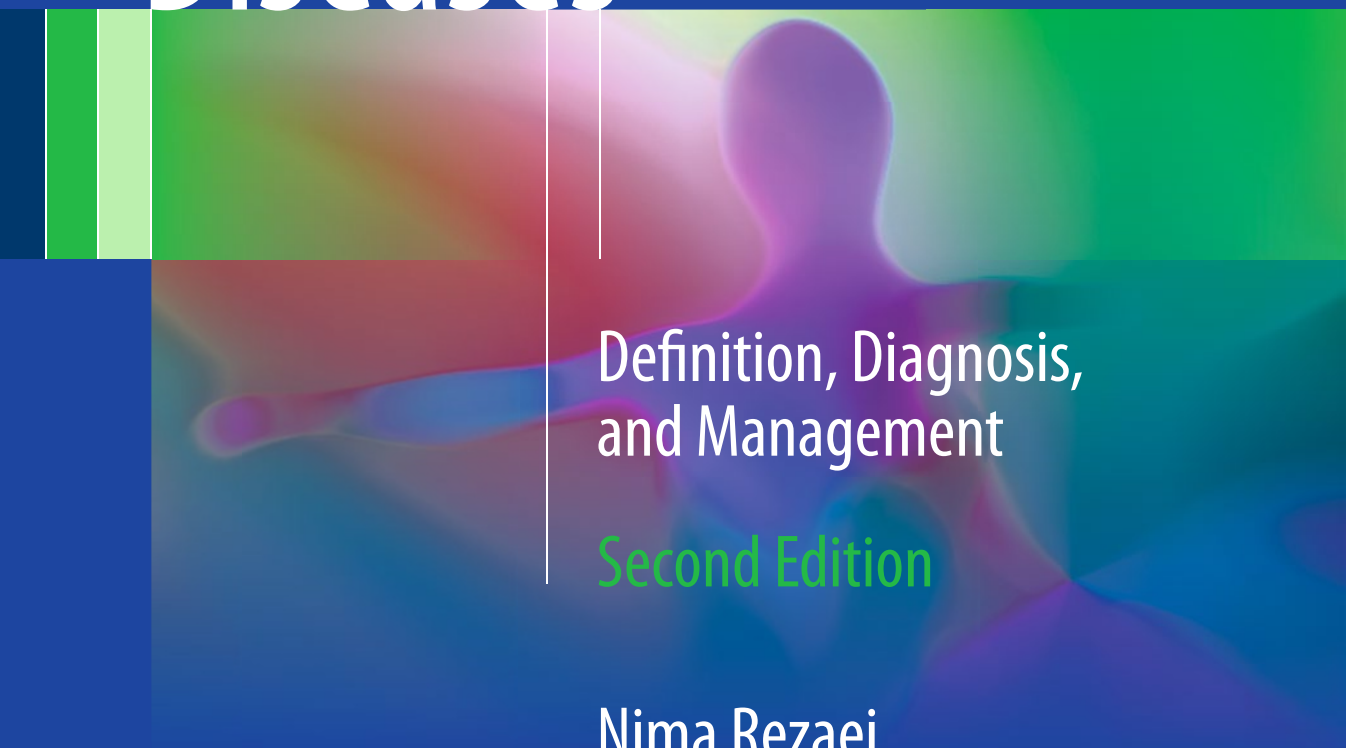
Primary Immunodeficiency Diseases



Definition, Diagnosis, and Management

Second Edition

Nima Rezaei
Asghar Aghamohammadi
Luigi D. Notarangelo
Editors

Springer

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This book would not have been possible without the continuous encouragement by our parents and our wives, Maryam, Soheila, and Evelina.
We wish to dedicate it to our children, Ariana, Arnika, Hamid Reza, Fatemeh, Claudio, Marco, and Giulia, with the hope that progress in diagnosis and management of these diseases may result in improved survival and quality of life for the next generations, and at the same time that international collaboration in research will happen without barriers.
Whatever we have learnt, comes from our mentors. This book is therefore dedicated also to all of them, but most importantly to our patients and their families whose continuous support has guided us over the years.

Foreword

With the advent of whole exome sequencing, the field of primary immunodeficiencies has exploded over the past 5 years. This updated edition of *Primary Immunodeficiency Diseases* by Nima Rezaei and a number of collaborators from around the world does a superb job of updating our knowledge of these fascinating disorders and covers all aspects for each of the diseases discussed, including current recommendations on treatment. A great deal of basic immunology has been learned from studies of these patients and much more has still to be discovered. This book addresses the need to increase awareness of the conditions worldwide and to define the resource requirements for diagnosis, genetic counseling, and treatment.

The commitment of Iranian pediatric immunologists to patients with primary immunodeficiency diseases and their collaborative efforts to discover novel genetic defects and to apply state-of-the-art methods for their diagnosis and treatment are demonstrated in the many chapters in this volume authored jointly by Iranian investigators and recognized international authorities in the subject. It is a tribute to the establishment of modern facilities in Tehran to diagnose and treat such patients that this second edition includes the latest discoveries in the field, and thus is up to date as well as practical.

The wide coverage of all aspects of primary immunodeficiency diseases provides a comprehensive text and will serve as a tool for experts who care for these patients in other geographical areas and who wish to spread awareness and understanding of this rapidly expanding field. It will be of great value to pediatric immunologists and will serve as a "Google-in-print" for primary immunodeficiency diseases.

Boston, MA, USA — Raif Geha
Seattle, WA, USA — Hans Ochs
Oxford, UK — Helen Chapel

Preface

Primary immunodeficiency diseases (PIDs) are a heterogeneous group of inherited disorders with defects in one or more components of the immune system, characterized by increased incidence of infections, autoimmunity, and malignancies. PIDs are not considered as rare conditions anymore, while the number of diagnosed patients has significantly been growing up. Nevertheless, because of inadequate medical awareness, it is estimated that a significant number of patients with PIDs are not recognized or are diagnosed late. This latency leads to a substantial increased rate of morbidity and mortality among the affected individuals. It should also be added that more than 300 different forms of PIDs have already been identified. Considering the fact that only 150 different types of PIDs had been described in the first edition of the book, it can show that how much efforts have been made during last decade in the identification of novel PIDs, which led to a twice increase in the number of described PIDs.

Our understanding on PID is rapidly improving, and this may facilitate the accuracy of diagnosis and efficiency of management. This book is an attempt to gather the most recent advances in this field and tries to provide a concise and structured review of hitherto known PIDs. Although the ultimate orientation of this book is toward practical diagnosis and management, the pathophysiology of diseases is also discussed. For this purpose, this book consists of 10 chapters. The first chapter gives an overview on PIDs and presents a classification of these disorders. In Chaps. 2, 3, 4, 5, 6, 7, 8, and 9, definition, etiology, clinical manifestations, diagnosis, and management of each disease are discussed separately. Syndromic immunodeficiencies are also briefly presented in Chap. 10, while some of them are explained in greater detail in other chapters.

This book is the result of the valuable contribution of 55 PID experts from top centers of five continents. We would like to acknowledge the expertise of all contributors, for generously giving their time and considerable effort in preparing their respective chapters. We are also grateful to Springer for giving us the opportunity to publish this book.

We hope that this book will be comprehensible, cogent, and manageable for physicians and nurses, who wish to learn more about PIDs. We were very pleased that the first edition of the book was very welcomed by the scientists from all over the world. It is our hope that second edition of

the book continues to represent a useful resource for doctors in training as well as for specialists and subspecialists in clinical decision-making and treatment planning.

Tehran, Iran — Nima Rezaei
Tehran, Iran — Asghar Aghamohammadi
Boston, MA, USA — Luigi Notarangelo

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Introduction on Primary Immunodeficiency Diseases

1

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1.1 Definition

1.1.1 Background

The immune system is a complex network of cells and organs which cooperate to protect individual against infectious microorganisms, as well as internally-derived threats such as cancers. The immune system specializes in identifying danger, containing and ultimately eradicating it. It is composed of highly specialized cells, proteins, tissues, and organs. B- and T- lymphocytes, phagocytic cells and soluble factors such as complement are some of the major components of the immune system, and have specific critical functions in immune defense.

When part of the immune system is missing or does not work correctly, immunodeficiency occurs; it may be either congenital (primary) or acquired (secondary). Secondary immunodeficiency diseases are caused by environmental factors such as infection with HIV, chemotherapy,

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irradiation, malnutrition, and others; while primary immunodeficiency diseases (PIDs) are hereditary disorders, caused by mutations of specific genes.

Primary immunodeficiency diseases are a heterogeneous group of inherited disorders with defects in one or more components of the immune system. These diseases have a wide spectrum of clinical manifestations and laboratory findings; however, in the vast majority of cases, they result in an unusually increased susceptibility to infections and a predisposition to autoimmune diseases and malignancies [44, 82, 83, 120, 214, 218, 251, 278]. Primary immunodeficiencies constitute a large group of diseases, including more than conservatively defined hereditary disorders [14, 120, 218, 278], affecting development of the immune system, its function, or both [24]. The number of known PIDs has been increased considerably over the last two decades, through two lines of research: the genetic dissection of known clinical phenotypes and the investigation of new clinical phenotypes [41, 64, 89, 239, 284]. Some of these clinical phenotypes are more common than traditional PID phenotypes. In particular, new PIDs conferring a specific predisposition to infections with one or a few pathogens have been described [61], including genetic predisposition to EBV [294], *Neisseria* [142], papillomavirus [228], *Streptococcus pneumonia* [236], weakly virulent mycobacteria [24, 146], herpes simplex virus [64], and *Candida albicans* [118]. Mendelian predisposition to tuberculosis has even been reported [114, 296]. In addition, various non-infectious phenotypes, as diverse as allergy, angioedema, hemophagocytosis, autoinflammation, autoimmunity, thrombotic microangiopathy and cancer, have been shown to result from inborn errors of immunity, in at least some patients [61]. Although the number of patients diagnosed with PIDs is growing, many physicians still know little about these disorders. Thus, many patients are diagnosed late; many cases suffer from complications by chronic infections, irretrievable end-organ damage, or even death before the definitive diagnosis is made. Timely diagnosis and appropriate treatment remain the keys to the successful management of patients with PIDs [68, 136, 246].

1.1.2 History

The birth of the primary immunodeficiency field is attributed to Col. Ogden Bruton in 1952, who reported a male patient with early onset recurrent infections and an absent gammaglobulin peak on serum protein electrophoresis. This child had an excellent response to immunoglobulin replacement therapy [53]; later, the condition ultimately became known as X-linked agammaglobulinemia (XLA) or Btk (Bruton's tyrosine kinase) deficiency. However, several patients with characteristic clinical manifestations of immunodeficiency disorders had been reported before 1950; e.g. Ataxia-telangiectasia (AT) in 1926 [283], chronic mucocutaneous candidiasis (CMCC) in 1929 [288], and Wiskott-Aldrich syndrome (WAS) in 1937 [315]. The first patient with cellular deficiency was initially reported in 1950 [124], the first case of a phagocytic defect (severe congenital neutropenia: SCN) was reported in 1956 [155], and the first case of complement deficiency (C2 deficiency) was initially reported in 1966 [154].

The discovery of PIDs and characterization of these diseases led to crucial contributions to understanding the functional organization of the immune system and molecular biology. Thus, the study of PIDs has contributed to progress in immunological and molecular diagnostic techniques. These advances enabled increased recognition and characterization of new types of PIDs, and identification of about 300 different types of PIDs in the ensuing years (Tables 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, and 1.8) [235].

1.1.3 Epidemiology

Several PID registries have been established in different countries during the last three decades [2, 4, 9, 13, 18, 20, 35, 37, 49, 60, 106, 107, 110, 111, 119, 128, 130, 143, 145, 152, 160, 161, 164, 166, 174, 180, 181, 190, 196, 207, 243, 246, 248,

Table 1.1 Modified IUIS classification of combined T- and B-cell immunodeficiencies [235]

Diseases		Inheritance	Genetic defects
T-B+ Severe combined immunodeficiency	*γc deficiency*	XL	IL-2 receptor gamma (*IL2RG*)
	JAK3 deficiency	AR	Janus-associated kinase 3 (*JAK3*)
	IL7-Rα deficiency	AR	IL-7 receptor (*IL7-R*) alpha
	CD45 deficiency	AR	Leukocyte-common antigen (*LCA*) or *CD45*
	CD3γ deficiency	AR	T-cell antigen receptor, Gamma subunit of T3 (*CD3G*)
	CD3δ deficiency	AR	T-cell antigen receptor, Delta subunit of T3 (*CD3D*)
	CD3ε deficiency	AR	T-cell antigen receptor, Epsilon subunit of T3 (*CD3E*)
	CD3ξ deficiency	AR	T-cell antigen receptor, Zeta subunit of T3 (*CD3Z*) or *CD247*
	Coronin-1A deficiency	AR	Coronin 1A (*CORO1A*)
T-B− Severe combined immunodeficiency	*RAG 1 deficiency*	AR	Recombination-activating gene 1 (*RAG1*)
	RAG 2 deficiency	AR	Recombination-activating gene 2 (*RAG2*)
	Artemis deficiency	AR	Artemis or DNA cross-link repair protein 1C (*DCLRE1C*)
	DNA PKcs deficiency	AR	Protein kinase, DNA-activated catalytic subunit (*PRKDC*)
	DNA ligase IV deficiency	AR	DNA ligase IV (*LIG4*)
	Cernunnos/XLF deficiency	AR	Nonhomologous end-joining 1 (*NHEJ1*) or *CERNUNNOS*
Omenn syndrome		AR	*RAG1/2*, *DCLRE1C*, *LIG4*, *IL2RG*, *IL7-R*, *ADA*, *AK2*, *RMRP*
Purine salvage pathway defects	*ADA deficiency*	AR	Adenosine deaminase (*ADA*)
	Purine nucleoside phosphorylase (PNP) deficiency	AR	Purine nucleoside phosphorylase (*PNP*)
Reticular dysgenesis	*AK2 deficiency*	AR	Adenylate kinase 2 (*AK2*)
DOCK2 deficiency		AR	Dedicator of Cytokinesis 2 (*DOCK2*)
Immunoglobulin class switch recombination deficiencies affecting CD40-CD40L	*CD40 ligand deficiency*	XL	Tumor necrosis factor ligand superfamily, member 5 (*TNFS5B*) or CD40 antigen ligand (*CD40L*)
	CD40 deficiency	AR	Tumor necrosis factor receptor superfamily, member 5 (*TNFRSF5*)
Complete DiGeorge syndrome		De novo, AD	22q.11.2 deletion, T-box 1 (*TBX1*)
CHARGE syndrome	*CHD7 deficiency*	AD	Chromodomain helicase DNA-binding protein 7 (*CHD7*)
	SEMA3E deficiency	AD	Semaphorin 3E (*SEMA3E*)
Combined immunodeficiency with alopecia totalis	*WHN deficiency*	AR	Winged-helix-nude (*WHN*) or Forkhead box N1 (*FoxN1*)

(continued)

Table 1.1 (continued)

Diseases		Inheritance	Genetic defects
Immuno-osseous dysplasias	*Schimke syndrome*	AR	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A-like (*SMARCAL1*)
	Cartilage hair hypoplasia	AR	RNA component of mitochondrial RNA-processing endoribonuclease (*RMRP*)
Combined immunodeficiency with intestinal atresias	*TTC7A deficiency*	AR	Tetratricopeptide repeat domain.containing protein 7A (*TTC7A*)
MHC class II deficiency	*CIITA deficiency*	AR	Class II transactivator (*CIITA*)
	RFX5 deficiency	AR	MHCII promoter X box regulatory factor 5 (*RFX5*)
	RFXAP deficiency	AR	Regulatory factor X-associated protein (*RFXAP*)
	RFXANK deficiency	AR	Ankyrin repeat containing regulatory factor X-associated protein (*RFXANK*)
MHC class I deficiency	*TAP1 deficiency*	AR	Transporter associated with antigen processing 1 (*TAP1*)
	TAP2 deficiency	AR	Transporter associated with antigen processing 2 (*TAP2*)
	TAPBP deficiency	AR	Tap-binding protein (*TAPBP*)
	β2-microglobulin deficiency		Beta-2 microglobulin (*B2M*)
CD8 deficiency	*ZAP-70 deficiency*	AR	Zeta-chain-associated protein of 70 kd signaling kinase (*ZAP70*)
	CD8α chain defect	AR	CD8 antigen, alpha polypeptide (*CD8A*)
Lck deficiency		AR	Lymphocyte-specific protein-tyrosine kinase (*LCK*)
Idiopathic CD4 lymphocytopenia		Variable	Unknown
TCRα deficiency		AR	T-cell receptor alpha chain constant region (*TRAC*)
CRAC channelopathy	*ORAI-I deficiency*	AR	ORAI1 or Calcium release-activated calcium modulator 1 (*CRACM1*) or Transmembrane protein 142A (*TMEM142A*)
	STIM-1 deficiency	AR	Stromal interaction molecule 1 (STIM1)
STK4 deficiency	*MST1 deficiency*	AR	Macrophage stimulating 1 (*MST1*)
CARD11/BCL10/MALT1 (CBM) complex deficiencies		AR	Caspase recruitment domain-containing protein 11 (*CARD11*), B-cell CLL/lymphoma 10 (*BCL10*), Mucosa-associated lymphoid tissue lymphoma translocation gene 1 (*MALT1*)
RHOH deficiency		AR	Ras homolog gene family, member H (*RHOH*)
OX40 deficiency		AR	Tumor necrosis factor receptor superfamily, member 4 (*TNFRSF4* or *OX40*)

IL21/IL21R deficiency	*IL21 deficiency*	AR	Interleukin 21 (*IL21*)
	IL21R deficiency	AR	Interleukin 21 receptor (*IL21R*)
IKAROS deficiency		AD de novo	Family zinc finger (*IKZF*)
IKK2 deficiency	*IKBKB deficiency*	AR	Inhibitor of kappa light chain gene enhancer in B cells, kinase of, beta (*IKBKB*)
NIK deficiency		AR	Mitogen-activated protein 3 kinase 14 (*MAP3K14*)
CTPS1 deficiency		AR	Cytidine 5-prime triphosphate synthetase 1 (*CTPS1*)
Other combined immunodeficiencies	*DOCK8 deficiency*	AR	Dedicator of cytokinesis 8 (*DOCK8*)
	ITK deficiency	AR	IL2-inducible T-cell kinase (*ITK*)
	MAGT1 deficiency	XL	Magnesium transporter 1 (*MAGT1*)
	CD25 deficiency	AR	Interleukin 2 receptor, alpha (*IL2RA*) or *CD25*
	STAT5b deficiency	AR	Signal transducer and activator of transcription 5B (*STAT5B*)
	MTHFD1 deficiency	AR	Methylenetetrahydrofolate dehydrogenase 1 (*MTHFD1*)
	ICOS deficiency	AR	Inducible costimulator (*ICOS*)
	LRBA deficiency	AR	Lipopolysaccharide-responsive, beige-like anchor protein (*LRBA*)

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

Table 1.2 Modified IUIS classification of predominantly antibody deficiencies [235]

Diseases		Inheritance	Genetic defects
X-linked agammaglobulinemia	*Btk deficiency*	XL	Bruton tyrosine kinase (*BTK*)
Autosomal recessive agammaglobulinemia	*μ heavy chain deficiency*	AR	Ig heavy mu chain (*IGHM*)
	λ5 deficiency	AR	Immunoglobulin lambda-like polypeptide 1 (*IGLL1*)
	Igα deficiency	AR	CD79A antigen (*CD79*A)
	Igβ deficiency	AR	CD79B antigen (*CD79B*)
	BLNK deficiency	AR	B cell liker protein (*BLNK*) or SH2 domain containing leukocyte protein, 65-KD (*SLP65*)
Other forms of agammaglobulinemia with absent B-cells	*TCF3 deficiency*	AD	Transcription factor 3 (*TCF3*)
	LRRC8 deficiency	AD	Leucine-rich repeat-containing protein 8 (*LRRC8*)
	Other forms of agammaglobulinemia	Variable	Unknown
PI3K syndrome		AR, AD gain-of-function	Phosphatidylinositol 3-kinase, catalytic, delta (*PIK3CD*), Phosphatidylinositol 3-kinase, regulatory subunit 1 (*PIK3R1*)
Common variable immunodeficiency		Variable	Unknown
LRBA deficiency		AR	Lipopolysaccharide-responsive, beige-like anchor protein (*LRBA*)
CD19 complex deficiencies	*CD19 deficiency*	AR	CD19 antigen (*CD19*)
	CD21 deficiency	AR	Complement component receptor 2 (*CR2* or *CD21*)
	CD81 deficiency	AR	CD81 antigen (*CD81*)
CD20 deficiency		AR	Membrane-spanning 4 domains, subfamily A, member 1 (*MS4A1* or *CD20*)
Other monogenic defects associated with hypogammaglobulinemia	*ICOS deficiency*	AR	Inducible costimulator (*ICO*S)
	TACI deficiency	AD or AR	Tumor necrosis factor receptor superfamily, member 13B (*TNFRSF13B*)
	BAFF receptor deficiency	AR	Tumor necrosis factor receptor superfamily, member 13C (*TNFRSF13C* or *BAFFR*)
	TWEAK deficiency	AD	Tumor necrosis factor ligand superfamily, member 12 (*TNFSF12* or *TWEAK*)
	NFKB2 deficiency	AD	Nuclear factor kappa-b, subunit 2 (*NFKB2*)
	MOGS deficiency	AR	Mannosyl-oligosaccharide glycosidase (*MOGS*)
	TRNT1 deficiency	AR	tRNA nucleotidyltransferase CCA-adding, 1 (*TRNT1*)
	TTC37 deficiency	AR	Tetratricopeptide repeat domain-containing protein 37 (*TTC37*)

Immunoglobulin class switch recombination deficiencies affecting B-cells	*AICDA deficiency*	AR	Activation-induced cytidine deaminase (*AICDA*)
	UNG deficiency	AR	Uracil-DNA glycosylase (*UNG*)
	MMR deficiency	AR	MutS E. coli homolog of 6 (*MSH6*)
	INO80 deficiency	AR	INO80 complex subunit (*INO80*)
Selective IgA deficiency		Variable	Unknown
Other immunoglobulin isotypes or light chain deficiencies	*Isolated IgG subclass deficiency*	Variable	Unknown
	IgA with IgG subclass deficiency	Variable	Unknown
	Ig heavy chain mutations/deletions	AR	Chromosomal deletion at 14q32
	k light chain deficiency	AR	Ig kappa constant region (*IGKC*)
Specific antibody deficiency with normal immunoglobulin concentrations		Variable	Unknown
Transient hypogammaglobulinemia of infancy		Variable	Unknown

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

Table 1.3 Modified IUIS classification of phagocytes defects [235]

Diseases		Inheritance	Genetic defects
Chronic granulomatous disease	*gp91 ^{phox} deficiency*	XL	Cytochrome b(−245), beta subunit (*CYBB*)
	p22 ^{phox} deficiency	AR	Cytochrome b(−245), alpha subunit (*CYBA*)
	p47 ^{phox} deficiency	AR	Neutrphil cytosolic factor 1 (*NCF1*)
	p67 ^{phox} deficiency	AR	Neutrophil cytosolic factor 2 (*NCF2*)
	p40 ^{phox} deficiency	AR	Neutrophil cytosolic factor 2 (*NCF4*)
Leukocyte adhesion deficiency	*ITGB2 or CD18 deficiency*	AR	Integrin, beta-2 (*ITGB2*)
	SCL35C1 or CDG-IIc deficiency	AR	Solute carrier family 35, member C1 (*SLC35C1*) or GDP-fucose transporter 1 (*FUCT1*)
	FERMT3 or Kindlin3 deficiency	AR	Fermitin family (Drosophila) homolog 3 (*FERMT3*)
RAC-2 deficiency		AD	Ras-related C3 botulinum toxin substrate 2 (*RAC2*)
β-Actin deficiency		AD	Actin, beta (*ACTB*)
Localized juvenile periodontitis		AR	Formyl peptide receptor 1 (*FRP1*)
Papillon-Lefèvre syndrome		AR	Cathepsin c (*CTSC*)
Specific granule deficiency		AR	CCAAT/enhancer-binding protein, epsilon (*CEBPE*)
Shwachman-Diamond syndrome		AR	Shwachman-Bodian-Diamond syndrome (*SBDS*)
Severe congenital neutropenias	*ELANE deficiency*	AD	Elastase, neutrophil-expressed (*ELANE*)
	GFI1 deficiency	AD	Growth factor-independent 1 (*GFI1*)
	HAX1 deficiency	AR	HCLS1-associated protein X1 (*HAX1*)
	G6PC3 deficiency	AR	Glucose-6-phosphatase, catalytic, 3 (*G6PC3*)
	VPS45 deficiency	AR	Vacuolar protein sorting 45, yeast, homolog of, A (*VPS45A*)
	X-linked neutropenia	XL	Wiskott-Aldrich syndrome protein (*WASP*)
	p14 deficiency	AR	Late endosomal/lysosomal adaptor, MAPK and MTOR activator 2 (*LAMTOR2*)
	JAGN1 deficiency	AR	Jagunal, drosophila, homolog of, 1 (*JAGN1*)
	G-CSF receptor deficiency	AR	Colony-stimulating factor 3 receptor, granulocyte (*CSF3R*)
Cyclic neutropenia		AD	Elastase, neutrophil-expressed (*ELANE*)
Glycogen storage disease type 1b		AR	Glucose-6-phosphatase transporter 1 (*G6PT1* or *SLC37A4*)
3-Methylglutaconic Aciduria	*Type II* (*Barth syndrome*)	XL	Tafazzin (*TAZ*)
	Type VII	AR	Caseinolytic peptidase B (*CLPB*)
Cohen syndrome		AR	Vacuolar protein sorting 13, yeast, homolog of, B (*VPS13B* or *COH1*)
Poikiloderma with neutropenia		AR	Chromosome 16 open reading frame 57 (*C16ORF57*)
Myeloperoxidase deficiency		AR	Myeloperoxidase (*MPO*)

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

Table 1.4 Modified IUIS classification of genetic disorders of immune regulation [235]

Diseases		Inheritance	Genetic defects
Familial hemophagocytic lymphohistiocytosis	*Perforin deficiency*	AR	Perforin 1 (*PRF1*)
	UNC13D deficiency	AR	*MUNC13-4* or *UNC13D*
	Syntaxin 11 deficiency	AR	Syntaxin 11 (*STX11*)
	STXBP2 deficiency	AR	Syntaxin-bnding protein 2 (*STXBP2*)
Autoimmune lymphoproliferative syndrome	*FAS defect*	AD, AR	Tumor necrosis factor receptor superfamily, member 6 (*TNFRSF6*) or *CD95* or *FAS*
	FASLG defect	AR	Tumor necrosis factor ligand superfamily, member 6 (*TNFSF6*) or *CD95L* or *FASL*
	CASP10 deficiency	AD	Caspase 10, apoptosis-related cysteine protease (*CASP10*)
	CASP8 deficiency state	AR	Caspase 8, apoptosis-related cysteine protease (*CASP8*)
	RAS-associated autoimmune leukoproliferative disease	AD	Unknown, Neuroblastome RAS viral oncogene homolog (*NRAS*)
	FADD deficiency	AR	FAS-associated via death domain (*FADD*)
	CTLA4 deficiency	AD	Cytotoxic T lymphocyte-associated 4 (*CTLA4*)
Chediak-Higashi syndrome		AR	Lysosomal trafficking regulator (*LYST*)
Griscelli syndrome, type 2		AR	Ras-associated protein rab27a (*RAB27A*)
Hermansky-Pudlak syndrome	*HPS type 2*	AR	Adaptor-related protein complex 3, beta-1 subunit (*AP3B1*)
	HPS type 9	AR	Biogenesis of lysosome-related organelles complex 1, subunit 6 (*BLOC1S6*)
	HPS10	AR	Adaptor-related protein complex 3, delta-1 subunit (*AP3D1*)
Other immunodeficiencies associated with hypopigmentation	*p14 deficiency*	AR	MAPBP-interacting protein (*MAPBPIP*) or *P14*
	Vici syndrome	AR	Ectopic P-granules autophagy protein 5, C. elegans, homolog of (*EPG5*)
X-linked lymphoproliferative syndromes	*SAP deficiency*	XL	src homology 2-domain protein (*SH2D1A*)
	XIAP deficiency	XL	Inhibitor-of-apotosis, X-linked (*XIAP*) or Baculoviral IAP repeat-containing protein 4 (*BIRC4*)
	MAGT1 deficiency	XL	Magnesium transporter 1 (*MAGT1*)
Autosomal recessive lymphoproliferative syndromes	*ITK deficiency*	AR	IL2-inducible T-cell kinase (*ITK*)
	CD27 deficiency	AR	Tumor necrosis factor receptor superfamily, member 7 (*TNFRSF7* or *CD27*)
Immunodysregulation, polyendocrinopathy, enteropathy, X-linked	*IPEX*	XL	Forkhead box P3 (*FOXP3*)

(continued)

Table 1.4 (continued)

Diseases		Inheritance	Genetic defects
CD25 deficiency		AR	Interleukin 2 receptor, alpha (*IL2RA*) or *CD25*
STAT5B deficiency		AR	Signal transducer and activator of transcription 5B (*STAT5B*)
ITCH deficiency		AR	Itchy E3 ubiquitin protein ligase, mouse, homolog of (*ITCH*)
TPP2 deficiency		AR	Tripeptidyl peptidase II (*TPP2*)
COPA deficiency		AD	Coatamer Protein Complex, Subunit Alpha (*COPA*)

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

Table 1.5 Modified IUIS classification of defects in intrinsic and innate immunity: receptors and signaling components [235]

Diseases		Inheritance	Genetic defects
Anhidrotic ectodermal dysplasia with immunodeficiency	*NEMO deficiency*	XL	Inhibitor of kappa light polypeptide gene enhancer in B cells, kinase of, gamma (*IKBKG*) or NF-kappa-B essential modulator (*NEMO*)
	IkBA gain-of-function mutations	AD	Inhibitor of kappa light polypeptide gene enhancer in B cells, kinase of, alpha (*IKBA*)
HOIL1 and HOIP deficiencies	*HOIL1 deficiency*	AR	Heme-oxidized IRP2 ubiquitin ligase 1 (*HOIL1*)
	HOIP deficiency	AR	HOIL1-interacting protein (*HOIP*)
IRAK-4 and MyD88 deficiencies	*IRAK-4 deficiency*	AR	Interleukin 1 receptor-associated kinase 4 (*IRAK4*)
	MyD88 deficiency	AR	Myeloid differentiation primary response gene 88 (*MYD88*)
Herpes simplex encephalitis	*TLR3 deficiency*	AD	Toll-like receptor 3 (*TLR3*)
	UNC93B deficiency	AR	*UNC-93B*
	TRAF3 deficiency	AD	TNF receptor-associated factor 3 (*TRAF3*)
	TRIF deficiency	AR, AD	Testis-specific ring finger protein (*TRIF*)
	TBK1 deficiency	AD	Tank-binding kinase 1 (*TBK1*)
	IRF3 deficiency	AD	Interferon regulatory factor 3 (*IRF3*)
Mendelian susceptibility to mycobacterial diseases	*IFN-γ receptor 1 deficiency*	AR, AD	Interferon, gamma, receptor 1 (*IFNGR1*)
	IFN-γ receptor 2 deficiency	AR, AD	Interferon, gamma, receptor 2 (*IFNGR2*)
	IL-12/IL-23 receptor β1 chain deficiency	AR	Interleukin 12 receptor, beta-1 (*IL12RB1*)
	IL-12p40 deficiency	AR	Interleukin 12B (*IL12B*)
	DP-STAT1 deficiency	AR, AD	Signal transducer and activator of transcription 1 (*STAT1*)
	LZ-NEMO deficiency	XL	NF-kappa-B essential modulator (*NEMO*)
	Macrophage-specific CYBB deficiency	XL	Cytochrome b(−245), beta subunit (*CYBB*)
	AD-IRF8 deficiency	AD	Interferon regulatory factor 8 (*IRF8*)
	ISG15 deficiency	AR	Ubiquitin-like modifier ISG15 (ISG15)

Table 1.5 (continued)

Diseases		Inheritance	Genetic defects
Genetic defects of interferon type I and III responses other than TLR3 pathway	*AR STAT1 deficiency*	AR	Signal transducer and activator of transcription 1 (*STAT1*)
	STAT2 deficiency	AR	Signal transducer and activator of transcription 2 (*STAT2*)
	TYK2 deficiency	AR	Protein-tyrosin kinase 2 (*TYK2*)
	IRF7 deficiency	AR	Interferon regulatory factor 7 (*IRF7*)
Warts, hypogammaglobulinemia infections, myelokathexis (WHIM) syndrome		AD	Chemokine, CXC motif, receptor 4 (*CXCR4*)
Epidermodysplasia verruciformis	*EVER1 deficiency*	AR	Epidermodysplasia verruciformis gene 1 (*EVER1*)
	EVER2 deficiency	AR	Epidermodysplasia verruciformis gene 2 (*EVER2*)
Chronic mucocutaneous candidiasis	*IL17RA deficiency*	AR	Interleukin 17 receptor A (*IL17RA*)
	IL17F deficiency	AD	Interleukin 17 F (*IL17F*)
	IL17RC deficiency	AR	Interleukin 17 receptor C (*IL17RC*)
	STAT1 gain-of-function mutation	AD	Signal transducer and activator of transcription 1 (*STAT1*)
	ACT1 deficiency	AR	Nuclear factor kappa-B activator 1 (*ACT1*)
CARD9 deficiency		AR	Caspase recruitment domain-containing protein 9 (*CARD9*)
Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy		AR	Autoimmune regulator (*AIRE*)
RORC deficiency		AR	RAR-related orphan receptor C (*RORC*)
Monocyte/dendritic cell deficiencies	*AD GATA2 deficiency*	AD	GATA-binding protein 2 (*GATA2*)
	AR IRF8 deficiency	AR	Interferon regulatory factor 8 (*IRF8*)
NK cell deficiencies	*MCM4 deficiency*	AR	Minichromosome maintenance complex component 4 (*MCM4*)
Pulmonary alveolar proteinosis		AR	Colony-stimulating factor 2 receptor, alpha (*CSF2RA*)
		AR	Colony-stimulating factor 2 receptor, beta (*CSF2RB*)
Isolated congenital asplenia		AD	NK2 homeobox 5 (*NKX2-5*)
		AD	Ribosomal protein SA (*RPS*)

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

Table 1.6 Modified IUIS classification of autoinflammatory disorders [235]

Diseases		Inheritance	Genetic defects
Familial mediterranean fever		AR	Mediterranean fever (*MEFV*)
Mevalonate kinase deficiency	*Hyper-IgD and periodic fever syndrome*	AR	Mevalonate kinase (*MVK*)
	Mevalonic aciduria	AR	Mevalonate kinase (*MVK*)
TNF receptor-associated periodic syndrome		AD	Tumor necrosis factor receptor superfamily, member 1a (*TNFRSF1A*)
Cryopyrin-associated periodic syndrome	*Chronic infantile neurological cutaneous articular syndrome*	AD	NLR family, pyrin domain containing 3 (*NLRP3*) or Cias1 gene (*CIAS1*) or Nacht domain-, leucine-rich repeat-, and pyd-containing protein 3 (*NALP3*) or Pyrin domain-containing APAF1-like protein 1 (*PYPAF1*)
	Muckle-Wells syndrome	AD	
	Familial cold autoinflammatory syndrome	AD	
Blau syndrome	*Pediatric granulomatous arthritis*	AD	Caspase recruitment domain-containing protein 15 (*CARD15*) or Nucleotide-binding oligomerization domain protein 2 (*NOD2*)
Pyogenic arthritis, pyoderma gangrenosum and acne syndrome		AD	Proline/Serine/Threonine phosphatase-interacting protein 1 (*PSTPIP1*) or CD2 antigen-binding protein 1 (*CD2BP1*)
NLRP12 associated periodic fever syndrome		AD	Nacht domain-, leucine-rich repeat-, and pyd-containing protein 12 (*NLRP12*)
Deficiency of ADA2		AR	Cat eye syndrome chromosome region, candidate 1 (*CECR1*)
STING-associated vasculopathy with onset in infancy		AD	Transmembrane protein 173 (*TMEM173*)
Deficiency of the IL-1 receptor antagonist		AR	Interleukin 1 receptor antagonist (*IL1RN*)
Majeed syndrome		AR	Lipin 2 (*LPIN2*)
Deficiency of IL-36 receptor antagonist		AR	Interleukin 36 receptor antagonist (*IL36RN*)
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature		AR	Proteasome subunit beta type 8 (*PSMB8*)
Early onset inflammatory bowel diseases	*IL-10 deficiency*	AR	Interleukin 10 (*IL10*)
	IL-10Rα deficiency	AR	Interleukin 10 receptor alpha (*IL10RA*)
	IL-10Rβ deficiency	AR	Interleukin 10 receptor beta (*IL10RB*)
	NFAT5 haploinsufficiency	AD	Nuclear factor of activated T cells 5 (*NFAT5*)
	ADAM17 deficiency	AR	A disintegrin and metalloproteinase domain 17 (*ADAM17*)
Autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation		AD	Phospholipase Cγ2 (*PLCG2*)

Table 1.6 (continued)

Diseases		Inheritance	Genetic defects
Sideroblastic anemia, immunodeficiency, fevers, and developmental delay		AR	tRNA nucleotidyl transferase, CCA-adding, 1 (*TRNT1*)
Aicardi-Goutieres syndromes (AGS)	*AGS1*	AR, AD	Three prime repair exonuclease 1 (*TREX1*)
	AGS2	AR	Ribonuclease H2 subunit A (*RNASEH2A*)
	AGS3	AR	Ribonuclease H2 subunit B (*RNASEH2B*)
	AGS4	AR	Ribonuclease H2 subunit C (*RNASEH2C*)
	AGS5	AR	SAM domain and HD domain 1 (*SAMHD1*)
	AGS6	AR	Adenosine deaminase, RNA-specific (*ADAR*)
	AGS7	AD	Interferon induced with helicase C domain 1 (*IFIH1*)
CARD14 mediated psoriasis		AD	Caspase recruitment domain family member 14 (*CARD14*)
Haploinsufficiency of A20 (HA20)		AR	TNF alpha induced protein 3 (*TNFAIP3*)
Episodic fevers, enteropathy, and MAS due to NLRC4 hyperactivity		AD	NLR family, CARD domain containing 4 (*NLRC4*).
TNFRSF11A-associated disease		AD	Tumor necrosis factor receptor superfamily member 11a (*TNFRSF11A*)
Histiocytosis-lymphadenopathy plus syndrome		AD	Soluble carrier family 29, member 3 (*SLC29A3*)
Cherubism		AD	SH3 domain-binding protein 2 (*SH3BP2*)
Spondyloenchondro-dysplasia with immune dysregulation		AD	Phosphatase, acid, type 5, tartrate-resistant (*ACP5*)

AR autosomal recessive, *AD* autosomal dominant

Table 1.7 Modified IUIS classification of complement deficiencies [235]

Diseases		Inheritance	Genetic defects
Deficiencies of classical pathway components	*C1q deficiency*	AR	Complement component 1, q subcomponent, alpha, beta and gamma polypeptides (*C1QA*, *C1QB*, *C1QG*)
	C1r deficiency	AR	Complement component *C1R*
	C1s deficiency	AR	Complement component 1, s subcomponent (*C1S*)
	C4 deficiency	AR	Complement component 4A and 4B (*C4A*, *C4B*)
	C2 deficiency	AR	Complement component 2
Deficiencies of lectin pathway components	*MBL deficiency*	AR	Lectin, mannose-binding, soluble, 2 (*MBL2*) or Mannose-binding protein, Serum (*MBP1*)
	MASP-2 deficiency	AR	Mannan-binding lectin serine protease 2 (*MASP2*)
	MASP-3 deficiency	AR	Mannan-binding lectin serine protease 1 (*MASP1*)
	Ficolin 3 deficiency	AR	Ficolin 3 (*FCN3*)
	Collectin 11 deficiency	AR	Collectin 11 (*COLEC11*)
Deficiencies of alternative pathway components	*Factor D deficiency*	AR	Complement factor D (*CFD*)
	Properdin deficiency	XL	Properdin P factor, complement (*PFC*)
Deficiency of complement component C3		AR	Complement component 3 (*C3*)
Deficiencies of terminal pathway components	*C5 deficiency*	AR	Complement component 5
	C6 deficiency	AR	Complement component 6
	C7 deficiency	AR	Complement component 7
	C8a deficiency	AR	Complement component 8, alpha subunit (*C8A*)
	C8b deficiency	AR	Complement component 8, beta subunit (*C8B*)
	C9 deficiency	AR	Complement component 9
Deficiencies of soluble regulatory proteins	*C1 inhibitor deficiency*	AD	Complement component 1 inhibitor (*C1NH*)
	Factor I deficiency	AR	Complement factor I (*CFI*)
	Factor H deficiency	AR	Complement factor H (*CFH*)
Deficiencies of the regulatory proteins and complement receptors	*MCP deficiency*	AD	Membrane cofactor protein (*MCP*) or *CD46*
	DAF deficiency	AR	Decay-accelerating factor for complement (*DAF*) or *CD55* antigen
	CD59 deficiency	AR	CD59 antigen p18-20 (*CD59*)
	PIGA deficiency	XL	Phosphatidylinositol glycan, class A (*PIGA*)
	CR3 deficiency	AR	Integrin, beta-2 (*ITGB2*)

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

Table 1.8 Modified IUIS classification of other well-defined immunodeficiencies [235]

Diseases		Inheritance	Genetic defects
Ataxia-telangiectasia		AR	Ataxia-telangiectasia mutated gene (*ATM*)
Ataxia telangiectasia-like disorder		AR	Meiotic recombination 11, S. cerevisiae, homolog of, A (*MRE11A*)
Nijmegen breakage syndrome		AR	Nijmegen breakage syndrome gene (*NBS1*)
RAD50 deficiency		AR	RAD50, cerevisiae, homolog of (*RAD50*)
Radiosensitivity, immunodeficiency, dysmorphic features and learning difficulties (RIDDLE) syndrome		AR	Ring finger protein 168 (*RNF168*)
Bloom syndrome		AR	Bloom syndrome (*BLM*)
Dyskeratosis congenita	*Dyskerin deficiency*	XL	Dyskerin (*DKC1*)
	NHP2 deficiency	AR	Nucleolar protein family A, member 2 (*NOLA2*) or (*NHP2*)
	NHP3 deficiency	AR	Nucleolar protein family A, member 3 (*NOLA3*) or (*NOP10*, *PCFT*)
	RTEL1 deficiency	AD, AR	Regulator of telomere elongation helicase 1 (*RTEL1*)
	TERC deficiency	AD	Telomerase RNA component (*TERC*)
	TERT deficiency	AD, AR	Telomerase reverse transcriptase (*TERT*)
	TINF2 deficiency	AD	TRF1-interacting nuclear factor 2 (*TINF2*)
	TPP1 deficiency	AD, AR	ACD, mouse homolog of (*ACD*)
	DCLRE1B deficiency	AR	DNA cross-link repair protein 1B (*DCLRE1B*) or (*SNM1/APOLLO*)
	PARN deficiency	AR	Polyadenylate-specific ribonuclease (*PARN*)
Rothmund-Thomson syndrome		AD	RECQ protein-like 4 (*RECQL4*)
Other well defined immunodeficiencies with DNA repair defects	*DNA ligase IV deficiency*	AR	DNA ligase IV (*LIG4*)
	Cernunnos-XLF deficiency	AR	Nonhomologous end-joining 1 (*NHEJ1*) or *CERNUNNOS*
	XRCC4 deficiency	AR	X-ray repair, complementing defective, in Chinese hamster, 4 (*XRCC4*)
	DNA PKcs deficiency	AR	Protein kinase, DNA-activated catalytic subunit (*PRKDC*)
	DNA ligase I deficiency	AR	DNA LIGASE I (*LIG1*)
	Fanconi anemia	AR, XL	FANCEF gene (*FANCF*)
	PMS2 deficiency	AR	Postmeiotic segregation increased S. cerevisiae, 2 (*PMS2*)
	MCM4 deficiency	AR	Minichromosome maintenance complex component 4 (*MCM4*)

(continued)

Table 1.8 (continued)

Diseases		Inheritance	Genetic defects
Immunodeficiency, centromere instability and facial abnormalities syndrome	*ICF1*	AR	DNA methyltransferase 3b (*DNMT3B*)
	ICF2	AR	Zinc finger and BTB domain-containing protein 24 (*ZBTB24*)
	ICF3	AR	Cell division cycle-associated protein 7 (*CDCA7*)
	ICF4	AR	Helicase, lymphoid-specific (*HELLS*)
Hyper-IgE syndrome	*STAT3 deficiency*	AD	Signal transducer and activator of transcription 3 (*STAT3*)
DOCK8 deficiency		AR	Dedicator of cytokinesis 8 (*DOCK8*)
PGM3 deficiency		AR	Phosphoglucomutase 3 (*PGM3*)
Comel Netherton syndrome		AR, XL	Serine protease inhibitor, Kazal-type, 5 (*SPINK5*)
Other forms of hyper-IgE syndrome	*Tyk2 deficiency*	AR	Protein-tyrosin kinase 2 (*TYK2*)
Wiskott-Aldrich syndrome		XL	Wiskott-Aldrich syndrome gene (*WAS*)
WIP deficiency		AR	WASP-interacting protein (*WIP*)
Hepatic veno-occlusive disease with immunodeficiency		AR	Nuclear body protein SP110 (*SP110*)
POLE deficiency	*POLE1 deficiency*	AR	Polymerase, DNA, epsilon-1 (*POLE1*)
	POLE2 deficiency	AR	Polymerase, DNA, epsilon-2 (*POLE2*)
Defects of vitamin B12 and folate metabolism	*Transcobalamin 2 deficiency*	AR	Transcobalamin 2 (*TCN2*)
	SLC46A1/PCFT deficiency	AR	Soluble carrier family 46 member 1 (*SLC46A1*)
	MTHFD1 deficiency	AR	Methylenetetrahydrofolate dehydrogenase 1 (*MTHFD1*)

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

309, 322, 325]. They provide valuable epidemiological information and demonstrate wide geographical and racial variations in the prevalence of PIDs in general and of its different types (Table 1.9). Considering the reports from major databases, including ESID (European Society for Immunodeficiencies) [110], LASID (Latin American Society for Primary Immunodeficiency Diseases) [164], USIDnet (US Immunodeficiency Network) [296], as well as selected reported registries from Asia [9, 13, 18, 20, 37, 107, 130, 143, 160, 166, 174, 246, 248, 309, 322, 325], Africa [35, 49, 161, 207, 243], and Australia [153], on about 35,000 PID patients, predominantly antibody deficiencies are the most common PID, which comprise more than half of all patients (Fig. 1.1). Other well-defined immunodeficiencies, combined T- and B- cell immunodeficiencies, and phagocytes defects are also relatively common. Among them, common variable immunodeficiency (CVID) seems to be the most common symptomatic PID. Meanwhile, it seems that the distribution of diseases varies by geographical regions/ethnicities. For example, it seems that the people living in the countries located in northern earth's equator region (0 to 30° latitude to the northern equator) are more susceptible to combined immunodeficiencies rather than other parts of the world with dominance of predominantly antibody deficiencies (Fig. 1.2).

The exact prevalence of PIDs in the general population is unknown. Although the overall prevalence of PIDs had been estimated to be 1 per 10,000 individuals, excluding asymptomatic

Table 1.9 Frequency of different types of PID, reported in several registries

	Region/report	Year of report	Number of patients[a]	Combined T- and B-cell immunodeficiencies (%)	Predominantly antibody deficiencies (%)	Congenital defects of phagocytes (%)	Genetic disorders of immune regulation (%)	Defects in innate immunity (%)	Autoinflammatory disorders (%)	Complement deficiencies (%)	Other immuno-deficiencies (%)	Unclassified (%)	Reference
1	JMF Referral Centers	2016	89,634	5.3	53.0	5.2	2.9	1.1	7.1	5.5	12.9	6.8	[202]
2	ESID	2015	19,355	7.5	56.7	8.7	3.9	1.0	2.1	4.9	13.9	1.4	[110]
3	LASID	2015	5695	9.4	62.9	7.6	2.4	1.8	–	3.4	9.5	3.0	[164]
4	France	2010	3083	17.4	42.8	18.4	6.6	0.2	–	0.5	14.1	–	[128]
5	USIDnet	2015	2858	20.2	55.1	15.2	0.2	0.7	0.1	0.4	8.1	0.0	[296]
6	UK	2014	2229	9.9	59.6	4.8	1.3	0.0	1.0	9.2	13.8	0.3	[106]
7	Spain	2001	2030	8.3	69.1	4.6	0.5	1.4	–	10.2	5.0	0.8	[196]
8	Iran	2006, 2014	1661	16.0	35.7	22.6	2.4	2.9	2.3	1.9	16.2	–	[9, 246]
9	Turkey	2013	1441	3.0	73.6	2.9	1.4	1.7	13.3	0.4	3.7	–	[152]
10	Germany	2013	1368	8.4	62.7	7.7	3.4	1.3	3.1	5.4	3.9	4.0	[119]
11	Argentina	2007	1246	10.4	68.4	3.9	2.9	1.4	–	1.0	12.0	–	[171]
12	Japan	2011	1217	10.8	41.2	18.5	4.0	3.0	8.9	2.6	11.0	–	[143]
13	Australia and New Zealand	2007	1209	8.9	77.4	3.2	–	1.6	–	5.9	2.9	0.2	[153]
14	Brazil	2013	1008	9.9	60.8	7.3	4.3	8.3	1.3	2.9	5.2	–	[60]
15	Italy	1983	797	14.2	66.6	4.9	2.4	–	–	1.6	9.5	0.8	[181]
16	Netherlands	2015	743	8.5	60.6	8.6	4.3	3.1	–	1.5	9.3	4.2	[145]
17	Tunis	2015	710	28.6	17.7	25.4	4.8	0.4	–	0.4	22.7	–	[193]
18	Czech	2000	518	8.1	78.0	1.2	–	–	–	11.5	1.2	–	[2]
19	China	2006, 2011, 2013	485	21.4	38.8	10.9	2.3	0.8	–	0.2	25.4	0.2	[309, 324, 325]
20	Morocco	2014	423	24.1	22.7	15.1	2.1	5.2	2.8	3.1	23.9	0.9	[49]
21	Saudi Arabia	2013	357	53.8	15.4	10.6	6.4	–	–	4.5	9.2	–	[18]
22	Switzerland	2015	348	11.5	61.5	8.9	2.3	2.0	3.4	4.6	4.3	1.4	[190]
23	Mexico	2007	399	15.0	36.3	14.0	3.5	2.5	–	1.5	27.1	–	[171]

(continued)

Table 1.9 (continued)

	Region/report	Year of report	Number of patients[a]	Combined T- and B-cell immunodeficiencies (%)	Predominantly antibody deficiencies (%)	Congenital defects of phagocytes (%)	Genetic disorders of immune regulation (%)	Defects in innate immunity (%)	Autoinflammatory disorders (%)	Complement deficiencies (%)	Other immuno-deficiencies (%)	Unclassified (%)	Reference
24	Norway	2000	372	3.5	50.8	6.7	–	–	–	21.0	18.0		[280]
25	Poland	2000	322	24.8	55.0	14.3	–	–	–	0.3	5.6		[2]
26	Chile	2007	279	23.7	43.0	6.8	6.1	3.2	–	1.8	15.4	–	[171]
27	India	2012	275	12.0	28.4	14.5	17.1	4.7	0.7	1.8	18.2	2.5	[130]
28	Taiwan	2011	215	15.8	25.1	11.6	2.3	–	0.5	7.0	37.7	–	[166]
29	Portugal	2000	208	6.3	76.9	3.8	–	–	–	6.7	6.3	–	[2]
30	Korea	2012	152	10.5	53.3	28.9	–	–	–	–	7.2	–	[248]
31	Costa Rica	2007	193	18.1	24.9	4.1	4.7	1.0	–	0.5	46.6	–	[171]
32	Sweden	1982	174	13.8	43.7	21.8	1.1	8.0	–	0.6	10.9	–	[111]
33	South Africa	2011	168	25.0	50.6	5.4	–	0.6	–	4.2	14.3	–	[207]
34	Russia	2000	161	29.8	59.6	6.2				0.0	4.4		[2]
35	Greece	2014	147	38.8	20.4	17.0	2.0	4.1	0.7	1.4	15.6	–	[194]
36	Colombia	2007	145	21.4	46.2	8.3	3.4	4.1	–	2.8	13.8	–	[171]
37	Qatar	2013	131	22.9	23.7	12.2	12.2	9.9	–	–	19.1	–	[107]
38	Hong Kong	2005	117	16.2	42.7	16.2	1.7	1.7	–	3.4	7.7	10.3	[160]
39	Republic Ireland	2005	115	12.2	46.1	9.6	–	2.6	–	27.8	1.7	–	[4]
40	Uruguay	2007	95	8.4	58.9	3.2	–	3.2	–	9.5	16.8	–	[171]
41	Oman	2012	90	14.4	17.8	38.9	3.3	3.3	–	5.6	10.0	6.7	[20]
42	Hungary	2000	90	0.0	22.2	14.5	–	–	–	63.3	0.0	–	[2]
43	Kuwait	2008	76	31.6	30.3	7.9	6.6	–	–	3.9	19.7	–	[13]
44	Austria	2000	71	26.8	67.6	2.8	–	–	–	1.4	1.4	–	[2]
45	Thailand	2009	67	32.8	52.2	9.0	–	3.0	–	–	3.0	–	[37]
46	Iceland	2015	66	4.5	39.4	12.1	–	1.5	3.0	28.8	10.6	–	[180]
47	Egypt	2009	64	31.3	35.9	12.5	3.1	–	–	–	17.2	–	[243]

48	Belgium	2000	64	10.9	64.1	17.2	–	–	–	4.7	3.1		[2]
49	Panama	2007	59	15.3	55.9	8.5	–	1.7	–	3.4	15.3	–	[171]
50	Finland	2000	48	8.3	71.1	10.4	–	–	–	4.2	0.0	–	[2]
51	Singapore	2003	39	15.4	40.0	15.4	–	2.6	–	25.6	0.0	–	[174]
52	Paraguay	2007	39	10.3	38.5	33.3	–	2.6	–	–	15.4	–	[171]
53	Honduras	2007	37	16.2	32.4	10.8	2.7	16.2	–	–	21.6	–	[171]
54	Croatia	2000	30	6.7	63.3	0.0	–	–	–	30.0	0.0	–	[2]
55	Venezuela	2007	22	9.1	40.9	4.5	13.6	–	–	9.1	22.7	–	[171]
56	Peru	2007	17	17.6	17.6	5.9	–	5.9	–	11.8	41.2	–	[171]

JMF Jeffrey Modell Foundation Diagnostic and Referral Centers, *ESID* European Society of Immunodeficiency, *LASID* Latin American Society for Primary Immunodeficiency Diseases, *USIDnet* US Immunodeficiency network

[a]There may be some overlapping between registries; i.e. JMF Referral Centers, ESID, LASID and other databases

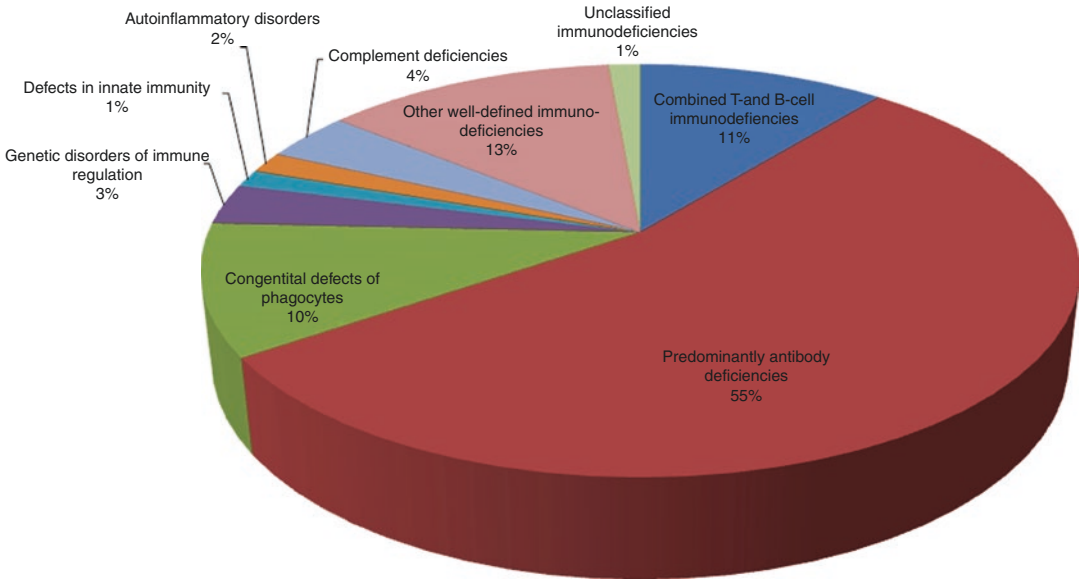

Fig. 1.1 Relative frequencies of primary immunodeficiency diseases (Extracted from data of the reports from major databases, including ESID (European Society for Immunodeficiencies), LASID (Latin American Society for Primary Immunodeficiency Diseases), USIDnet (US Immunodeficiency network), as well as selected reported registries from Asia, Africa, and Australia)

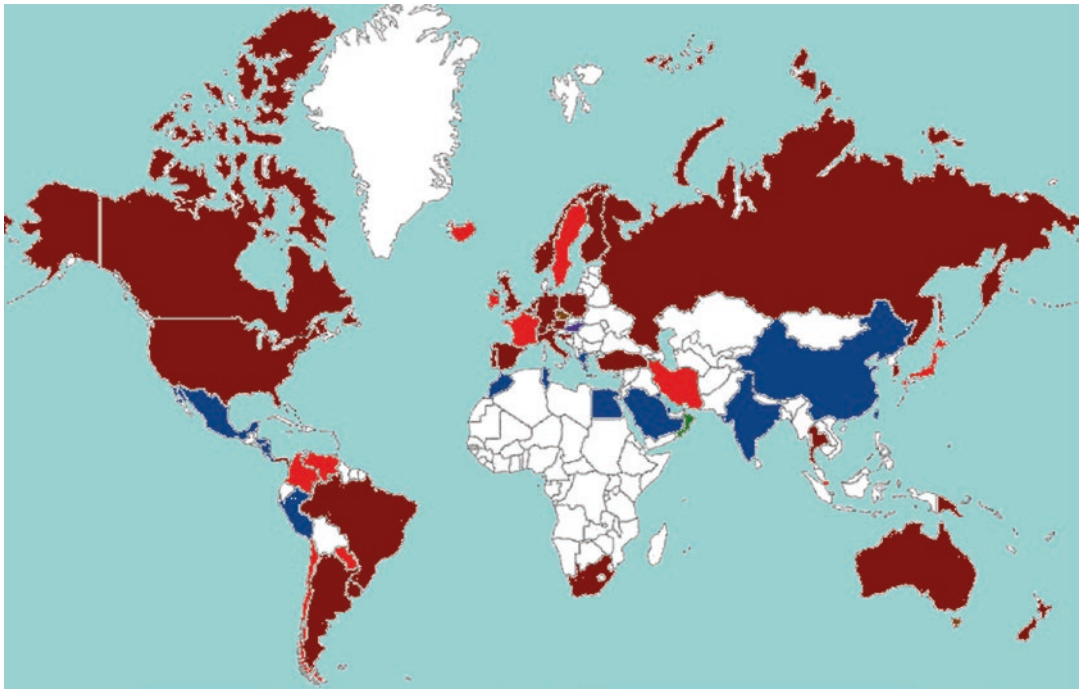

Fig. 1.2 Distribution of different types of primary immunodeficiency diseases in the world. *Dark red*: dominancy of predominantly antibody deficiencies (>50%); *Light red*: dominancy of predominantly antibody deficiencies (<50%); *Dark blue*: dominancy of Combined T- and B-cell immunodeficiencies and other well-defined immunodeficiencies; *Green*: dominancy of congenital defects of phagocytes; *Purple*: dominancy of complement deficiencies

IgA deficiency, recent reports indicated a higher prevalence of PIDs worldwide [48, 50, 278]; this prevalence may differ among different ethnic groups and countries [278], while the discovery of new PIDs, infectious and otherwise, may necessitate a revision of previous estimates of the frequency of PIDs in the general population.

Meanwhile, conservatively defined PIDs are commonly thought to be individually and collectively rare. Rare diseases are defined as having an incidence of less than 1/2000 live births in the EU [164] or a prevalence of less than 200,000 patients in the US. However, it remains unclear whether the prevalence and incidence of PIDs have been estimated accurately. Many studies, based on different methodologies, have attempted to estimate the prevalence of PIDs in various countries and have generated inconsistent results. For example, the most recent estimates obtained were 5.93/100,000 inhabitants in France in August 2013 [152], 5.6/100,000 in Australia in 2007 [107], and 3.71/100,000 in the UK in 2013 [20]. These estimates of prevalence were based on data from registries and seem to be much lower than recently reported estimates based on specific population surveys in the US, such as prevalence of 86.3/100,000 inhabitants by a telephone survey [17] or incidence of 10.3/100,000 person-years at the Mayo Clinic epidemiologic study [207].

In the Europe, prevalence data can be easily obtained from the ESID registry. Indeed, this international registry is documented by 126 centers all around Europe by mid-2015, and its statistics are regularly updated on the ESID website [110]. However, when we go through the data, there is a relatively high heterogeneity in PID prevalence from a country to another, ranging from 0.06/100,000 inhabitants in Romania to 5.93/100,000 in France. This can be explained by the different approaches in the use of this registry. Actually, only 8 of the 29 participating countries have developed a national registry, included in the ESID registry, namely France, Spain, Italy, the Netherlands, Poland, Czech Republic, Austria and Belgium. Moreover, even national registries can miss out diagnosed patients in non-documenting centers. The prevalence produced by their data collection should be interpreted with caution, and that the observed differences are mostly due to underreporting [165].

In the USA, the national registry, USIDnet only account for 3430 patients in mid-2015 [296]. However, only 10 diagnosis accounts for about 85 % of the patients. Besides, the ImmuneDeficiency Foundation (IDF) performed several surveys to define PID prevalence in US. In the IDF National Survey, in 2005, they estimated that at least 250,000 PID cases would be diagnosed in the US with the prevalence of about 1 in 1200 persons in the United States [325]. On another hand, an epidemiologic study providing an estimate of PID incidence in the USA based on a survey in Olmsted County, Minnesota [160], using data of all patients treated between 1976 and 2006 whose medical records contained at least one of the ICD (International Classification of Diseases) codes relating to PIDs, showed overall incidence of 4.6/100,000 person-years for a 30-years period (1976–2006), and 10.3/100,000 person-years for the most recent period (2001–2006). Immunodeficiency Canada, a national registered charity, estimated that 13,000 people (1/2500) would have a PID in Canada [77].

In the Middle East, until recently, very few data were available on the PID epidemiology. Only two countries have developed a PID registry: the Iranian Primary Immunodeficiency Registry (IPIDR), established in 1999 [7], and the National Primary Immunodeficiency Registry in Kuwait (KNPIDR), founded in 2007 [12]. The second report from the IPIDR in 2006 [246] estimated the occurrence of PID as 6 per 100,000 live births, with a cumulative incidence of about 1.2/100,000 in the last 10 years. In Kuwait, the prevalence of PID was estimated about 12/100,000 in children [13].

In Asia, no international registry is available. Likewise, diagnosis and management vary from a country to another. In Japan, a nationwide survey was performed and published in 2011 [143]. The estimated prevalence from this survey was 2.3/100,000 inhabitants, with estimated regional prevalence ranged from 1.7 to 4.0/100,000 [143]. In China, several single-centers published their series [75, 175, 322, 326]. A single-center study from 2011 observed a PID incidence of 1/2850 children [309]. When gathering these cases, we

estimated a PID prevalence of 0.4/100,000 inhabitants in 2009 in China, which should be lower than the reality. In Taiwan, a recent population-based survey reported a minimal prevalence of 0.78/100,000 [167]. In Singapore, an incidence of 2.65 per 100,000 live births was reported, which was similar to PID incidence in Australia at the time of publication [174]. On total population, prevalence reached 0.89/100,000 inhabitants. In India, some single-centers published their series recently [77, 184]. However, these series are not large enough to estimate PID prevalence in India. The observed prevalence of PID in Australia and New Zealand was 4.9/100,000 [153]. The regional estimated prevalence ranged from less than 1/100,000 in Tasmania to 12.4 in South Australasian. After adjustments, PID prevalence is estimated around 13.2–14.5/100,000 inhabitants.

In Africa, very few data are available on the PID prevalence. Indeed, definite diagnosis of PIDs and appropriate care are developed only in a few countries, such as Tunisia, Egypt, Morocco, Algeria and South Africa. Likewise, only Morocco and South Africa have established a National Registry. The African Society of Immunodeficiency (ASID) registry and the North African registry initiatives have begun, but are still in their first steps.

The Jeffrey Modell Foundation (JMF) has created a worldwide network of centers specialized in PIDs: the Jeffrey Modell Centers Network (JMCN). Every other year, a survey is sent to this network to assess PID distribution and management. The last publication reported the results from the 2015 survey, where 253 centers representing 84 countries responded. A total of 89,634 patients with PIDs who were referred to a JMCN institution was reported [202]. In another report from the JMF with 60,364 PIDs [201], a worldwide prevalence of at least 1.14/100,000 inhabitants was estimated. To be more specific, if we only consider the population of the participating countries, the prevalence should be no less than 1.56/100,000. Here again, huge variations are observed between regions, with low PID prevalence in Asia (0.22/100,000 inhabitants), Africa (0.39/100,000) and Latin America (0.86/100,000), and higher prevalence in regions involved in the field since the beginning: Europe (3.76), USA (4.98), Australia (5.35) and Canada (9.97/100,000).

Estimates of PID prevalence from registry data [e.g. 5.9/100 000 in France [142], 5.6/100,000 in Australia [153]] are much lower than the estimates based on the data from a telephone survey in the USA (86.3/100,000) [50]. Considering the estimate prevalence of PID on the later survey [50], the predicted total number of PID patients reaches six million, while considering the reported incidence data [146], more than 700,000 new cases annually could be calculated. However, more data relying on population studies are needed to define the exact prevalence and incidence of PIDs to avoid both underestimation and overestimation of these diseases.

1.2 Etiology

1.2.1 Classification

There is no single system of classification of the large and heterogeneous group of primary immunodeficiencies that suffices for every educational or clinical purpose [16, 43, 217]. Most texts utilize a functional classification wherein distinct disease entities are grouped according to the immunological mechanism whose perturbation is responsible for the principal clinical and laboratory manifestations of those diseases or syndromes [45]. One may distinguish, for example, antibody or humoral immune defects, combined immunodeficiencies (affecting both specific humoral and cellular immunity), phagocytic cell defects, complement deficiencies, and other defects of innate immunity or immune dysregulation. Note that these types of descriptive functional categories may overlap to varying degrees, for example, phagocytic cells and complement may be considered elements of innate immunity, but are usually considered separately due to the convenience of their mechanistic distinction. The assignment of one entity to a particular category is occasionally arbitrary and may have a historical basis.

The foundation for the organization of this text is the most recent classification of immunological diseases reported by the World Health

Organization (WHO) in conjunction with the International Union of Immunological Societies (IUIS) [14]. This classification is conveyed in Tables 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, and 1.8. This scheme includes combined T- and B-cell immunodeficiencies (Table 1.1), predominantly antibody deficiencies (Table 1.2), phagocytes defects (Table 1.3), genetic disorders of immune regulation (Table 1.4), defects in intrinsic and innate immunity: receptors and signaling components (Table 1.5), autoinflammatory disorders (Table 1.6), complement deficiencies (Table 1.7), and other well-defined immunodeficiencies (Table 1.8). Some disease entities may be listed more than once, if they have characteristics of more than one group or for historical reasons.

The usefulness of any classification scheme depends mainly on the ultimate purpose for which it was developed [43]. The WHO/IUIS system is well suited as a framework for organizing a knowledge base on the general clinical and immunologic features of disease entities arising "primarily" from dysfunction of the immune system. This classification may be cumbersome in other contexts, for example, developing a differential diagnosis based on particular clinical or immunologic features. Other systems have been proposed or formulated with these kinds of considerations in mind [5, 257]

1.2.2 Genetic Defects

More than 200 distinct genes have been associated with clinical immunodeficiency (Tables 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, and 1.8). This number is even larger when one takes into consideration the many genetically-determined syndromes in which some fraction of individuals has been found to have a degree of immune compromise or infection susceptibility. (*See* Chap. 10 *for more details*) As can be readily seen (and not surprisingly) by surveying the genes listed in Tables 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, and 1.8, immunodeficiency may arise from disruption of a wide range of biochemical functions including transcription factors, cytokines and their receptors, cell surface and cytoplasmic signaling mediators, cell cycle regulators, DNA modifying enzymes, intracellular chaperones and transport proteins, and a variety of other specialized enzymatic functions. One may broadly generalize that perhaps more than half of these molecular species are active principally or predominantly in blood cells, lymphocytes and leukocytes, in particular, although that relative restriction clearly does not apply in many instances.

Clearly, having a molecular genetic focus adds precision to a diagnosis, although there are important practical caveats to the use of such information, some of which will be introduced here. In addition, a large proportion of patients with recurrent infections, or "clinical immunodeficiency" have syndromes whose molecular genetic basis is unknown.

The ability to assign genes and molecular functions to an observable characteristic leads to the concept of the genotype-phenotype correlation. Common examples include the genetic basis of traits such as eye color, or ABO blood group. This also applies in a general way to disease associations, for example, mutations of *BTK* lead to Bruton's agammaglobulinemia (Chap. 3) while mutations of *WAS* lead to Wiskott-Aldrich syndrome (Chap. 9). However, the concept may also be applied in a more detailed way. Within a group of individuals having any specific immunodeficiency diagnosis, one may distinguish a spectrum of clinical phenotypes. This may relate to the degree of frequency or severity of infections ("severity" of the immunodeficiency), or to the expression of other associated features of the disease such as autoimmunity or malignancy. Thus, one may ask: "does the identification of a particular genetic change affecting even submolecular functions (ligand binding, association with signaling intermediates or chaperones, enzymatic activity, cellular transport, etc.) permit one to predict the severity of the immunodeficiency, the occurrence of autoimmunity or malignancy, etc.?" In some cases, "yes", although there are many important exceptions making a generalization difficult. In some instances, identical mutations may lead to a severe phenotype in one individual, and may be mild, or may not even be expressed at all, in another. For example, some

entirely well people have been found incidentally to have mutations of *BTK*, while siblings carrying the same mutation have classic clinical X-linked agammaglobulinemia. (*See* Chap. 3 *for more details*) Does an individual who is completely well and who has a "disease-causing" mutation of *BTK* have X-linked agammaglobulinemia? The answer is not a simple one because we do not know if it is possible for any such individual to be "completely healthy" with a "normal" lifespan.

It is axiomatic that many (all?) gene products, as well as the environment, interact to determine phenotype. Thus, the clinical and immunologic heterogeneity that we observe with identical genotypes is due to the influence of these interactions. Given the possibility of molecular diagnosis, and the heterogeneity of expression of genotypes, then all syndromes defined solely by clinical and immunologic criteria should be considered diagnoses of exclusion [45]. Common variable immunodeficiency (CVID, Chap. 3) is a useful illustration of this point. CVID is defined primarily by recurrent infections with hypogammaglobulinemia and impaired antibody response to natural and/or intentional immune challenge [72, 86]. Several genetic lesions have been identified in individuals "diagnosed" with CVID including *BTK*, *SH2D1A* (mutated in X-linked lymphoproliferative syndrome), *ICOS* (inducible T cell costimulator), *CD19*, *CD20*, *CD81* and *BAFFR* [259]. The particular natural history associated with each of these mutations is distinct, so it is most beneficial for patients to know their molecular diagnosis whenever possible. This also creates opportunities for more informed genetic counseling. Note that the principal presenting phenotype associated with X-linked lymphoproliferative syndrome (Chap. 5) is fulminant infectious mononucleosis. This is a good example of how an environmental factor (Epstein-Barr virus infection) may interact with a gene defect (*SH2D1A*) to affect the clinical presentation.

Some individuals expressing mild or variant forms of immunodeficiency have a reversion of a deleterious mutation. These patients are mosaics, they have abnormal mutant cells and another population of cells with normal or near-normal function that have arisen from a precursor that has repaired the defect, either from a second "corrective" mutation, or possibly gene conversion. This has been found in rare cases of adenosine deaminase deficiency, X-linked severe combined immunodeficiency, Wiskott-Aldrich syndrome, leukocyte adhesion deficiency type I, and possibly X-linked chronic granulomatous disease [88, 157, 204, 298, 318].

Some X-linked immunodeficiencies affect females through extreme non-random X chromosome inactivation. In most females, roughly half of all somatic cells will inactivate one X chromosome, and half inactivate the other. In some individuals, 95–100 % of cells will all have inactivated the same X chromosome. If the remaining active X carries a mutation causing immunodeficiency, that disease will become manifest. This phenomenon has been observed with chronic granulomatous disease, Wiskott-Aldrich syndrome, X-linked agammaglobulinemia, and X-linked immunoglobulin class switching recombination (CSR) deficiency [25, 141, 173, 285].

1.2.3 Pathophysiology

The infection susceptibility and other clinical features of a given immunodeficiency arise from the absence or altered function of one or more gene products. All of the details of these aspects of each disorder depend on the biochemical roles of these gene products and the cells or tissues in which they are expressed. As discussed above, the products of interacting genes and their polymorphisms and environmental factors also play a role. For most immunodeficiencies, we still have very much to learn regarding all of the biochemical, cellular, organic, and systemic consequences of a particular defect. The majority of the genetically defined immunodeficiencies will be discussed in the remainder of this book. Here we give a few examples of an interesting phenomenon in immunodeficiency: syndromes having identical or very similar clinical and immunologic phenotypes may arise from the disrupted function of molecular entities that interact with one another to subserve a single biochemical function or pathway.

Bruton's disease, or X-linked, agammaglobulinemia (XLA) was one of the first immunodeficiencies to be defined at the molecular level [39].

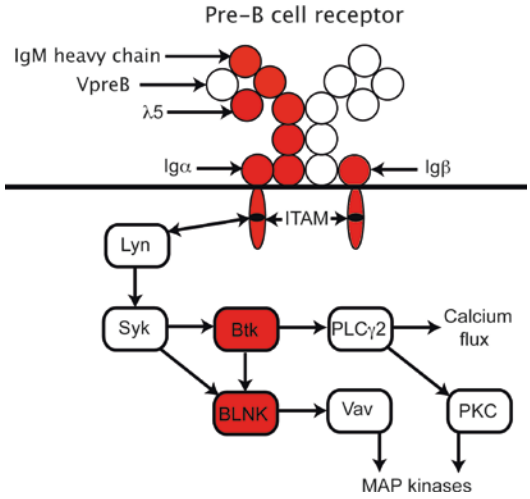

Fig. 1.3 This is a highly simplified diagram summarizing the relationships of several molecules whose absence is associated with agammaglobulinemia. All of the defects indicated here in red affect signaling through the pre-B cell receptor and block B cell development at the pre-B cell stage in the bone marrow. The pre-B cell receptor itself is made up of an IgM heavy chain, the surrogate light chain heterodimer of λ5 and VpreB, and the signal transducers Igα and Igβ which bear the immunoreceptor tyrosine based activation motifs (ITAMs). The ITAMs are phosphorylated by Lyn, a Src family tyrosine kinase, while Syk is the prototype of the tyrosine kinase family that bears the same name. Btk is a member of the Tec family of tyrosine kinases. B cell linker protein (BLNK) is a scaffold or adaptor protein, while Vav is a guanine nucleotide exchange factor for downstream GTPases. PLCγ2 is phospholipase C γ2; PKC is protein kinase C

The Bruton's tyrosine kinase (BTK) is critical for transducing a signal from the B cell surface immunoglobulin receptor (Fig. 1.3). In the pre B cell, this receptor consists of an immunoglobulin M heavy chain, the heterodimeric surrogate light chain containing lambda 5 and VpreB, and the signal transducers Ig alpha, and Ig beta. Within the cytoplasm, BTK interacts with other kinases, and with so-called scaffold or adaptor proteins that serve to juxtapose other signaling molecules, permitting activation to proceed downstream along the pathway. One of these is B cell linker protein (BLNK). Several of these interacting molecules have been associated with autosomal forms of agammaglobulinemia that are indistinguishable from XLA in their clinical and laboratory characteristics; these are IgM heavy chain, lambda 5, Ig alpha, Ig beta, and BTK [39]. Agammaglobulinemia is the subject of Chap. 3.

X-linked severe combined immunodeficiency (XSCID) is the result of a defect in the cytokine receptor common gamma chain (gamma$_c$, Fig. 1.4) [212]. This molecule is a signal-transducing component of the multimeric receptors for 6 different cytokines: interleukins 2, 4, 7, 9, 15, and 21. Gamma$_c$ signals through the kinase JAK3. Mutation of the *JAK3* gene results in a very similar form of SCID with autosomal recessive inheritance [301]. Mutations in the genes

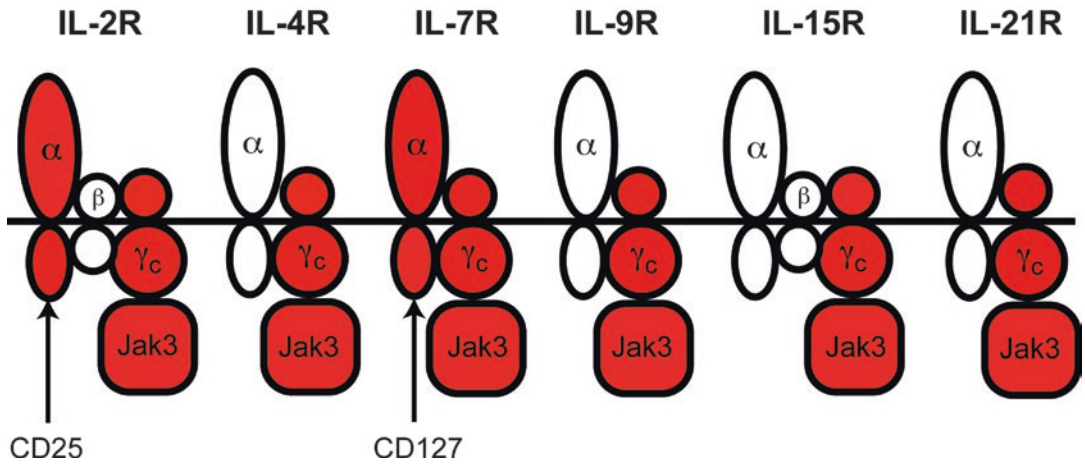

Fig. 1.4 The cytokine receptor common γ chain (γ_c) is a signal transducing component of the six cytokine receptors shown. In every case, its immediate downstream partner is the Jak3 tyrosine kinase. Absence of function of either of these molecules leads to severe combined immune deficiency (SCID) with similar phenotypes. Four of these receptors have only two components, a ligand-biding α chain and γ_c. Two (IL-2R and IL-15R) have an additional β chain. IL-2 is a critical autocrine mediator of T cell activation and proliferation and mutations of the IL-2R α chain lead to SCID. IL-7 is required for early T cell development, and mutations of IL-7R α have also been associated with SCID

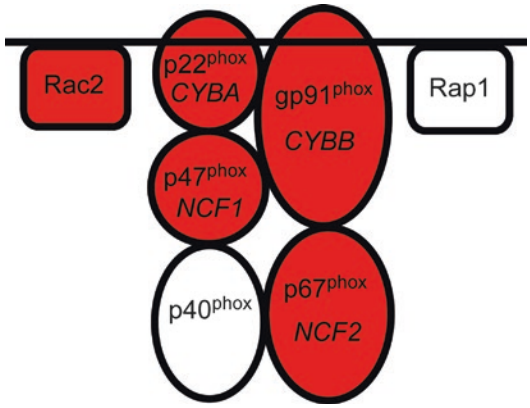

Fig. 1.5 The phagocyte oxidase complex is an electron transporter that is required for effective intracellular killing in the phagolysosomes of neutrophils and macrophages. This enzyme is comprised of 5 distinct subunits. Absence of four of these (*shaded red*) have been associated with chronic granulomatous disease (CGD). The $gp91^{phox}$ (also called cytochrome b558 β, gene CYBB) is encoded by a gene on the X-chromosome, the other subunits are encoded by autosomal genes ($p22^{phox}$ = cytochrome b558 α, gene CYBA; $p47^{phox}$ = neutrophil cytosolic factor 1, gene NCF1; $p67^{phox}$ = neutrophil cytosolic factor 2, gene NCF2). A neutrophil defect similar to CGD is also associated with mutations of the gene encoding the GTPase Rac2

encoding the ligand binding chains of the receptors for IL-2 and IL-7 also lead to forms of SCID [301]. Severe combined immunodeficiency is the subject of Chap. 2.

Mutations in genes encoding distinct components of multimeric enzymes may also lead to similar disease phenotypes. Chronic granulomatous disease (CGD) results from absent function of the phagocyte oxidase complex (Fig. 1.5) [249]. This complex has four subunits, the gp91phox subunit is encoded by a gene on the X chromosome. The other three subunits are all encoded by autosomal genes. A mutation of any of these leads to CGD, although the phenotype of the X-linked form tends to be more severe. CGD and other phagocyte defects are the subject of Chap. 4.

1.3 Clinical Manifestations

1.3.1 Infections

While the strongest warning sign for PID is positive family history, most PIDs are to be suspected if 1) recurrent or opportunistic infections, 2) organ specific inflammation/autoimmunity or continuous systemic immune activation and/or 3) benign or malignant, potentially virally induced lymphoproliferation or tumors are seen together, in various combinations [26, 281]. Though most PIDs become symptomatic in childhood, onset is delayed in most patients with common variable immunodeficiency diseases [307]. The onset may also be delayed in PIDs with progressive damage to the immune system (like GATA2) or due to various genetic mechanisms (e.g. hypomorphic mutations, age-related skewing in random X-chromosome inactivation) [81, 208]. Before PID screening, one must exclude HIV infection. During assessment, not-readily-apparent secondary immunodeficiency (e.g. occult hematologic malignancy, protein loss) should be excluded.

Opportunistic or recurrent infections are seen in most PID (Tables 1.10, 1.11, 1.12, and 1.13). Traditionally, screening for PIDs has heavily relied on this feature, yet with unsatisfactory results [84]. (*See* Sect. 1.4 *for more details*) Especially in respiratory and skin infections, there is considerable overlap between recurrent infections in antibody deficient patients and in those with Th2-dominant immune response [6, 317]. If other members of a large family are perfectly healthy, this argues against common polygenic traits like chronic asthma or severe atopy that predispose to recurrent rhinosinusitis, skin infections and – to an extent – to recurrent pneumonias [148, 216].

In one study, in addition to positive family history the use of intravenous antibiotics for sepsis identified neutrophil PIDs and failure to thrive identified T cell PIDs with satisfactory results [281]. Combining these three signs correctly identified neutrophil, complement and T cell PIDs in approximately 90% of patients [26]. Since using solely recurrent infections as screening criteria is neither specific nor sensitive, other features that suggest PID should actively be sought [85]. As an example, common infectious complications of antibody deficiencies – the most common of all PIDs – are shown in Fig. 1.6, while Fig. 1.7 lists immune disorders seen in CVID.

Most PIDs predispose the subjects to infections caused by a limited array of pathogens,

Table 1.10 Bacterial infections seen in various primary immunodeficiency diseases

Infections	PID	Notes
Encapsulated extracellular bacteria	Predominantly antibody deficiencies	Pneumococci, other streptococci, *Haemophilus spp.*, *M. catarrhalis* Upper and lower respiratory infections, sepsis Also: *Campylobacter spp.*, *Giardia lamblia*, *Salmonella spp.*, enteroviruses
	Complement deficiencies	Recurrent meningitis and bacteremia, *Neisseria spp.* Neisserial infections only: *C9*, *CFD*, *PFC* Neisserial infections + SLE: *C5*, *C6*, *C8A*, *C8B* Pulmonary bacterial infections: *FCN3* Pneumococcal and meningococcal infections: *CFB*
	Isolated congenital asplenia and FADD deficiency	ICA: *RPSA*, *NKX2-5* FADD: Early onset invasive *S. pneumoniae*, splenic dysfunction, also VZV and neurologic symptoms
U. urealyticum and *Mycoplasma spp.*	Predominantly antibody deficiencies	Often as large-joint monoarthritis or osteomyelitis, occasionally polyarthritis
S. aureus and gram-negative bacteria, (+fungal infections)	Chronic granulomatous disease	Early-onset recurrent bacterial infections by mainly catalase-positive micro-organisms, invasive fungal infections *B. cepacia*, *S. marcescens*, *Nocardia spp.*, *Klebsiella spp.*, *Proteus spp.*, *Salmonella spp.*, *E. coli*, *Pseudomonas*, *Chromobacterium violaceum*, *Granulobacter bethesyndromeensis* Also: CNS candidiasis, *Aspergillus spp.*, *M. tuberculosis*, BCG-itis, *Leishmania spp.*, *Penicillium spp.*, *Scedosporium spp.* depending on local epidemiology
	Other phagocyte defects	Early-onset recurrent bacterial infections primarily localized to skin and mucosal surfaces, omphalitis, aphthous ulcers, deep abscesses, pneumonias Also: invasive candidiasis and aspergillosis in SCN and LAD1
	AD hyper-IgE syndrome	Severe, deep visceral *S. aureus* infections, recurrent pneumonia and pneumatocele formations. Extremely high IgE, typical structural findings and early-onset eczema Also: chronic mucocutaneous candidiasis and invasive aspergillosis
	GATA2 deficiency	Onset may be delayed to adulthood Also: nontuberculous mycobacteria, HPV, VZV, EBV, CMV, streptococci, dimorphic and filamentous fungi, candidiasis
	ORAI1 deficiency	Also: viruses, fungi
	KID syndrome (*GJB2*, others)	Also: candidiasis, CMV, other viral infections
Pseudomonas aeruginosa	Neutropenia and specific granule deficiency	Besides SCN, various PIDs associated with symptomatic neutropenia, *LRBA*

(continued)

Table 1.10 (continued)

Infections	PID	Notes
Nontuberculous mycobacteria	Mendelian susceptibility to mycobacterial diseases (IL12/23-IFN-γ circuit)	For complete list, see relevant chapter. Recurrent nontuberculous mycobacteriosis and salmonellosis, BCG-itis, osteomyelitis. Includes *RORC*, *TYK2*, *ISG15*, *IKBKG*, *IKBKB*, GOF *NFKBIA/IKBA*, reported in *STAT3* GOF Also: occasionally *Klebsiella spp.*, various intracellular bacteria and viruses, invasive dimorphic fungi, leishmaniasis
	GATA2 deficiency, IRF8 (AR, AD) deficiencies	GATA2: also bacterial pneumonias especially in patients with primary alveolar proteinosis, histoplasmosis, HPV-, EBV-associated diseases. Some have primary lymphedema (Emberger syndrome), risk of myelodysplastic syndrome, AML, CMML IRF8: Candida, myeloproliferation
Streptococcus spp., *S. aureus*, *P. aeruginosa*	MyD88/IRAK4 deficiency	Very early-onset invasive pyogenic infections, meningitis, sepsis, arthritis, osteomyelitis, superficial skin infections, deep tissue infections of respiratory tract, low grade fever and slow development of inflammatory reaction. Also: invasive gram-negative bacterial infections (e.g. Enterobacteriaceae, *A. baumannii*, *H. influenzae*, *N. meningitides*, *M. catarrhalis*, *C.septicum*), no increased susceptibility to toxoplasmosis, mycobacterial, viral or fungal infections
Legionella spp.	TLR5 deficiency	Legionella penumonias, recurrent urinary tract infections by common pathogens. In up to 10% of Europeans, phenotype mild.
	SCID, T cell deficiencies	Also a wide range of intracellular micro-organisms (viruses, fungi)

Table 1.11 Relatively common infections and their complications that most likely should result in screening for immunodeficiency

Infection	Warning signs	Note
Pyogenic pneumonia	Failure to thrive	Susceptibility to a wide array of gram-positive and gram-negative micro-organisms (also to viruses, fungi, parasites), interstitial pneumonitis: SCID and T cell deficiencies
	Recurrent	>2–3 pneumonias during lifetime, earlier if warning signs: In various loci, leads to bronchiectasis or bronchial dilatation. In-between-episodes bronchial wall thickening, signs of cryptogenic organizing pneumonia, lymphoid interstitial pneumonitis, follicular bronchiolitis or granulomas without clear sarcoidosis (or low immunoglobulins) Concurrent invasive infections, recurrent bacterial rhinosinusitis, very early-onset recurrent otitis media, adult-onset recurrent otitis media, slow systemic inflammatory response, or no demonstrable serum IgE Exclude a wide range of PIDs
	Complicated	Pneumatocele formation: STAT3 deficiency Empyema or abscess: CGD, other phagocyte defects, STAT3 deficiency Bronchiectasis or interstitial pneumonitis: wide range of PIDs
	Early-onset (<3–4 months)	Phagocyte deficiencies, MyD88/IRAK4 deficiency, SCID, T cell deficiencies, congenital asplenia (*RPSA*, *NKX2-5*), FADD deficiency (functional hyposplenism)
Pyogenic sepsis	Recurrent	Phagocyte deficiencies, complement deficiencies, MyD88/IRAK4 deficiency, SCID, antibody deficiencies, CD40/CD40L deficiency, congenital asplenia, NEMO, GATA2 deficiency
	Early-onset (<3–4 months)	SCID, phagocyte deficiencies, complement deficiencies, MyD88/IRAK4 deficiency, congenital asplenia (*RPSA*, *NKX2-5*), FADD deficiency (functional hyposplenism)
Pyogenic meningitis	Recurrent	Complement deficiencies, MyD88/IRAK4 deficiency, antibody deficiencies, congenital asplenia (*RPSA*, *NKX2-5*), FADD deficiency (functional hyposplenism), MKL1 deficiency
Upper respiratory tract	Deep tissue infection	For example, mastoiditis after otitis media or tonsillar abscess in infant: MyD88/IRAK4 deficiency, phagocyte and antibody deficiencies
Infectious colitis	Persistent/recurrent, in childhood	Most commonly reported in SCID, LADs, CGD
	Persistent/recurrent	Salmonella spp., Campylobacter spp.: antibody deficiencies, MyD88/IRAK4 deficiency, MSMD, combined immunodeficiencies
		Rotaviruses, adenovirus, CMV: SCID, other T cell deficiencies, CVIDs, Ig CSR deficiencies
		Enteroviruses: agammaglobulinemias, CVIDs
	Necrotizing enterocolitis	Ficolin 3 deficiency in infancy
	Severe *C. difficile*	GATA2 deficiency
Skin	Deep-seated abscesses	Phagocyte deficiencies Skin, muscle, lacrimal, dental or salivary abscesses with hypogammaglobulinemia, consider *PIK3CD* GOF, *LRBA* MKL1 deficiency: early-onset cutaneous and subcutaneous abscesses, invasive systemic infections
	Superficial	If invasive infections, phagocyte deficiencies, MyD88/IRAK4 deficiency, antibody deficiencies, GATA2 deficiency.
Visceral abscess	In childhood (mostly)	Phagocyte deficiencies, STAT3 deficiency, often by *S. aureus*

Table 1.12 Opportunistic viral and parasitic infections suggestive of primary immunodeficiency diseases

Infection	Clinical setting	Note
EBV	Chronic EBV viremia ± EBV-driven Malignancy ± hemophagocytic Lymphohistiocytosis	Familial hemophagocytic lymphohistiocytosis 1–5 (unknown, *PRF1*, *UNC13D*, *STX11*, *STXBP2*) X-linked lymphoproliferative disease 1–2 (*SH2D1A*, *XIAP*) *CTLA4*, *LRBA*, *PIK3CD* GOF, *PIK3R1* Chediak-Higashi (*LYST*), Griscelli syndrome 2 (*RAB27A*), Hermansky-Pudlak 2 (*AP3B1*) ITK deficiency, CD27 deficiency, MAGT1 deficiency, STK4 deficiency, Coronin-1A deficiency, GATA2 deficiency, p110δ deficiency, PRKCδ deficiency, LRBA deficiency, DNA ligase IV deficiency, STIM1 deficiency, TRAC deficiency, CD25 deficiency, PGM3 Chronic active EBV disease Occasionally: AT (*ATM*), WAS (*WASP*), CHH (*RMRP*; late onset), SCID, NK deficiencies, WHIM (*CXCR4*), MCM4 deficiency, γc deficiency, 22q11 deletion syndrome, schlafen deficiency (late onset) In CD16a deficiency (*FCGR3A*) EBV-associated Castleman disease
CMV, VZV, HSV	Severe generalized or CMV viremia	Various PIDs with significant T/NK deficiency, CVIDs with secondary immunodeficiency May also incite HLH. Presenting feature in for example P110δ deficiency, VODI and KID, TYK2 deficiency, *CTLA4*, *PIK3R1*, *PIK3CD* GOF, *PIK3R1*
HSV	Encephalitis	TLR3-IFN pathway deficiency (*TLR3*/*UNC93B1*/*TRIF*/*TRAF3*/*TBK1*), more likely if recurrent
HHV8	Kaposi sarcoma in young subjects	OX40 deficiency (*TNFRSF4*), STIM1 deficiency, *STAT4* Occasionally: AR complete IFNγR1 deficiency, WAS
HPV	Severe/recalcitrant Warts Flat or verrucous Often trunk, face, neck, extremities, genital	Epidermodysplasia verruciformis (*EVER1*, *EVER2*, *RHOH*, *MST1*) Commonly: WHIM (*CXCR4*), DOCK8 deficiency, GATA2 deficiency (late onset), *PIK3CD* GOF, *LRBA* STK4 deficiency, Netherton syndrome (*SPINK5*; late onset), CASP8 deficiency syndrome, idiopathic CD4 lymphopenia (ICL, late onset). Some ICL caused by *IL7* mutations. Occasionally: WAS (*WASP*), NEMO deficiency (*IKBKG*), AT (*ATM*), SCID (*ADA*, *CD3G*, *JAK3*), LAD1 (*ITGB2*), MHC II deficiency (*CIITA*, *RFX5*, *RFXAP*, *RFXANK*), CVIDs, CD40L deficiency, LRBA deficiency, TWEAK deficiency, 11q terminal deletion
Molluscum contagiosum	Recalcitrant, widespread	WAS, NEMO deficiency (*IKBKG*), STAT1 deficiency, DOCK8 deficiency, TYK2 deficiency, LRBA deficiency, CASP8 deficiency syndrome, STK4 deficiency, LRBA Idiopathic CD4 lymphopenia
Common viruses	Severe infection	SCIDs, other significant T cell deficiencies. Influenza: IRF7 deficiency
Toxoplasmosis	Severe	Severe T cell deficiencies, Ig CSR deficiencies
Cryptosporidium spp., *Isospora spp.*	Recurrent or persistent infections	CD40L deficiency, CD40 deficiency, CVIDs, *CTLA4*, NIK (*MAP3K14*) deficiency
	Ascending cholangitis	CD40L deficiency, CD40 deficiency
Giardiasis	Recurrent/recalcitrant	Antibody deficiencies

Table 1.13 Opportunistic fungal infections in primary immunodeficiencies

Infection	Clinical setting	Primary immunodeficiencies
Pneumocystis jirovecii	Pneumonia	SCID (>30 genes), MHC II deficiency (*CIITA*, *RFANK*, *RFXC*, *RFXAP*)
		CID (*CD40LG*, *CD40*, *CARD11*, *DOCK8*, *FOXP3*, *CTLA4*)
		Syndromic: WAS (*WASP*), NEMO deficiency (*IKBKG*), VODI (*SP110*)
Candida spp.	Invasive	SCN (*ELA2*, *HAX1*, *VPS45*), LAD 1 (*ITGB2*)
	CNS infection	CGD (*CYBB*, *CYBA*, *NCF1*, *NCF2*, *NCF4*), CARD9 deficiency
	Chronic mucocutaneous	SCID (>30 genes), MHC II deficiency (*CIITA*, *RFANK*, *RFXC*, *RFXAP*)
		CID (*STAT1* GOF, *IL2RA*, *IKBG*, *IKBA*, *IKBB*, *TCRA*, *DOCK8*, *CRACM1*, *STK4*, *TRAC*, *RORC*, *LRBA*)
		Idiopathic CD4 lymphopenia
		Syndromic: APECED, *STAT3* haploinsufficiency and GOF, NEMO deficiency, VODI (*SP110*), KID (*GJB2*)
		With CNS candidiasis and dermatophytic infections: CARD9 deficiency
		As part of MSMD: IL12Rβ1 deficiency, IL12p40 deficiency
		Isolated: IL17RC deficiency; with susceptibility to *S. aureus*: IL17A deficiency, IL17F deficiency (partial), *ACT1* mutation
Aspergillus spp.	Invasive	CGD (*CYBB*, *CYBA*, *NCF1*, *NCF2*, *NCF4*)
		Syndromic: STAT3 deficiency, GATA2 deficiency[a]
		SCN (*ELA2*, *HAX1*, *VPS45*), LAD 1 (*ITGB2*)
	Deep dermatophytosis	CARD9 deficiency
Cryptococcus spp.	CNS	Syndromic: GATA2 deficiency[a]
		CD40L deficiency, *IL7*
		As acquired defect due to cytokine antibodies (anti-GM-CSF, anti-IFNγ)
Dimorphic fungi[b]	Invasive	As part of MSMD : IL12Rβ1 deficiency, IFNγR1 deficiency
		CID (*STAT1* GOF, *DOCK8*, *CD40LG*)
		Syndromic: GATA2 deficiency[a]
		Idiopathic CD4 lymphopenia

[a]GATA2 deficiency patients may have primary alveolar proteinosis, primary lymphedema, myelodysplastic syndrome
[b]Histoplasmosis, coccidioidomycosis, paracoccidioidomycosis

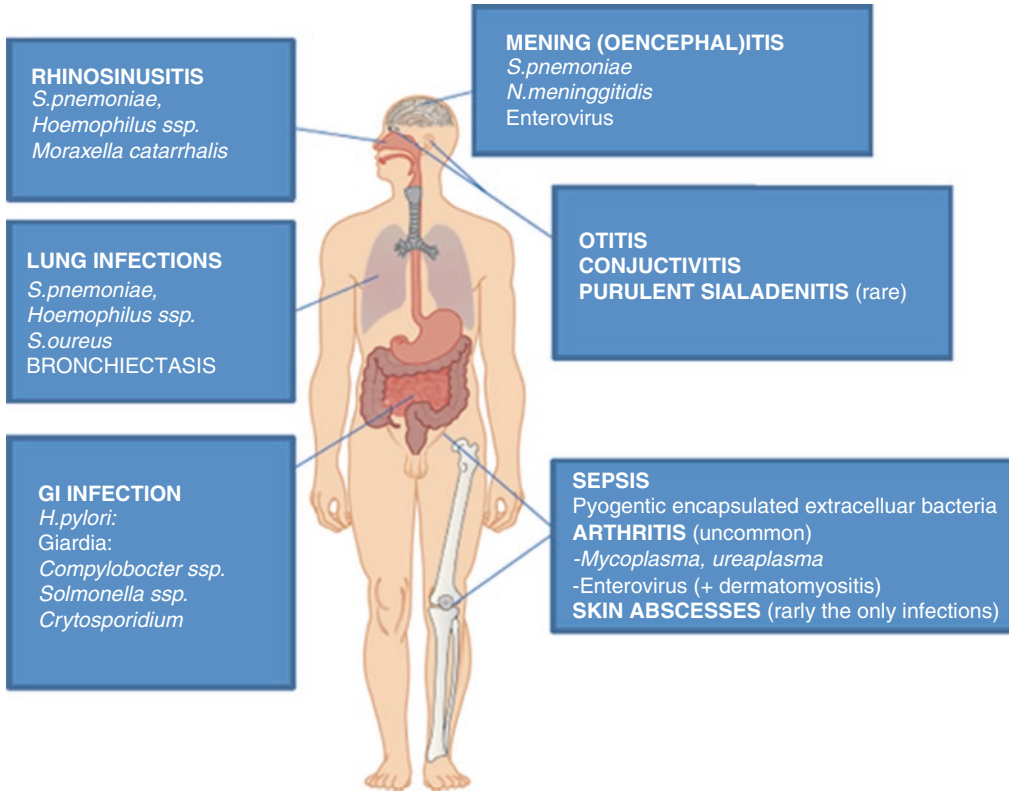

Fig. 1.6 Infections in antibody deficiencies (Adapted with permission from an open domain figure by Hautala T, Seppänen M. Aikuisen infektioalttius. Lääkärin käsikirja 2013. Kainulainen L, Seppänen M. Immunologia 2010, Mikko Seppänen/HumanArt Helena Schmidt, sponsored by Sanquin Finland, open domain)

often at typical sites of infection. Examples of bacterial infections seen in various PIDs are listed in Table 1.10 [6, 85]. As single episodes, most of these are relatively common in the population. Notably but not solely, in PID predisposing to purulent infections an acute infection episode may not differ in any way from infections in immune competent individuals. Only a careful, chronological and methodical patient history will uncover subject's predisposition to recurrent infections, its time of onset and whether this manifested early after birth or concurs with the loss of maternal antibodies (5–7 months after birth). If the onset of infections is very early (2–6 months of age), a combined immunodeficiency, phagocyte disorder or pattern recognition receptor deficiency should be suspected [6]. Individuals with various genetic autoinflammatory or immune regulation disorders often show mild or no predisposition to infections.

Partly due to the less developed immune system of infants and small children, they commonly suffer frequent, uncomplicated respiratory infections [6, 85]. More than 10–14 yearly episodes of infection in children and more than 5–7 yearly episodes in adults with healthy immune system can be seen if the infectious burden is high (e.g., occupation, day care), especially in subjects exposed to tobacco smoke or with concurrent asthma, chronic obstructive pulmonary disease (COPD), allergy or atopic dermatitis [6]. Atopy causes chronic inflammation of the airways that facilitates the adherence of pathogens to the respiratory epithelium and development of respiratory infections; >30 % children admitted to PID screening can have allergy as the main culprit and 50 % may be found to have normal immunity [6]. However, severe atopy is a feature of several rare PIDs. (*see below*) Atopic dermatitis was seen in 1.25 % of all UKPID Registry

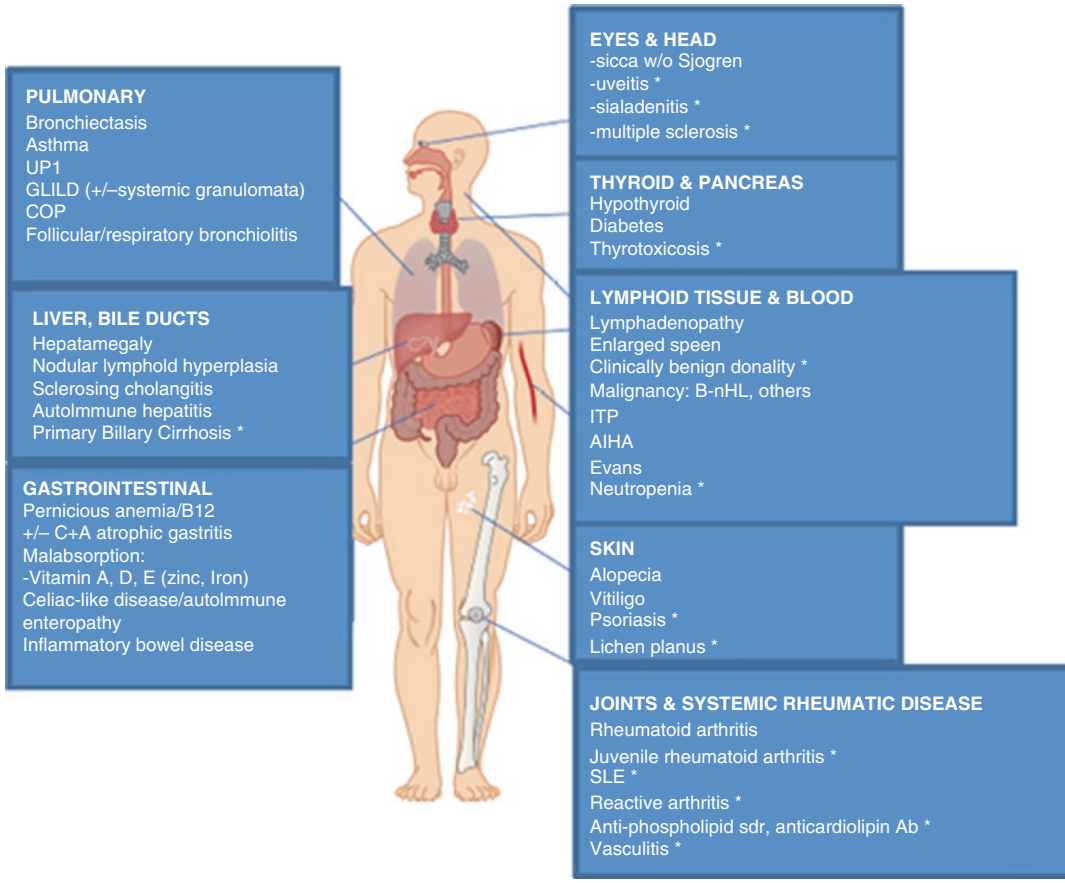

Fig. 1.7 Immune disturbances in common variable immunodeficiency. * Uncommon (generally <2 % in large series) (Adapted from an open domain figure by Hautala T, Seppänen M. Aikuisen infektioalttius. Lääkärin käsikirja 2013. Vaarala O, Seppänen M, Miettinen A. Immunologia 2010, Mikko Seppänen/HumanArt Helena Schmidt, sponsored by Sanquin Finland, open domain)

patients and asthma in 7 % [106]. Recurrent upper respiratory tract infections are also common in adult patients with long-standing negative stress or depression.

Based on mostly retrospective or epidemiologic data, also certain common recurrent infections and their complications should most likely result in screening for PID (Table 1.11) [6, 85, 87, 319]. Regardless of age, these include frequently recurrent pneumonias and/or bronchiectasis, recurrent septicemias, recurrent pyogenic meningitis and the rare recurrent viral encephalitis. If chronic or invasive opportunistic infections without apparent secondary cause (e.g., cutaneous candidiasis, invasive aspergillosis) are found, these should always lead to a search for PID (Tables 1.11, 1.12, and 1.13). If PID is thought probable, a clinical diagnosis of suspected infection like purulent rhinosinusitis or pneumonia is not sufficient. Instead, one should actively search for radiologic and microbiologic evidence.

In common respiratory infections, very early onset of symptoms before the age of 3–4 months and association with invasive diseases like mastoiditis after otitis media or recurrent sinusitis together with recurrent pneumonias may point to a potential PID [85].

Deep-seated abscesses and complicated pneumonias in childhood (empyema, lung abscess) indicate screening. In addition to antibody deficiencies, screened PIDs – at least in children – should include phagocyte, MyD88/IRAK4

deficiencies and congenital asplenia or hyposplenism (Table 1.11). For example p47^{phox} -deficient CGD patients (and X-CGD carriers) may become symptomatic only in early adulthood or later [34, 36]. Pattern recognition deficiencies cause susceptibility to severe early-onset infections with distinctly normal findings in routine immunologic tests, with the lack of autoimmune diseases and disappearance of infections in adulthood. (*See* Chap. 6 *for more details*) MyD88 and IRAK4 deficiencies cause severe early-onset susceptibility to both gram-positive and gram-negative bacteria (e.g., pneumococci, staphylococci, *Pseudomonas*) mainly during infancy and early childhood [308]. In patients without HIV infection but with recurrent blood-culture positive pneumococcal pneumonia, up to 50 % of patients may have some form of antibody deficiency [108]. Depending on the setting (e.g., primary care or tertiary referral center), in chronic bronchiectasis patients up to 7–30 % of adults and one-third of children may have some form PID. Bronchiectasis, bronchial wall thickening and different forms of interstitial pneumonitis are common in a wide range of PIDs and should thus alert to the possibility of PID (Table 1.11) [6, 85, 292].

Chronic recurrent rhinosinusitis is common both in allergy and in antibody deficiencies [85, 319]. In allergic patients, total serum IgE and specific IgE are never missing and tend to be high. Patients with agammaglobulinemia or class-switch recombination deficiencies are not able to produce IgE. In CVID, chronic recurrent rhinosinusitis is usually accompanied by infections of the lower respiratory tract, autoimmune diseases or recurrent or chronic diarrhea, and in approximately 90 % patients by undetectable total serum IgE levels when routine methods are used [6, 255]. Asthma in itself does not exclude antibody deficiency (Fig. 1.7) or other PIDs [6, 10, 106, 292, 295, 319]. Asthma is seen in approximately 6 % of CVIDs patients and atopy in 1 %; severe atopic eczema can be the presenting feature of several PIDs (Table 1.14) [10, 106].

If a patient has had earlier invasive infections or there is a failure to thrive, opportunistic pathogens listed in Tables 1.12 and 1.13 should be actively sought [97, 245]. For example, EBV or CMV viremia or their presence in tissues may not be clinically readily obvious in undiagnosed various combined PIDs and in genetic disorders of immune regulation [220, 232]. These should be systematically sought, if PIDs are suspected. Viremia caused by various herpesviruses has also been described in various monogenic, predominantly antibody deficiencies (e.g., *PKCD*, *PIK3CD*, *LRBA*). Depending on the subjects travel history, local epidemiology and current geographic area, one may need to consider pathogens that are not traditionally listed as opportunistic infections (Tables 1.12 and 1.13) [85].

Severe gingivitis and chronic periodontitis are seen in phagocyte defects and may be seen in other PIDs with symptomatic chronic neutropenia. (*See* Chap. 4 *for more details*) Chronic diarrhea is common in PIDs. In these, diarrhea is often accompanied by malabsorption, hepato(spleno)megaly and generalized lymphadenopathy [6, 85]. Diarrhea is often caused by noninfectious causes. Apart from antibody deficiencies, susceptibility to infectious colitis is most commonly reported in various forms of SCID, in leukocyte adhesion deficiencies and CGD [300]. Necrotizing enterocolitis in infancy is associated with Ficolin 3 deficiency [235]. In SCID, oral, esophageal and perianal candidiasis, chronic rotavirus infection and chronic CMV or adenovirus colitis (in GI biopsies) have been reported. Chronic enteroviral shedding, encephalitis and muscle, skin, liver or joint involvement may be seen in agammaglobulinemias and less commonly in CVIDs [162, 300]. Persistent enteric *Salmonella*, cholangitis by *Cryptosporidium* or recurrent giardiasis may be seen in for example immunoglobulin class-switch recombination deficiencies (Ig CSR) and CVIDs, while susceptibility to *Salmonella* and *Cryptococcus* may point to γ-IFN/IL-12 axis defect [57, 85].

Osteomyelitis or pyogenic arthritis is seen most commonly in various forms of antibody deficiency, but have also been reported in for example CGD, WAS and SCIDs. Enteroviral arthritis and dermatomyositis may develop in XLA. Infections by *Ureaplasma urealyticum* and *Mycoplasma ssp*. may lead to erosive, mostly

Table 1.14 Inflammatory skin conditions in primary immunodeficiencies

Inflammatory condition	Primary immunodeficiency	Note
Mild eczema	In most PIDs	
Generalized exfoliative erythroderma of infancy	SCID (>30 genes)	With diffuse alopecia. Omenn syndrome, occasionally due to GVHD from maternofetal transfusion
	Comèl-Netherton syndrome (*SPINK5*)	Bamboo hair may be hard to detect. Evolves into ichtyosis linearis circumflexa, superimposed atopic dermatitis common
Diffuse early-onset eczema and erythroderma and muscle amylopectinosis	HOIL-1 deficiency	Desquamative dermatitis, early-onset recurrent fever, chronic bloody diarrhea, hepatosplenomegaly, invasive pyogenic infections, CMV viremia, candidial sepsis
Psoriasiform erythroderma	*ADAMS17* deletion	Starts as pustular perioral and perianal dermatitis
Generalized pustular psoriasis	Deficiency of IL-36 receptor antagonist (DITRA, *IL36RN*)	Recurrent skin pustulation, systemic inflammation and psoriasis vulgaris
Atypical ichthyosiform erythroderma	KID syndrome (*GJB2*, others)	KID: keratitis, ectodermal dysplasia, deafness, chronic mucocutaneous candidiasis, viral infections
Severe, early-onset atopic eczema	Atopic/CID: WAS, IPEX, Comèl-Netherton syndrome, DOCK8 deficiency, LRBA deficiency, PGM3, *STAT1* GOF, IPEX, CD25, ITCH and STAT5b deficiencies Atopy unclear/CID: WIP deficiency, STAT5b deficiency, TRAC deficiency	WIP: high IgE, papulovesicular rash and clinically severe eczema STAT5b: early-onset diarrhea, growth-hormone insensitivity, of autoimmune PIDs least allergy and high IgE. Lung disease in ITCH, STATb and CD25 deficiencies commonest.
	STAT3 deficiency	Diminished allergic response (food allergy, anaphylaxis) due to impaired basophil activation and mast cell degranulation
Periodic eczema	NAID (adult-onset *NOD2*)	Spongiotic dermatitis, fever, arthritis, serositis, sicca, abdominal pain
Vesiculobullous dermatitis	Acrodermatitis enteropathica (*SLC39A4*)	Alopecia, diarrhea, zinc deficiency
Alopecia and vitiligo	Antibody deficiencies with autoimmunity	Most common in CVIDs and monogenic antibody deficiencies with autoimmunity, occasionally in various others.
Alopecia	Various	SCIDs (Omenn syndrome, *FOXN1*), AT (*ATM*), CID (*TRAC*), acrodermatitis enteropathica TTC7A deficiency: enteropathy, lymphocytopenia, alopecia
Congenital livedo	FILS syndrome (*POLE1*)	Mild facial dysmorphism, immunodeficiency, short stature
Aseptic skin granulomas	AT, MHC I deficiency (*TAP1*, *TAP2*, *B2M*)	Relatively common

(continued)

Table 1.14 (continued)

Inflammatory condition	Primary immunodeficiency	Note
	CVIDs, CD40L deficiency, *LRBA*, *BTK*, *BIRC4*, CGD, ALPS, CHH, NBS, Rothmund-Thomson syndrome, Griscelli syndrome, Blau syndrome, hypomorphic SCID (*RAG1*, *RAG2*, *JAK3*, *DCLRE1C*), PLAID, HOIL1, 22q11 del, *PRKCD*	Occasionally, often late-onset. In Blau syndrome, minimal or low-grade fever attacks. In PLAID, child may be born with them. In NAID (adult-onset *NOD2*) usually eczema, may be granulomatous.
Urticaria	CAPS (*NLRP3*; FCAS, MWS, NOMID), other autoinflammatory syndromes (*NLRP12*, *PLCG2*), HAE (*SERPING1*)	FCAS triggered by cold, in FCAS and MWS periodic fever is of short duration, in NOMID continuous low grade. PLAID: hypogammaglobulinemia. HAE: angioedema.
Erysipelas-like erythema	FMF (*MEFV*), TRAPS (*TNFRSF1A*)	FMF: serositis, fever 1–3 days TRAPS: periorbital edema, migratory rash, fever lasts >7 days
Maculopapular or purpuric exanthema	HIDS (*MVK*)	Painful bilateral cervical lymphadenopathy, fever 3–7 days, may have hypogammaglobulinemia
Ichthyosis-like exanthema	PGA (*NOD2*)	Skin rash, uveitis, chronic arthritis, granulomatous.
Pustular dermatitis	DIRA (*IL1RN*), Majeed syndrome (*LPIN2*),	DIRA: early-onset rash, multifocal osteomyelitis Majeed: early-onset rash, multifocal osteomyelitis, dyserythropoetic anemia
Pyoderma gangrenosum and cystic acne	PAPA (*PSTPIP1*)	PAPA: deforming sterile pyogenic arthritis and skin abscesses
Hidradenitis suppurativa (acne inversa)	*PSENEN*, *PSEN1*, *NCSTN*	Gamma-secretase gene mutations affecting Notch-signalling. With pyoderma gangrenosum (PASH): *NCSTN*
Folliculitis	Early-onset inflammatory bowel disease (*IL10*, *IL10RA*, *IL10RB*)	Failure to thrive, early-onset, severe bloody diarrhea, recurrent fever and infections
Psoriasis	DITRA (*IL36RN*), CAMPS (*CARD14*)	DITRA: recurrent, sudden generalized erythematous pustular psoriasis, high grade fever, secondary skin infections and sepsis CAMPS: familial plaque/pustular psoriasis or pityriasis rubra pilaris, no systemic symptoms if no superinfection
Nodular exanthema, panniculitis, lipodystrophy, histiocytic-like infiltrates	PRAAS (*PSMB8*)	Recurrent fever with diffuse annular plaques, violaceous edema of eyelids, myositis, arthralgia, arthritis, joint contractures, lymphadenopathy, hepatosplenomegaly, basal ganglia calcifications
Cold-induced urticaria	PLAID (*PLCG2*)	Super-imposed atopy, organ-specific autoimmunity, recurrent sinopulmonary infections and hypogammaglobulinemia
Erythematous plaques, vesicopustular lesions, cellulitis	APLAID (*PLCG2*)	Early-onset, together with arthralgia, corneal erosions and interstitial pneumonitis, mild antibody deficiency.

large-joint monoarthritis in patients with severely low immunoglobulin levels; polyarthritis has been reported infrequently [271]. Chronic multifocal sterile osteomyelitis is seen in Majeed and DIRA syndromes (Table 1.14) [23].

If severe, chronic or recurrent viral or fungal infections of the skin are seen, they point to combined or phagocyte defects (Tables 1.12 and 1.13) [6, 85]. Deep dermatophytosis is seen in CARD9 deficiency [163]. PIDs with recurrent, widespread and numerous warts or *Molluscum contagiosum* are listed in Table 1.12 [170, 275].

Skin microbiomes in PID patients with eczema (STAT3, DOCK8, WAS) are altered and more permissive to fungal, gram negative and anaerobic bacterial species [219]. Superficial abscesses are seen in these as well as in phagocyte deficiencies, together with deeper abscesses and other opportunistic infections (Table 1.11) [6]. Recurrent cellulitis or superficial abscesses without concurrent invasive bacterial, viral or fungal infections in PIDs seem rare [6, 184]. Anatomical, functional and microbiologic causes like secondary lymphedema, dry atopic skin or Panton-Valentine leukocidin (PVL) positive MRSA should be sought in such patients. Often helping to exclude PID, PVL-positive MRSA causes mini-epidemics in close contacts. MyD88 and IRAK4 deficiencies need to be excluded if a child develops severe ulcerative skin infections and invasive infections [209, 308]. Poor wound healing and skin pustules or abscesses leading to pyoderma gangrenosum (PG)-type ulcerations are seen in leukocyte adhesion deficiencies, PG is also seen in autoinflammatory diseases [6, 85]. (*See below*) Systemic lymphangiectasia points to HOIP mutation, while primary lymphedema (Emberger syndrome) and monocytopenia point to GATA2 deficiency [81, 274]. Severe, chronic, recalcitrant and painful skin ulcers of the lower extremities and telangiectasias of the face and hands are seen in prolidase (*PEPD*) deficiency.

Reported incidence of complement deficiencies in patients with a single episode of meningococcal meningitis varies greatly between populations, but may exceed 10 % (Tables 1.10 and 1.11) [1, 100, 282]. Complement deficiencies are more commonly found during epidemics, in African Americans and in patients infected with uncommon strains (X, Y, W135 or ungroupable), possibly reflecting the increased susceptibility of deficient patients to become symptomatic [100, 327].

Narrow susceptibility to severe viral infections is seen in impaired TLR3-IFN immunity (*TLR3*, *UNC93B1*, *TRIF*, *TRAF*, *TBK1*, *IRF3*, *HYOU1*), which causes susceptibility to HSV-1 encephalitis, this may become recurrent (Table 1.12) [323]. In FADD deficiency, fever, encephalopathy, generalized seizures and mild liver dysfunction lasting several days may be triggered by viral infections or immunizations [42].

Careful history of received vaccines may also reveal side effects that point to monogenic diseases. Side effects of Bacillus Calmette-Guérin (BCG) occur in SCID and MSMD patients, and may reveal unexpectedly high incidence of SCID in ethnic groups [254]. Adverse reactions to other live attenuated vaccines like those against polio, yellow fever or rotavirus may be seen in PIDs with low T cell function and in antibody deficiencies [84]. Granulomatous skin lesions caused by vaccine-strain rubella is seen in T deficiencies and generalized vaccine-strain measles is seen in STAT2 deficiency [135]. In HIDS (*MVK*), vaccines may trigger autoinflammatory symptoms [23].

PIDs are rarely to be expected, if recurrent infections are not caused by opportunistic pathogens or if there is no invasive or chronic course nor the tendency to recur soon after antimicrobial therapy is stopped [8, 84, 319]. A single episode of pneumonia or invasive group A streptococcal infection is not predictive of PID [139, 140]. In clinical practice, PIDs are not found in patients with solely recurrent urinary tract infections. If infections strictly recur in the same anatomical foci (e.g., sinuses, lung lobe), one should first look for anatomical or functional defects like primary or secondary ciliary dyskinesia, cystic fibrosis, gastro-esophageal reflux, infantile bronchomalacia, lung sequesters, localized bronchiectasis, tracheobronchial foreign bodies or middle-lobe syndrome [292]. Of opportunistic fungi, especially *Aspergillus fumigatus* is capable of causing chronic pulmonary disease even in

non-PID patients, most commonly allergic bronchopulmonary aspergillosis. Pre-existing structural lung disease and minor immunologic defects predispose patients to chronic cavitary, necrotizing or fibrosing pulmonary aspergillosis [269].

1.3.2 Autoimmunity and Inflammatory Conditions

Autoimmunity and other manifestations of dysregulated immunity are common in many PIDs (Table 1.15). At the office, these are most commonly seen in CVID due to its incidence (Fig. 1.7).

Various hypomorphic SCIDs cause Omenn syndrome (OS), most often RAG1 and RAG2 deficiencies [28, 289]. In OS, expansion of oligoclonal T cells and defective AIRE expression in thymus lead to autoreactivity, lymphadenopathy, hepatosplenomegaly, alopecia, exudative erythroderma, hypereosinophilia and increased serum levels of IgE despite the absence of B cells [305]. In addition to OS, autoimmunity is more common in so-called leaky (atypical) SCID like in delayed-onset ADA and PNP deficiencies [28, 129]. The term leaky SCID is used when incomplete mutation(s) in a typical SCID gene lead to T cell counts above that seen in classical SCIDs, ranging from 300 to 1500 cells/L. In leaky SCID, the patient may also have a later age of onset of clinical symptoms. Among more typical autoimmune manifestations, hematologic cytopenias, hepatitis, vitiligo and villous atrophy have been reported [126, 211]. In villous atrophy, GI biopsies show hypocellular lamina propria, without plasma cells or lymphocytes. If OS and SCID have been excluded, severe early onset non-infectious diarrhea may point to other PIDs with autoimmunity or autoinflammation (Table 1.15) [117, 293].

Autoimmunity is reported frequently in various combined immunodeficiencies. In WAS, impaired cytoskeletal movement leads to impaired T cell signaling leading to autoimmunity in 40–72 % of patients. Autoimmune neutropenia and hemolytic anemia are common, in PID generally rare phenomena like Henoch-Schönlein vasculitis, uveitis, renal disease, myositis and dermatomyositis are also seen [289]. In immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), *STAT5B* and *LRBA* mutations, the frequency of autoimmunity may be close to 100 % at least with increasing age; autoimmune cytopenias are common [28, 211]. In ataxia-telangiectasia, autoimmune cytopenias, thyroiditis and alopecia are occasionally seen [233]. In 22q11 deletion syndrome, autoimmune manifestations like autoimmune hypothyroidism or cytopenia are seen in approximately 9 % of patients (Table 1.15) [122, 289].

Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED), IPEX, CD25 deficiency, STAT5b deficiency, ITCH deficiency, *STAT1* GOF and *STAT3* GOF mutations belong to PIDs with predominantly autoimmune manifestations [117]. (*See* Chap. 5 *for more details*) These may present with slightly differing combinations of autoimmune polyendocrinopathy, severe early-onset diarrhea due to autoimmune enteropathy, severe mostly allergic eczema and/or multisystem autoimmune disease (Tables 1.14 and 1.15) [211, 306]. In autoimmune polyendocrinopathy, variable combinations of hypoparathyroidism, hypoadrenalism, type I diabetes, hypothyroidism, ovarian failure, vitiligo and autoimmune hepatitis are seen [211]. Autoimmune enteropathy leads to blunted villi, intraepithelial lymphocytosis, malabsorption and severe diarrhea [117, 289, 306]. Many of these diseases also cause concurrent lung damage, for example lymphocytic interstitial pneumonitis and bronchiectasis. Infections are mainly associated with impaired gut integrity. However, APEX, CD25 deficient and *STAT1* GOF patients have candida infections, CD25, STAT5b and *STAT1* GOF patients infections caused by bacteria and herpesviruses and *STAT3* GOF patients have generalized mycobacterial infections (Table 1.15) [306].

Autoimmunity is common in primary antibody deficiencies [211, 266, 289]. In the largest published CVID cohorts, inflammatory conditions were seen in approximately 70 % of patients [266]. Progressive pulmonary lymphocytic and/or granulomatous infiltrates with a component of tertiary lymphoid neogenesis are the most

Table 1.15 Organ-specific and hematologic autoimmune/autoinflammatory disorders associated with primary immunodeficiencies

Inflammatory condition	Primary immunodeficiency	Note
Organ-specific autoimmunity	Hypomorphic SCID (*ADA*, *PNP*, *CD3G*, *RAG1*, *RAG2*, possibly others)	May present early with Omenn syndrome or delayed, villous atrophy. STIM1 deficiency: close to 100 % with increasing age
	XLA	Occasionally arthritis, nodular regenerative liver hyperplasia
	Hypogammaglobulinemia with thymoma	Good syndrome
	CVIDs	*See* Fig. 1.7
	IgAD	Celiac disease, type I diabetes, thyroid diseases, juvenile arthritis (JRA, JIA), also SLE, atopy, others.
	Monogenic predominantly antibody deficiencies (*LRBA*, *TACI*, *CD19*, *CD81*, *PKCD*)	Like in Fig. 1.7, rare manifestations seem more common than in classical CVID. Non-granulomatous nephropathy described in *CD19*, *CD81*, *PRKCD* -mutations.
	Ig CSR deficiencies (*AICDA*, *CD40LG*)	AID deficiency, autoimmunity in one-third, uveitis 10 % CD40L deficiency: sclerosing cholangitis, arthritis
	COPA	Arthritis and interstitial lung disease
	22q deletion syndrome	Autoimmune hypothyroidism, some AI disease in approximately 9 %. May be seen in other deletional PIDs as well (e.g. 11q terminal).
	CID (*WASP*, *ATM*, *STAT5B*, others)	WAS: AI diseases in 40–72 % (e.g. Henoch-Schönlein vasculitis, uveitis, renal disease, myositis, dermatomyositis).
	CGD	SLE, DLE, JIA, sarcoidosis. In X-CGD carriers, multiple autoimmune phenomena including photosensitivity and DLE.
	ALPS	Rare (e.g. nephritis, autoimmune liver diseases, uveitis)
	PKCδ deficiency	Benign lymphoproliferation, autoimmunity (organ-specific, antiphospholipid syndrome)
Hematologic autoimmunity	SCID (*ADA*, *PNP*, *STIM1*, *ORAI1*, *AK2*, others), MHC II deficiency	Clinical presentation may be delayed in hypomorphic mutations.
	CVIDs	*See* Fig. 1.7
	IgAD	
	Monogenic predominantly antibody deficiencies (*LRBA*, *TACI*, *ICOS*, *CD19*, *CD81*, *PKCD*)	
	Ig CSR deficiencies (*AICDA*, *CD40LG*, *CD40*)	CD40L deficiency: autoimmune neutropenia in up to 40 %
	22 q deletion syndrome	Syndromic findings
	CID (*WASP*, *ATM*, *STAT5B*, *TRAC*, others)	Syndromic findings in *WASP*, *ATM*, *STAT5B*
	CGD	ITP
	IPEX	Eczema

(continued)

Table 1.15 (continued)

Inflammatory condition	Primary immunodeficiency	Note
Hematologic autoimmunity with non-virally induced lymphoproliferation	ALPS	Chronic lymphoproliferation in all, AI cytopenias in 70% of patients, autoimmune neutropenia least common
	ALPS-associated disorders	RALD (*NRAS*, *KRAS*): AI cytopenias and autoantibodies CEDS (*CASP8*): mild combined PID, pronounced lymphocyte accumulation and infiltration, minimal autoimmunity PKCδ deficiency: AI cytopenias not described
	CD25 deficiency	Eczema, polyendocrinopathy, enteropathy, early-onset opportunistic infections
	SCID (e.g. *JAK3*, *STIM1*), 22q11 deletion, 10p deletion	Clinical immunodeficiency
Hematologic autoinflammation with hemophagocytic lymphohistiocytosis	HLH mainly seen in FHL1-5, also in *LYST*, *RAB27A*, *SH2D1A*, *XIAP*, *ITK*, *CD27* and *NLRC4* mutations	Occasionally: *WASP*, *LIG4*, *AP3B1*, *IL2RG* mutations, 22q11 deletion syndrome) Hypopigmentation in *LYST*, *RAB27A*, *AP3B1* mutations
Histiocytosis	*SLC29A3*	H syndrome: Lymphadenopathy or skin lesions, sensorineural hearing loss, hyperpigmentation/ hypertrichosis
Sterile arthritis	CVIDs	
	Ig CSR deficiencies (*AICDA*, *CD40LG*)	
	CID (*WASP*, *STAT5B*, others)	Eczema, in STAT5b prominent forehead, saddle nose
	ALPS	Rare
	Autoinflammatory syndromes	In all, rare in some (*IL36RN*, *PLCG2*, *HOIL1*)
Sterile pericarditis	Autoinflammatory syndromes	*MEFV*, *TNFRSF1A*, variant *NLRP3*, *SLC29A3*
Autoimmune polyendocrinopathy ± autoimmune enteropathy ± CMC, with failure to thrive	APECED	Chronic mucocutaneous candidiasis, hypoparathyroidism, adrenal insufficiency
	IPEX	Enteropathy, eczema, type I diabetes, thyroid, cytopenias, high IgE, other organ-specific autoimmunity
	STAT1 GOF mutations	Enteropathy, type I diabetes, thyroid, cytopenias
	ITCH deficiency	Enteropathy, type I diabetes, hypothyroidism, hepatitis, interstitial pneumonitis, macrocephaly, dysmorphic features
	CD25 deficiency	Enteropathy, mucous candidiasis, lymphadenopathy, hepatomegaly, eczema, no polyendocrinopathy reported, recurrent/persistent viral infections, IgE normal
	STAT5b deficiency	Growth failure, interstitial pneumonitis, eczema, enteropathy, thyroid, recurrent/severe viral infections, prominent forehead, saddle nose
	STAT3 GOF mutations	Cytopenias, lymphoproliferation, enteritis, eczema, some with type I diabetes, lung or thyroid disorders, arthritis, macular degeneration. Short stature, recurrent infections and hypogammaglobulinemia common. Candidiasis possible.

Inflammatory bowel disease, often Crohn disease like	CVIDs, IgAD, CGD, CGD, ALPS	Usually not early-onset except in IL-21 deficiency, other forms of CVIDs: Fig. 1.7
	Ig CSR deficiencies (*CD40LG*, *AICDA*)	Variable onset, rare
	Monogenic antibody deficiencies (*ICOS*, *LRBA*, possibly others)	Variable onset, also villous atrophy, lymphocytic colitis
	SCN (*G6PC3*)	Typically several years of delay
	HIDS	Not rare, variable onset (>6 months appr. 10%), recurrent fevers
	FMF	Atypical, rare, if present may be early-onset ulcerative colitis.
Early-onset inflammatory bowel disease	SCID	Omenn syndrome
	Agammaglobulinemia (*BTK*, *PIK3R1*)	May also be delayed. With CVID phenotype: IL-21 deficiency.
	Neutropenia (*SLC37A4*), LAD 1 (*ITGB2*)	Crohn disease -like
	CID (*WASP*, *IKBKG*)	WAS: eczema, thrombopenia, immunodeficiency NEMO: variable presentation, ectodermal dysplasia, enteropathy
	FHL5 (*STXBP2*), XLP1 (*SH2D1*)	Atypical manifestations, diffuse colitis
	XLP2 (*XIAP*)	Crohn disease-like, perianal, fistulising
	Early-onset inflammatory bowel disease syndrome (*IL10*, *IL10RA*, *IL10RB*)	Bloody diarrhea, abscesses, perianal fistula, oral aphthous lesions, arthritis, reminiscent or Crohn disease
	APLAID (*PLCG2*)	Enterocolitis, bloody diarrhea (by 6 months of age), blistering skin lesions, NSIP, arthralgias, eye inflammation
	Trichohepatoenteric syndrome (*SKIV2L*, *TTC37*)	Colitis, very early-onset, hepatopathy, trichorrhexis nodosa (woolly hair), hypogammaglobulinemia
	ADAM17 deficiency	Psoiriasiform erythroderma starting as pustular perioral and perianal dermatitis, short and broken
	VODI (*SP110*)	Occasional
	Prolidase (*PEPD*) deficiency	Occasional
Early-onset diarrhea and malabsorption	Shwachman-Diamond syndrome, ICF	SDS (*SBDS*): exocrine pancreatic insufficiency ICF (*DNMTB3*, *ZBTB24*, *CDCA7*, *HELLS*): immunodeficiency centromeric instability, facial anomalies

common findings, even in CVID patients under therapy (Fig. 1.7) [185]. Granulomatous disease undistinguishable from sarcoidosis in biopsy is seen in approximately 10 % of CVID patients; unlike in sarcoidosis these patients have low not high immunoglobulin levels [27]. There is considerable geographic variation in the frequencies (12–46 %) of reported inflammatory complications [71].

Hematologic autoimmune cytopenias are most commonly found in CVIDs and autoimmune lymphoproliferative syndrome (ALPS) [287]. In a nation-wide cohort of childhood autoimmune anemia patients, PID was concurrently diagnosed in 2.8 % and later during follow-up in 6.2 % of subjects. In these, CVID accounted for 59 % of PID cases, and the likelihood of finding PID increased if the patient developed also immune thrombocytopenia [21]. In the US studies on Evans syndrome, 30–40 % of children had ALPS [287]. Splenomegaly may precede the onset of clinical symptoms of PIDs.

Inflammatory liver diseases are seen in approximately 9 % of CVID patients and include autoimmune hepatitis, primary biliary cirrhosis, nodular regenerative hyperplasia and granulomas [71, 310]. In a French cohort, nodular regenerative hyperplasia was seen in approximately 5 % of all CVID patients [115, 188]. Sterile arthritis is most commonly seen in CVIDs, Ig CSRD deficiencies, IgA deficiency, WAS, 22q deletion syndrome, autoinflammatory syndromes (AIS) and occasionally in XLA (Table 1.15) [23, 271].

In addition to the PIDs with predominantly autoimmune manifestations listed above, early-onset diarrhea is seen in various other monogenic diseases. These patients often display inflammatory and/or granulomatous bowel diseases resembling Crohn disease with formation of fistulae, abscesses, pustules and perianal disease (Table 1.15). Infantile chronic diarrhea and small stature have been described in *STAT5B*, *SBDS*, *TTC37*, *SKIV2L*, and *RTEL1* mutations. Early-onset severe hypogammaglobulinemia with hepatobiliary and/or inflammatory bowel disease may be caused by *LRBA*, *ICOS*, *CD40LG*, *AICDA*, *SP110*, *BTK* or *PIK3R1* mutations and by AISs (Table 1.15) [23, 33, 293].

Inflammatory bowel diseases and other autoimmune diseases of the gastrointestinal tract are also seen in 10–32 % of classical CVID patients (Fig. 1.7) and in immunoglobulin class-switch recombination (Ig CSR) deficiencies, often with somewhat delayed onset. In CVIDs, GVHD-mimicking colitis and nodular lymphoid intestinal hyperplasia containing expanded B cell numbers, but reduced plasma cells are seen regularly. A subset of CVID patients suffers from coeliac sprue-resembling enteropathy [86, 293]. The association of antibody deficiencies with bowel, liver and granulomatous complications is still omitted by most gastroenterology and hepatology textbooks.

Chronic airway damage is frequently seen in most PIDs, including SCID, various combined immunodeficiencies, CVIDs and monogenic antibody deficiencies. Most commonly, interstitial pneumonitis, bronchiectasis, granulomas and cryptogenic organizing pneumonia are encountered (Table 1.11) [292]. Deficiencies of *LRBA*, *CD81*, *PRKCD* and *ICOS* seem strongly associated with both common and uncommon autoimmune and inflammatory manifestations described in CVID (Fig. 1.7) [22, 156, 178, 256, 302, 320]. Non-granulomatous nephropathy with low immunoglobulin levels, uncommon in classical CVID, may point to a monogenic disease (e.g., *CD19*, *CD81*, *PRKCD*, *AICDA*). Recurrent mucosal aphthae may point to *NFKB1* mutations. Autoimmune conditions are also found in IgA deficiency and in Ig CSR, mostly in AID and CD40L deficiencies [266, 289]. Autoimmunity is infrequent in agammaglobulinemias, but besides inflammatory bowel disease, arthritis and nodular regenerative hyperplasia may be found [289].

PIDs presenting with lymphoproliferation, autoimmunity and/or autoinflammation infrequently display infectious complications. (*See* Chap. 5 *for more details*) Typical clinical presentations in these patients include chronic lymphoproliferation leading to hepatosplenomegaly and generalized lymphadenopathy or hemophagocytic lymphohistiocytosis (HLH; Tables 1.12 and 1.15). In ALPS caused by defects in FAS pathway apoptosis, increased double-negative αβ T cells, nonmalignant

lymphadenopathy, hypergammaglobulinemia, B cell lymphocytosis and splenomegaly are typically found together with autoimmune cytopenias. Vitamin B12 levels are high. Other autoimmune manifestations like uveitis, autoimmune hepatitis or Guillain-Barré are infrequently reported (Table 1.15) [183, 211, 289]. ALPS may occasionally be found in adults with autoimmune complications and no previous diagnosis. ALPS-like findings are seen in *STAT3* GOF mutations. The so-called ALPS-related disorders not fulfilling ALPS criteria usually present with autoimmunity, lymphadenopathy and/or splenomegaly [113, 156, 183]. (*See* Chap. 5 *for more details*) Briefly, these include RAS-associated autoimmune leukoproliferative disorder (RALD) caused by somatic mutations in *NRAS* or *KRAS*, *CASP8* deficiency syndrome (CEDS), the newly described protein kinase C delta deficiency and Fas-associated protein with death domain (FADD) deficiency. CEDS patients do have recurrent viral and bacterial infections. In FADD deficiency, the main symptoms are periodic fever and inflammatory encephalopathy lasting a few days together with functional hyposplenism [42, 221]. Importantly, in various SCIDs (e.g., *JAK3*, *STIM1*) lymphoproliferation leading to hepatosplenomegaly and lymphadenopathy may also be seen (Table 1.15) [58, 65].

Hemophagocytosis refers to a biopsy finding of activated macrophages engulfing erythrocytes, leukocytes, platelets and their precursor cells. It may be seen as an autoinflammatory reaction [250, 297]. HLH may be secondary to infections (e.g., EBV, other herpesviruses except HHV7) or primary [182]. In familial hemophagocytic lymphohistiocytoses (FHL1-5), genetic defects of CTL and NK cell cytotoxic function result in HLH [263]. By definition, HLH patients have an unremitting fever, splenomegaly and cytopenia in at least 2 lineages. These may be accompanied by various cutaneous, liver and neurologic manifestations, coagulopathies and acute respiratory failure. Symptoms may resemble severe bacterial sepsis or Kawasaki disease. In biopsies, HLH is not always discernible. If clinical suspicion is moderate, systematic testing and follow-up of laboratory markers for HLH is recommended [182, 297]. (*See* Chap. 5 *for more details*) Untreated HLH may rapidly lead to death. Chronic EBV viremia and lymphomas are seen in FHL2 and FHL5. Hypogammaglobulinemia occurs in FHL2-3 [232]. FHL is typically manifested during the first months of age, adult cases have been diagnosed in FHL2, FHL3 and FHL5 [231].

HLH occurs also in genetic conditions associated with pigmentary dilution/albinism and/or platelet dysfunction and abnormal cytotoxic granule trafficking in different cell types (Table 1.15). These include Chediak-Higashi (CHS), Griscelli type 2 (GS2) and Hermansky-Pudlak type 2 (HPS2) syndromes. EBV-associated HLH is further seen in genetic PIDs with defective T cell signaling or T-B cell interaction (Table 1.12) [232]. (*See* Chap. 5 *for more details*) Hypogammaglobulinemia occurs in all these, as well as EBV viremia in ITK and CD27 deficiencies. Risk of lymphoma is increased in all except X-linked lymphoproliferative disease type 2 (XLP2; *XIAP*) [232]. XLP2 patients display prominent splenomegaly and may develop severe colitis [232, 273]. XLP1 has been diagnosed in adults [263]. Further infrequent monogenic causes of HLH are listed in Table 1.15.

Mild eczema is commonly seen in various PID. Severe erythroderma occurs in 7 % of PIDs [15]. While autoimmune cytopenias, interstitial lung diseases, inflammatory bowel diseases and enteropathy may be seen in B cell, T cell and combined immunodeficiencies, severe newborn dermatitis is generally a sign of significant T cell deficiency [15, 169]. Erythroderma of infancy with diffuse alopecia is a hallmark of SCID. In these patients, exfoliative erythroderma is usually caused by Omenn syndrome and occasionally by GVHD due to maternofetal transfusion [15, 169, 264].

Numerous inflammatory skin manifestations that occur in PIDs are listed in Table 1.14. Severe early-onset atopic or atopic-like eczema is a presenting feature in WAS, in autoimmune PIDs covered above (e.g., IPEX, GOF *STAT1*), hyper-IgE syndromes (*STAT3* LOF, *DOCK8*, *PGM3*), Comèl-Netherton syndrome, and occasional in *LRBA* [169, 264, 306]. Severe atopic-like eczema from birth occurs in *STAT3* LOF mutations. Despite very

high IgE levels, severe IgE-mediated allergy or anaphylaxis is rare; mast cell degranulation and basophil activation are compromised [262]. Comèl-Netherton patients have congenital ichthyosis and sometimes hard-to-detect bamboo hair. Various rashes are almost universal in AISs [271]. Aseptic skin granulomas occur most commonly in ataxia-telangiectasia, TAP1/2 deficiencies, late-onset hypomorphic SCIDs (*RAG1*/*2*, *JAK3*, *DCLRE1C*) and in CVIDs, occasionally in other PIDs (Table 1.14) [76, 91, 150]. Congenital livedo is seen in FILS syndrome (*POLE1*) and generalized bullous epidermolysis in APLAID (*PLCG2*).

In addition to CVIDs and IgAD, certain monogenic PIDs predispose to systemic, renal and neurologic autoimmune diseases. Early classical complement component deficiencies cause systemic lupus erythematosus (SLE) and SLE-like glomerulonephritis. Various gain and loss of function mutations of *C3*, *CFB*, *CFH*, *CFI* and *MCP* and autoantibodies to factor H and factor I result in over-activation of the alternative pathway and cause atypical hemolytic uremic syndrome. C1s, C7, C2 and complement regulatory protein deficiencies have been associated with multiple autoimmune diseases (e.g., SLE, glomerulonephritis, vasculitis, polymyositis) [151, 211]. (*See* Chap. 8 *for more details*) XLP1 is associated with aggressive lymphoid vasculitis. Carriers of X-CGD may develop photosensitivity and discoid lupus. They may also develop other features of mild CGD and occasionally invasive infections [34]. Chronic or recurrent aseptic (meningo)encephalitis may be seen in CAPS/NOMID and has been described together with vasculitis in a single case of factor I deficiency [23, 133]. Episodes of recurrent fever and encephalopathy with difficult-to-control generalized seizures are seen in FADD deficiency; progressive brain atrophy may ensue [42]. Excess type I interferon production in a subgroup of autoinflammatory syndromes, so-called interferonopathies, may cause lupoid findings.

Autoinflammatory syndromes are characterized by periodic or fluctuating fever and systemic activation of innate immunity against affected tissues together with a general lack of involvement of adaptive immunity (e.g., autoantibodies, antigen-specific T cells) or susceptibility to infections. (*See* Chap. 6 *for more details*) Multisystem sterile neutrophilic or granulomatous inflammation may affect skin, eyes, joints, bone, gut, serosal surfaces, sebaceous glands and fat tissue (Table 1.15). Skin manifestations, seen in all AIS, may worsen by cold, heat or sun exposure (Table 1.14) [23]. Though chronic sterile multifocal osteomyelitis lesions are frequently associated with polygenic diseases (psoriasis, Crohn disease, SAPHO syndrome), they may be seen in the monogenic Majeed and DIRA syndromes as well as in hypomorphic *RAG1* mutations (Table 1.15) [260].

1.3.3 Malignancies

Together with infections and autoimmunity, malignancies form the triad defining the most common findings in various PIDs. Despite this, we lack systematic data on the cancer risk and type of malignancies seen in most genetic PID. Generation of this and data on the remaining risk of malignancy after HSCT are among the most important functions of international and national PID registries and treatment consortiums [112, 126]. PIDs most commonly associated with malignancies are CVIDs, defects in immunodeficiency genes regulating DNA repair, cell cycle, apoptosis, or bone marrow maturation as well as those predisposing to virally-induced malignancies.

Based on what we know of cancer immune surveillance, increased frequency of malignancy could theoretically be considered likely in all PID populations with significant T cell or NK cell compromise. Only a few known NK cell and limited numbers of T cell defects have reliably been linked to early-onset cancers [147, 168, 211, 299, 303]. Since infections may cause early death in significantly T and NK cell deficient patients without HSCT and since with HSCT the risk of malignancy may be altered in the subjects, this concept may be hard to prove. Lack of genetic diagnosis in a significant subset of patients and the rarity of many PID further complicate reliable assessment.

Available population-based cohort studies suggest that an excess cancer risk is confined to specific rare genetic PIDs and to CVIDs, and is mainly caused by increased lymphoma risk [192, 247, 286, 299]. In published cases, the highest risks for lymphomas have been reported in NBS (49 %), XLP (24–30 %), AT (15–19 %), CHH (7 %), ALPS-FAS (7 %) and in CVID (1.8–8.2 %) [168, 211, 299]. In ALPS-FAS with defective apoptosis, the increased relative risk is 51-fold for Hodgkin disease and 14-fold for non-Hodgkin lymphoma, various other types of lymphomas are seen as well. Risk is not known for other ALPS forms. Unlike in other immunodysregulatory PIDs, malignancies in ALPS show no evidence of generally being virally driven, though EBV-associated lymphoproliferation has sporadically been reported (Table 1.12) [113, 213].

The immune system relies on genetic diversity generated by somatic recombination of antigen-binding T and B cell receptors. This is dependent on controlled genetic rearrangements by multiple repair and damage response complexes. Defect damage response leads to dsDNA breaks causing a high rate of malignancies, chromosomal instability and abnormal gene rearrangements [93, 121]. AT is a typical DNA repair defect with a high rate of malignancy and chromosomal instability. Various DNA repair deficiencies that affect lymphocyte-specific V(D)J rearrangements, class switch recombination and/or somatic hypermutation (*ATM*, *NBN*, *DCLRE1C*, *LIG4*, *LIG1*) give rise to combined immunodeficiencies and malignancies, most often lymphomas [93, 168]. DNA repair defect patients may be radiosensitive and often display neurodevelopmental and structural features. (*See* Chap. 9 *for more details*) *SMARCAL*, the mutated gene in Schimke immune-osseous dysplasia (SIOD), also participates in DNA damage response; SIOD patients display chromosomal instability and an increased risk of malignancy [265]. Rothmund-Thomson syndrome (*RECQL4*) is caused by mutations in the DNA helicase gene. Patients are prone to osteosarcoma, basal and squamous cell carcinomas. Bloom syndrome (*BLM*) patients age prematurely and are prone to non-Hodgkin's lymphomas. *BLM* is involved in unwinding and separation of DNA complementary structures, making the strands accessible for DNA replication and repair [93, 192]. MCM4 deficiency predisposes to EBV-associated lymphomas [63]. MCM4 is involved in DNA replication. Mismatch repair gene mutations (*PMS2*, *MSH6*, *MSH5*, *MLH1*) impair the fidelity of DNA replication and cause Lynch syndrome. Patients are prone to gastrointestinal, genitourinary and brain tumors, lymphomas and leukemias and may develop antibody deficiencies of variable severity. Some DNA repair-associated PIDs (*NHEJ1*, *PRKDC*, *MRE11A*, *RNF168*, *RAD50*) have not yet been found to intrinsically predispose to malignancies; the numbers of reported patients are small. Since DNA-PKcs deficiency completely stalls B and T cell development, lymphoid malignancies seem unlikely. Ataxia-telangiectasia like disease (*MRE11A*) causes radiosensitivity, which in itself predisposes to radiation-induced oncogenesis [93].

Malignancies associated with impaired telomere maintenance are seen in the genetically heterogeneous dyskeratosis congenita and its clinically severe variant Hoyeraal Hreidarsson syndrome, in Nijmegen breakage syndrome and ataxia-telangiectasia. (*See* Chap. 9 *for more details*) Impaired telomerase maintenance leads to defective function of rapidly dividing cells and to increased susceptibility to hematologic malignancies and solid tumors [93]. It is presently not known whether immunodeficiency with centromere instability and facial anomalies (ICF, *DNMTB3*, *ZBTB24*, *CDCA7*, *HELLS*) predisposes to malignancies.

Various PIDs that intrinsically affect hematopoiesis cause susceptibility to malignancies. Intrinsic genetic bone marrow failure leading to pancytopenia, hematologic malignancies, solid tumors and an immunodeficiency phenotype is seen in Fanconi anemia, a genetically heterogeneous disorder. In Wiskott-Aldrich syndrome, myelodysplasia, leukemias and lymphomas are seen with increased frequency. Mutated WASP disrupts the link between the GTPases and the actin cytoskeleton, impairing regulation of signaling in hematopoietic cells [93, 150, 168]. Hematologic transcription factor GATA2 deficiency leads to a variable phenotype of

immunodeficiency, primary alveolar proteinosis, Emberger syndrome with lymphedema and/or susceptibility to myelodysplastic syndrome, AML, CMML and EBV-driven lymphomas [274]. Histiocytic skin infiltrates and neutrophilic panniculitis occurs in Lck deficiency, while myelofibrosis and histiocytosis occur in H syndrome (*SLC29A3*) [203]. For example in WAS, HSCT may correct the susceptibility to malignancies [126, 230].

Risk for leukemia is increased in certain severe congenital neutropenias (*ELANE*, *HAX1*, *WASP*), but is not increased by those *ELANE* mutations causing cyclic neutropenia. Increased risk of leukemia has not been reported in other PIDs with neutropenia [270]. Complement deficiencies have not been found to confer increased risk of malignancy. Deficiencies of *IL10R1* and *IL10R2* are associated with a high risk of EBV-negative B cell non-Hodgkin's lymphoma [210].

Almost 20% all human malignancies are associated with chronic infections by HBV, HCV, HPV, EBV, HHV8/KSHV, HTLV-I, HIV-1, HIV-2, JCV, Merkel cell virus (MCV), *Helicobacter pylori*, schistosomes or liver flukes [90]. Unsurprisingly, chronic infections are often associated with malignancies arising in PID patients. These have mostly been described together with HPV, EBV and HHV8 [232, 247]. HPV may induce cancer of the cervix, vagina, vulva, anus and penis as well as oral squamous cell carcinoma [170]. EBV in PID subjects may induce chronic EBV viremia, hemophagocytic lymphohistiocytosis, dysgammaglobulinemia, atypical EBV-associated lymphoproliferative disorders (polymorphic B cell hyperplasia, plasmacytic hyperplasia) and EBV-associated lymphomas [67, 168, 220, 232]. HHV8 is associated with primary Kaposi sarcoma (*TNFRSF4*, *IFNGR1*, *WAS*, *STIM1*), and a child from consanguineous marriage with HHV8-associated primary multicentric Castleman disease has been described [59, 172]. EBV-associated Castleman occurs in homozygous FcγRIIIA deficiency [98, 125]. Also patients with CHH (*RMRP*) have an increased risk of basal cell carcinoma and of EBV-associated lymphoproliferation [186]. Mutations in *RMRP* affect cell growth by impairing ribosomal assembly and altering cyclin-dependent cell-cycle regulation. In the rare heterogeneous KID (keratitis, ichtyosis, deafness) syndrome, mostly caused by mutations in connexin 26 gene (*GJB2*), 15% of patients develop squamous cell carcinoma, often to sun-exposed areas [80]. Whether these are virally induced is not known. Table 1.12 lists EBV- and HPV-associated PIDs [170, 220, 232]. In PID patients, hepatocellular carcinoma associated with chronic HBV or HCV infection has rarely been reported. This might be due to the rapid progression of hepatitis to liver failure in patients with T cell dysfunction [241]. In a single patient, MCV has been linked to a disrupted cell cycle and development of Merkel cell carcinoma and EBV-associated angioimmunoblastic lymphoma associated with Schlafen gene deletions and mutations [159].

In CD40L and CD40 deficiencies, *Cryptosporidium* infection of the biliary tree may lead to sclerosing cholangitis, liver cirrhosis and an increased risk of hepatocellular and bile duct carcinomas [19, 314]. CD40L deficiency also predisposes to neuroendocrine cancer [109]. Possibly due to the missing secreted IgA, CVID patients have seven to ten-fold increase in gastric carcinoma; a gastroscopy screening protocol has been suggested [101, 240]. The risk of stomach cancer appears to be decreasing, possibly due to eradication of *H. pylori* in CVID patients. In the available patient series, lymphoma has developed in 1.8–8.2% of CVID subjects, extranodal non-Hodgkin B cell and mucosa-associated lymphomas are most commonly reported [86]. Unlike in most PID, lymphomas in CVID are more common in subjects in the fourth to seventh decade of life and are usually EBV-negative [86, 307]. IgA deficiency predisposes to lymphomas and solid cancers (e.g., prostate, colon, lung) [179].

1.3.4 Other Manifestations

In infancy, failure to thrive, severe diarrhea, erythroderma and/or opportunistic infections call for exclusion of serious PIDs. Structural, functional and neurodevelopmental features offer

important clues to the genetic defect(s) causing a PID in a patient. Careful history may unveil a secondary immunodeficiency caused by drugs or procedures (e.g., earlier splenectomy, Fontan procedure causing lymphocyte, protein and antibody loss, irradiation). However, potentially predisposing structural features like bronchiectasis or previous heart surgery may also point to PIDs associated with these (antibody deficiency, 22q11.2 deletion syndrome). Absent tonsils, adenoids or lymph nodes point directly to XLA or to T cell deficiencies that prevent germinal center formation [291] [6, 84, 317]. Generalized lymphadenopathy and splenomegaly suggest OS, CVIDs, AR Ig CSR defects, ALPS, FHL or other autoimmune PIDs. Gingivitis may point to phagocyte defects. Heart murmurs, cyanosis or finger clubbing suggest concomitant heart defects (e.g., chromosome deletions, *STK4*), rhonchi or rhales suggest chronic lung disease and bronchiectasis seen in various PIDs, but most often in antibody deficiencies, neutrophil defects and STAT3 deficiency. Flared costochondral junctions in lateral view of lung X-ray point to SCID and ADA deficiency [291, 317]. Purpura and petechiae suggest PIDs with bleeding tendency, for example WAS, LAD3, Ikaros deficiency, SDS or PIDs with hematologic autoimmunity/autoinflammation (Table 1.15) [47].

During clinical assessment, the general structure of the patient, potential proportionate or disproportionate short stature or head size, facial dysmorphism, limb dysplasias, dysplastic or dysmorphic changes of ectodermal structures (hair, skin, teeth, sweat glands), pigmentary changes (e.g., oculocutaneous hypopigmentation, café-au-lait spots) and oculocutaneous telangiectasias deserve special attention [197, 199]. (*See* Chap. 10 *for more details*) Asymmetrical face, high palate, skin and midline findings and hyperextensibility of joints suggest STAT3 deficiency but may not be readily apparent during childhood [272]. Limb defects in PIDs may be seen in Fanconi anemia (radial ray abnormalities affecting thumbs) and in Nijmegen breakage and Cornelia de Lange syndromes [78, 92, 149]. Camptodactyly, a fixed flexion deformity of the interphalangeal joints of fingers, may be seen in Blau (*NOD2*) and Jacobsen syndromes (11qter) [23, 191]. Metaphyseal dysplasia is seen in ADA deficiency, cartilage hair hypoplasia and Shwachman-Diamond syndrome [47, 104, 187].

Poikiloderma is the combination of hypopigmentation, hyperpigmentation, telangiectasias and atrophy of skin. It may be seen in AT, Rothmund-Thomson as well as in poikiloderma with immunodeficiency syndrome [47, 169]. Ectodermal dysplasia describes primary dysplasia of skin, hair, teeth and/or sweat glands. The dystrophic nail and hair findings in APECED/APS1 may be secondary to candidiasis and autoimmune conditions [169]. In KID syndrome, true ichthyosis with scaling is not seen but rather ectodermal dysplasia [80]. Ectodermal dysplasia and anhidrosis (EDA) is seen in XL- and AD-EDA (*IKBKG*, *IKBKB*, GOF *NFKBIA*/*IKBA*), and together with myopathy in calcium channel deficiencies (*ORAI1*, *STIM1*) [47]. In addition, epidermal dysplasia may be seen in cartilage hair hypoplasia, in the genetically heterogeneous dyskeratosis congenita (DKC) syndrome and in Papillon-Lefèvre syndrome [169]. Café-au-lait spots are seen in Lynch syndrome genes that cause Ig CSR defects and hereditary cancers [93, 150]. Syndromic immunodeficiencies and DNA repair defects with structural, cutaneous, ocular and neurological findings are systematically covered in Chaps. 9 and 10.

Syndromic features are also found in certain congenital neutropenias and help in targeted genetic testing [270]. (*See* Chap. 4 *for more details*) Delayed separation of umbilical cord is characteristic of LAD1 and LAD3. LAD3 patients also display bleeding tendency. In an HLH patient, hypopigmentation and hair shaft anomalies point to CHS, GS2, and HPS types 2 or 9. CHS patient has areflexia and progressive neurodegeneration; in HPS 2 bleeding tendency and neutropenia occur.

Specific neuromuscular features are most often seen in deletional disorders (e.g. 22q11, 10p, 11qter), in selected SCIDs (*ADA*, *PNP*, *NHEJ1*, *LIG4*, *ORAI1*, *STIM1*), in CIDs (e.g. *MTHFD1*, *EPG5*), in DNA repair defects, some phagocyte deficiencies (e.g. *ACTB*, *VPS13B*, *SLC35C1*), immunodysregulatory (FHLs, *LYST*,

AP3B, *FADD*), and autoinflammatory syndromes (*MVK*, *NLRP3*, *NOD2*, *NLRP12*) [47, 99]. Sensorineural hearing deficit may be seen in $T^-B^-NK^-$ SCIDs (*AK2*, *ADA*), FHL5, in some AISs (*NLRP3*, *NAPS12*), in the combined *BTK* and *TIMM8A* deletion that causes XLA with Mohr-Tranebaerg syndrome, in Di George syndrome (10p) and together with CHARGE (coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital and urinary abnormalities, ear abnormalities and/or hearing loss) association [23, 47, 231].

Patients may also have non-inflammatory gastrointestinal and endocrine manifestations. Multiple atresias are seen in familial intestinal polyatresia (*TTC7A*) [74]. Hepatic veno-occlusive disease suggests VODI [79]. Shwachman-Diamond (*SBDS*) syndrome patients have exocrine pancreatic insufficiency with pathognomonic MRI findings of pancreas [290]. Growth hormone insensitivity or deficiency may sometimes be seen in non-*BTK*-XLA, CSRDs, APS1, Shwachmann, SIOD, AT, NFJB2 deficiency, STAT5b deficiency, this may be seen as well in various combinations with hypogonadism and adrenal insufficiency in various syndromic defects covered mostly in Chap. 10 [47].

ESID and IUIS have published highly useful tables and flow charts of most classes of PIDs that combine laboratory findings with various phenotypic features. In the end, the combination of meticulous taking of patient history and clinical assessment will most often lead to a correct tentative diagnosis of PID and to the judicious use of targeted testing.

1.4 Diagnosis

1.4.1 Warning Signs and Symptoms

First and foremost: infections are the hallmark of immunodeficiency [277]! This should always be kept in mind. However, other symptoms may be more prominent at first, and this can be misleading. Widely varying events such as failure-to-thrive in children, weight loss in adults, intractable diarrhea, autoimmune manifestations, granulomatous diseases … (*see* Sect. 1.3 *for more details*), all these and many more can point to immunodeficiency, but may not.

Young children suffer regularly from infections [195], and even in older children and adults, infections are not uncommon [253]. It is of course impossible, and also unnecessary, to screen every patient with an infection for primary immunodeficiency. Only when the clinical presentation differs from the usually encountered pattern should the physician be alerted to possible immunodeficiency. This is the case when infections recur more frequently then expected, especially when these infections are bacterial in origin. Physicians should also be alerted by infections that present atypically, infections that are unusually severe or chronic, infections that are caused by an unexpected or opportunistic pathogen, or infections that fail regular treatment [277]. However, when infections recur at the same anatomical site, an anatomical defect may be the underlying problem, and this should be investigated first. Periodic fever syndromes can be another pitfall: it can be difficult to distinguish the recurrent episodes of fever from recurrent infections. A thorough investigation for the causative organism – which in the case of periodic fever will not be found – can help to make the distinction [176]. This will also help in case a primary immunodeficiency is indeed present, because the underlying immunodeficiency generally determines which types of pathogen are found [277]. Opsonization with specific antibody and complement and subsequent elimination by phagocytosis is needed for clearance of extracellular encapsulated bacteria that cause sinopulmonary infections. Thus, these infections will continue to recur in agammaglobulinemia, specific antibody deficiency, complement deficiency, neutropenia, and defects in granulocyte function. Local phagocytosis is important for clearance of fungi and bacteria on the skin and mucosal surfaces. If this is impaired, as in neutropenia and defects in granulocyte function, pyogenic skin infections with potential systemic spread occur, as well as candidiasis and pulmonary aspergillosis. Intracellular and slow-growing pathogens are eliminated by activated T- lymphocytes in interaction with macrophages.

Viruses, parasites, mycobacteria, and opportunistic bacteria may, therefore, cause problems in case of T-cell deficiency, SCID, or impaired interaction between T-lymphocytes and macrophages (Table 1.10). Time is also a distinguishing factor when assessing the possibility of an immunodeficiency. In the first months of life, maternal immunoglobulin will mask antibody deficiency in a child, but not a deficiency of T-lymphocytes. So, a child with SCID will mostly start to have problems related to the T-lymphocyte deficiency. A child with agammaglobulinemia generally starts to have recurrent infections in the second part of the first year of life, when maternal antibodies are waning. But if the immunodeficiency develops later in life, as in CVID, the infections will also start later.

Besides infections, there are many other signs and symptoms that can point to immunodeficiency. They may be a complication of the repeated infections, or be entirely unrelated to them. Unusual complications of vaccination, unexplained bronchiectasis, absence of immunological tissues, difficult-to-treat obstructive lung disease, abnormal hair, delayed shedding of the umbilical cord or the primary teeth, eczema, and many more may be symptoms of immunodeficiency.

It is of paramount importance to thoroughly explore the family history. A good family history may reveal consanguinity in the parents, unexplained early infant deaths in the family, or familial occurrence of similar symptoms. This is important for the prompt recognition of genetic disorders. Several affected siblings in the same family point to autosomal recessive inheritance, whereas transmission from parent to child fits autosomal dominant inheritance. Male patients with a disease that is transmitted along the female line, on the other hand, is suggestive for an X-linked recessive disorder. However, many mutations may be new and the family history is not necessarily positive, even if a genetic defect is present.

All in all, it is not an easy task to efficiently identify PID within the large pool of potential cases. Especially for non-immunologists, it works best to rely on pattern recognition of clinical presentations of patients. The better the knowledge about what is normal, the easier it becomes to identify abnormal patterns. Then, by focusing on the characteristic clinical presentations of PID, the attending physician can be guided to the right laboratory tests.

1.4.2 Diagnostic Approach

Primary immunodeficiency generally presents with one of eight characteristic clinical presentations (Table 1.16) [94, 95]. So, once such a clinical presentation is encountered, PID is a possibility that should be explored further. This does not necessarily mean immunological tests have to be performed. In patients with recurrent ENT and airway infections other non-immunological problems like bronchial hyperreactivity, allergy and asthma occur much more frequently and should be investigated first. On the other hand, only a few children with failure to thrive will have PID, but delay in diagnosis and treatment will greatly impair their survival, and immunological tests have to be performed at an early stage. In general, severe defects should be ruled out (or identified) promptly with widely available screening tests, whereas less severe forms of PID can safely be identified later. The advice of an immunologist can be very useful during this diagnostic process.

It is not necessary to fully understand the underlying immunological mechanisms to be

Table 1.16 The eight characteristic clinical presentations of PID [94, 95]

1	Recurrent ENT (ear, nose, throat) and airway infections
2	Failure to thrive from early infancy
3	Recurrent pyogenic infections
4	Unusual infections or unusually severe course of infections
5	Recurrent infections with the same type of pathogen
6	Autoimmune or chronic inflammatory disease and/or lymphoproliferation
7	Characteristic combinations of clinical features in eponymous syndromes
8	Angioedema

able to use the different clinical presentations for reliable early suspicion of potential PID. Practice parameters can be used to link the clinical presentation to the right set of laboratory tests. The American practice parameter for the diagnosis and management of primary immunodeficiency offers diagnostic guidelines for immunologists with extensive decision trees [43]. The ESID has published a multi-stage diagnostic protocol that was especially designed for use by non-immunologists [94, 95]. A simplified version can be found in Table 1.17. From the eight characteristic clinical presentations of immunodeficiency in column 1 of this table, the user is guided through the first essential steps in the diagnostic work-up in column 2 with the aid of screening tests that ensure identification of severe defects in an early phase in column 3. If a diagnosis of severe immunodeficiency is made, further identification of the defect is illustrated in columns 4 and 5. If no diagnosis is found in the first screening and problems persist, columns 4 and 5 enable further elaborate tests to characterize milder defects. Not all tests in column 5 need necessarily be done. If in doubt, consult an immunologist!

Recurrent ENT (ear, nose, throat) and airway infections Recurrent ENT and airway infections are normal in young children, especially in case of passive smoking and day care attendance. Only when their frequency is out of the ordinary, or if the child is unable to lead a life like its peers, is it necessary to look for an underlying cause. Older children and adults can suffer from the occasional ENT or airway infection, but in them, recurrent infections should be considered abnormal. Non-immunological underlying causes such as mucosal swelling caused by allergy and/or bronchial hyperreactivity or anatomical obstruction caused by adenoidal hypertrophy in a young child are frequent. Sometimes gastro-oesophageal reflux or iron deficiency plays a role in children. Infrequently, a more severe problem like bronchopulmonary dysplasia, cystic fibrosis, a foreign body, a congenital anomaly, ciliary dyskinesia or α1-antitrypsindeficiency is present. These generally present in childhood. Only seldom, a PID like antibody deficiency, complement deficiency, neutropenia or phagocyte function deficiency will be present. IgA-deficiency, IgG-subclass deficiency, and anti-polysaccharide antibody deficiency are the most frequently encountered PID, but their clinical relevance is often unclear. In young children, this may be temporary, but in older children and adults this is seldom the case. They may even be a sign of developing CVID, resulting in profound hypogammaglobulinemia in the following years. So, if problems persist, it is essential to repeat the immunological investigations.

Failure to thrive from early infancy Failure to thrive, often combined with intractable diarrhea, can have many causes. One of them is SCID, which nowadays can have a good prognosis if stem cell transplantation is performed in time. Therefore, prompt investigation of T-lymphocyte number and function are of paramount importance in children presenting with failure to thrive. The lymphopenia can most typically be detected in a routine leukocyte differential count.

Recurrent pyogenic infections Superficial pyogenic infections can be expected on damaged skin, as in eczema or burns, and are not related to immunodeficiency. Deep-seated pyogenic infections, especially in combination with granulomatous inflammation and poor wound healing, point to phagocyte deficiency. This is mostly due to neutropenia, which is often iatrogenic (chemotherapy and other drugs). Sometimes a true phagocyte function defect such as CGD is present.

Unusual infections or unusually severe course of infections Unusual infections or an unusually severe course of an infection should always trigger the physician to consider possible immunodeficiency. However, an uncommon presentation of a common disease is much more frequent then an uncommon disease like PID. In spite of that, screening investigations should be done, because early recognition of immunodeficiency prevents sequelae and thereby improves the patient's prognosis.

Table 1.17 From clinical presentation to laboratory tests [94, 95]

Clinical presentation	First step in the diagnostic process	Screening laboratory tests[a]	Next steps in the diagnostic process[b]	More elaborate laboratory tests[a,b,c]
1. Recurrent ENT and airway infections	Rule out severe antibody deficiency and neutropenia	IgG, IgA and IgM. Blood count and differential (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts)	Identify milder forms of antibody deficiency and complement defects.	IgG-subclasses. CH_{50} and AP_{50}. MBL. Specific antibody responses to tetanus and unconjugated pneumococcal vaccine. M-proteins. Lymphocyte subpopulations. Lymphocyte proliferation tests. CD40/CD40L after stimulation. ANA. Specific complement components. Chromosomal analysis. α-fetoprotein
2. Failure to thrive from early infancy and 3. Unusual infections or unusually severe course of infections	Rule out severe combined immune deficiency and AIDS	Blood count and differential (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts). IgG, IgA and IgM. Lymphocyte subpopulations. Tests for HIV	Identify the different forms of (severe) combined immunodeficiency.	Extended protocol for lymphocyte subpopulations. Lymphocyte proliferation tests. CD40/CD40L after stimulation. IL12, IL12-receptor, IFN-γ-receptor, STAT1. IkBα. If no agammaglobulinemia: IgG-subclasses, booster responses, M-proteins. Tests for chimerism. *In vitro* cytokine production. *In vivo* tests of T-lymphocyte function. Analysis of bone marrow, lymph node biopsy. NK cell cytotoxicity. Uric acid, ADA, PNP, α-fetoprotein, X-ray of long bones if short stature or disproportional growth, thymus size (chest X-ray, ultrasound), chromosomal analysis, radiosensitivity tests, 22q11 analysis, clonality studies (Vβ-gene usage)
4. Recurrent pyogenic infections	Identify neutropenia, and – if present – its cause	Blood count and differential (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts)	Identify defects in phagocyte function	Phagocyte function tests. Repeated blood count and differential for cyclic neutropenia. Autoantibodies, ANA, C3/C4, RF, ANCA, Coombs, IgG, IgA and IgM. Analysis of bone marrow (morphology, chromosomes, culture), mobilization tests (GCSF, prednisone), pancreatic function tests. Metabolic tests. IgD. IgE. Hair evaluation. Electron microscopy. CD11/18, sLeX, kindlin3 expression (flow cytometry, in case of neutrophilia).

(continued)

Table 1.17 (continued)

Clinical presentation	First step in the diagnostic process	Screening laboratory tests[a]	Next steps in the diagnostic process[b]	More elaborate laboratory tests[a,b,c]
5. Recurrent infections with the same type of pathogen	Consider PID	–	Dependent on type of pathogen: (a) Intracellular bacteria; (b) Meningococci; (c) Candida; (d) Encapsulated bacteria; (e) Viruses	(a) IL12, IL12-receptor, IFN-γ-receptor, STAT1. (b) CH_{50} and AP_{50}. (c) Rows 1 and 2. (d) Row 1; splenic ultrasound. (e) Row 2
6. Autoimmune or chronic inflammatory disease and/or lymphoproliferation	Consider PID	Immunoglobulins. CH50. Blood count and differential (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts). Lymphocyte subpopulations. Acute phase proteins during fever. Organ-specific autoantibody screen	Identify specific PID syndrome	Dependent on particular PID
7. Characteristic combinations of clinical features in eponymous syndromes	Consider PID	Dependent on particular syndrome (*See* Chap. 10)	Identify specific PID syndrome	Dependent on particular PID Chromosomal analysis. α-fetoprotein. 22q11 analysis
8. Angioedema	Consider specific complement deficiency	–	Identify specific complement deficiency	C1-inhibitor. C4 during an attack

[a]Use age-matched reference values for the interpretation of laboratory tests
[b]Consult an immunologist, not all tests mentioned need necessarily be done!
[c]Perform genetic characterisation of the defect if possible

Recurrent infections with the same type of pathogen Without an anatomical defect, increased exposure, or inadequate treatment, recurrent infections with the same type of pathogen can be caused by immunodeficiency, even if the patient is otherwise healthy. Generally, only one specific pathway is then affected, but the resulting infection can be life threatening. Recently, several defects have been described, and more can be expected [62].

Autoimmune or chronic inflammatory disease and/or lymphoproliferation Generally, autoimmunity, chronic inflammation, and lymphoproliferation are not associated with an immunodeficiency. This is possible, however, especially but not exclusively if recurrent infections occur. Common variable immunodeficiency, complement deficiency, and T-lymphocyte deficiency can be complicated by these phenomena. In certain diseases, autoimmunity (APECED, IPEX) or lymphoproliferation (XLP) are core symptoms. Therefore, immunodeficiency should be kept in mind in atypical cases.

Characteristic combinations of clinical features in eponymous syndromes Many eponymous syndromes are associated with immunodeficiency [198, 199]. These can be of varying severity. Mostly, the immunodeficiency is not the presenting symptom in these patients. However, adequate treatment of the immunodeficiency may significantly improve their quality of life.

Angioedema Classical hereditary angioedema occurs after a trigger like stress or an infection activates the complement system in people who lack the C1 inhibitor. It is often not recognized, especially if the swelling occurs in an internal organ, leading to unnecessary treatment (e.g. exploratory laparotomy). The differential diagnosis includes allergy, malignancy, and autoimmunity.

1.4.3 Approach to Laboratory Tests

Laboratory tests that are useful for the identification of PID are listed in Table 1.17. With a limited set of tests that is available in most hospitals, a first screen for PID can be reliably performed (column 3). Neutropenia and lymphopenia can be easily identified by a blood count and differential. Serum levels of IgG, IgA, and IgM can show a/hypogammaglobulinemia, and CH_{50} and $AP(AH)_{50}$ can identify most complement defects. T-lymphocytes with $CD4^+$ helper and $CD8^+$ cytotoxic subsets, B-lymphocytes and NK-cells can be determined by flow cytometry. Absolute counts and age-related reference values are needed for accurate interpretation of the results; relative counts can lead to misinterpretations [96]. This is sufficient for identification of most patients with SCID, agammaglobulinemia, neutropenia and complement deficiencies. Serology is usually sufficient to identify an HIV-infection, but in young children with possible perinatal exposure, or in those suspected to have a deficiency of humoral immunity viral load should be determined because antibodies can be maternal in origin, or may not be present.

More elaborate tests (column 5) can be performed in immunological laboratories; their results are generally more difficult to interpret. IgG-subclass deficiencies as well as mannose binding lectin deficiency are found more often in patients with recurrent infections, but can be asymptomatic. Specific antibody responses to protein (tetanus) or polysaccharide (pneumococci) antigens can be diminished or absent despite normal immunoglobulin serum levels. This can be found in isolation, or be part of a more severe defect such as common variable immunodeficiency. Lymphocyte proliferation tests can be performed with mitogens that stimulate lymphocytes nonspecifically, or with stimulators that selectively activate calcium entry into the cell (for example), or antigens that must be recognized by the T-cell receptor. Advanced immunophenotyping can help to elucidate which parts of the immune system are disturbed. Random migration, chemotaxis, adherence, phagocytosis, and intracellular microbial killing by phagocytes can be measured in specialised laboratories by conventional methods or flow cytometry. Superoxide generation can be measured by the nitroblue tetrazolium (NBT) dye

reduction test, a chemiluminescence assay, or by dihydrorhodamine (DHR) oxidation.

1.4.4 Phenotypic Approach

Considering the rapid progress in identification of novel PIDs, diagnosis of all types of PIDs is not easy in the clinic. Therefore phenotypic classification, proposed by IUIS, based on the selection of key phenotypes could help the clinicians at the bedside to have a better approach to patients (Figs. 1.8, 1.9, 1.10, 1.11, 1.12, 1.13, 1.14, and 1.15) [47].

1.5 Management

1.5.1 General Considerations

Since primary immunodeficiency diseases represent a vast array of defects that differentially impair host defenses, there would ideally be an equally vast number of therapeutic options to specifically address each of the deficiencies in these individual conditions. Unfortunately this is not the case, and there are a limited, but expanding number of therapeutic modalities and management strategies available to patients. In some instances the available treatments are quite

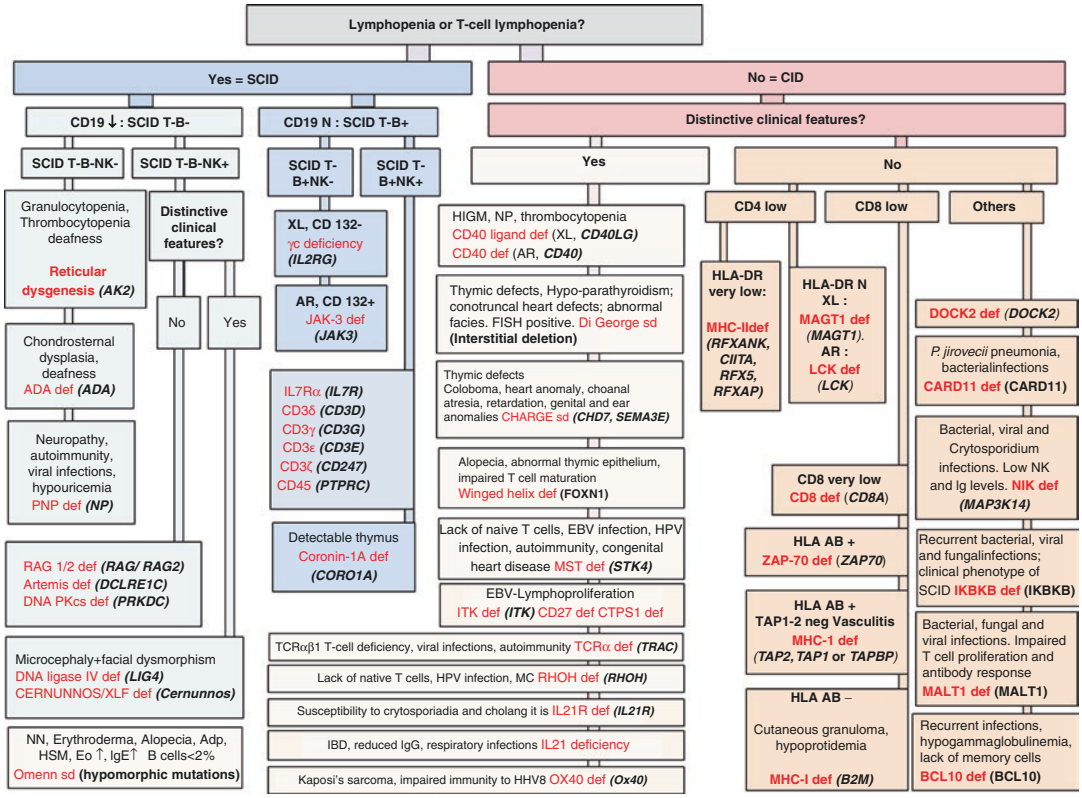

Fig. 1.8 Modified IUIS phenotypic classification of combined T- and B-cell immunodeficiencies [47]. *ADA* adenosine deaminase, *Adp* adenopathy, *AR* autosomal recessive, *CD* cluster of differentiation, *CID* combined immunodeficiency, *EBV* Epstein-Barr Virus, *EO* eosinophils, *HHV8* human herpes virus type 8, *HIGM* hyper IgM syndrome, *HLA* human leukocyte antigen, *HSM* hepatosplenomegaly, *HPV* human papilloma virus, *IBD* inflammatory bowel disease, *Ig* immunoglobulin, *MC* Molluscum contagiosum, *N* normal, *NK* natural killer, *NN* neonatal, *NP* neutropenia, *SCID* severe combined immunodeficiency, *Staph* staphylococcus sp., *TCR* T-cell receptor, *XL* X-linked (© Springer Science + Business Media New York 2015)

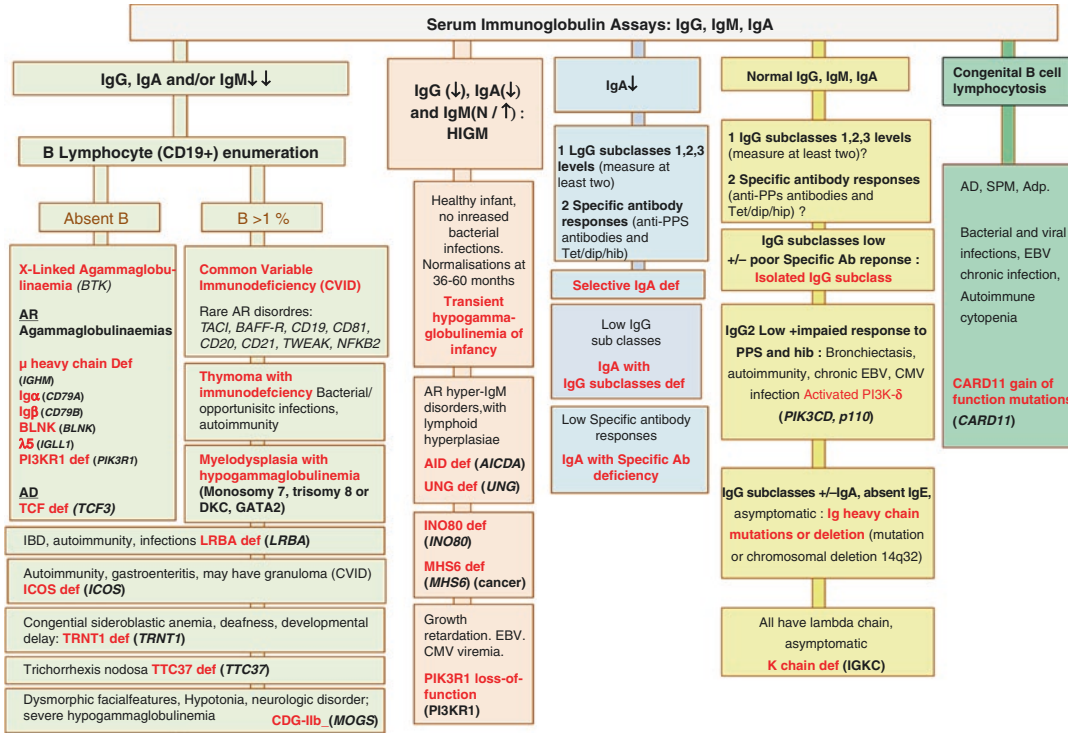

Fig. 1.9 Modified IUIS phenotypic classification of predominantly antibody deficiencies [47]. *Ab* antibody, *Adp* adenopathy, *Anti PPS* anti- pneumococcus antibody, *AR* autosomal recessive, *CD* cluster of differentiation, *CDG-IIb* congenital disorder of glycosylation, type IIb, *CMV* cytomegalovirus, *CT* computed tomography, *EBV* Epstein-Barr virus, *Dip* Diphtheria, *GI* gastrointestinal, *Hib* haemophilus influenzae serotype b, *Hx* medical history, *Ig* immunoglobulin, *SPM* splenomegaly, *subcl* subclass, *Tet* tetanus, *XL* X-linked (© Springer Science+Business Media New York 2015)

appropriate for "closing the gap" in host defense created by a given PID, while in others the treatments fall unacceptably short and patients suffer excessive morbidities and even premature death. There is high quality scientific evidence supporting certain specific therapeutic interventions applied to particular PID, however, in many, the evidence is extrapolated from other PID-specific data, data from other medical conditions affecting immunologic function, or even consensus among experts caring for patients with PID. Here, general concepts in therapy for PID are introduced so that many of the disease-specific details provided elsewhere throughout this volume can be placed within a broader context.

PID results in an ineffective immunological balance between the patient and environment. Thus, interventions to bias this balance toward host defense and away from allowing for pathogen success should be considered a general goal. In some instances of PID, specific holes in host defense can be filled through therapeutic intervention, while in others treatments are more directed at globally reducing susceptibility to infection. It can be critical to the well being of the patient to strive towards striking this balance as perfectly as possible, while maintaining the general health of the patient and their family. As the variety of treatments and management options available to patients affected by the different diagnoses is often specific to a particular diagnosis, this section is only focused upon more general concepts of the expert care applied to and range of options available for PID patients. Essential general issues in the care of PID patients that can help create an effective structure to prevent and contend with disease morbidity include edu-

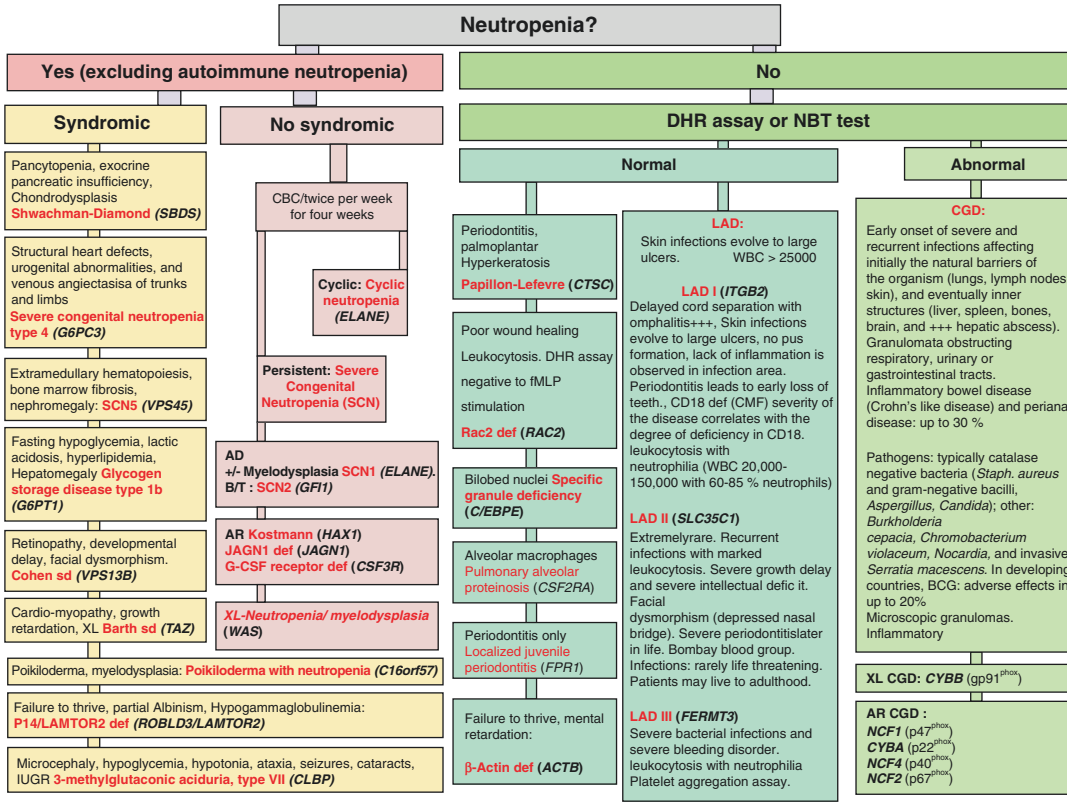

Fig. 1.10 Modified IUIS phenotypic classification of phagocytes defects [47]. *AD* autosomal dominant, *AML* acute myeloid leukemia, *AR* autosomal recessive, *BCG* Bacilli Calmette-Guérin, *CD* cluster of differentiation, *CGD* chronic granulomatous disease, *CMML* chronicmyelomonocytic leukemia, *DHR* dihydrorhodamine, *IUGR* intrauterine growth retard, *LAD* leukocyte adhesion deficiency, *SCN* severe congenital neutropenia, *WBC* white blood cells, *XL* X-linked (© Springer Science+Business Media New York 2015)

cating the patient about their diagnosis, insuring general health maintenance, and providing continuity in sub-specialty care.

A definite priority for the clinical immunologist is to serve as teacher and educator for patients affected by these relatively rare diseases. If a patient is unable to comprehend the challenges they face from their environment, it is unlikely that they will be able to successfully navigate them. In most cases, this involves some general introduction to the immune system, how it functions to facilitate host defense, the specific component or components that are defective in the given patient's disease, and what strategies are best to close the gap in immunity created by the deficiency. Often this information is overwhelming and needs to be reiterated and provided in multiple formats over time. In this regard, there are a number of resources available to the physician including a number from patient organizations such as the Jeffrey Modell Foundation (JMF), the International Patient Organization for Primary Immunodeficiencies (iPOPI) and the Immune Deficiency Foundation (IDF). In particular, the latter organization has a patient and family handbook covering both general and disease specific topics. It is available in print and as a free download from the IDF website (http://primary-immune.org/idf-publications/patient-family-handbook). Similarly, the virtual book "Living with Primary Immunodeficiencies" is available for free download from the IPOPI website (http://www.ipopi.org). Another source that can be useful for explaining the immune system and its

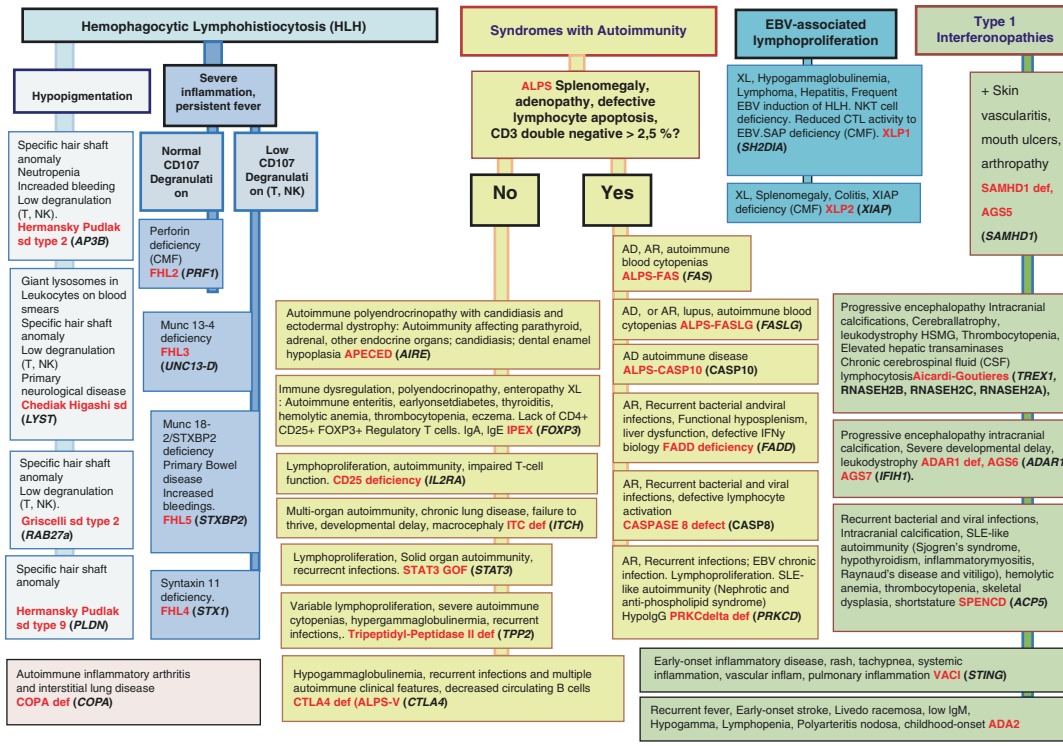

Fig. 1.11 Modified IUIS phenotypic classification of genetic disorders of immune regulation [47]. *AD* autosomal dominant, *ALPS* autoimmune lymphoproliferative syndrome, *AR* autosomal recessive, *CD* cluster of differentiation, *CMF* flow cytometry available, *CSF* cerebrospinal fluid, *CTL* cytotoxic T lymphocyte, *EBV* Epstein-Barr virus, *GOF* gain-of-function, *HLH* hemophagocytic lymphohistiocytosis, *HSM* hepatosplenomegaly, *IBD* inflammatory bowel disease, *IFNγ* interferon gamma, *Ig* immunoglobulin, *IL* interleukin, *Inflam* inflammation, *NK* natural killer, *NKT* natural killer T cell, *T* T lymphocyte, *XL* X-linked (© Springer Science+Business Media New York 2015)

defects to children affected by PID are a number of superb children's-style books, such as the independently published book "Cell Wars" [31], the "Our Immune System" pamphlet available through the IDF website (http://primaryimmune.org/wp-content/uploads/2011/04/Our-Immune-System.pdf) and the "Play Your Best Defense" picture book available from the JMF. Collaborating with the patient and their family to understand the intricacies of the immune deficiency can lead to an important and effective therapeutic alliance.

Another important part of managing PID patients is to insure adequate basic health maintenance. General guidelines for the health maintenance for children and adolescents as well as those for adults promoted by organizations such as the American Academy of Pediatrics, the American College of Physicians, and the American Academy of Family Physicians are an important baseline and should be respected. It is unfortunate that the highly complex PID patient can sometimes overwhelm a primary care provider resulting in primary care being shifted to the sub-specialist. There are many disadvantages to this paradigm. It can be very useful for the patient to have a strong primary care provider who is informed by the sub-specialist regarding the intricacies of the PID diagnosis. These providers are routinely considering age-specific guidelines for general health maintenance and likely have practices equipped to provide such care. Specific additions and modifications to such general guidelines, however, need to be introduced for the different PID diagnoses. Thus, an active dialogue between the sub-specialist and

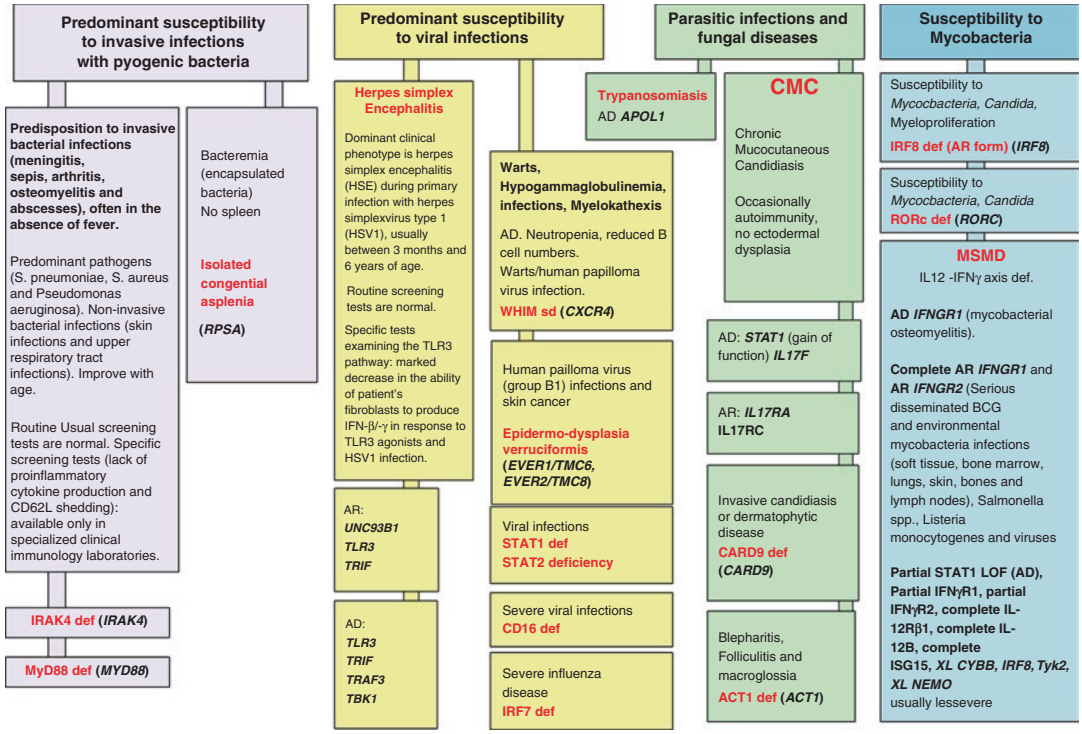

Fig. 1.12 Modified IUIS phenotypic classification of defects in intrinsic and innate immunity: receptors and signaling components [47]. *AD* autosomal dominant, *AR* autosomal recessive, *BCG* Bacilli Calmette-Guérin, *BL* B lymphocyte, *CMC* chronic mucocutaneous candidiasis, *HSV* herpes simplex virus, *Ig* immunoglobulin, *IL* interleukin, *LOF* loss-of-function, *MSMD* Mendelian susceptibility to mycobacterial disease, *XL* X-linked (© Springer Science + Business Media New York 2015)

the primary physician regarding these alterations as indicated for the patient's diagnosis are invaluable. There are a number of resources available to a sub-specialist to facilitate their effort in educating a primary care physician regarding the patient's diagnosis and requirements for care. These include a number of excellent reviews by clinical immunologists in the generalist medical literature [29, 54, 83], as well as the educational materials of the Immune Deficiency Foundation specifically tailored to generalist physicians (http://primaryimmune.org/wp-content/uploads/2011/04/IDF-Diagnostic-Clinical-Care-Guidelines-for-Primary-Immunodeficiency-Diseases-2nd-Edition.pdf)

Finally, providing continuity in sub-specialist care is a critical part of the comprehensive care and presumed well-being of a PID patient. Despite this seemingly obvious conclusion, there are few data demonstrating the effectiveness of regular sub-specialist care, or demonstrating an effective frequency of patient visits. Guidelines exist [43] and in many cases are disease-specific and are typically updated every 5–10 years (a most recent update is anticipated, but has not been published yet at the completion of this chapter). Ideally, the sub-specialist will actively contribute to the health maintenance of the patient and help guide the patient, family, generalist and other health care providers along a course that will be mindful of the pitfalls inherent to a given PID. Extensive familiarity with the most recent disease-specific literature will enable the sub-specialist to recommend and provide the most current and effective therapies for the patient. Although it is difficult to define exactly how often a PID patient should be evaluated by a sub-specialist it is important for the sub-specialist to be considered more than a diagnostician and to participate in the formation

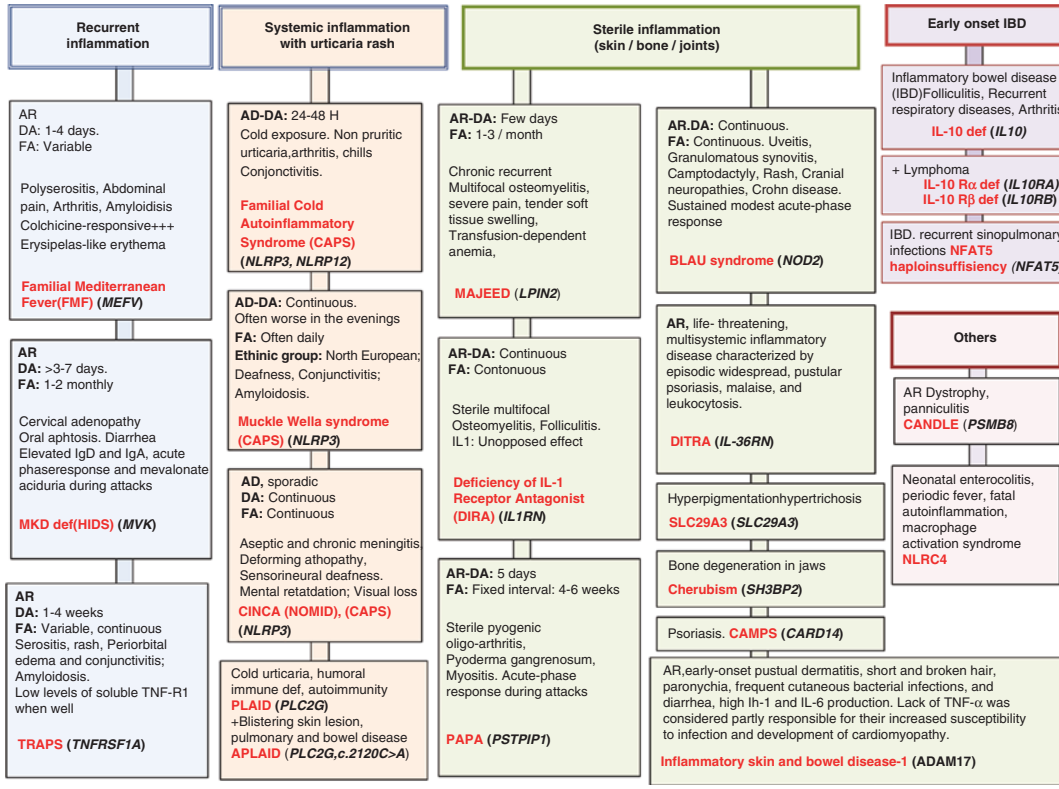

Fig. 1.13 Modified IUIS phenotypic classification of autoinflammatory disorders [47]. *AD* autosomal dominant, *AR* autosomal recessive, *CAMPS* CARD14 mediated psoriasis, *CANDLE* chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome, *CAPS* cryopyrin-associated periodic syndromes, *CINCA* chronic infantile neurologic cutaneous and articular syndrome, *DA* duration of attacks, *DITRA* deficiency of interleukin 36 receptor antagonist, *FA* frequency of attacks, *HIDS* hyper IgD syndrome, *Ig* immunoglobulin, *IL* interleukin, *MKD* mevalonate kinase deficiency, *MWS* Muckle-Wells syndrome, *NOMID* neonatal onset multisystem inflammatory disease, *PAPA* pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome, *SPM* splenomegaly, *TNF* tumor necrosis factor, *TRAPS* TNF receptor-associated periodic syndrome (© Springer Science+Business Media New York 2015)

and execution of ongoing care plans for PID patients.

1.5.2 Vaccination

Vaccines are an essential part of health maintenance for the general population and are required by law in many countries. In general, widespread vaccination programs only stand to benefit patients with PID. These programs reduce the burden of and exposure to diseases that present significant risks to PID patients suffering from ineffective defenses against them. A notable exception is certain live viral vaccinations that have the potential to infect PID patients during a period of viral shedding in the otherwise healthy vaccinee. One for which direct national guidance exists and has gained publicity in discussions of bioterrorism is small pox (Variola) vaccination. Here according to the US centers for disease control (CDC), the household contacts of immunodeficient individuals are not to be vaccinated [311]. Furthermore, casual contacts of vaccinated individuals are not to include immunodeficient individuals until the vaccination lesion has fully scabbed.

In terms of the direct vaccination of PID patients, immunizations have the potential to be helpful or harmful depending upon the vaccine

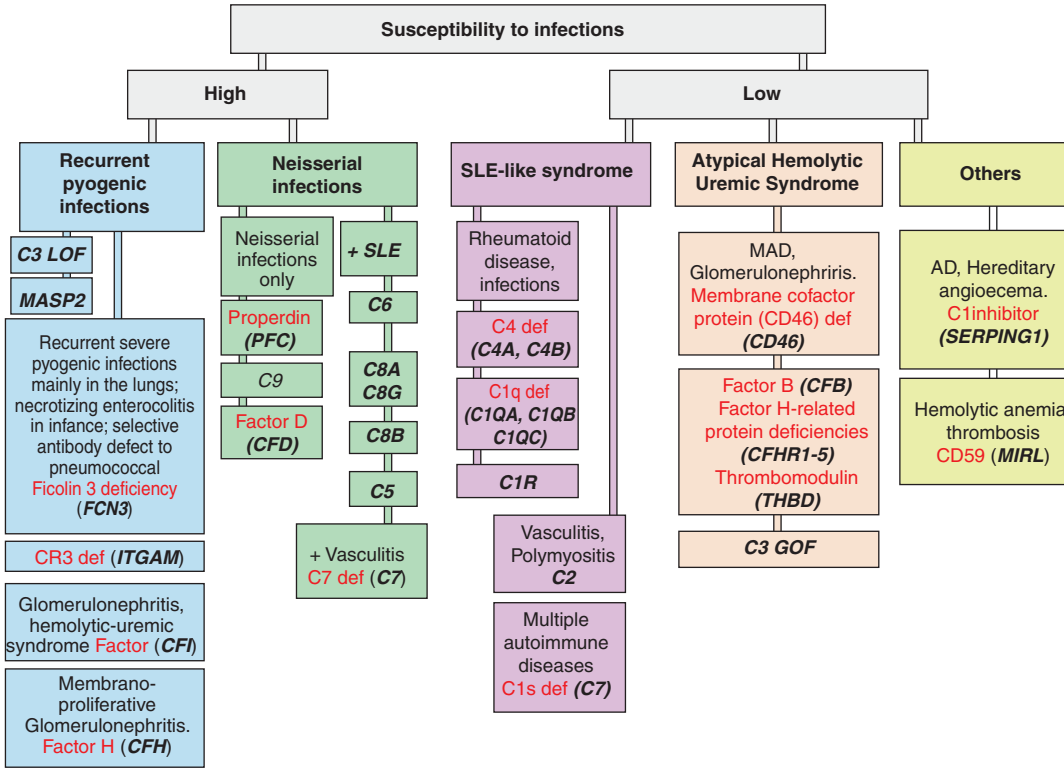

Fig. 1.14 Modified IUIS phenotypic classification of complement deficiencies [47]. *AD* autosomal dominant, *GOF* gain-of-function, *LOF* loss-of-function, *LAD* leukocyte adhesion deficiency, *SLE* systemic lupus erythematosus (© Springer Science+Business Media New York 2015)

and specific disease of the patient. In general, killed or subunit vaccines are safe for PID patients although they may be ineffective. Live vaccines can be useful, but must be carefully considered as they have the potential to cause disease in their own right in some PID patients. There are cases documented across the range of live vaccines [123, 138]. In this light the advisory committee on Immunizations Practices (ACIP) of the US Centers for Disease Control and Prevention (http://www.cdc.gov/vaccines/recs/acip/) has included a number of recommendations specific to patients with immunodeficiency. This broadly covers the avoidance of live viral vaccination for patients with significant immunodeficiency. More specifically, patients with T-cell or combined PID should be considered at relative risk for vaccine complications and the degree of immunodeficiency need be carefully evaluated prior to clearing a patient for immunization. There are a number of disease-specific recommendations that exist based upon scientific studies [30, 205, 234] and should be considered in individual cases. It is also essential that the subspecialist communicates a very clear plan to the primary care provider so that an at-risk patient is not incidentally immunized in the routine process of health maintenance. Important vaccines presenting risk to PID patients that should be carefully considered, include Measles, Mumps, Rubella, Varicella, Rotavirus, Poliovirus, BCG, intranasal Influenza, yellow fever, and Variola.

To comprehensively address the topic of risk to PID patients through live viral vaccination, a more recent expert consensus has been offered [261]. This perspective delineates the PID by category and provides existing recommendations for live vaccine avoidance as well as a PID-specific expert perspective on the recommendations. The existing recommendations are: avoidance of oral

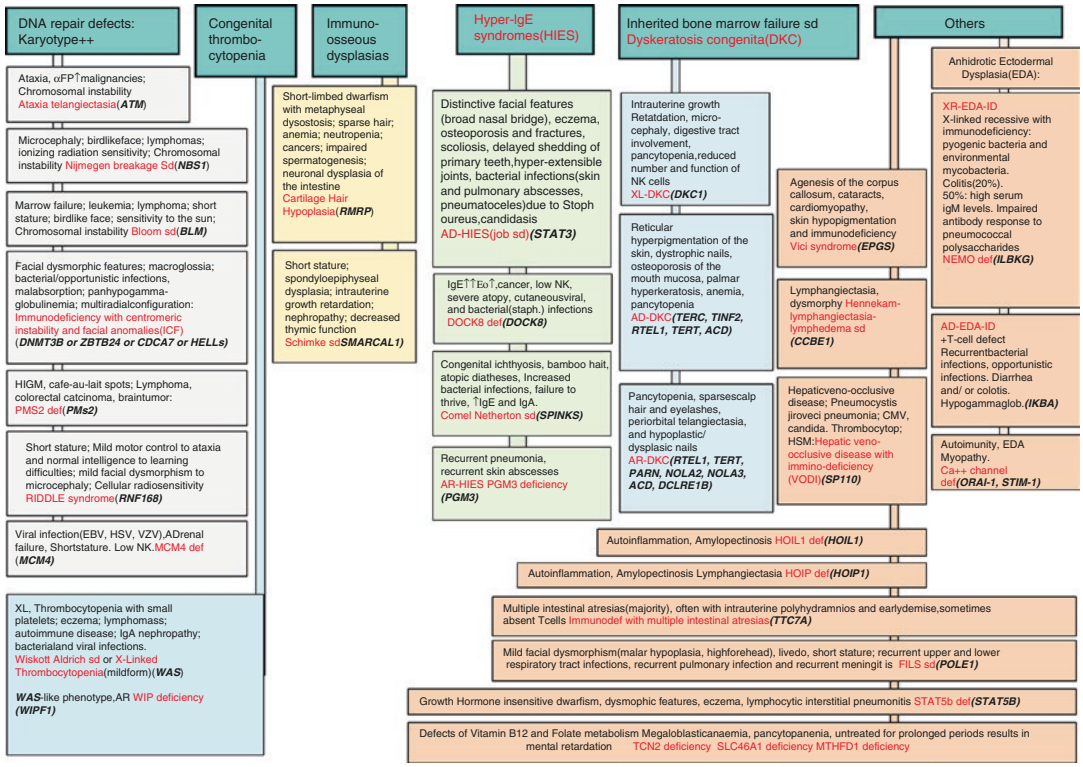

Fig. 1.15 Modified IUIS phenotypic classification of other well-defined immunodeficiencies [47]. *αFP* alpha fetoprotein, *AD* autosomal dominant, *AR* autosomal recessive, *CMF* flow cytometry available, *EDA* anhidrotic ectodermal dysplasia, *EDA-ID* anhidrotic ectodermal dysplasia with immunodeficiency, *FILS* facial dysmorphism, immunodeficiency, livedo, and short stature, *FISH* fluorescence in situ hybridization, *HSM* hepatosplenomegaly, *HSV* herpes simplex virus, *Ig* immunoglobulin, *VZV* varicella zoster virus, *WAS* Wiskott-Aldrich syndrome, *XL* X-linked (© Springer Science + Business Media New York 2015)

polio vaccine, smallpox, live attenuated influenza, Yellow fever and live bacterial vaccines in severe humoral immunodeficiencies; avoidance of live vaccines in combined immune deficiency; avoidance of live bacterial vaccines in phagocytic cell defects; and avoidance of BCG vaccination in IFN-γ/IL-12 pathway defects. In general the consensus document authors concur with the existing recommendations as stated above for live viral vaccine avoidance with the following exceptions: 1) Humoral deficiency recommendations should be applied to XLA but more selectively to CVID as "little vaccine-related viral infection is seen in patients with CVID"; 2) Strict avoidance is not indicated in partial T cell defects (such as DiGeorge syndrome) when adequate T cell numbers can be documented; and 3) that there are not enough data to make a formal recommendation regarding all live vaccines in IFN-γ/IL-12 pathway defects.

Although the use of live viral vaccines can potentially be harmful, the use of non-live vaccines may have the potential to provide some prophylactic or even therapeutic efficacy. An important example is influenza. The injectable killed influenza vaccine may have limited effectiveness in PID patients, but may provide some important protection against this very common infection. This may be especially relevant as the antigenic drift and shift inherent to influenza means that neutralizing antibodies against the season's influenza virus may be absent from the plasma pool used for antibody replacement therapy. For this reason, annual non-live influenza vaccination is a consideration for PID patients. One vaccine indication that is often overlooked is

the use of pneumococcal polysaccharide vaccine for PID patients who are not receiving immunoglobulin replacement therapy. In particular, the ACIP states, "Persons who have conditions associated with decreased immunologic function that increase the risk for severe pneumococcal disease or its complications should be vaccinated". Improving the range and quantity of anti-pneumococcal polysaccharide antibodies may help reduce the incidence of pneumococcal infection in PID patients. Given that this is an significant morbidity in patients with even mild humoral immune defects, it is an important recommendation to consider. A listing of recommended vaccines according to specific category of PID is available from the ACIP and is a reasonable starting point in considering this practice (http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/A/immuno-table.pdf).

Importantly, non-live vaccines are also routinely used in the diagnosis of humoral PID. This practice is commonplace because non-live vaccines represent standard doses of antigen that generate a well-defined immune response in immunologically normal individuals and they are generally safe for PID patients. Since children are routinely vaccinated with according to a specified schedule with an expected response, the measurement of vaccine-antigen specific antibodies can be of diagnostic utility in considering abnormal humoral immunity. Furthermore, non-viral vaccines may be applied to individuals of all ages in the consideration of humoral PID since an ineffective response may be consistent with a humoral defect. The most commonly utilized vaccine for this purpose is the 23-valent pneumococcal polysaccharide vaccine. A consensus document regarding the application and interpretation of vaccines for diagnostic purposes in PID was published in 2012 and the reader is referred to that source for a more definitive perspective on this topic.

One final concern relative to vaccines in PID is vaccination for individuals who are on, or who have been on immunoglobulin therapy. As a general rule, patients on immunoglobulin replacement therapy do not need to receive immunizations. The live viral vaccines in particular, are actually neutralized by exogenous antibody. There may be utility however, to still providing non-live influenza vaccination as discussed above. It is also important to consider when to re-immunize a patient after they have received immunoglobulin. Here specific recommendations vary according to country but include waiting as long as 11 months (in the US) before administering a live viral vaccine. A study of measles vaccines efficacy in patients treated with IVIG for Kawasaki Disease is useful in that it demonstrated the return of protective responses in all patients by 9 months after treatment [200].

1.5.3 Antibiotics

Antibiotics are essential to the survival of most PID patients and have in many cases allowed patients to survive to the point of receiving a diagnosis. Appropriately diagnosing infection in as timely a fashion as possible and then treating with appropriate antibiotics is fundamental. For this reason, it is critical that the sub-specialist be familiar with the range of infectious susceptibilities inherent to a particular PID as well as the most appropriate diagnostic approaches to these infections. These individual topics are covered throughout this volume in detail.

In addition to antibiotics used for the specific therapy of clinically apparent infections, there is an important and frequently underappreciated role for prophylactic antibiotics in PID patients. In some PID the use of antibiotics prophylactically is very clear and is based upon evidence derived from placebo-controlled trials, such as in chronic granulomatous disease [116, 189]. In other PID, however, the use of antibiotic prophylaxis is based only upon data extrapolated from other conditions [313], anecdotal experience [102], and/or expert recommendations [43]. This said, a majority of sub-specialist immunologists in the US [224] as well as in the Europe [137] use prophylaxis for at least some PID patients. A majority also uses it for at least some PID patients as an adjunct therapy to IVIG. Better high-quality data regarding the efficacy of prophylactic antibiotics for PID is

most certainly needed, but at present should be considered an option for patients who are experiencing frequent infection that requires repeated use of treatment-dose antibiotics. It should also be considered for patients who are at extreme risk for particular type of infections, or severe infections. An example would be *Mycobacterium avium* prophylaxis for patients with NEMO deficiency [227].

1.5.4 Immunoglobulin Replacement Therapy

Immunoglobulin (Ig) replacement therapy is a mainstay for PID patients who do not have the ability to generate or maintain effective antibody responses. In this regard, it represents one of the truly immediate life altering interventions that can be offered to appropriate patients with PID. In fact, when patients with antibody deficiencies are treated with Ig, their infection frequency can be reduced to that of baseline populations [267].

It is important to use Ig replacement therapy for PID diagnoses that are characterized by an inability to produce antibody, produce specific antibody, or maintain specific antibody [3, 222, 279]. These include XLA, Ig CSR deficiencies, CVID, and specific antibody deficiency. There are other diagnoses, however, in which anecdotal experience supports the use of Ig therapy, but it is unclear if it represents the best evidenced-based practice. In some, this is due to the ambiguity of the diagnosis and in others the limited experience in treating the diagnosis, or the efficacy of available alternative treatments. There are several guidelines available, which can help navigate the evidence underlying the different indications for Ig therapy [43, 177, 222, 226, 276].

Once a decision has been made to provide Ig replacement therapy, there are a number of options regarding its administration that can affect clinical outcome. These options should be considered and decisions made in accordance with best evidence and patient characteristics. One is the route of therapy, which can be either intravenous (IVIG) or subcutaneous (SCIG). There are important considerations relative to each, but they should at least be considered therapeutically equivalent [38, 73]. Other important variables include the dose of Ig, frequency of Ig, residual trough level (especially in diagnoses characterized by hypogammaglobulinemia or agammaglobulinemia), which apply for either of the intravenous or subcutaneous routes of administration [223, 225], and management of infusion-associated adverse events. Again, many of these variables will be discussed later in this text, but they are also specifically considered according to evidence elsewhere [32, 226, 279].

1.5.5 Transplantation

Some of the more severe PID that weaken host defense outside of the B cell system cannot be effectively treated using only antibiotics and other relatively conservative measures. In these diseases the patients affected by them are expected to die prematurely if only these therapeutic strategies are employed. Fortunately hematopoietic stem cell (HSC) transplantation (HSCT) has emerged over recent decades as a very viable and effective option for many of these patients [215]. A clear example is SCID, which is uniformly fatal without this intervention [56]. Other PID can also be treated with HSCT, some more successfully than others. These include Ig CSR deficiencies, NEMO deficiency, familial hemophagocytic lymphohistiocytosis (FHL), IPEX, WAS, CGD, and LAD among others. The specifics, merits and outcomes of HSCT for these diseases are the subject of numerous reviews and primary articles and will also be covered elsewhere in this volume. It is important, however, to mention a few general considerations.

Unfortunately, there is no PID in which HSCT is 100 % successful and therefore the risk-benefit relation for the particular patient must be carefully considered. In some situations, it is very clear that nearly any risk must be accepted to provide HSCT for the patient, such as for a classic SCID. In others, however, particular variables should be weighed before proceeding to transplant. These include suitability of a donor, health

of the patient and in some cases, support available to the patient. In terms of donor suitability, there are some diseases that appear to be much more effectively treated through the use of an HLA-identical related donor. In others there is more flexibility and a matched unrelated donor, or haploidentical donor can be quite effective. These decisions may impact the conditioning regimen selected for the patient and therefore have the potential to affect the transplantation experience and long-term consequences. In some patients, cord blood sourced HSCT can be highly effective [268], while in others bone marrow sourced HSCT is preferred. There are important attributes of each of these options including potentially different HSC/Kg dose, incidence of graft failure, incidence of graft vs. host disease and time to engraftment that need to be evaluated for each patient. Essential overall considerations in HSCT for PID have been collectively considered by global experts and these consensus guidelines provide guidance useful for all clinical immunologists [127]. Although the science of transplantation has advanced remarkably in recent years, HSCT does create a disease state in and of itself and the decision to transplant need be evaluated very carefully. As a result, HSCT is best performed in centers with expertise and preferably in centers with expertise in PID and better still, for the specific disease being treated.

1.5.6 Gene Therapy

Advances in gene therapy for PID have at times predominated the popular media, but have advanced substantively in recent years to the point where it is beginning to emerge as a legitimate therapy for PID [40]. Immunologic deficiencies are superb candidates for gene therapy because the HSC can be removed and manipulated in vitro and then carry the therapeutic gene through successive cell divisions and differentiation. Some of the PID are ideally suited as the deficiency of the causative gene results in a selective disadvantage of the affected immune cells. In other words, if the normal gene can be replaced, even into a subset of cells, they will have a superior proliferative or survival capacity and be able to fill the space in the immune system that was otherwise void or occupied by weaker disadvantaged cells. A clear example is lymphocytopenic SCID, in which lymphocytes fail to proliferate. Here provision of the normal gene into patient HSCs can provide them with the ability to proliferate and fill otherwise unoccupied space. This approach has been successful in patients with X-linked SCID due to *IL2RG* mutation [131]. The limitation in this setting, and a true challenge to gene therapy, has been in developing and using optimal and controllable gene vector systems. In the *IL2RG* patients receiving "first generation" retroviral-vector based gene therapy, a subset developed hematopoietic malignancy that was believed to be due to insertion of the gene therapy vector near the *LMO2* oncogene, thus promoting abnormal growth of the gene transduced cells containing this insertion event [132]. Although this has been debated [316], it is believed that the Retroviral-vector system is to blame [237]. Gene therapy success has also been reported for CGD, but unexpected and preferential insertion of the vector was prerequisite for success [229]. This result helped reconcile the success in CGD, as the defective phagocytes typically do not have a survival disadvantage as demonstrated by carrier females. Thus, the selective immunologic pressure to provide an advantage to gene-transduced cells was now introduced through vector-induced enhanced transcription of specific genes.

Difficulties relating to the retroviral vector system, have been all but confirmed in the context of gene therapy for Wiskott-Aldrich syndrome. Here the approach has been highly effective in restoring immunologic function and platelet counts to affected patients having received therapy [51]. Unfortunately, those patients having received the WASP gene in retroviral-vector were also increasingly diagnosed with vector-insertion related malignancy [51].

Despite these initial successes and increased understanding, it is commonly held that more elegant gene therapy vector systems are needed to provide additional assurance and control over this very promising means of treating PID [66].

The use of self-inactivating lentiviral systems seem to have proven this hypothesis true as spectacular successes without the retroviral vector-associated malignancies have been documented in X-linked SCID, ADA-SCID and Wiskott-Aldrich Syndrome [11]. Future objectives will clearly include expansion of the lentiviral approaches and may include vectors specifically designed to control an integration site for the therapy vector, the ability selectively destroy cells containing the vector (in the case of abnormal expansion), exogenously control the expression of the transduced gene and even removal and replacement of a diseased gene.

1.5.7 Adjunct Therapies

The health of PID patients can also be improved by a number of more indirect interventions that are believed to provide slight benefits. Again in most cases these have not been directly studied in the context of PID and are based upon data extrapolated from other conditions affecting immunologic function, or from the opinion and consensus of expert immunologists. In general, these measures are believed to help reduce the susceptibility to infection, or improve host defense. Although they may not be perceived as substantial interventions, they can be considered as part of a holistic approach to a PID patient. Firstly, it is important to effectively manage co-morbidities or unrelated conditions that increase the susceptibility to infection that a given patient may have. These include allergic rhinosinusitis, asthma, gastroesophageal reflux and challenges presented by sinus anatomy. In patients without PID, effective management of these diagnoses can be associated with beneficial outcomes.

In PID patients, one often-discussed intervention is hygiene. In some cases, there is a very clear rationale for hygiene, such as excluding mold sources from the environment of CGD patients. In others, however, a rationale for hygiene is based upon studies of hygiene interventions in otherwise healthy individuals, such as the use of regular hand washing or alcohol-based hand gels [312]. Also in this category it can be useful to discuss nasal/sinus irrigation with saline as this has been demonstrated to have effectiveness in patients with chronic sinusitis, presumably through removing irritants, bacteria, and debris [242]. At a minimum, discussing reasonable hygiene interventions with a PID patient may have benefit and may prevent them from inappropriately diverting their focus from more effective measures. In particular, having a discussion about the social and developmental merits of participation in school is important, as the immunologic benefit of avoiding school is almost never warranted. Many of these interventions are utilized by expert immunologists with a perceived benefit to their patients [321].

It is also relevant to discuss the use of botanicals and other remedies aimed at reducing the incidence of infection and or improving immunity. In the United States, the sale of botanicals represents a multi-billion dollar industry and one not subject to the same evidence-based and marketing controls as standard pharmaceuticals. Since many of these formulations are marketed directly to patients, it is important to have a working knowledge of some of the more common preparations and to be prepared to hold a discussion about the benefits and risks of such remedies. It is also important to advise patients in protecting their financial resources when considering therapies promising great return based upon scarce or no evidence. With this said, some of these therapies are perhaps useful. One worthy of mention is the use of lactobacillus. The use of lactobacillus has been shown to reduce the incidence of infectious diarrhea as well as upper respiratory infection in susceptible non-PID populations [244, 258]. Caution need be advised regarding the very wide-range of lactobacillus preparations available, some of which are associated with significant financial costs.

A final very important consideration is the psychosocial well being of the PID patient. Psychosocial stress is well documented to adversely affect immune function [328], and PID patients can only benefit from minimizing this impact. A variety of measures are worth consideration including psychosocial therapy, massage

therapy and even acupuncture in the appropriate setting. The onus of a life-long chronic illness is tremendous and being faced with the uncertainty of infectious susceptibility can truly take its toll. It is critical therefore to recognize this, acknowledge it to both patient and family, and provide the patient with the best available resources. Many are available through the national and international patient organizations representing primary immunodeficiency diseases, the IDF, JMF and IPOPI. Others are available through local or disease specific groups. In addition local resources for patients with chronic diseases may be very effective and useful for PID patients and the sub-specialist need become familiar with the availability of resources in a given region. Although there are an array of appropriate options, these need to be matched to the individual patient, and discussing these issues should be viewed as a requirement in PID patient care.

1.5.8 Prevention

Genetic counseling begins with obtaining a family history. Documentation of a complete family pedigree is essential when a proband is diagnosed with immunodeficiency. The kindred may have other individuals who were known, or who in retrospect can be surmised to have had the same condition, and the inheritance pattern may be discerned—whether autosomal recessive, dominant, X-linked recessive, or complex. This information can be used by prospective parents to understand their recurrence risks when planning further children. Prenatal diagnosis may be possible by sampling amniotic cells or chorionic villous cells early enough in pregnancy, making the option of terminating an affected pregnancy available. Sex selection or pre-implantation diagnosis are options that have become available when a specific gene mutation causing disease in an affected family member is known.

However, families for whom pregnancy termination or genetic selection is not an option also benefit from counseling, and physicians caring for the affected individual will gain insight from learning how family members approach a serious immunodeficiency disease. Optimal care for patients and their families depends on understanding what the disease means to them. In previous generations or when the initial diagnosis has been delayed and treatment ineffective, children with immunodeficiencies are likely to have died, leading to parental feelings of guilt, secrecy, and other family stresses. Important family events or beliefs also strongly influence the outlook of family members and influence the type of genetic testing that may be used. Those at genetic risk of bearing further affected children may choose not to reproduce, or may have their infants tested and treated promptly after birth to optimize successful treatment.

Now that many males with X-linked immunodeficiency diseases have been successfully treated and are reaching adulthood, it is important for them to understand their reproductive risks, which remain even if the disease in their blood cells has been permanently treated, such as by bone marrow transplantation. Affected males will pass on their mutation-bearing X chromosome to all of their daughters, who will be carriers; however, none of their sons will be affected because they will inherit the Y chromosome, and not the X chromosome from their father.

1.5.9 Newborn Screening

All PID should be diagnosed as early as possible, because available treatments are optimally successful when instituted early, before the onset of serious or life threatening complications. This is perhaps most obviously true for SCID, for which diagnosis at birth or even prenatally in the setting of a recognized positive family history has allowed infants to receive definitive immune restoration prior to developing infections [52, 69, 105, 206]. Routine population-based screening of newborns for treatable genetic conditions has been a successful public health measure to facilitate prompt intervention, and the first primary immunodeficiencies for which newborn screening (NBS) has been applied are SCID and other disorders characterized by lack of the normal diverse repertoire of T lymphocytes.

A PCR test for SCID carried out on DNA isolated from infant dried blood spots (DBS) universally collected for NBS was developed in 2005 by [70]. The test quantitates T cell receptor excision circles (TRECs), a biomarker for T cell lymphopoiesis [103]. The test was first piloted on a large scale in Wisconsin, followed by Massachusetts, California, New York and other states in the USA [55, 238, 252, 304]. Upon finding absent or abnormally low TRECs in the DBS sample, screening programs and immunologists obtain a liquid blood sample to measure T cell numbers, as well as B and NK cells and naïve and memory phenotype T cells to confirm the diagnosis. Further immune testing and treatment can then follow without delay by the time the infant is 3 to 4 weeks of age. At this writing over half of the infants born in the USA are screened with a TREC test, and other countries are also adding SCID to their NBS panels. Dozens of infants with SCID have been diagnosed while healthy and rescued with hematopoietic cell transplantation (HCT), gene therapy, or, in the case of adenosine deaminase deficiency, enzyme replacement therapy [134, 158, 304].

In addition to typical SCID, a spectrum of cases with very low T cells have been detected, including leaky SCID and Omenn syndrome, which also require treatment by HSCT as well as additional primary and secondary immunodeficiencies. Examples of the latter are syndromes, such as chromosome 22q deletion, trisomy 21, cartilage hair hypoplasia and ataxia telangiectasia, in which T cell numbers may be dangerously low, as well as secondary T lymphocytopenias associated with T cell loss due to hydrops or vascular permeability. Extremely premature infants may also have low T cells with low birth weight, but their T cells normalize over time. Another secondary cause of T lymphocytopenia has been congenital leukemia, and severe HIV infection is hypothesized to potentially be detected, though no confirmed cases have been reported to date.

The institution of NBS for SCID has made possible a true measurement of its incidence, about 1/58,000 in the general population, nearly double prior estimates [158]. Certain groups with restricted genetic diversity or high rates of consanguinity may have much higher incidence, such as Navajo Native Americans, who have a founder mutation causing SCID in up to 1/2000 births [144]. The proportion of autosomal recessive as compared to X-linked cases with population-based SCID screening has been greater than anticipated, as has the number of cases that remain without a molecular genetic diagnosis despite sequencing of many of the well recognized SCID genes. While the test was designed for SCID, the additional cases of infants with T lymphocytopenia have also benefited from early detection by receiving indicated antibiotics or immunoglobulin and by avoiding being exposed to infections from live vaccinations, such as the attenuated live rotavirus vaccine, as well as CMV positive transfusions or community acquired infections [158].

Of course most primary immunodeficiencies are not characterized by insufficient generation of T cells, and these disorders will not be detected by TREC NBS. Disorders such as ZAP70 deficiency or MHC class II deficiency affect T cell function at a later stage of differentiation than the T cell receptor recombination events, and thus infants with these conditions will have normal TRECs. Beyond T cell disorders, the rest of the primary immunodeficiencies are also in need of early recognition. B cell deficiencies may be detectable by screening with a PCR test for kappa light chain excision circles (KRECs) [46], although it is not certain whether the sensitivity and specificity of this addition to TREC testing will be sufficient for their widespread adoption in NBS programs. The rapid advances in genomic technology may in the future make deep sequencing sufficiently inexpensive, accurate and interpretable to consider whole exome or even genome sequencing in the newborn period to identify immunodeficiencies among other treatable conditions.

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Combined T- and B-Cell Immunodeficiencies

2

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2.1 Introduction

Combined T and B lymphocytes immunodeficiencies (CID) are a group of rare genetic disorders characterized mainly by profound deficiencies of T-lymphocyte counts and/or function, with or without B-lymphocyte defect. The incidence of CID is estimated to be 1 in 75,000–100,000 live births [390]; however, the true incidence is unknown because many patients die before diagnosis. Since most forms of CID are inherited as AR traits, they would be expected to be more common in areas with high rate of consanguinity [12]. Unfortunately, many physicians lack the knowledge to early diagnose these patient. This results into significant organ damage before diagnosis, which affects the overall prognosis. *(See* Table 1.1 *and* Fig. 1.8 *for updated classification of combined T- and B-cell immunodeficiencies)*

The first description of a child with a deficiency in cellular immunity was made by Glanzmann and Riniker in 1950 [253]. Some years later Hitzig et al. identified patients with a combined deficiency of the cellular and humoral immunity, the so called "Swiss Type" Agammaglobulinemia with the clinical triad of mucocutaneous candidiasis, intractable diarrhea and interstitial pneumonia [297]. As immunodeficiencies with autosomal recessive and also X-linked transmission were observed subsequently, soon a heterogeneous etiology was suspected.

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Most patients with this group of PID present early in life with severe infections caused by opportunistic organisms, chronic diarrhea, failure to thrive or GVHD due to engraftment of maternal T cells. However, patients with hypomorphic mutations usually present with profound combined immunodeficiency beyond the age 1 year [205, 553]. Beside recurrent and severe infections, these patients usually present with immune dysregulation characterized by granulomatous infiltrations of the skin and lungs among other organs, lymphadenopathy, hepatosplenomegaly, autoimmune cytopenias and/or lymphoproliferative disease and malignancy. Another group of patients have underlying defects in genes involved in late T cell activation [11, 392] and present with features of functional CID with a severe impairment of immune response to pathogens, prominent signs of immune dysregulation and increased risk of malignancy. Depending on the underlying gene defect, some patients may present other clinical features such as ectodermal dysplasia and congenital myopathy, warts, chronic mucocutaneous candidiasis, severe allergy/food intolerance, and heart defects [481].

Patient suspected to have CID should undergo urgent evaluation. A complete and differential blood count is crucial to detect lymphopenia, and measurement of serum IgG, IgA, IgM and IgE levels has to be done to look for hypo or agammaglobulinemia. If the patient has received any vaccine, the assessment of the specific antibody production is also needed. Enumeration of T lymphocyte subsets, B lymphocytes and NK cells constitutes the most important part in diagnosing CID patients. Enumeration of naïve T cells and T cell functional studies can be helpful to further clarify immune status in cases where T cell numbers are normal. It should be noted that the results need to be compared with the normal age-matched ranges and normal immunoglobulin level and lymphocyte counts do not exclude the diagnosis.

Newborn screening (NBS) for a number of T and B lymphocyte deficiencies is now available and has already been implemented in a few countries [449, 520]. NBS is performed using real-time polymerase chain reaction on DNA extracted from blood collected on newborn-screening cards [345, 361]. T lymphocyte deficiencies such as severe combined immunodeficiency (SCID) can be detected using the T cell receptor excision circle (TREC) assay, while kappa-deleting recombination excision circles (KREC) can detect abnormalities in B cell development in primary B cell immunodeficiencies [72]. Both tests were found to be cost effective and sensitive [114, 674]. Hence, their implementation in countries with a high frequency of PIDs is crucial and will remarkably improve long-term survival and decrease mortality for these disorders.

2.2 T-B+ Severe Combined Immunodeficiency

(γc deficiency, JAK3 deficiency, IL7-Rα deficiency, CD45 deficiency, CD3γ/CD3δ/CD3ε/CD3ξ deficiencies, Coronin-1A deficiency)

2.2.1 Definition

Severe combined immunodeficiency (SCID) is the most severe forms of inborn immunodeficiencies, which are characterized in most cases by complete absence of T-cell-mediated immunity and by impaired B-cell-function [121, 123, 220]. The over-all incidence is about 1:50,000 to 1:100,000 newborns, possibly there may be a higher incidence due to early lethality in undiagnosed cases in the case of patients who succumb in the course of overwhelming infections before the diagnosis of immunodeficiency is made. The differential diagnostic to "pure" cellular immunodeficiencies might be difficult in some conditions.

T-B+ SCID (OMIM*600802) are characterized by impaired development of mature T-cells while B-cells are present but non-functional. This form presents the most frequently observed SCID phenotype and can be observed in 30–50 % of all cases [88, 627]. T-B+ SCID can be further

distinguished according to the presence or absence of NK-cells.

In the case of γc-deficiency and JAK3 deficiency, NK-cells are virtually absent (T-B + NK- SCID), whereas NK cell development is intact in SCID patients with T-B + NK+ phenotype. While NK cells are present in normal number in the IL-7 receptor α deficiency and in defects of the different subunits of the TCR, the CD3 γ, δ, ε and ξ-chain, NK cells are reduced in number in the CD45 deficiency.

γc deficiency Patients with X-linked recessive SCID (XL-SCID, OMIM*300400) present with absent T- and NK-cells while B-cell counts are normal or high (T-B + NK- SCID). Affected males present combined impairment of T and B cell immunity. In vitro proliferative responses to mitogens and antigens are abolished and immunoglobulin synthesis is deeply impaired despite detectable B-cells. Mutations in the gene coding for the interleukin (IL)-2 receptor gamma chain cause the XL-SCID which is responsible for about half of the cases of all SCID patients explaining why a male predominance can be observed in SCID patients. The incidence of XL-SCID is estimated to 1:150,000 to 1:200,000 live births. A positive family history can lead to the confirmation of the diagnosis before or early after birth, but often XL-SCID occurs as sporadic cases that are discovered upon infectious complications.

JAK3 deficiency Patients with mutations in *JAK3* (OMIM*600173) present with an autosomal recessive form of T-B + NK- SCID [400, 485, 569].

IL7-Rα deficiency A selective impairment of T-cell development is found in deficiency of the Interleukin-7 receptor alpha (*IL7R-ALPHA*, OMIM*146661), also known as CD127. B- and NK-cells are present; patients may show elevated B-cell-counts. This condition is due to mutations in the Interleukin-7 receptor alpha (IL-7Rα) gene located on chromosome 5p13 [398], it follows an autosomal recessive inheritance.

CD45 deficiency CD45 deficiency generates T-B + NK+ SCID due to mutations in the *CD45* (OMIM + 151460) tyrosine phosphatase.

CD3/TCR complex deficiencies Some rare cases of T-B+ SCID may be due to mutations affecting the CD3/T-cell receptor (TCR) complex (γ: *CD3G*, OMIM*186740; δ: *CD3D*, OMIM*186790; ε: *CD3E*, OMIM*186830; ξ: *CD3Z*, OMIM*186780) [217].

Coronin-1A deficiency Coronin-1A deficiency is a recently recognized autosomal recessive T-B+ SCID [604], caused by mutations in *CORO1A* gene (OMIM*605000) [452, 453, 631].

2.2.2 Etiology

γc deficiency De Saint Basile et al. mapped the X-linked SCID to the proximal long arm of the chromosome X (Xq12-13.1) [160]. After the cloning of the gamma c gene (*IL2RG*, OMIM*308380) [644] and its localization in the same region on the X-chromosome, mutations in the gamma-c gene have been identified in X-linked SCID patients [477, 522].

The gene *IL2RG* covers 4,5kB of genomic DNA in Xq13.1 and contains a coding sequence of 1124 nucleotides distributed into eight exons. It is constitutively expressed in lymphoid cells including both T-, B- and NK-cell-lineages [378] and encodes the gamma c chain of the interleukin-2 receptor. The gamma c is a type I transmembrane protein which is transported to the cell membrane after cleavage of a signal peptide.

Defective production of interleukin-2 had been observed in an immunodeficient patient who had detectable circulating T-cells [698]. The observation that the knock-out mouse for IL-2 shows disturbed peripheral T-cell homeostasis and autoimmunity, but does not display a SCID phenotype [590], suggested already that XL-SCID is not caused exclusively by impaired IL-2 mediated signaling. This hypothesis has further been confirmed by the identification of

mutations in the *IL-2RA* gene encoding the interleukin-2 receptor alpha chain (CD25), a subunit of the tripartite high-affinity receptor for interleukin, in a patient who showed decreased numbers of peripheral T cells and abnormal T-cell proliferation but normal B cell development and autoimmune features [597] like the murine IL-2 knock-out. The complex XL-SCID phenotype can be explained by the fact, that the interleukin-2 receptor gamma chain is not only part of the interleukin-2 receptor, but also of the IL-4, IL-7, IL-9, IL-15 and IL-21 receptors [406] [185] and has been therefore also designated "common gamma chain" [378]. Multiple cytokine mediated pathways are thus abrogated in the gamma C deficiency giving rise to the pronounced defect in T-cell maturation. Exceptionally patients with gamma c deficiency may develop some autologous T-cells which may be associated to a milder clinical phenotype [174, 436, 568].

JAK3 deficiency The human *JAK3* gene maps to chromosome 19p12-13.1 [299, 571] and is organized in 23 exons. Its cDNA is composed of 4,064 nucleotides encoding for a protein of 1,124 amino acids [591]. JAK3 is a lymphoid tissue-specific tyrosine kinase and belongs to the Janus family of protein kinases [332]. It is involved in the signal transduction pathway of several cytokines, such as IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 [36, 320], thus the same cytokines which are affected by the lack of the common gamma chain in the case of XL-SCID. In fact, JAK3 interacts intracellularly with the common gamma c chain. This explains why the clinical manifestations of XL-SCID and JAK3 deficiency are virtually identical, besides the fact that JAK3 deficiency can be observed in both female and male patients, as it follows an autosomal recessive inheritance. Upon association of the gamma c with JAK3, crossphosphorylation of the JAK proteins and of the cytokine receptor take place. The STAT proteins are then recruited and themselves phosphorylated. This allows their dimerization, nuclear translocation and binding to regulatory elements in the nucleus. Finally, the transcription of target genes is induced [482].

IL7-Rα deficiency An important step during lymphoid development is the interaction between IL-7 and the γ-c containing IL-7 receptor complex. This is underscored by the fact that IL-7 or the IL-7 receptor α chain deficiency generates impaired lymphoid maturation with a SCID phenotype in mice [173, 510]. Whereas IL-15 is important for NK-cell development [353] and IL-21 is implicated in innate and adaptive immune functions [277], the physiological significance of IL-4 or IL-9 impairment during lymphoid maturation is not yet fully elucidated.

IL-7 provides survival and proliferative signals through the IL-7 receptor and plays thus a critical role in early T-cell development. SCID with T-B+NK+ phenotype in humans due to mutations in the Interleukin-7 receptor alpha gene was first described by Puel et al. in 1998 in two patients with failure to thrive, diarrhea, recurrent otitis, viral infections and candidiasis [525]. Other patients with defect in the IL-7Rα have subsequently been described [85, 524, 554].

CD45 deficiency The cell-surface coreceptor CD45, or common Leukocyte Surface Protein, is a hematopoetic-cell-specific transmembrane protein that is implicated in the regulation of src kinases involved in T- and B-cell antigen receptor signaling. Mice with a CD45 deficiency display a profound immunodeficiency. The thymocyte maturation is blocked at the transitional stage from immature CD4+CD8+ to mature CD4+ or CD8+ cells, and only a few T cells are detected in peripheral lymphoid organs [341].

Up to now few cases of CD45 deficiency have been identified. A 2-month-old infant with mutations in the CD45 tyrosine phosphatase gene was described by Kung et al. [356]. This patient presented with low CD4 numbers while B-cell counts were normal and NK cells were found albeit in reduced number (T-B+NK+ SCID). The

TCR αβ T cells were lacking, but γδ-cells were present. More recently a second case was reported by Tchilian in 2001 [648]. CD45 deficiency has thus to be examined in T-B + NK+ SCID phenotype when the more common etiologies have been ruled out.

CD3/TCR complex deficiencies The antigen specificity of the TCR is based on a heterodimer composed either of the αβ- or γδ-chain. This heterodimer is associated to four polypeptide chains, the CD 3 γ, δ, ε and ξ-chain. Mutations of each of these transmembrane proteins may occur and may generate an abnormal or absent expression of the TCR causing moderate to severe immunodeficiency [16]. The phenotypic expression may be variable and depends on the degree of the residual expression of the defective TCR-subunit. Patients display thus variable susceptibility to infection and autoimmunity. They have very few or completely undetectable circulating CD3+ T-cells, poor responses to T-cell mitogens and various levels of immunoglobulins.

CD3γ deficiency has been described in Turkish and Spanish patients [32, 509]. A defect of the δ chain has been found in a Canadian patient [144]. A French patient presented a CD3ε deficiency [616, 651]. Complete CD3δ and γ-deficient patients who present with SCID-symptoms have been described [161, 643]. A 4-month-old boy with primary immunodeficiency was reported to have a homozygous germ-line mutation of the gene encoding the CD3ξ subunit of the T-cell receptor-CD3 complex [542]. Interestingly, the CD3ξ-deficiency was partially corrected by somatic mutations resulting in a milder phenotype and in decreased numbers of circulating T cells. A second patient with complete CD3ξ deficiency resulting in T-B + NK+ SCID was described recently [547].

Coronin-1A deficiency Up to now, only few cases of Coronin-1A deficiency have been identified [452]. In addition to significant decreased number of naive T-cells, impaired development of a diverse T-cell repertoire, absent invariant natural killer T cells, and severely diminished mucosal-associated invariant T cells have also been reported [453]. It has also been shown that coronin 1A can play a role in NK cell cytotoxic function [452]. Recently, compound heterozygous *CORO1A* mutations have already been reported [631].

2.2.3 Clinical Manifestations

Despite the huge heterogeneity on the molecular level, the clinical manifestations of the different SCID forms are comparable, as shown by the observations in large cohorts of SCID patients in Europe and the United States of America which has revealed that the clinical presentation with regard to the infectious events is quite similar [88, 627]. The onset of manifestations is characteristically early, often already before the third month of life. Despite the protection through maternal antibodies, SCID patients develop recurrent infections with protracted course and unexpected complications. Before the age of 6 months the SCID patients develop chronic diarrhea, interstitial pneumonia and/or therapy-resistant mucocutaneous candidiasis. Infections with opportunistic germs like *Pneumocystis jiroveci* (beforehand *Pneumocystis carinii*) or Cryptosporidium are currently present. But also intracellular microorganisms like Listeria, *Salmonella typhi*, Toxoplasma and Mycobacteria can be found. Other manifestations are due to infections due to Aspergillus sp or viral infections like Adenovirus, Respiratory Syncytial Virus (RSV), CMV, Herpesvirus or EBV. The suspicion of SCID is always to be considered as a "pediatric emergency" with the risk of a rapidly fatal evolution if the immunodeficiency remains undetermined.

The clinical alarm signs in an infant which should direct our attention to a possible immunodeficiency or failure to thrive or loss of weight (often observed between the 3rd and the 6th

month of age), chronic diarrhea, atypical eczematous skin manifestations, absence of adequate response to current antibiotics, recurrent candidiasis and persistent respiratory symptoms (chronic cough, chronic respiratory obstruction, progressive tachypnea or dyspnea). The clinical examination of a "classical" SCID patient reveals a hypoplasia of the lymphatic tissues (lymph-nodes, tonsils), there is no thymic shadow in the chest radiography. Consanguineous setting is in favor of an inborn error of the immune system as many deficiencies follow an autosomal recessive inheritance-pattern and are thus more frequently observed in consanguineous families. Lymphopenia and hypogammaglobulinemia are additional factors that should lead to further immunological investigations.

Vaccination with live vaccines is contraindicated in SCID patients. BCG vaccination in SCID patients causes disseminated infections that may be fatal. Infiltrating and ulcerating lesions at the impact of the vaccination and in the regional lymph nodes, but also systemic propagation with papular cutaneous lesions, osteolytic lesions and organ impairment of liver, spleen, lymph-node and lung may occur. As the BCG vaccination is no longer generally recommended in many countries, it should be checked if a patient has been exposed to BCG vaccination, and if so, adequate antibiotic treatment should be initiated even in the absence of any clinical manifestation. In the case of oral live polio vaccine or upon contact to recently vaccinated persons, central nervous poliomyelitis-infections and carditis may occur.

Other SCID manifestations concern in rare cases chronic hepatitis or sclerosing cholangitis. Cutaneous manifestations interests consist in recurrent warts, Molluscum contagiosum, atypical eczematous skin lesions, alopecia, seborrhoic skin manifestations as well as cellulitis.

The maternal alloreactive T-cells may lead to the clinical picture of "Graft versus host disease" (GVHD). Habitually asymptomatic, the so-called "materno-fetal" may touch different organs. Frequently exist maculopapular rush and hypereosinophilia, more rarely found are liver involvement with disturbed liver enzymes, profuse diarrhea or pancytopenia. Transfusion of non-irradiated blood-products can generate a fatal GVHD, thus only irradiated products should be used.

γc deficiency XL-SCID is characterized by early onset of severe infections starting during the first months of life, typically between 3 and 6 months of age. The clinical manifestations do not differ substantially from the general presentation of SCID patients. Milder phenotypes exist.

JAK3 deficiency While most JAK3-deficient patients present with a clinical phenotype virtually indistinguishable from boys affected by X-linked SCID, some JAK3 patients reveal an unexpected clinical heterogeneity, emphasizing the need for adequate investigations in order to rule out JAK3 deficiency even in atypical clinical presentations [483].

IL7-Rα deficiency, CD45 deficiency Patients present the same clinical phenotype as the other SCID patients.

CD3/TCR complex deficiencies Recio et al. studied recently two new Turkish patients with complete CD3gamma deficiency. The comparison with three formerly described CD3gamma-deficient patients of Spanish and Turkish origin revealed for all patients a similar immunological phenotype with a partial TCR/CD3 expression defect, mild αβ- and γδ-T lymphocytopenia, poor in vitro proliferative responses to antigens and mitogens at diagnosis, and very low TCR rearrangement excision circles and CD45RA(+) alpha beta T cells [530]. Interestingly, an important intrafamilial and interfamilial clinical variability was observed in patients with the same CD3G mutations, two of them reaching the second or third decade respectively in healthy conditions, whereas the other three died early in life with typical SCID features

associated to enteropathy. In contrast, all reported patients with complete CD3δ (or CD3ε) deficiencies show clearly the life-threatening SCID phenotype with very severe αβ and γδ T lymphocytopenia. These data confirm the observation of Roifman et al., who showed that the absence of CD3 delta in humans results in a complete arrest in thymocyte development at the stage of double negative to double positive transition and in impaired development of gamma delta T-cell receptor-positive T cells [550]. Interestingly, the three studied patients with CD3delta deficiency showed a normal sized thymus shadow on chest radiography, but biopsy revealed abnormal thymus structure [550].

Coronin-1A deficiency The first described case with coronin-1A deficiency experienced recurrent respiratory infections and oral thrush since early infancy. She developed severe mucocutaneous chickenpox after varicella vaccine [603, 604]. The second family with three siblings, who suffered from hypomorphic *CORO1A* mutations, all presented aggressive EBV-associated B cell lymphoproliferation at early infancy [453]. The very recent reported case with compound heterozygous *CORO1A* mutations, suffered from epidermodysplasia verruciformis-HPV, molluscum contagiosum and granulomatous tuberculoid leprosy [631].

2.2.4 Diagnosis

Anamnesis is a central element in the establishment of diagnosis and allows the identification of those children for whom immediate immunological explorations are indicated. As in most cases SCID follows autosomal recessive or X-linked inheritance, it is very important to perform an exact inquiry of family history and to analyze the genealogical background of the patient. Attention has to be paid to any other family member presenting infectious susceptibility, auto-immune manifestation or tumor-disease. Cases of unidentified infant death have to be reported. Obviously, autosomal recessive inborn errors are more frequent in a consanguine setting.

Basic investigations should contain a complete white blood count. Eosinophilia can be frequently observed in SCID patients. Absolute lymphocyte counts are often less than 1000/μl, but normal lymphocyte counts do not exclude SCID, as some forms of SCID present with absolute lymphocyte counts which may be within normal range. This may be the case on one hand in SCID-forms in which T-cell maturation is only impaired in a limited way (e.g. PNP deficiency), on the other hand in patients with "leaky" or atypical SCID who present hypomorphic mutations, which allow a residual function of the defective protein.

A special situation is the persistence of maternal T-cells after transplacental materno-fetal transfusion. In these cases, the presence of maternal T-cells should be eliminated through chimerism analysis: in male patients by in situ XX/XY hybridization of the CD3 positive cells, in girls by molecular biological methods (HLA or VNTR analysis of CD3 positive cells). In some cases, skin-, liver- or intestinal biopsies may be necessary to rule out a materno-fetal GVHD. HIV-infection should be ruled out systematically in all cases of suspected SCID.

Analysis of humoral immunity should be performed by dosage of immunoglobulins IgG, IgA and IgM. Antibody production in SCID patients is deeply reduced or completely abolished. In the first months of life a normal IgG-level may be observed due to the transmission of maternal antibodies during pregnancy, whereas a reduced IgM level is more significant. A detailed exploration of humoral immunity through analysis of specific antibody-levels following vaccination, allohemagglutinins or IgG-subclass is not useful before the second year of life, but should be done in older infants with suspected immunodeficiency. In case of enteropathy it is important to determine values for albumin in order to rule out an exudative enteropathy that may generate a

"secondary" hypogammaglobulinemia through enteral protein loss. Sometimes intestinal biopsies may be justified, as lymphopenia may be observed in the context of lymphangiectasia.

In order to perform precise immunological diagnostic, a center for pediatric immunology should be contacted promptly. The characterization of the lymphocyte subpopulations can be achieved by flow cytometry and allows in most cases a first diagnostic classification of the SCID type with regard to the presence or absence of the different lymphocyte-populations (CD4+ and CD8+ T lymphocytes, CD19+ B-cells and CD3-CD16/56+ Natural Killer cells). It is important to determine in the same time the absolute lymphocyte count. Normal range of the different lymphocyte subpopulations are age dependent. For age-related normal values see [131, 165, 601].

The T-cell function can be assessed in specific laboratory assays in vitro by testing the lymphocyte proliferation upon stimulation through so-called mitogens or through specific antigens, the latter is only meaningful after vaccination (e.g. tetanus, tuberculin) or after infection (e.g. Candida, CMV or VZV). T cell receptor excision circles or TREC are episomal DNA circles that are generated during V(D)J recombination by endjoining of the removed genomic DNA segments, they attest continuing thymic output. These TREC can be analyzed by polymerase chain reaction [180], patients with impaired T-cell maturation lack TREC.

Depending on the characterization of the specific immunophenotype of the patient, different diagnostic hypothesis can be formulated. A molecular diagnosis should be achieved based on the identification of the underlying gene defect, but in no case should the adequate treatment be postponed because the definitive diagnosis is pending. Enzymatic determination of ADA and PNP should always be performed in distance to eventual blood-transfusions.

Ultrasound of the thymus or chest radiography allows the evaluation of the size of the thymus which is generally reduced in the SCID patients. In the case of ADA-SCID patients, an alteration of the anterior rips may be observed. Additional imaging may be necessary in the context of infectious complications. In all cases a detailed microbiological work-up should be performed. Direct identification through culture or with the help of polymerase chain reactions (PCR) should be privileged as serological analysis is not significant in immunodeficient patients with abolished antibody production. Bronchoalveolar lavage or digestive endoscopy with biopsies may be necessary in order to attempt microbiological documentation.

γc deficiency Gamma c deficiency is suspected in male patients with or without positive family history upon immunophenotyping of peripheral blood. Typically, but not always, patients display a T-B+NK- phenotype and lack the expression of the gamma c chain on peripheral blood lymphocytes as analyzed with the help of monoclonal gamma-c antibodies [311]. Some patients may express a non-functional gamma c chain which may be detected by the monoclonal antibody. Maternal T-cells can also complicate the interpretation of the results. While XL-SCID patients usually present with absent or low NK cell counts and poor NK cell cytotoxicity, there have been observations of patients with confirmed mutations in the gamma c gene who possess NK cells with a certain NK cytotoxicity [508].

Theoretically, gamma c deficiency could be present exceptionally in females in the case of Turner syndrome (45X0), and in the very rare females with constitutionally unbalanced X-chromosome inactivation. Diagnosis should be confirmed by genetic analysis of the IL2RG. IL2RG mutations have been reported in different ethnical groups. IL2Rgbase [521], a database of identified mutations, is available on the web http://www.genome.gov/DIR/GMBB/SCID. The majority of mutation concerns single nucleotide changes leading to nonsense and missense-mutations, but there are also insertions, deletions and splice mutations. Mutations are not evenly distributed within the gene. There exist recurrent mutations at several positions, so-called

"hot-spots", most mutations concern the exon 5, followed by exon 3 and 4 [521]. Prenatal diagnosis at 11 weeks of gestational age is possible once the mutation is identified in a given family.

Female carriers remain healthy, they show non-random X-inactivation in T-, B- and NK-cells with the non-mutated X-chromosome being the active X-chromosome in their lymphocytes [133, 523], whereas myeloid cells show random inactivation. This underlines the important function of the common gamma c for the development of the lymphoid cell-lineages. This non-random X-inactivation in lymphoid cells has been used for the diagnosis of the carrier status.

JAK3 deficiency Diagnosis is based on immunophenotyping and molecular diagnosis. The mutations found in JAK3 deficiency have been collected in a database, the "JAK3base" that is accessible through the World Wide Web at http://bioinf.uta.fi/JAK3base.

IL7-Rα deficiency IL-7R alpha-deficiencies should be looked for in patients with a T(-)B(+) NK(+) phenotype. Confirmation of the diagnosis can be achieved by identification of the mutation.

CD45 deficiency Diagnostic procedures are the same as for other SCID-forms.

CD3/TCR complex deficiencies Diagnostic is confirmed by sequencing of the genes coding for the different transmembrane subunits of the CD3 complex (the CD3 γ, δ, ε and ξ-chain).

Coronin-1A deficiency Diagnostic procedures are the same as for other T-B+ SCID-forms, while specific described phenotypes could also be considered for the cases.

2.2.5 Management

At the slightest suspicion of SCID, adequate prophylaxis and treatment has to be initiated immediately, with the aim to treat acute infections and to prevent their recurrence. It is essential to isolate any suspected SCID patient in a sterile environment and to apply drastic hygienic measures. Suspicion of SCID is always a "pediatric-immunological emergency", as exclusively a rapid and adequate treatment in specialized centers allows the initiation of a curative therapy. The preparations for hematopoietic stem cell transplantation (HSCT) should be launched immediately at diagnosis of SCID, a specialized center should be contacted and the patient should be transferred promptly. HLA-typing of the patient, his eventual siblings and his parents has to be performed as soon as possible. The guideline written by the Primary Immune Deficiency Treatment Consortium (PIDTC) is a useful protocol, which could be considered in treatment of SCID [600].

As soon as the blood drawing for the exploration of the humoral immunity has been performed, the substitution of immunoglobulins should be started. Residual levels of IgG >8 g/l should be obtained. Aggressive antibiotic treatment of acute infectious complications has to be started. A *Pneumocystis jiroveci*-pneumonia must be ruled out or treated respectively, a prophylactic treatment with Sulfamethoxazol/Trimethoprim has to be initiated. If necessary, antimycotic treatment has to be started. Antiviral therapy may be indicated in the case of CMV- or Adenovirus-infection, in case of RSV-infection Palivizumab may be useful. Attention has to be paid to children who were vaccinated with the BCG vaccine, in these children a treatment by Isoniazid and Rifampicin has to be initiated. In the case of signs of BCGitis, anti-tuberculosis treatment including four or more drugs is necessary. Systemic BCGitis can be fatal.

Exclusively irradiated blood-products should be transfused; CMV negative patients should receive only CMV negative blood-products.

At diagnosis, SCID patients are often in poor a nutritional condition and present chronic intestinal infection and inflammation which lead to impaired intestinal absorption. A high caloric parenteral nutrition is justified to cover the energetic requirement especially as due to infections

energy requirement is higher in SCID patients than in age matched controls. The parenteral nutrition and anti-infectious intravenous therapy requires a central venous line. During central venous line placement tracheal secretions for additional microbiological analysis should be obtained in children with respiratory symptoms. In some cases a fibroblast biopsy for further genetic or functional investigations with regard to the underlying immunodeficiency can be justified.

Except for infants with complete Di George syndrome who lack an HLA identical donor and who need a cultured allogenic thymic transplantation, all children with inborn immunodeficiencies may be cured by allogenic HSCT, which is actually the treatment of choice for severe combined immunodeficiencies.

Up to now, only a few patients were treated by somatic gene therapy in clinical studies. For ADA-SCID enzyme replacement therapy is available. The first successful bone marrow transplantations were performed in 1968 [41, 237] shortly after the description of the „major human histocompatibility system"[24]. Since then more than 1300 patients with primary immunodeficiency have been transplanted worldwide. In the beginning, only unfractionated HSCT with HLA identical donors could be performed. Only about 20 % of the patients dispose of an HLA identical sibling. The development of T-cell depletion techniques starting in the beginning of the 1980's [532] allowed the transplantation from haploidentical parental donors. Bone marrow, peripheral blood stem cells (PBSC) harvested by cytapheresis or cord blood can be used as source for HSCT.

Best results with regard to survival and immune reconstitution can be observed when using HLA-identical sibling-donors. In some cases the search for an HLA identical unrelated donor can be justified, if the patient's HLA-type allows the identification of an HLA-matched unrelated donor in a reasonable time span. In clinically critic situations or in the case of a rare HLA-type in the patient, no time should be wasted with an unrelated donor search and haploidentical HSCT with one of the parents should be prepared.

Considerable progress has been observed with regard to survival rates: the first report in 1977 on the outcome of SCID patients showed survival with functional graft in only 14 out of the 69 transplanted patients [73]. In 2004, Buckley et al. report survival rates of 84 % in the case of HLA identical siblings, 71 % in HLA-matched unrelated donors and 63 % in haploidentical donors [82, 83]. The most frequent reasons of death concern infectious complications, veno-occlusive disease and graft versus host disease. In isolated cases *in utero* transplantation has been reported, but there seems to be no advantage in comparison to HSCT performed early after birth.

The first successful treatment by gene therapy was observed in the case of X-linked SCID, this was the proof of principle that gene therapeutic correction of the hematopoietic stem cell is feasible [106] and results in sustained immune reconstitution [278]. However, the occurrence of severe adverse effects has been observed subsequently [279, 280] with the appearance of leukemic transformation in actually 4 patients out of 10 in the French patient group and one patient treated at the Great Ormond Street Hospital. Occurrence of genotoxicity with retroviral vectors led to development of new generations of safer and efficient vectors such as self-inactivating gammaretroviral or lentiviral vectors as well as major advances in integrome knowledge [107, 218].

γc deficiency Unless treated, XL-SCID is usually lethal in the first year of life, in very rare cases mild courses have been observed, so that exceptionally the diagnosis may be made after 2 years of age. Rare isolated cases have been reported in which a particular mutational profile seems to be responsible for an atypical mild phenotype [174].

Allogenic HSCT is a curative treatment for XL-SCID patients and shows good success with regard to survival [30, 82]. The best results are achieved with an HLA identical related donor. In the case of haploidentical donors the immune reconstitution with regard to humoral immunity might be mediocre as patients often present only

partial chimerism after HSCT with persistence of autologous B-lymphocytes, so that immunoglobulin-substitution has to be continued after HSCT [30]. Two isolated cases have been reported of successful *in utero* bone marrow transplantation, in which fetuses between 17 and 20 weeks of gestation received haploidentical T-depleted BMT via intraperitoneal infusion [221, 702]. In the follow-up, both patients showed adequate immune reconstitution and independence from immunoglobulin substitution [50, 53].

The observation in a single patient that spontaneous reversion of the genetic defect may occur *in vivo*, probably within a T-cell progenitor, and can generate functional T-cells [628], and a stable T-cell repertoire [76], was a powerful argument for the selective advantage of the corrected cell and opened the way for the development of gene therapy, an innovative therapy option for inborn immunodeficiencies. In 1999 a first clinical gene therapy trial was initiated in the Necker Hospital in Paris with inclusion of XL-SCID patients who lacked HLA-identical donor. The XL-SCID was the first disease in humans which was treated successfully by gene therapy. It could be demonstrated that the retroviral-mediated gene transfer of the gamma-c gene allowed sustained restoration of the patients' immune function [106, 278]. This was the proof of principle that gene-transfer in hematopoietic stem cells can restore the development of the immune system. The appearance of severe adverse events due to insertional oncogenesis with development of uncontrolled T-cell proliferation were first observed in two patients [279, 280], at the time of this writing in total 4 patients have been identified with leukemic transformation which appeared after gene therapy.

Additional gene therapy trials for XL-SCID were launched by Thrasher et al. at the Great Ormond Street Hospital [236]. Until recently, no severe adverse events have been documented in this trial in which a similar protocol to the French one is used; the differences regard essentially the culture conditions and the vector design. However, Thrasher et al. reported a case of leukemia caused by the gene therapy in December 2007. Chinen et al. reported also on gene therapy for XL-SCID [119]. Such unfortunate adverse events led to extensive investigations to define the retrovirus integration profiles, which led to development and implementation of new generations of safer vectors [107].

JAK3 deficiency Treatment options are similar to the ones available for gamma c SCID patients and allogenic HSCT is the treatment of choice. The specific interaction of JAK3 and gamma c represents the biochemical basis for the similarities between these two immunodeficiencies and thus it is not surprising, that the rationale for feasibility of gene therapy is the same for both disorders. Candotti et al. reported on *in vitro* retroviral-mediated gene correction for JAK3-deficiency [98], Bunting et al. showed the restoration of lymphocyte function in JAK3-deficient mice by retroviral mediated gene transfer [90]. Clinical trials are though not yet available.

IL7-Rα deficiency, CD45 deficiency Therapeutic procedures are the same as for other forms of SCID.

CD3/TCR complex deficiencies Therapeutic procedures depend on the degree of immunodeficiency and are substantially the same as for other SCID-forms.

Corononin-1A deficiency Although HSCT seems to be the only curative therapy for SCID, only the first patient with corononin-1A deficiency received a successful matched unrelated cord blood HSCT following cytoreductive conditioning [603, 604].

Prognosis Without treatment SCID patients will succumb to infections early in life, usually within the first year. The prognosis of SCID patients depends particularly on the moment of diagnosis that is the time at which adequate treatment is initiated to treat and limit deleterious infectious complications. Thus early diagnosis is crucial for prognosis. Today it can be considered that about two-third of the SCID

patients will survive. No general newborn screening has been available, but has been repeatedly discussed in the past [82, 83]. The Department of Health and Family Services of Wisconsin, USA, approved that screening for SCID is added to the current panel for newborn screening starting from January 2008. This collaborative effort from the Jeffrey Modell Foundation, the Wisconsin State Laboratory of Hygiene and Children's Hospital of Wisconsin opens the way for to prompt identification of SCID patients allowing fast access to life saving treatment and will allow evaluation of effectiveness and outcome of this early testing for SCID.

2.3 T-B- Severe Combined Immunodeficiency

(RAG 1/2 deficiencies, Artemis deficiency, DNA PKcs deficiency, DNA Ligase IV deficiency, Cernunnos deficiency)

2.3.1 Definition

As it has been explained in the 2.2 section, SCID is a heterogeneous group of diseases that affect cellular and humoral immune function. Twenty to thirty percent of all SCID patients have a phenotype where circulating T cells and B cells are almost entirely absent but natural killer (NK) cells are present (T-B-NK+ SCID, OMIM*601457) [216]. This particular form of SCID has an autosomal recessive pattern of inheritance and is most commonly caused by a defect in the Recombination Activating Genes (*RAG1*, OMIM*179615; *RAG2*, OMIM*179616) [238, 480]. There are also some types of T-B-NK+ SCID with sensitivity to ionizing radiation (OMIM*602450), which are caused by mutation in the gene encoding Artemis (*DCLRE1C*, OMIM*605988), *CERNUNNOS* (OMIM*611290), *LIG4* (OMIM*601837), and *PRKDC* (OMIM*600899). Moreover such phenotype in addition to microcephaly and growth retardation (OMIM*611291) is due to mutations in the *NHEJ1* gene (OMIM*611290). DNA ligase IV deficiency (OMIM*606593) is another form of T-B- SCID, which is characterized by a profound but not complete defect in the development of T and B lymphocytes (T-B-NK+ SCID) associated with various degrees of microcephaly, developmental defects and growth delay. There is a high heterogeneity with level of immunodeficiency in DNA Ligase IV deficiency, ranging from no immunodeficiency to profound SCID phenotypes. Patients with Cernunnos deficiency are characterized by severe T lymphopenia, progressive B lymphopenia and microcephaly [80].

2.3.2 Etiology

The immune system encounters a vast array of foreign antigens, the recognition of which is facilitated by antigen-specific immunoglobulins (Ig)/B cell receptors (BCR), or T cell receptors (TCR). Immunoglobulins and B cell receptors control humoral immunity, recognizing soluble antigens, while T cell receptors are responsible for binding and reacting against antigens presented via cells using the human leukocyte antigen molecule. The diversity in the variable region of antigen receptors is created through random somatic recombination of genetic elements, forming a contiguous coding segment for a functional unit. This receptor also serves as a checkpoint in lymphocyte development; lack of it causes T cells to be blocked at the CD4, CD8 double negative stage and B cells do not mature past the pro B compartment [706]. T-cells lacking receptors cannot undergo selection in the thymus to become $CD4^+$ or $CD8^+$ immunocompetent cells, and IgM^+ B cells are not exported from the bone marrow, resulting in T-B- SCID.

The principle genes that control the mechanism responsible for recombination of the antigen receptors are called Recombination Activating Genes 1 and 2 (RAG1 and RAG2). The RAG genes are convergently expressed specifically in

lymphocytes and the RAG proteins that are produced act as a heterodimer, targeting the variable (V), diversity (D) and joining (J) components of T cell receptors (TCR) and immunoglobulins (Igs) which are then randomly selected from pre-existing gene segments and joined together through a process of recombination.

There are seven antigen receptor loci in mammals; TCR α, β, γ and δ loci along with Immunoglobulin receptors H, k and λ loci. The N-terminal variable part of TCR β and δ, and Ig heavy chain (H) are assembled through V, D and J recombination, while TCR α and γ and the Ig light chains are produced from V and J segments only. These gene fragments are recombined together and then joined, through RNA splicing, to a constant (C) region to produce a functional receptor. Because each locus comprises numerous copies of each V, D or J segment, random joining of these different regions of DNA can produce in excess of 10^{14} possible receptor combinations which are capable or recognizing the array of antigens encountered.

Each V, D and J gene are flanked by a recombination signal sequence (RSS) which is recognized by the RAG complex. Each RSS comprises a conserved palindromic seven base pairs (bp), followed by an AT-rich nine base pair motif, separated by either 12 or 23 bp of weakly conserved DNA. The length of the spacer is vital for producing functional receptors because recombination occurs only between RSS with 12 and 23 bp spacers [658]. Hence, V and J regions are flanked by RSS with different spacers so that V-J recombination occurs in preference to a non functional V-V or J-J arrangement. If the D segment is involved, such as for the IgH antigen receptor loci, appropriate spacers flank it to ensure the regions are joined in the correct order.

As demonstrated by experiments *in vitro* [425], RSS with unlike spacers are joined when the RAG complex produces a double strand break at the border of the palindromic heptamer motif, leaving a 3' hydroxyl group that is then covalently joined to the same nucleotide position on the opposite strand. This results in DNA with a conserved coding sequence and a hairpin structure on the coding terminus. This action also excises the DNA between the recognition sites to produce a blunt 5' phosphorylated signal terminus on the section that is looped out. The RAG proteins remain associated with all the cleaved ends of DNA [7]. The blunt signal ends are then ligated, typically without any modification [385], to form an excision circle with an exact signal joint (Fig. 2.1) [669]. These DNA circles are generally lost from the genome through dilution during cell division.

The second stage of V(D)J recombination requires the resolution of the hairpin ends to form a functional, rearranged reading frame. The ligation of the coding joint is imprecise compared to that of the signal ends with the loss or addition of approximately 15 nucleotides. This adds further variation to the receptor domain, although it does carry the risk of producing non-functional genes through frameshift mutations or introduction of premature stop codons. The addition or loss of nucleotides arises firstly by the random opening of the hairpin within the coding region, rather than exactly at the covalently closed terminus [562, 733]. If the hairpin is opened asymmetrically, the overhang can be filled in by the addition of short palindromic (P) repeat nucleotides upon resolution of the structure [381]. RAG1/2 can mediate hydrolysis of hairpins *in vitro* [58, 605] but while their presence appears to be required [323, 562, 721], Artemis (DCLRE1C) is the most likely candidate to open the RAG-generated coding hairpin [450]. This protein is phosphorylated by the DNA protein kinase catalytic subunit (DNA-PKcs) activating an endonuclease capable of cleaving hairpin DNA [183, 399]. Coding ends are also modified through template-independent addition of random N (GC rich) nucleotides by terminal deoxynucleotidyl transferase (TdT) [251, 347, 561]. Joining of homologous regions or truncation of random nucleotides at the ends of the free DNA are further mechanisms implicated in producing additional junctional diversity [563].

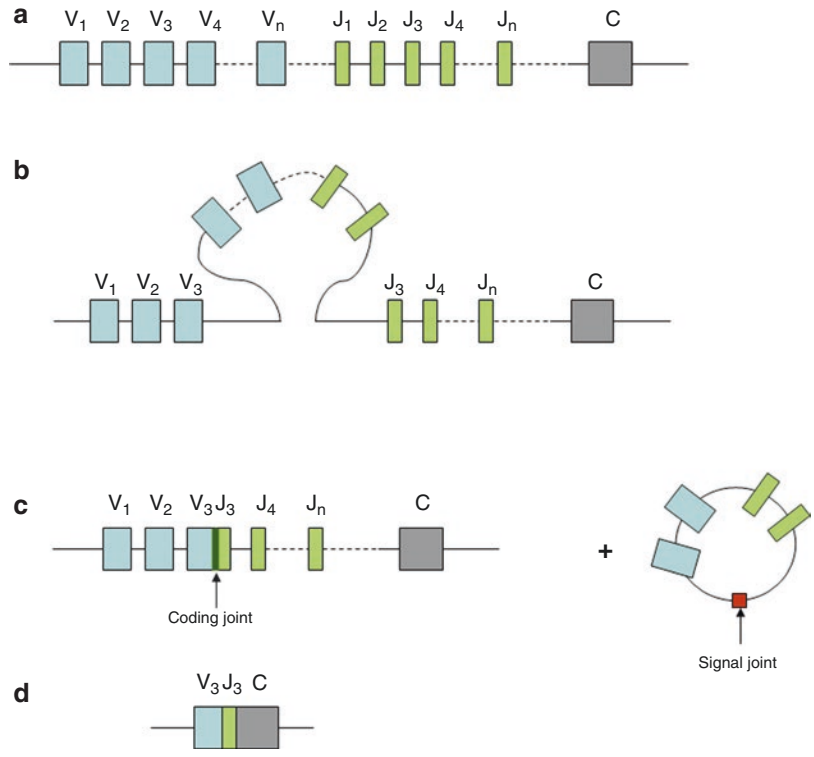

Fig. 2.1 RAG 1 and RAG 2 recognize the V and J regions of light chains and recombine them together randomly to produce an array of antigen receptors. In germline DNA, Igk comprises approximately 40 V and 5 J segments, while Igλ has about 30 V and 4 J segments (**a**). The RAG complex randomly selects a V and J region, bringing them into close proximity and most commonly, loops out the intervening DNA (**b**). The V and J genes are then recombined together, and joined with an imprecise coding joint, while the blunt ends of the excised DNA are ligated together to form a signal joint (**c**). The DNA is then transcribed and the recombined V- J region is spliced to the constant or C region to form the mature message RNA (**d**). After translation, a leader sequence at the start of the V region enables transport of the light chain to the endoplasmic reticulum. The process is very similar for heavy chain and TCR β/δ recombination, only the additional D segments separating V and J are firstly recombined with a J region, before V is randomly joined to the D-J segment produced initially

The lose ends of the modified coding signal are joined by ubiquitous proteins involved in the non-homologous end joining (NHEJ) pathway. DNA-dependent protein kinase (DNA-PK) recognizes open DNA ends, mediated by the DNA-binding subunits KU70 and KU80 and catalytic subunit DNA-PKcs. The final joining of the double strand breaks of RAG-associated cleavages is probably due to a complex of several factors [266]: a novel protein, XRCC4 [384] associates with DNA ligase IV [139, 266] and the protein Cernunnos or XLF [9, 80, 96] to ligate double strand breaks. Mutations of these NHEJ factors can lead to immunodeficiency [80, 372].

The observation of patients presenting a T-B-NK+ phenotype with increased sensitivity to ionizing radiation without mutations in the known factors involved in non homologous end joining (NHEJ) in mammals (Ku70, Ku80, DNA-dependent protein kinase catalytic subunit, XRCC4, DNA ligase IV, or Artemis) [145] indicated that there were still other NHEJ-repair-factors to be discovered. Recently a new factor was identified through the study of five human SCID patients with severe progressive T and B

cell lymphopenia and increased sensitivity to ionizing radiation: *CERNUNNOS* or XRCC4-like factor (*XLF*), was cloned contemporarily via a complementation strategy in Cernunnos deficient patients' fibroblasts [80] and via its capacity to interact with XRCC4 [9], respectively. Cernunnos is located on the long arm of chromosome 2 (2q35) and its cDNA comprises 2063 nucleotides giving rise to a protein of 299 amino acids. Cernunnos shows homology to XRCC4 [96] and forms a complex with XRCC4 and DNA-ligase IV, its precise molecular function remains to be elucidated, but it can be considered as a "new" factor of the NHEJ pathway. With regard to V(D)J recombination, the fidelity of signal joints is impaired in Cernunnos deficiency with various length of nucleotide deletions [80, 145].

RAG1 and RAG2 are located on chromosome 11p13, 8 kb apart. The proteins are the only lymphoid specific factors required for recombination of RSS sites. When the genes are artificially expressed in non-lymphoid cells where rearrangement does not normally occur, a test substrate is recombined [491, 587], suggesting that the remaining required factors are available in all cell lineages. Equally, lack of either RAG 1 or RAG 2 in humans or mice [444, 602] leads to an absence of mature T and B cells with no other defects, implying that RAG genes function only in lymphoid cells.

As homozygous or compound heterozygous mutation cause disease, this form of SCID follows an autosomal recessive pattern of transmission. RAG1 and RAG2 are arranged in an unusual tail-to-tail configuration, sharing a 3' untranslated region and both lacking introns [6]. There is no homology between the genes, but they are highly conserved in animals, emphasising their importance. In addition to this genomic configuration, the close arrangement of the genes suggests the genes may have appeared at the same time in early vertebrates through an insertion of a mobile genetic element [56, 655].

In addition to mutations of *RAG1* or *RAG2*, T-,B- SCID in humans has been caused by aberrant expression of Artemis [450], Ligase IV [56, 81, 489, 536] and Cernunnos/XLF [80]. Because these genes are also involved in DNA double strand break repair, SCID caused by their disruption is also associated with radiosensitivity [615].

Out of 174 cases of SCID examined at one American Medical Center, 3.4 % were due to RAG mutations, 1.1 % due to Artemis and 16.1 % caused by ADA deficiency [87] although worldwide, RAG mutations account for approximately 50 % of T-B- SCID [86].

Mutations of a given gene can generate a multitude of clinical phenotypes depending on the type of mutation and additional somatic mutations, environmental and regulatory factors. Hypomorphic mutations in the genes *RAG1* or *RAG2* have been shown to generate an oligoclonal T-cell repertoire which in the case of Omenn syndrome will expand and display self-reactivity [159, 679]. The observation, that identical mutations in *RAG1* or *RAG2* can be observed in Omenn syndrome but also in typical and atypical SCID patients [478, 592, 679], sometimes in the same kindred [134], suggests the involvement of one or more modifying factors.

An interesting phenotype of hypomorphic *RAG1* mutations was described in several patients with TCRαβ T cell lymphopenia, severe cytomegalovirus (CMV) infection and autoimmunity [163, 191]. T cells have been shown to be of autologous origin. De Villartay et al. describe four unrelated patients from consanguineous families who present hypomorphic mutations in Rag1, three of the four identified mutations have already been described in patients with Omenn syndrome (del T631, del 368-369 and R841W). The missense mutation Q981P found in the forth patient involves amino acids within the minimal core of RAG1 leading to a protein with residual RAG1 activity [163]. The remaining patient developed EBV-associated lymphoproliferation and presented an R561H RAG1 mutation [191] which had also been described previously in Omenn syndrome patients. It can be speculated that in these patients due to hypomorphic mutations in Rag1, a limited T cell repertoire is generated. The early occurrence of CMV infection may then induce a huge expansion of oligoclonal non γδ T cell clones.

Patients with attenuated forms of T-B-NK + SCID have been described, for example a patient who survived for 6 years without HSCT carrying mutations in RAG1, an R559S substitution on one allele and an R897X substitution on the second allele [354]. This patient presented maternal derived T cells and autologous peripheral B cells which were shown to be functional as specific anti HSV antibodies were observed. In fact, it has become obvious that the clinical spectrum for Rag1/Rag2 defects comprises not only complete abolition of V(D)J recombination leading to typical T-B-NK + SCID patients and hypomorphic mutations giving rise to Omenn Syndrome: more and more "atypical" SCID forms are identified [680, 681]. Thus genetic analysis of the Rag1 and Rag2 genes should be considered also in atypical clinical presentations.

Hypomorphic mutations in the Artemis gene may be found in patients that show clinical and immunological features that are indistinguishable from Omenn syndrome due to mutations in Rag1 or Rag2 [190].

In our patient group, four patients of two different kindreds showed a combined immunodeficiency with profound B- and T-lymphopenia and severe hypogammaglobulinemia generated by mutations in the last exon leading to truncation of the Artemis-protein and thus leaving intact the metallo-beta-lactamase domain [451, 454]. These "hypomorphic" mutations display a partial V(D)J recombination activity as assessed in the functional V(D)J assays in patients' fibroblasts and have an incomplete complementation of the sensitivity to ionizing radiation compared with a cell line fully deficient in Artemis. The patients present polyclonal T and B lymphocyte populations albeit in low number. Interestingly, two out of the four patients developed EBV-associated B-cell lymphoma; in three of the four patients a general genomic instability was found. It has thus been hypothesized that Artemis may play an important role in genome stability. According to the hypothesis of Kinzler and Vogelstein [338], Artemis may be considered as genomic "caretaker" involved in the repair of genomic lesions and thus guaranteeing genomic stability. This hypothesis was emphasized by the observations of chromosomal fragments, fusion and detached centromers in different cell lines of Artemis knock-out mice [559] indicating genomic instability in these mice [557]. Artemis/p53-deficient mice succumb to progenitor B cell tumors [558]. Furthermore, it has recently been described that tumorigenesis in several tissues is accelerated in Artemis deficient mice in a Trp 53 heterozygous setting, emphasizing the tumor suppression role for nonhomologous end-joining in lymphoid and non lymphoid cells [490, 714]. These findings suggest that Artemis deficient patients may be at risk for the development of lymphoid and non-lymphoid malignancies.

DNA ligase IV (*LIG4*) which is located on chromosome 13.q22-q34: the cDNA encoding a polypeptide of 844 amino acids [697] is essential for embryonic development and its complete deficiency causes early lethality accompanied by defective lymphogenesis and defective neurogenesis in knock-out mice [226, 235]. DNA ligase IV is a component of the non homologous end-joining and participates thus in the repair of DNA double strand breaks (dsb) that arise during DNA damage induced by ionizing radiation but also in the context of endogenously induced DNA dsb during V(D)J recombination. As detailed in the Sect. 2.3, V(D)J recombination is initiated by the lymphoid specific proteins RAG1 and RAG2 that introduce a DNA dsb between a coding segment (V, J or D) and the specific recombination signal sequence (RSS). This generates four different extremities: two blunt signal ends and two hairpin sealed coding ends, which are then resolved by the NHEJ-DNA repair pathway composed of at least six factors: DNA-PKcs, Ku70, Ku80, Artemis, DNA-ligase IV and XRCC4. Whereas the signal ends can be directly ligated by the complex formed by DNA-ligase IV with XRCC4 [139, 265] giving rise to a precise signal joint, the coding ends have to be processed prior to their ligation which generates an imprecise coding joint.

V(D)J recombination in patients' fibroblasts shows only moderate impairment with an almost normal recombination frequency of coding- and signal joint formation, but the fidelity of the signal joint formation in DNA ligase IV deficient patients is highly compromised [81].

The *Lig4* ^{Y288C} mouse strain presents hypomorphic mutations in the DNA ligase IV gene and is characterized by growth retardation and immunodeficiency. The diminished DNA double-strand break repair in *Lig4* ^{Y288C} mice causes a progressive loss of hematopoietic stem cells and bone marrow cellularity during ageing [476], thus it can be speculated that DNA ligase IV may be required beyond V(D)J recombination for lymphoid homeostasis explaining why DNA ligase IV deficiency can cause profound immunodeficiency despite the fact that there is only moderate *in vitro* impairment of V(D)J recombination in DNA ligase IV deficient patients.

Hypomorphic mutations of DNA ligase IV have been described in humans, first in a 14 year old leukemia patient who overresponded to radiotherapy [536, 537]. The observed increased cellular sensitivity to ionizing radiation was the clue to the diagnosis of DNA ligase IV deficiency. Interestingly, this patient did not display developmental or immunological abnormalities before the onset of leukemia.

Van der Burg et al. identified a homozygous missense mutation in the *PRKDC* (*DNA-PKcs*) gene in a girl with T-B- SCID and increased cellular sensitivity to radiation [666]. Few years later, Woodbine et al. showed compound heterozygous mutations of that gene in a case with severe neurologic abnormalities. Functional studies revealed a loss of function, resulting in decreased protein expression, loss of kinase activity, and impaired NHEJ and DSB repair [716].

2.3.3 Clinical Manifestations

Symptoms of T-B- SCID are similar to all other SCID and are generally manifested as early opportunistic infections with impaired growth by the second or third month after birth. Patients often present with candidiasis, chronic persistent infections of the airways, and local or systemic bacterial infections. These most commonly cause rhinitis, otitis, mastoiditis, abscesses, conjunctivitis and meningitis. Chronic diarrhea associated with gram-negative enteric bacterial sepsis causes a failure to thrive.

Maternal T cells are engrafted in half of all patients and Natural killer cells are present in this form of SCID. After decline of maternal immunoglobulins, no antibodies circulate in the peripheral blood and the lack of mature B and T cells is often accompanied by an absence of a thymus, tonsils and cervical lymph nodes.

DNA ligase IV deficient patients with a varying degree of T and B immunodeficiency, microcephaly, facial dysmorphy, growth retardation and developmental delay have been described [56, 81, 199, 489]. Some patients present exclusively a T-B-NK+ SCID phenotype without any growth or developmental defects [667]. After the first leukemia patient, who had been reported to have a mutation in DNA Ligase IV, several other patients have been identified with DNA ligase IV deficiency and lymphoproliferation or lymphoid malignancy: EBV associated B cell lymphoproliferation in two patients [81, 657], and acute T-cell leukemia in another patient [56].

Cernunnos deficient patients present recurrent bacterial, viral and/or parasitic infections like those observed in other SCID patients. Developmental defects, microcephaly, bone and urogenital malformations, and a "bird like face" could be other features of Cernunnos deficiency.

2.3.4 Diagnosis

To diagnose T-B- SCID, a full lymphocyte count and flow cytometry should be performed on peripheral blood, including markers for B, T and NK cells. RAG and Artemis deficient patients will generally lack T cells and B cells with NK cells present.

For full T-B- SCID, patients generally lack a thymus on X-ray or ultrasound imaging. Once an

initial diagnosis has been determined based on physical examination, further investigation can be performed to establish the molecular basis of disease. DNA sequencing can reveal the mutation responsible and if parental mutation has been previously determined, prenatal diagnosis can be offered [642, 678].

The immunophenotype of DNA ligase IV deficient patients may be very heterogeneous, ranging from an almost complete T-B-NK+ SCID phenotype to milder presentation with various degrees of lymphopenia and hypogammaglobulinemia [241, 489]. Radiosensitivity and microcephaly are important clues to diagnosis, but there may be rare cases without the typical microcephaly. Other characteristic features that should lead to the suspicion of DNA ligase IV deficiency are developmental retardation and growth delay.

The diagnosis can be confirmed by sequencing of the genes.

2.3.5 Management

Upon presentation, management of life-threatening infection is the immediate concern and is treated with antibiotics and antifungal drugs specific for the pathogen (often *Candida spp*, *Pneumocystis jiroveci* or *Staphylococcus aureus*). Antiviral agents should be used only if necessary.

Isolation of the patient with meticulous skin and mucosal hygienic practice is essential to prevent further infection. Prophylactic antibiotics, antifungal agents and intravenous immunoglobulins are usually required. Parenteral or enteral nutrition is an option when patients have severe diarrhea and are failing to thrive through malnutrition.

Patients should not be immunized with live viral vaccines, as they can cause fatal symptoms.

If left untreated, all forms of T-B- SCID are fatal. Bone marrow or stem cell transplantation is the only curative therapy available, although the mortality rate with this treatment is higher when compared to other types of SCID [30]. However, HSCT outcome in DNA ligase IV deficiency may be limited by complications due to increased sensitivity to conditioning regimens, even if "reduced intensity" conditioning is chosen, and more severe GVHD due to the DNA repair deficiency. It can be speculated that long-term outcome may be compromised by occurrence of secondary malignancies; nevertheless the observation period after the few performed HSCT for DNA ligase IV deficiency is still too short to draw final conclusions.

Gene therapy is a possibly future option for treating this disease. Advances treating other types of SCID have been made [10, 106, 236, 278, 494], using retroviruses to deliver functional copies of the affected gene to patients' stem cells *ex vivo*. The treated cells can then be re-implanted and give rise to an effective immune system. Gene therapy vectors to treat T-B- SCID are currently being tested [365, 455, 722] and may soon provide an alternative treatment in situations when bone marrow donors are unavailable. Occurrence of genotoxicity with retroviral vectors led to development of retroviral vectors devoid of its enhancer element, which showed safety and efficacy of this method [218]. The guideline written by the Primary Immune Deficiency Treatment Consortium (PIDTC) is a useful protocol, which could be considered in treatment of SCID [600]

2.4 Omenn Syndrome

2.4.1 Definition

Omenn syndrome (OS, OMIM*603554) is a related disease first described by Gilbert Omenn in 1965 after observing a consanguineous family with an unusual skin disorder [493].

2.4.2 Etiology

Omenn syndrome is caused primarily by missense mutations in RAG1 or RAG2, which do not entirely abrogate V(D)J recombination [679, 685]. Partial activity of the recombination acti-

vating genes allows some T cell clones develop and survive, but because of the oligoclonal nature of the population, patients remain immunodeficient. The severity of disease is variable and can be partially attributable to genotype although there are exceptions: identical mutations in RAG genes have been discovered in both T-B- SCID and OS patients [134, 240]. As OS describes a heterogeneous range of symptoms and is not a molecular definition, the disease can be the result of mutations in genes other than the RAGs [243], such as Artemis [190] or IL-7Rα [238, 480].

2.4.3 Clinical Manifestations

Symptoms are similar to other SCID but also characterized by lymphadenopathy and hepatosplenomegaly which are problems unusual in other types of SCID. Patients also suffer from alopecia and an exudative erythrodermia that is associated with episodes of *Staphylococcus aureus* sepsis. This skin condition becomes apparent as pachydermia which progresses to desquamation, resulting in protein loss through the skin which, in conjunction with diarrhea, causes hypoproteinaemia and edema. Normal to elevated levels of T cells can be present but these cells have a skewed T-helper-2 (Th2) profile [118] and due to their highly oligoclonal nature [159, 287], are poorly functional. Th2 cells produce elevated levels of interleukins 4 and 5 which lead to hypereosinophilia and despite the absence of B cells, increased serum levels of IgE.

2.4.4 Diagnosis

To diagnose OS, lymphocyte count and flow cytometry should be performed on peripheral blood. An initial misdiagnosis of atopic dermatitis or a food allergy is possible in Omenn syndrome. Engraftment of maternal T cells *in utero* can cause a skin condition with a similar appearance to graft-*versus*-host type illness, but OS can be differentiated by lack of T cell chimerism and eosinophilia, where lymphadenopathy and hepatosplenomegaly are also hallmarks of the syndrome. In OS, B cells are absent but an oligoclonal population of T cells is present with an activated antigen stimulated Th2 cell profile, as shown by presence of CD30 of the T cell surface with a CD45RO positive phenotype. These cells are responsible for the increased IL-4 and IL5 levels in serum.

Immunoglobulins A and M are absent whilst levels of IgE and maternal IgG will be elevated. OS T cell lymphocyte stimulation assays against concanavalin A (conA), pokeweed mitogen (PWM) and phytohemagglutanin (PHA) are absent or greatly decreased. Lymphocytes will however show some response to stimulation with anti-CD3, superantigens and phorbol myristate acetate (PMA).

Patients with OS generally lack a thymus on X-ray or ultrasound imaging. DNA sequencing can reveal the mutation responsible and if parental mutation has been previously determined, prenatal diagnosis can be offered [642, 678].

2.4.5 Management

Therapeutic procedures are the same as for other forms of SCID. Dermatitis can be treated with immunosuppression and topical steroids. Immunosuppression of the patients' oligoclonal T cells has decreased incidence of graft *versus* host disease [281]. The guideline written by the Primary Immune Deficiency Treatment Consortium (PIDTC) is a useful protocol, which could be considered in treatment of SCID [600]

2.5 Purine Salvage Pathway Defects

(PNP deficiency, ADA deficiency)

2.5.1 Definition

PNP deficiency (OMIM*613179) is a combined immunodeficiency caused by mutations in the enzyme *PNP* (OMIM*164050) and subsequent

accumulation of purine metabolites such as deoxyguanosine. Patients typically present with recurrent infections, autoimmunity and ataxia. Presentation may be delayed beyond 1–2 years of life.

Adenosine deaminase (ADA) deficiency (OMIM*102700) is another form of combined immunodeficiency, caused by mutation in the adenosine deaminase gene (*ADA*, OMIM*608958).

2.5.2 Etiology

Purine nucleoside phosphorylase is a key enzyme in the purine salvage pathway. PNP catalyzes the phosphorylation of inosine, deoxyinosine, guanosine and deoxyguanosine to yield guanine or hypoxanthine and ribose -1- phosphate or 2'-deoxyribose 1-phosphate. These ubiquitous purine metabolic pathways are responsible for the proper balance between the production of dephosphorylated purines, detoxification by further degradation to uric acid, and salvage by metabolism back to the nucleotide level. PNP is also responsible for catalyzing guanosine and deoxyguanosine back into the GTP pool. Maintenance of low and balanced intracellular deoxynucleoside triphosphate pools is critical for the fidelity of DNA synthesis and repair [128, 197, 437, 531].

The metabolic consequences of the PNP deficiency is the accumulation of all four PNP substrates; inosine, deoxyinosine, guanosine and deoxyguanosine [127]. Because PNP activity is obligatory to purine degradation, no uric acid is produced [127]. Of the four metabolites only deoxyguanosine can be phosphorylated further in mammalian cells [201, 690]. As a result, cells from patients with PNP deficiency accumulate abnormally high levels of intracellular dGTP [127]. The high concentration of dGTP is believed to cause lymph toxicity in patients with PNP deficiency.

Much of these metabolic effects on the immune system were learned from animal models. Three mutant mice lines were generated with a single amino acid substitution and partial PNP enzymatic activity (1–5 % of wild-type) [614]. The PNP mutant mice developed partial immune deficiency after 2–3 months consistent with the partial reduction in PNP enzymatic activity. The total number of thymocytes was reduced with a decrease in the number of CD4+CD8+ double positive cells and an increase in immature CD4-CD8- double-negative cells. In parallel spleen, T cells were reduced by 50 % and their response to T-cell mitogen was impaired partially. The overall conclusion of this study was that the progressive T-cell defect is similar to the human disorder. It is likely that the partial nature of the mutations in the PNP may hinder direct comparison with the human disease and further insight into the mechanism of the immune deficiency.

The authors' group [33] generated a PNP-deficient mouse by gene targeting resulting in a complete absence of PNP enzymatic activity. The PNP-deficient mice develop severe immune deficiency at an early age characterized by abnormal intrathymic T-cell differentiation, progressively reduced peripheral T cell with impaired immune function, and minimal abnormalities of B lymphocytes or other tissues. The observed immune phenotype of the PNP-deficient mice is similar to clinical observations in patients with PNP deficiency.

The following observations of the immune phenotype of PNP-deficient mice shed light on the mechanism by which PNP deficiency may cause immune deficiency: (1) The development of T cells in PNP-deficient mice is affected at the CD4+CD8+ double-positive intrathymic stage of differentiation; (2) in PNP-/- mice, the double-positive thymocytes undergo enhanced apoptosis in vivo markedly increased rates of activation induced apoptosis in vitro; and (3) apoptosis of double-positive thymocytes can be induced by inhibition of PNP in the presence of deoxyguanosine. The deoxyguanosine-induced apoptosis of double-positive thymocytes is inhibited by over expression of Bcl-2 or by inhibition of caspase activity.

Together, the experimental evidence supports the following hypothesis explaining the mechanisms of the immune deficiency caused by PNP deficiency:

1. The accumulation of a PNP lymphotoxic substrate, rather than the lack of the product of the enzymatic reaction, is responsible for the immune deficiency [606, 608].

2. Deoxyguanosine is the only PNP substrate that is phosphorylated further and has been demonstrated to be lymphotoxic [273, 295].
3. To exert its lymphotoxicity, deoxyguanosine has to be phosphorylated first to dGTP, which in turn inhibits ribonucleotidase reductase activity, depletes dCTP, and inhibits DNA synthesis and repair [273].
4. There is evidence that deoxyguanosine-induced apoptosis is initiated in the mitochondria. There is a secondary loss of the mitochondrial deoxyguanosine kinase enzymatic activity in PNP mutant mice and in PNP-deficient mice [319, 501, 732]. Deoxyguanosine is produced or actively transported into the mitochondria [693, 694], phosphorylated by the mitochondrial deoxyguanosine kinase, and the end product dGTP likely destabilizes deoxyguanosine kinase protein. Mitochondrial dGTP is also likely to inhibit mitochondrial DNA repair and initiate apoptosis by way of cytochrome C release [383].
5. Any hypothesis explaining the biochemical mechanism of cytotoxicity of PNP deficiency must explain the lymphocyte and in particular T-cell specificity of the disease. One explanation for the T-lymphocyte specificity is the high deoxyguanosine phosphorylating activity in T lymphocytes as compared with lymphocytes or any other tissue [101, 333, 519].
6. A second explanation for the T-cell specificity of PNP deficiency lies in the inherent susceptibility of immature thymocytes to apoptosis during T-cell selection [427]. Immature double-positive T cells express low levels of Bcl-2 and are uniquely sensitive to apoptosis during negative selection [684]. Thymocytes at this stage of differentiation have been shown to be especially vulnerable to deoxyguanosine-induced apoptosis [95, 129]. According to this hypothesis, dGTP accumulation in PNP-deficient CD4+CD8+ thymocytes increases the proportion of thymocytes undergoing negative selection by increasing susceptibility to activation-induced apoptosis [684].

It should also be added that mutations in the *ADA* gene [3], which normally breaks down toxic products of the purine scavenging pathway, cause apoptosis in lymphocytes. As such this also results in a T-B- SCID, but patients also lack natural killer cells [250].

2.5.3 Clinical Manifestations

PNP deficiency is a rare disease with an estimated frequency of 4% among patients with SCID [95]. Patients with PNP deficiency typically have a triad of symptoms including neurologic abnormalities, autoimmune phenomena, and recurrent and unusual infections.

Similar to children with other types of severe immune deficiency, PNP deficiency may come to medical attention during the first year of life because of prolonged diarrhea, oral thrush, or respiratory infections [146, 295]. Other infections include meningitis, recurrent otitis, sinusitis, mastoiditis, pharyngistis, pneumonia, and skin infection [128, 146, 222]. Patients are extremely susceptible to viral infections such as varicella, cytomegalovirus, Epstein-Barr virus, parainfluenza [95], and the polyoma JC virus [504]. There is a considerable heterogeneity both in age of presentation and severity of symptoms. In some cases significant infections are delayed until later in life [128, 146, 189, 222, 504] or have only mild symptoms, which may be credited to residual PNP activity [283].

Neurologic abnormalities are common in PNP deficiency [146, 283], and more than 20% of cases seek medical consultation due to neurologic symptoms that can not be explained by infections or preceding signs of immune deficiency [617]. The majority of neurologic manifestations are related to the motor system dysfunction, such as non-progressive cerebral palsy, spastic paresis, or tonus abnormalities. Disequilibrium characterized by hypotonia, pronounced difficulty in maintaining posture and upright position, associated with spastic diplegia and ataxia [283] or spastic paraplegia have also been described [496, 641]. Other neurologic findings include tremor, developmental delay, hyperactivity, behavioral problems, and varying levels of mental retardation,

some of which may be related to recurrent brain infarcts.

One third of the patients manifest autoimmune phenomena, which may be the presenting feature [95, 222]. These include autoimmune hemolytic anemia (associated with autoantibodies to erythrocytes) [146], idiopathic thrombocytopenic purpura, autoimmune neutropenia, arthritis, pericarditis, and systemic lupus erythematosus [84]. Patients with autoimmune disorders may test positive for rheumatic factors and antinuclear antigens [100].

2.5.4 Diagnosis

PNP deficiency is an autosomal recessive disorder. The gene that encodes PNP is localized on chromosome 14Q13.1 [708]; and several disease-causing mutations have been identified [28, 38, 146, 441, 499, 585, 663]. Different mutations in the PNP gene produce proteins with variable degrees of enzymatic activity that correlate with accumulation of nucleoside substrates and with the clinical course. Retention of partial enzyme activity may lead in some patients to less severe metabolic abnormalities, delayed presentation, milder clinical symptoms, and immune dysfunction [128].

All patients with PNP deficiency have purine nucleoside abnormalities (elevated inosine and deoxyinosine, and also guanosine and deoxyguanosine in blood and urine). Uric acid blood level is typically below 2.0 mg. Normal or slightly decreased uric acid levels are found in few patients with partial enzyme activity [59, 283]. Low serum uric acid levels also may be caused by proximal renal tubular diseases (e.g., Fanconi syndrome) or xanthinuria, in which blood and urine levels are extremely low [301]. Other metabolic abnormalities found in patients with PNP deficiency include elevated dGTP, undetectable in normal individuals, and depletion of GTP in erythrocytes to about 10 % of normal levels [295].

PNP activity can be determined by measuring the rate of conversion of radioactivity labeled inosine to hypoxanthine [95] or by spectrophotometry in which the coupled conversion of inosine to uric acid in the presence of xanthine oxidase is tested [544]. Normal PNP activity varies in different human cell and tissues extracts; the diagnosis of PNP deficiency is based commonly on enzyme activity in hemolysate [249]. Undetectable or lower than 1 % activity is usually found in patients with PNP deficiency [100], but activity as high as 4.8 % of normal control was associated with immune deficiency, although with a mild course and delayed presentation [574]. Determination of PNP activity could be affected by recent erythrocyte transfusion [189]. It is advised in these instances to measure inosine, guanosine and their deoxy analogue concentrations in the urine, or PNP activity in mononuclear cells or peripheral blood T cells [283, 295].

Prenatal exclusion of PNP deficiency can be performed by measuring the enzyme activity in fetal red blood cells [222] and amniocytes or by determining the purine profile in amniotic fluid. The advantage of the latter is that purine levels are available within a short time after amniocentesis [100]. Assessing PNP activity in chorionic villi is an effective alternative that can be performed early in the course of pregnancy [100].

The thymus of patients with PNP deficiency is small; however, unlike most other types of SCID, occasional poorly formed Hassall's corpuscles can be demonstrated [95]. Lymph nodes seem depleted and lack paracortical fields. In most patients there is a low absolute lymphocyte count (frequently less than 500 cells/mL). T-cell function assessed by responses to mitogens and by skin test for Candida and other delayed hypersensitivity immunogens are reduced or absent [249, 295]. Decreased total lymphocytes and T-cells numbers were reported in PNP deficiency. In some patients, T-cell numbers and function fluctuate with time [222, 544], whereas in those with delayed presentation, mitogenic responses may be moderately reduced to normal [574]. Humoral immunity as assessed by B-cell number, immunoglobulin levels, and specific antibody formation are normal in most cases with PNP deficiency [128]. In a small group of patients, humoral aberrations including low levels of immunoglobulins, poor specific antibody production, reduced

isohemagglutinins [617] or monoclonal gammopathy were documented [538]. The number of NK cells varies among patients [283].

The differential diagnosis of PNP deficiency should particularly consider disorders that combine significant immune deficiencies and neurologic abnormalities, including A-T, zinc deficiency, and biotin-dependent carboxylase deficiency. Because a dysplastic marrow and anemia may be an early symptom of PNP deficiency [182], congenital hypoplastic anemia (Diamond Blackfan syndrome), transcobalamine 2 deficiency, and type I hereditary orotic aciduria, which may be associated with immunodeficiency, also should be considered in the differential diagnosis.

2.5.5 Management

The only available cure for patients with PNP deficiency is HSCT. There are a few reports of successful restoration of immune function in patients with PNP after HLA-matched sibling HSCT [43, 99]. Myeloablative conditioning is required in order to reduce the risk of rejection caused by residual immune function frequently documented in these patients. Conditioning regimens included cyclophosphamide and busulfan, without [43], or with ATG [167], or alternatively busulfan and fludarabine [124]. In the absence of a matched related donor, cord blood has been recently used successfully in a patient with PNP deficiency [459]. Whether these patients can benefit from matched unrelated donor marrow or cord blood transplants remains to be determined in a larger group of patients. In addition, HSCT may not reverse neurological manifestation as previously observed [43].

Regarding ADA deficiency, although HSCT is the treatment of choice, several patients benefit from enzyme replacement with PEG-ADA [42, 466].

When bone marrow transplant is unavailable, enzyme replacement using PEG-PNP could provide temporary remedy similar to the treatment of patients with ADA deficiency [295]. Its efficiency has been recently tested, demonstrating complete immune reconstruction of PNP-/- mice unfortunately, PEG-PNP is not commercially available [33]. Other future therapies such as enzyme replacement with TAT-PNP [659] or gene therapy are now undergoing pre-clinical studies.

In the past, several other modalities of therapy were proposed for PNP deficiency. Erythrocyte transfusions used as enzyme replacement were originally encouraging, but subsequently proved inefficient [621]. Other treatment including deoxycytidine and tetrahydrouridine [630, 695], guanine [695], adenine, uridine, and hypoxanthine [128, 621] showed no benefit. Attempts to restore immune function in patients with PNP deficiency with thymus transplant, or with thymosine fraction 5 were also unsuccessful.

Supportive treatment is warranted in patients with PNP deficiency, as in all immune deficiency states [222]. Immunoglobulin therapy should be considered in cases who have antibody deficiency or autoimmune manifestation [617].

The life expectancy of individuals with PNP deficiency has been poor. Most of the patients who did not receive a bone marrow transplant died during early childhood. The oldest reported patient reached the second decade of life [645]. Death has occurred from overwhelming infections, such as generalized chickenpox complicated by pneumonia and carditis, or pneumonia and chronic pulmonary disease. A high frequency of malignancy was also noted, including pharyngeal tumors, lymphoma, and lymphosarcoma [128, 429, 585].

2.6 AK2 Deficiency

2.6.1 Definition

Reticular dysgenesis (OMIM*267500) or AK2 deficiency is the most severe form of combined immunodeficiency, characterized by congenital agranulocytosis, lymphopenia. The disease was first described by de Vall and Seyneheve in 1959 [164]. The patients also suffer from lymphoid and thymic hypoplasia with absent cellular and humoral immunity functions.

2.6.2 Etiology

Reticular dysgenesis is due to mutations in the *AK2* gene (OMIM*103020), which is an adenylate kinase, a mitochondrial enzyme [364, 498].

2.6.3 Clinical Manifestations

In addition to severe infections that can be seen in other combined immunodeficiencies, affected newborns with AK2 deficiency have bilateral sensorineural deafness [364].

2.6.4 Diagnosis

Severe neutropenia as well as severe T- and NK-cell lymphopenia are characteristics for AK2 deficiency, while the B cell lineage could variably be affected [364].

2.6.5 Management

HSCT is the treatment of choice for those with AK2 deficiency. A recent study suggested potential use of antioxidants as a supportive therapeutic modality for these patients as well [545].

2.7 DOCK2 Deficiency

2.7.1 Definition

DOCK2 deficiency (OMIM*616433) is a very recently described autosomal recessive combined immunodeficiency, affecting T-cell number and function, with variable defects in B- and NK- cell function.

2.7.2 Etiology

DOCK2 deficiency (OMIM*616433) is due to homozygous or compound heterozygous mutations in the *DOCK2* gene (OMIM*603122). Five patients with DOCK2 deficiency have already been reported [175].

2.7.3 Clinical Manifestations

Patients with DOCK2 deficiency suffer from early onset severe invasive bacterial and viral infections.

2.7.4 Diagnosis

Three reported patients experienced invasive bacterial and viral infections, associated with T-cell lymphopenia and reduced *in vitro* T-cell proliferation, while remaining two patients also had B-cell lymphopenia, and poor antibody responses [175].

2.7.5 Management

HSCT is the treatment of choice in patients with DOCK2 deficiency. Two patients with DOCK2 deficiency died, while three who underwent HSCT, which was successful [175].

2.8 Immunoglobulin Class Switch Recombination Deficiencies Affecting CD40-CD40L

(CD40LG deficiency, CD40 deficiency)

2.8.1 Definition

Hyper IgM (HIGM) syndrome, originally termed "dysgammaglobulinemia" is immunodeficiency conditions, characterized by defective production of Ig requiring a switch process, i.e. IgG, IgA and IgE, whereas the IgM concentration is either normal or increased. Although rare cases of HIGM with autosomal recessive inheritance have been reported recently, most cases are inherited as an X-linked recessive trait and are due to a mutation in the CD40 ligand encoding gene [21, 35, 171, 231, 296, 348]. The gene responsible for some autosomal recessive forms was identified as CD40 [206]. The clinical and biological characteristics of both HIGM syndromes associated

with a defect in the CD40 ligand-CD40 interaction are very similar and point to the importance of this interaction in the immune response. These characteristics distinguish them from other HIGM with Ig CSR deficiencies (see Chap. 3 for more details) [203, 207, 484].

2.8.2 Etiology

The X-linked form of HIGM (XHIGM or HIGM1) syndrome (OMIM*308230) is due to a mutation in CD40 ligand (CD40L also called CD154). The *CD40L* gene (OMIM*300386), also called tumor necrosis factor superfamily 5, *TNFS5*) maps on the X chromosome region q26 and is organized in five exons and four introns. CD40L is a type II transmembrane glycoprotein 261 amino acids long that is mainly expressed on activated CD4 T lymphocytes as a trimer. The crystal structure of the extracellular part of CD40L shows that hydrophobic and hydrophilic residues are crucial for CD40 binding [327]. Different mutations of the gene have been described in a large number of patients, including missense mutations, deletion, insertions, nonsense mutations and splice site mutation [375, 486, 594]. Although the mutations described involve all parts of the gene, most of them are located in exon 5, affecting regions that are conserved in sequence analogy with tumor necrosis factor [486]. The majority of missense mutations described affect the folding and stability of the molecule rather than the CD40-binding site directly [327, 486]. There is no a clear phenotype–genotype correlation, however, some mutations allowing a residual binding of CD40 are associated with a less severe phenotype [148, 594]. Some rare cases of XHIGM have been described in girls secondary to a skewed X inactivation chromosome [162, 307].

In 2001, Ferrari et al. [206] identified *CD40* gene (OMIM*109535) mutation in three patients from two unrelated families with autosomal recessive HIGM syndrome (HIGM3) (OMIM:606843). It is a rare situation and less than 20 patients are reported [15, 326, 358, 395, 424]. So far, all patients described had homozygous mutations. CD40 is a type I transmembrane protein 277 amino acids long and is included in the TNF-R superfamily. CD40 is constitutively expressed on B cells, monocytes, macrophages, dendritic cells and non-hematopoietic cells. The *CD40* gene displays 9 exons. *CD40* mutations affect splice sites or consist of amino acid substitution or deletion. In most cases, CD40 is not expressed at the membrane level. However, recently a homozygous *CD40* deletion was described, including the stop codon, resulting presumably to a longer non-functional protein, which is detected at the membrane level.

The CD40-CD40L interaction plays a major role in the cross talk between immune cells. Engagement by CD40L induces CD40 signal transduction in B and dendritic cells. CD40 could already be trimerized independently of CD40L engagement by its pre-ligand-associated domain (PLAD) identified in the extracellular regions of TNFR members [113].I). The CD40L-CD40 interaction plays a crucial role in T cell-dependent B cell proliferation and differentiation in the presence of a second signal (such as IL-4 or IL10). It is consequently critical for germinal center formation and for the generation of a secondary antibody repertoire. The latter results from two main processes. First, there is class switch recombination that leads to the expression of different immunoglobulin isotypes. The second process consists of the somatic hypermutations characterized by a high rate accumulation of point mutations in the V regions of Ig genes and allows the selection of B cells bearing a high affinity antigen specific BCR. Altogether, these processes lead to high affinity antibody production and to the generation of memory B cells and of long-life plasma cells. Although rare somatic mutations can be detected in IgM-bearing B lymphocytes [700], the main consequence of a defect in CD40/CD40L interaction is the absence of generation of a secondary antibody repertoire. However, several sources of evidence indicate that XIGM1 and HIGM3 are not solely a humoral immunodeficiency. CD40 triggering also plays a central role in T cell mediated activation of monocytes-dendritic cells [18, 104, 223, 315]. Engagement of CD40 on dendritic cells leads to their maturation and the secretion of IL-12 a cytokine with a major role in TH1 immunity.

Failure to produce IL-12 and thereby interferon γ [108] is a likely event in the T cell immunity defect observed in HIGM affecting CD40-CD40L interaction.

2.8.3 Clinical Manifestations

This section summarizes the clinical manifestations observed in HIGM1 patients; the disorder has been recognized since 1993 and has been the object of many reports [375, 380, 710]. However, the clinical manifestations observed in the patients with HIGM3 are very similar [15, 206, 326, 395, 424].

In most cases, age at the time of diagnosis is between 3 months and 2 years and the clinical presentation evokes a combined immunodeficiency. However, it seems that variability in susceptibility to opportunistic infection in HIGM1-deficient patients could exist since some patients develop such infection early in life while others do not, at least not until adulthood.

The most common clinical manifestations observed in HIGM-1 patients are infections, especially infections involving the respiratory tract. First of all, the pneumonias that occur in more than 80 % of patients, and *pneumocystis jiroveci,* accounts for most of the cases in infancy. It is noticeable that this infection is the first manifestation of the disease in over one-third of patients. The occurrence of such an infection in a young patient has to evoke this diagnosis, especially if hypogammaglobulinemia is associated. Lung infections can also be due to viruses including CMV, adenovirus, herpes simplex or bacteria such as *pseudomonas* or *staphylococcus*. Finally, mycobacteria including bacillus *Calmette-Guerin* (BCG) and fungi such as *Histoplasmosis* and *Cryptococcus* can be responsible for lower respiratory tract infections. Upper respiratory tract infections including sinusitis and otitis are also common and affect more than 40 % of patients.

Gastrointestinal problems also affect over 50 % of patients. These problems are often of infectious origin especially due to *Cryptosporidium.* Diarrhea associated with *Gardia lamblia, Salmonella* or *Entamoeba histolytica* have been reported [380]. Inflammatory bowel disease and intestinal hyperplasia may cause chronic diarrhea in some patients. The intestinal problems follow a chronic course leading to failure to thrive, and parenteral nutrition is required. The liver is often affected. The common lesion is sclerosing cholangitis that is most often related to *Cryptosporidium* infection and that may require liver transplantation. Hepatitis has been reported either with or without a proven viral etiology. As with other immunodeficiencies, the risk of neoplasm, especially lymphoma, is increased. But in HIGM1 the risk of neoplasm also includes carcinomas affecting the liver, pancreas, biliary tree [293, 380, 462]. These observations suggest that physiological CD40 expression on regenerating or inflamed bile duct epithelium could play a role in triggering local immune response. [293].

The most typical hematological abnormality is neutropenia that is observed in over 60 % of patients. It is usually chronic and can be exacerbated by infectious episodes and be associated with oral ulcers and gingivitis. Chronic infections can lead to anemia, but some of them are related to Parvovirus B19 infection [61].

Neurologic problems including meningitis and encephalitis have also been reported. Despite the frequent absence of identification, several organisms are involved such as Toxoplasma, Cryptococcus and Mycobacteria [380]. Moreover, viruses including enterovirus and JC virus are responsible for some neurological features [284, 639].

Some cases of arthritis, nephritis and hyperparathyroidism have been reported. The osteopenia observed in some patients suggests a regulatory role for CD40L in bone mineralization [393].

2.8.4 Diagnosis

The characteristic serum Ig profile observed in HIGM1 and HIGM3 consists in markedly decreased serum IgG, IgA and IgE and normal to increased IgM levels. Indeed, a normal IgM level is observed at the time of diagnosis in around 50 % of the patients, especially in young patients

[380]. However, nearly 70 % of patients will present a Hyper IgM during their lifetime. In some cases, the level of IgG, which is generally very low, can reach normal values. In the same way, some patients present normal or high IgA level as well as IgE. These near normal immunoglobulin profiles, sometimes associated with an antibody response to T cell-dependent antigens, could be associated with a milder phenotype [61, 148].

In both HIGM1 and HIGM3, T-cell counts were generally normal, although a low proportion of CD45R0 memory T cells is frequently observed [315]. Whereas total B cell count is normal in most cases, the B cell population is characterized by the lack of B cells that do not express IgD and that express CD27, which correlates with the failure of class switch recombination and of somatic hypermutation processes [5, 326, 395].

The screening assay for diagnosis of HIGM1 is based on the absence of CD40 binding on the patient's activated T cells. Usually, T-cell activation is driven by the association of phorbol ester and ionomycin, and the expression of a functional CD40 ligand is revealed by binding fluorescent chimeric CD40-Ig molecules assessed in flow cytometry. Some monoclonal fluorescent anti-CD40L antibodies which recognize the binding site of CD40 can be used cautiously for the diagnosis [375]. However, some CD40L mutations associated with milder phenotypes allow a residual CD40 binding and the level of fluorescent intensity has to be taken into consideration for a suitable interpretation. Moreover, when a defect of CD40 binding is detected, it is important to rule out a T cell activation defect which could lead to an absence of CD40Ligand expression without intrinsic defect in this molecule. The final diagnosis requires CD40L molecular analysis. Carrier detection in females has to be performed by direct sequencing when the searched-for mutation is known. Therefore, prenatal diagnosis can be offered by using a chorionic Villi biopsy taken at week 8–10 of pregnancy. Direct mutation identification, if known in the family at risk, or an intragenic polymorphic marker can be used [172].

The screening assay for the diagnosis of HIGM3 was founded on the absence of CD40 expression assessed by immunofluorescence. However, some mutant proteins can be expressed and recognized by monoclonal antibodies. Then, the diagnosis of CD40 deficiency requires genetic analysis.

2.8.5 Management

The treatment included immunoglobulin substitution that resulted in a marked decrease of upper and lower respiratory tract bacterial infections. In some cases, immunoglobulin replacement therapy also led to the resolution of lymphoid hyperplasia when it existed before treatment. Under immunoglobulin treatment, IgM level often drops to normal value. The neutropenia is also frequently corrected by this substitution. However, in some patients presenting severe and symptomatic neutropenia, treatment by granulocyte-colony-stimulating factor has been given, successfully in most cases. Depending on the frequency and the severity of opportunistic infection, especially by *Pneumocystis jiroveci,* a prophylactic antibiotherapy using trimethopim-sulfamethoxasazole is recommended, especially when the patient had presented a previous episode of opportunistic infection. In spite of these preventive measures, the survival rate is still poor, although variable from one series to another. An important cause of death is still opportunistic infections, including *Pneumocystis jiroveci,* CMV and mycobacteria. But it is noticeable that severe liver disease is responsible for many deaths, particularly in the European cohort. Indeed, in the US registry, these complications seem to be less frequent. This could reflect a lower incidence of *Cryptosporidium* infection. Neoplasm complications are also an important element in the prognosis. Consequently, more aggressive treatment such as HSCT has to be considered. Indeed, HSCT using either bone marrow from familial HLA identical [69, 314, 652] or matched unrelated donors [25, 244, 336, 380] or cord blood [735] has been performed in patients with HIGM1 with an overall cure rate of 58 %. Recently, a haploidentical T-cell depleted peripheral blood stem transplantation has been performed successfully

in a patient. Injection of donor T lymphocytes reverted a mix chimerism characterized by an increasing proportion of autologous cells [317]. The absence of preexisting liver or lung disease and an HSCT from HLA-matched sibling or closely mated unrelated donor may increase the success rate. [528, 535]. A careful follow-up of the lung and liver functions, with regular screening for *Cryptosporidium* infection and the monitoring of the neutropenia could allow proposing HSCT to at-risk patients before complications that constitute a pejorative factor especially when matched related donor is not available. According the CD40 expression on non-hematopoietic cells, stem cell transplantation as treatment in HIGM3 patients is more uncertain. However, three out of four patients with HIGM3 who received HSCT has been cured [15, 357, 424].

Recently, patients received therapeutics targeting the CD40 using either recombinant CD40 ligand or agonist anti-CD40 antibody [204, 316]. In the three patients treated by recombinant CD40 ligand, whereas the capability of T lymphocytes to synthesize IFN-γ and TNF-α was improved, the specific antibody response was not corrected. However, the architecture and size of lymph nodes changed, with an expansion of follicular dendritic cells, but no germinal center was observed. The decrease of the *Cryptosporidium* burden detected in two patients treated by agonist anti-CD40 antibody could be related to the improvement of the production of TNF-α and IFN-γ by T-cells. Perhaps, these treatments would open a new avenue allowing limitation of complications due to infections and consequently to perform HSCT in better conditions.

2.9 Complete DiGeorge Syndrome

2.9.1 Definition

Di George syndrome (DGS, OMIM*188400) is a developmental disturbance of neural crest occurring during the embryogenesis and is attributed to the haploinsufficiency of one or more of the genes located on the chromosomal region 22q11.2 [2, 153, 334]. This condition was first described by Angelo DiGeorge in 1965 as the association of immunodeficiency and congenital absence of thymus gland which had been noted early in the twentieth century [132]. The syndrome is classically defined as a congenital T-cell immunodeficiency secondary to aplasia or hypoplasia of the thymus gland associated with congenital heart defects and hypocalcaemia, due to small or absent parathyroid glands. The most common cause of the syndrome is a hemizygous deletion of 22q11.2, seen in approximately 90 % of DGS patients and may occur as frequently as once in 4000–6000 live births, affecting both sex equally [169]. It is one of the most frequent genetic diseases, considering that it may be underestimated because of the rate of perinatal deaths observed in many cases with a severe congenital heart defect.

The fact that same deletion has been linked to a heterogeneous group of disorders with an overlapping phenotype has led to further expansion of clinical spectrum of DGS. Although each presentation is very different, it is important to remember that these are not distinct disorders, but represent points along the continuum of the same genetic disease, more appropriately named *chromosome 22q11.2 deletion syndrome*.

DGS was originally distinguished from the other overlapping diseases because of a prominent component of immunodeficiency. It is known that defect in the immune system is seen in all patients with the deletion despite the other clinical features. However, the term *chromosome 22q11.2 deletion syndrome* should be used to describe patients where the deletion has been confirmed, whereas DGS is typically used for both patients with 22q11.2 deletion and those affected by the clinical triad of cardiac defects, immunodeficiency, and hypocalcaemia, but without a demonstrable deletion.

2.9.2 Etiology

DGS is characterized by malformations attributed to abnormal development of the pharyngeal arches and pouches. The common threat among all the organs involved in DGS is that their

development is dependent on migration of neural crest cells to the region of pharyngeal pouches. *Lammer and Opitz* described DGS as a field defect in which a group of tissues, that are interdependent on each other for normal growth, develop in an abnormal fashion [64, 339]. Although DGS has traditionally been described as abnormal development of the third and fourth pharyngeal pouches, defects involving the first to sixth pouches are also known to occur. Animal studies have shown that acute ethanol exposure in mice at a time when neural crest cells are migrating results in a craniofacial phenotype similar to DGS [696]. Exposure to teratogens during pregnancy, including alcohol, retinoids, bisdiamine, can result in similar phenotypic syndromes [264, 696]. Thus, it is postulated that any intrauterine insult to the facial neural crest can result in similar features of DGS.

A 3-Mb deletion within 22q11.2 is present in majority of cases, with a smaller 1.5-Mb deletion found in less than 10% and some unique smaller deletions in a few number of cases [198, 595]. Most deletions are de novo, with 10% or less inherited from an affected parent. At least 40 genes have been identified within this region. In spite of efforts to identify candidate gene(s), no single gene deletion has been shown to be sufficient for the development of DGS. Consequently, it is possible that more than one gene could contribute to the phenotype since DGS patients with different type of deletions have similar phenotypes.

Among the most investigated genes, *TUPLE1* (TUP-like enhancer of split gene-1) (OMIM*600237), reported by Halford et al. [282], is an attractive candidate for the central features of the syndrome. It shows evidence of expression during the critical period of development of the outflow tract of heart, and of the neural crest derived aspects of face and upper thorax.

Moreover, *TBX1* (OMIM*602054), encodes for a "T box" transcription factor, is involved in the regulation of developmental processes, and is mostly affected in the majority of DGS patients [45, 153]. Yagi et al. identified 3 mutations within *TBX1* in unrelated patients with 22q11.2 syndrome phenotype, but no detectable deletion in 22q11.2 [719]. One mutation was found in a case of sporadic velocardiofacial syndrome/conotruncal anomaly face, and a second in a sporadic case of Di George syndrome. The third mutation was shown in 3 patients from a family with velocardiofacial syndrome/conotruncal anomaly face. These findings indicated that *TBX1* mutations were responsible for five major phenotypes of the 22q11.2 syndrome, namely, abnormal facies (conotruncal anomaly face), cardiac defects, thymic hypoplasia, velopharyngeal insufficiency of the cleft palate, and parathyroid dysfunction with hypocalcaemia. These mutations did not appear to be responsible for typical mental retardation that is commonly seen in patients with the deletion form of 22q11.2 syndrome.

Other implicated genes include *Crkl* and *COMT* genes. *Crkl* encodes an adaptor protein, which is highly expressed in neural crest derived tissue during development. *Crkl*$^{-/-}$ mice die in uterus, whereas heterozygous ones survive [275, 387]. Catechol-*O*-methyltranferase (*COMT*), also located within the commonly deleted region [270], is involved in the metabolism of catecholamines. The V158M polymorphism (*COMT*158^{met}) seems to result in decreased enzyme activity and to be associated with the development of psychiatric disease in patients with *chromosome 22q11.2 deletion syndrome* [264, 362]. In contrast, some studies have shown that patients carrying the *met* allele have a better cognition performance and that *COMT* V158M polymorphism affects minimally the executive function in 22q11.2 deletion syndrome [254, 598]. Deletions on the short arm of chromosome 10 p13-14 are also associated with a DGS-like phenotype, but are much less common than 22q11.2 deletions with an estimated frequency of 1 in 200,000 live births. Other chromosomal abnormalities that have been found in patients with presumed DGS include deletions on chromosomes 17p13, and 18q21 [267].

2.9.3 Clinical Manifestations

Although many reports have greatly contributed to the understanding of the clinical features and the pathophysiology of the disease, the DGS phenotype is much more variable and extensive than

initially recognized, and several aspects still need to be clarified [49, 75, 132, 391, 456, 570, 671].

DGS has commonly been characterized as a triad of clinical features: congenital cardiac defects, immunodeficiency and hypocalcemia. A variety of cardiac malformations are seen, in particular affecting the outflow tract. These include tetralogy of Fallot, type B interrupted aortic arch, truncus arteriosus, right aortic arch and aberrant right subclavian artery.

Moreover, newborns and infants with DGS may have dysmorphic facial features. Ears are typically low set and deficient in the vertical diameter with abnormal folding of the pinna. Telecanthus with short palpebral fissures is seen. Both upward and downward slanting eyes have been described. The philtrum is short and the mouth relatively small. In older children the features overlap velocardiofacial (Shprintzen) syndrome with a rather bulbous nose, square nasal tip and hypernasal speech associated with submucous or overt palatal clefting.

Neonatal hypocalcaemia, due to hypoplasia of the parathyroid glands, is characteristic and may be sufficiently severe to present as tetany or seizures. However, it could be intermittent and resolve during the first year of life as the parathyroid glands hypertrophy. Latent hypoparathyroidism may occur in both children and adults [141].

Feeding difficulties and gastroesophageal reflux are also described. Renal abnormalities such us single kidney, multicystic dysplasic kidney, horseshoe kidney, and duplicated collecting system occur in approximately one-third of DGS patients. Short stature and variable mild to moderate learning difficulties are common. Other clinical features seen more rarely include hypothyroidism and deafness. Cases presenting later, tend to have a milder spectrum of cardiac defect with ventricular septal defect being common.

Various psychiatric disorders have been also described both in children and adults [248, 640]. Different behavioral, psychiatric, and communication disorders include attention deficit-hyperactivity disorder (ADHD), anxiety, language and speech delays, and affective disorders. An estimated 25 % of children with *22q11 deletion syndrome* develop schizophrenia in late adolescence or adulthood. A recent study on 112 individuals aged 8–45 years revealed diagnoses of psychosis in 11 % of cases with a peak occurrence of psychosis risk during adolescence [646]. Neurological abnormalities consist of structural brain anomalies (small vermis, small posterior fossa and small cysts adjacent to the anterior horns) and increased risk of developing seizures, in a minority polymicrogyria and periventricular nodular heterotopia have been observed [27, 439].

Thymic hypoplasia or aplasia leading to defective T-cell function is the hallmark of DGS. Patients with the chromosome 22q11.2 deletion have a broad range of T-cell counts and proliferative responses. Complete absence of thymus ('complete' DGS) accounts for less than 0.5 % of patients and exhibit a severe T-cell immunodeficiency, resembling a SCID phenotype. In 'complete' DGS few T cells are detectable in peripheral blood (1–2 %) and there is no response to T cell mitogenes. T-cell receptor excision circles (TRECs), as a measure of newly emigrated thymic cells, are reduced [292].A recent report has described two patients with absent T cells and DGS associated with 22q.11 deletion and carrying pathogenic mutations in the DCLRE1C (Artemis) gene [294]. Since TRECs are absent or low in complete DGS, newborn screening using TREC detection is useful for early diagnosis of the disease and for the prevention of infections [359, 564].

In contrast, the majority of patients with *22q11.2 deletion syndrome* and immune defects exhibit mild to moderate deficits in T cell numbers (so-called 'partial' DGS). Immunodeficiency in these patients is not caused by the absence of thymus, but due to abnormal thymic migration. Many patients have microscopic nests of thymic epithelial cells that account for their ability to produce T cells. A normal-sized thymus is not necessary for normal T cell development, and patients with a very small thymus, even in an ectopic location, may have a T cell response to mitogens that ranges from below normal to normal. As such, total T cell numbers may not accurately reflect immune [411]. The majority of

'partial' DGS patients have normal T cell proliferations, although some patients show low mitogen responses. Therefore, mitogen responsiveness should be considered the most important parameter to assess T cell function and to better discriminate DGS as 'partial' or 'complete'.

Most DGS patients have normal antibody levels, function and avidity. The aberrant regulation of B cells by the deficient T cells might also result in hypergammaglobulinemia. On the other hand, hypogammaglobulinemia, IgA deficiency, delayed acquisition of appropriate anti-tetanus and anti-diphtheria antibody titers have been described as well. In a cohort, 55 % of patients showed impaired specific antibody responses to pneumococcal polysaccharide antigen [242]. Impaired T–B cell interaction is likely to explain the defective T-dependent antibody responses. In another study 43 % of patients exhibited evidence of antibody deficiency (IgA deficiency, IgM deficiency, IgG subclass deficiency or specific antibody deficiency) and a significant correlation between the presence of recurrent infections and humoral abnormalities ($P<0.01$) was found. $CD27^+$ memory B cell subsets were reduced in patients with defective humoral immunity [215]. A recent study performed on over 1000 patients of partial DGS with a median age of 3 year, showed that 2.7 % were under immunoglobulin replacement. In the over 3 years age group, 6.2 % had IgG levels below 5 g/l. Amongst patients over 3 years of age, around 0.7 % had complete and 1 % partial IgA deficiency, while 23 % had low levels of IgM [506]. There was not association between low T cells counts and Immunoglobulin levels in any of the isotypes. Unfortunately this study did not evaluate the B cell numbers, although previous studies reported to be normal or sometimes low but normalizing during life [321]. The repertoire of IgH usage is normal; however, further studies are needed to clarify whether abnormalities in somatic hypermutation might occur.

Patients with DGS who present with infections as the first manifestation are unusual because cardiac malformations and hypocalcaemia are so severe that they usually manifest in the neonatal period. In fact, most of the early deaths are due to cardiac defects. However, recurrent infections are a major problem and an important cause of later mortality. Increased susceptibility to infections, caused by organisms typically associated with T-cell dysfunction, is observed. These include systemic fungal infections, *Pneumocystis jiroveci* infection, and disseminated viral infections [410, 581]. Moreover, the combination of impaired immune response and abnormal palatal anatomy may be associated with high frequency of upper respiratory tract infectious.

Immunodeficiencies are frequently associated with autoimmunity, and the incidence of autoimmune disorders is increased in Di George syndrome as well [318]. In one study of 20 patients with 22q11.2 deletion syndrome, 10 % had evidences of autoimmune disease [242]. In particular, autoimmune cytopenias [150, 379], juvenile rheumatoid arthritis–like polyarthritis [637] and autoimmune endocrinopathy [151] have been described. A number of immune defects may predispose to the development of autoimmunity in these patients including increased infection, persistent antigen stimulation. However, in partial DGS autoimmunity is not predominantly found in those with the most severe or frequent infections [433]. It is more likely that defective central tolerance or impaired development of natural $CD4^+CD25^+$ T-regulatory cells may have a role in predisposition to autoimmunity. Controversial data are reported in literature on peripheral tolerance. Indeed, one study performed on partial DGS patients demonstrated a significant decrease in the percentage of $CD4^+CD25^+$ T cells when compared to normal control, which was most marked in infancy. Another study reported $CD4^+$ $CD25^+$ cells in patients with pDGS. However, no difference was observed in the percentage of $CD4^+CD25^+$ T cells in *22q11.2 deletion syndrome* patients with and without evidence of autoimmune disease [636]. Abnormal thymic development in DGS may thus result in impaired expression of autoimmune regulator gene (*AIRE*) and potentially of other transcription factors that regulate expression of organ-specific antigens in the thymus, resulting in defective central tolerance [105, 150]. However, so far any report indicates

defect in AIRE expression in thymic tissue from partial DGS cases and indeed, since autoimmune disease is limited to one or two organs in patients with partial DGS, it is likely that negative selection most occur to most antigens [150].

There is a wide range of phenotypic variability associated with the *22q11.2 deletion syndrome* as conotruncal anomaly face (Takao syndrome), and isolated outflow tract defects of the heart. While some patients present with classic findings of DGS, others have relatively slight features such as minor dysmorphic facial traits or mild cognitive impairment. Consequently, none of the phenotypic features is considered pathognomonic for the *22q11.2 deletion*. Furthermore, the deletion does not predict the organ effects or disease severity and the phenotypic expression does not seem to be related to the deletion size, to date. In addition, there are many published examples of affected kindreds demonstrating that the clinical presentation can be broadly different even within a single family [330, 373].

2.9.4 Diagnosis

The dysmorphic facial appearance, in an individual with a major outflow tract defect of the heart or a history of recurrent infection, should raise suspicion. In infancy, hypocalcaemia, a characteristic feature, is usually evident with low parathyroid hormone (PTH) levels. Chest radiography may detect an absent thymic shadow, although this finding does not always correlate with immune function. Newborns should be evaluated for T cell production and function. A complete blood count (CBC) and the measurement of the CD4+ subset of T cells can assess the presence and severity of lymphopenia. Meanwhile it is important to evaluate T cell proliferative responses and not merely the number of T cells. *In vitro* studies of T cell function offer the most reliable estimate of the extent of immunodeficiency. Evaluation of humoral immunity reveals variable immunoglobulin levels and depends on the degree of T cell deficiency. Patients with partial DGS generate good antibody response to protein vaccines [40].

The investigation of choice is a standard karyotype to exclude major rearrangements, and fluorescence in situ hybridization (FISH) using probes within the deletion segment, preferably those close to the translocation breakpoint site. A 10p13-14 FISH study should also be considered if there is clinical evidence for DGS, but negative 22q11 FISH study. A positive FISH test for chromosome 22q11.2 deletion or a 10p deletion ascertains the diagnosis. For patients without the deletion diagnosis is based on the clinical phenotype, although precise diagnostic criteria are difficult to establish [75, 428, 570, 671] (Table 2.1). Parents should be screened for carrier status.

Table 2.1 Diagnostic criteria for *PARTIAL* and *COMPLETE* Di George Syndrome

Type of syndrome	Diagnostic category	Description
PARTIAL Di George Syndrome	Definitive	<500/mm^3 CD3+ T cells during the first 3 years of life, conotruncal cardiac defect and/or hypocalcemia possibly associated with chromosome 22q11.2 deletion.
	Probable	<1500/mm^3 CD3+ T cells during the first 3 years of life and deletion of chromosome 22q11.2
	Possible	<1500/mm^3 CD3+ T cells during the first 3 years of life associated with cardiac defect or hypocalcemia or dysmorphic facies/ palatal abnormalities.
COMPLETE Di George Syndrome	Definitive	Reduced/absent CD3+ T cells (less than 50/mm^3) and documented athymia, hypocalcemia and heart defect.

Adapted from: European Society for Primary Immunodeficiencies, DiGeorge Syndrome diagnostic criteria, Clinical Working Party

2.9.5 Management

The non-immunologic features of DGS often require a coordinated medical management early after birth. Calcium supplements and 1,25-cholecalciferol may be needed to treat hypocalcaemia. Cardiac defects are the usual focus of clinical management. Asymptomatic infants, where other features suggest the diagnosis, should be investigated with early echocardiography to search for cardiac defects. Unless the immunocompetence has been demonstrated, any affected child is at risk for opportunistic infections and should receive prophylaxis for *Pneumocystis jiroveci* pneumonia. Moreover, if undergoing major surgery, they should have a supply of irradiated blood to avoid graft-versus-host disease. Clefts may be submucous and should be sought. Speech therapy and additional educational assistance may be needed.

Several approaches have been attempted over time to achieve an immune reconstitution. Implantation of whole thymus was first described by Cleveland et al. in 1968. Later, several other trials of fetal thymic tissue implantation were performed [423, 656]. Recently success has been reported using allogeneic, partially HLA-matched postnatal thymus tissue to transplant infants with the complete DGS [411, 412].Thymic tissue is obtained from cardiac surgery and kept in culture for 2–3 weeks prior to transplantation that is performed into the quadriceps muscle of the patient [150].Two trails are currently ongoing and so far, of 60 patients treated the survival was 72%. Death after transplant is caused by systemic viral infections such as cytomegalovirus and chronic lung disease. Transplanted thymi show a normal morphology and in patients with successful transplantation, patients develop host derived naïve T cells with normal T cell repertoire, normal mitogen responses and a normalization of the TCR repertoire in circulating regulatory T cells [120]. However, there are other disappointing reports for thymus transplantation. In particular, development of autoimmunity represents the main problem, mainly hypothyroidism and immune-cytopenias [413] and importantly autoimmune signs mimick the spectrum of autoimmunity observed in partial DGS.

In complete DGS, bone marrow and peripheral blood T-cell transplantation from HLA-matched sibling donor has been also efficacious [57, 74, 259, 421]. Long term survival has been reported but with low rate (41–48%), as compared with survival after HSCT [245]. Mortality is referred to graft versus host disease or viral infections.

The prognosis of DGS patients varies significantly according to the degree of involvement of the cardiac and immune system. Heart problems are the major cause of deaths early in childhood and opportunistic infections are the second most fatal complication. In most children who survive, the number of T cells rises spontaneously as they mature. Children who were successfully bone marrow or peripheral blood transplanted as well as those who received thymus transplant and achieved a good immune reconstitution, remained free of infections long time after. Survivors are likely to be mentally retarded and to have other developmental and neurologic difficulties in later life.

2.10 CHARGE Syndrome

2.10.1 Definition

CHARGE syndrome (OMIM*214800) is association of Coloboma, Heart anomaly, choanal Atresia, Retardation, Genital and Ear anomalies.

2.10.2 Etiology

De novo heterozygous mutation in the CHD7 gene (OMIM*608892), on chromosome 8q12, resulting in haploinsufficiency has been reported in CHARGE syndrome [166, 582]. There is also a report showing that heterozygous in the SEMA3E gene (OMIM*608166), on chromosome 7q21, could cause this syndrome [366].

2.10.3 Clinical Manifestations

Coloboma of eye, heart anomaly, choanal atresia, mental retardation, microphallus, and abnormalities of ear are the main features of CHARGE

syndrome. Some other anomalies such as facial palsy, cleft palate, and dysphagia are also common.

2.10.4 Diagnosis

Distinctive clinical phenotype could help in making the diagnosis. Four major signs of diagnostic criteria are coloboma, choanal atresia, characteristic ear anomalies, and cranial nerve involvement [62, 675]. Various defects of thymus and associated T cell abnormalities have been reported in cases of with CHARGE syndrome [713].

2.10.5 Management

A combination of medical and surgical care is needed in patients with CHARGE syndrome [302].

2.11 Combined Immunodeficiency with Alopecia Totalis (WHN Deficiency)

2.11.1 Definition

The Combined Immunodeficiency with Alopecia Totalis due to FOXN1 deficiency (OMIM*601705) constitutes the human counterpart of the nude mouse.

2.11.2 Etiology

In 1994, the genetic basis of the well-known, "nude" mouse, associating hairlessness and congenital athymia, was reported for the first time. It involves a new gene, Winged Helix – Nude *whn* (also called *Foxn1*), and consists in a single base deletion in exon 3. This frameshift mutation leads to a predicted aberrant protein.

The protein FOXN1 is a member of the forkhead/winged-helix transcription factor family. It is mainly expressed in thymus epithelia and in skin [468] and plays a crucial role in the differentiation of thymic epithelial cells (TEC) [632] as well skin epithelial cells [434]. FOXN1 is involved in the morphogenesis of the three dimensional thymic structure and the development of cortical and medullary TEC is FOXN1-dependent in fetal life [555]. The expression of FOXN1 could be upregulated by wingless (wnt) proteins which play an important role in cell-fate specification [44, 555, 556, 662]. The mutation observed in nude mice leads to a protein deprived of the DNA binding domain.

Five years later, in 1999, J. Franck et al. identified a homozygous mutation of the human gene *FOXN1* (OMIM*600838), localized on the chromosome 17, in two siblings. This mutation, R255X, is a nonsense mutation and predicts complete absence of functional protein [225]. The two patients were born from consanguineous parents in a small community in southern Italy. It was secondarily shown that this mutation is present in 6.52 % of this population, and is related to a single ancestral origin [4]. More recently, this mutation has been found in another patient born from consanguineous Portuguese parents. Another FOXN1 homozygous mutation has been found in deficient patient born from mixed French/African parent. This missense mutation, C987T (R320W) alters the DNA binding site of the proteins [17, 414]. The study of a FOXN1 deficient fetal thymus confirm that *FOXN1* mutation abrogate prenatal T-development [677]. A novel *FOXN1* mutation has also been reported, resulting in SCID phenotype [122].

2.11.3 Clinical Manifestations

In the patients reported, alopecia affecting the scalp, the eyebrows and the eyelashes associated with nail dystrophy was noted at birth, as well as bilateral epicantal fold in two patients [414, 516].

Subsequently, between 2 and 4 months of age, they developed immunodeficiency symptoms. The first one had with a clinical picture mimicking Omenn's Syndrome, including erythroderma, diarrhea and hepatosplenomegaly, and died

at 12 months of age following recurrent infections and severe failure to thrive. Two patients developed erythrodermia probably related to the presence of circulating T lymphocytes. One out four patients reported had BCG invasion after vaccination and another one, a HHV6 infection associated with anemia and neutropenia. These two patients received thymus transplantation.

It is noticeable that in a FOXN1 deficient fetus, anencephaly and spina bifida were found to be associated with the absence of thymus [23].

2.11.4 Diagnosis

Only one patient had a total absence of T lymphocyte [414]. The others displayed a T-cell lymphopenia affecting mainly the CD4 population. However, in one patient who had a moderate lymphopenia, the non-maternal circulating T-lymphocytes, predominantly double negative CD4-CD8- displayed a restricted repertoire, and no TREC was detected consistent with the absence of naïve CD45RA T-lymphocytes like in atypical SCID or atypical DiGeorge syndrome. B and NK cell populations are present at normal or high level. Proliferations induced by PHA or anti-CD3 monoclonal antibody are variable from one patient to another.

2.11.5 Management

One out of the two patients received non depleted HLA identical bone marrow transplantation from her healthy heterozygous brother, with successful engraftment [517]. CD4 and CD8 T lymphocytes increased promptly and are stable 6 years later. However, the CD4 T population displays only a memory phenotype CD45RO. This suggests that, as expected, CD4 recovery mainly results from the expansion of graft T lymphocytes.

Moreover, the Vβ repertoire of CD4 lymphocytes is similar in the donor and the engrafted patient. Conversely, the prompt recovery of naïve CD45RA CD8 population suggests extrathymic lymphopoiesis. However, CD8 compartment reconstitution is poor as judged by restricted TCR-Vβ diversity. T cell proliferation restored early after transplantation has further decreased to reach 20 % of the normal value. In spite of this incomplete immune T reconstitution, humoral immunity is restored as judged by the production of specific antibodies after immunization, especially with antigen unknown by donor. However, the patient is free of infections at 6-year follow-up.

Taking advantage of the experience of thymus transplantation in DiGeorge syndrome, two patients with *FOXN1* mutation received this treatment at 14 and 9 months of age. The first patient, who had an atypical picture, received treatment with cyclosporin, steroids, rabbit antithymocyte globulin and daclizumab before the procedure. The second patient who had no circulating T-lymphocyte did not receive any immunosuppression treatment before transplant [414]. In both patients, the immune reconstitution evaluated at 5 and 2.9 years, respectively, after transplantation is characterized by the presence of naïve T-lymphocytes, diversified TCR repertoire, normal T-cell proliferative response, normal immunoglobulin levels and normal specific antibody response. As observed in some DiGeorge patients after thymus transplantation, one patient developed an autoimmune thyroid disease at 1.6 years after transplantation [412].

2.12 Combined Immunodeficiencies with Immuno-Osseous Dysplasias

(Schimke syndrome, Cartilage hair hypoplasia)

2.12.1 Definition

Immuno-osseous disorders are a heterogeneous group of disorders, characterized by combined abnormalities in immune and skeletal systems. These disorders are manifest at birth mainly because of skeletal abnormalities; however, there are variants that may present later in life (Table 2.2).

Table 2.2 Comparing the facts between schimke immuno-osseous dysplasia and cartilage-hair hypoplasia.

	Schimke immuno-osseous dysplasia	Cartilage-hair hypoplasia
Responsible gene	SMARCAL1	RNase RMRP
Chromosomal Locus	2q34-q36	9p21-p12
Inheritance	Autosomal Recessive	Autosomal Recessive
Stature	Mainly short neck and trunk	Mainly short limb dwarfism
Skin	Multiple hyperpigmented macules (Lentigines)	Hypopigmented skin with dysplastic, foreshortened nails
Skeletal system	Spondyloepiphyseal dysplasia, Dysplastic hips, Small capital femoral epiphysis	Chest deformities with flaring of ribs, Fixed flexion deformity in elbow, Long distal fibula, cone shaped epiphysis in the phalanges
Immune System	Lymphopenia, T-cell involvement, SCID (infrequently)	Lymphopenia, T-cell involvement
Infections	Recurrent fungal, viral and bacterial infections. Opportunistic infections	Mainly viral infections, Varicela and sever herpes infections
Kidneys	Proteinuria, FSGN, Renal failure in childhood	Not reported in literature
Hematopoietic system	Bone Marrow failure (very infrequent)	Defective erythropoiesis (spontaneous remission on adulthood), Diamond-Blackfan Aplastic Anemia
Cardio-vascular system	Early onset severe atherosclerosis, Ischemic attacks in childhood, Hypertension	Not reported in literature
Other organs/systems	Specific facial and habitual features, involvement of eyes, teeth, azospermia, Endocrine abnormalities	Hematopoietic malignancies, Hirschprung's disease, Splenomegaly, Dental abnormalities

Schimke syndrome or Schimke Immuno-Osseous Dysplasia (SIOD, OMIM*242900) was first classified as a new lysosomal storage disease by Schimke in 1974 [588]. He described a 6-year old girl with spondyloepiphyseal dysplasia, progressive renal failure, lymphopenia and signs of defective cellular immunity. The increased amounts of urinary chondroitin 6-sulphate, led him to speculate the condition as a new presentation of mucopolysaccharidosis, which was not confirmed in later studies [67, 619]. SIOD is an autosomal recessive multisystem disorder with invariant defining features of spondyloepiphyseal dysplasia, progressive proteinuria leading to renal dysfunction [66, 67, 584, 588]. T-cell immunodeficiency is frequently observed, associated with opportunistic infections, autoimmune diseases and non-Hodgkin's lymphoma [48, 66, 734].There are some other features, which are variable among patients, including hypothyroidism, bone marrow failure, numerous cutaneous lentigines, early-onset cerebral ischemic attacks, migraine type headaches, and peculiar faces [66, 67, 170, 196, 337, 584, 619].

Metaphyseal Chondrodysplasia, McKusick type, also known as Cartilage Hair Hypoplasia (CHH, OMIM*250250), was first described 1965 in Amish families [432] and later identified in multiple ethnic groups and particularly among the Amish and the Finns [540]. This condition is an autosomal recessive disorder that results in short-limb dwarfism. It is predominantly associated with cell-mediated immunodeficiency. Other associated conditions are chondrodysplasia, fine and sparse hair, Hirschprung disease, skin hypopigmentation, increased risk of malignancy, defective hematopoiesis [401, 404, 635].

2.12.2 Etiology

Several studies had postulated various pathogenesis for SIOD, such as autoimmunity [322, 619] or metabolic defects [65, 126, 396, 588], that could not explain all the features of SIOD. For example scientists noticed that the disease does not recur in the transplanted tissues, neither tissue transplantation protects other tissues from disease process [196, 512]. In 2002, Boerkoel showed that mutations in *SMARCAL1* gene (OMIM*606622), (SW1/SNF matrix-associated actin-dependent regulator of chromatin, subfamiliy a-like 1), encoding a DNA stress response enzyme, are the causative molecular defect of SIOD [67].However, the role of this gene in the pathogenesis was not recognized at that time. Using a murine model, it was later shown that *SMARCAL1* was expressed throughout development and is involved in all affected tissues [196].

The molecular defect of CHH has been identified in the gene for RNAase, *RMRP* (OMIM*157660), mapped to 9p21-p12. *RMRP* is a ribonucleoprotein present in the nucleus and mitochondria [541, 635]. RNase MRP has two functions: cleavage of RNA during the mitochondrial DNA synthesis and nuclear cleaving of pre-rRNA. Mutations in *RMRP* affect cell growth by impairing ribosomal assembly and altering cyclin-dependent cell-cycle regulation [649]. Four distinct skeletal disorders have found to be associated with RMRP mutations: CHH, metaphyseal dysplasia without hypertrichosis (MDWH; MIM 250460), kyphomelic dysplasia (MIM211350) and anauxetic dysplasia (MIM607095) [352, 650]. Furthermore, it has been shown that RMRP mutations are responsible for a variable spectrum of immunodeficiencies and should be considered even in patients without skeletal dysplasias.

2.12.3 Clinical Manifestations

Schimke immuno-osseous affects both sexes equally [66, 619]. Facial features in SIOD patients are characteristic with a broad-low nasal bridge and bulbous nasal tip. Spondyloepiphyseal dysplasia is a constant feature, which manifests as truncal short stature. Vertebrae are usually flattened and ovoid. Increased lumbar lordosis is invariant and leads to a protuberant abdomen. Thoracic kyphosis, short neck, skull and rib abnormalities have also been mentioned. Epiphyseal changes are most consistently observed in the proximal femurs. Capital femoral epiphyses are small and laterally displaced with hypoplastic iliac wings, and shallow dysplastic acetabular fossae [66, 360, 619].

Most of these children have multiple hyperpigmented macules, measuring a few millimetres, mainly on the trunk with extension to the extremities and face. These cutaneous lentigines usually progress with age [66, 584], but there is a report of regression during adolescence [66].

SIOD patients present with growth retardation and normal or nearly normal developmental milestones. There is invariable evidence of intrauterine growth retardation in them and maximum height of adult patients rarely reaches more than 150 cm; however, the bone age does not suggest hormonal deficiency. Growth hormone studies are normal in most cases and they do not respond to hormone supplementation. Up to 50 % of the patients may have high TSH levels with normal T4 and free T3 levels; however, L-Thyroxin supplementation improves TSH levels without any effect on the course of disease [66].

The other constant feature of SIOD is renal failure, which usually starts with proteinuria and progresses to an end-stage disease within 1–11 years. The renal failure is refractory to treatment with glucocorticoids, cyclosporin A and cyclophosphamide [66]. Histopathology specimens usually show focal, segmental glomerulosclerosis (FSGS) and interestingly, there is no report of recurrence of FSGS in transplanted kidney; neither of improvement in other organ systems after renal transplantation [66]. Hypertension is relatively common [66, 584].

Immune dysfunction in SIOD usually presents with lymphopenia and/or T-cell dysfunction. Lymphocytopenia might be episodic in some patients, but all the patients show evidence of T-cell dysfunction. The $CD3^+/CD4^+$

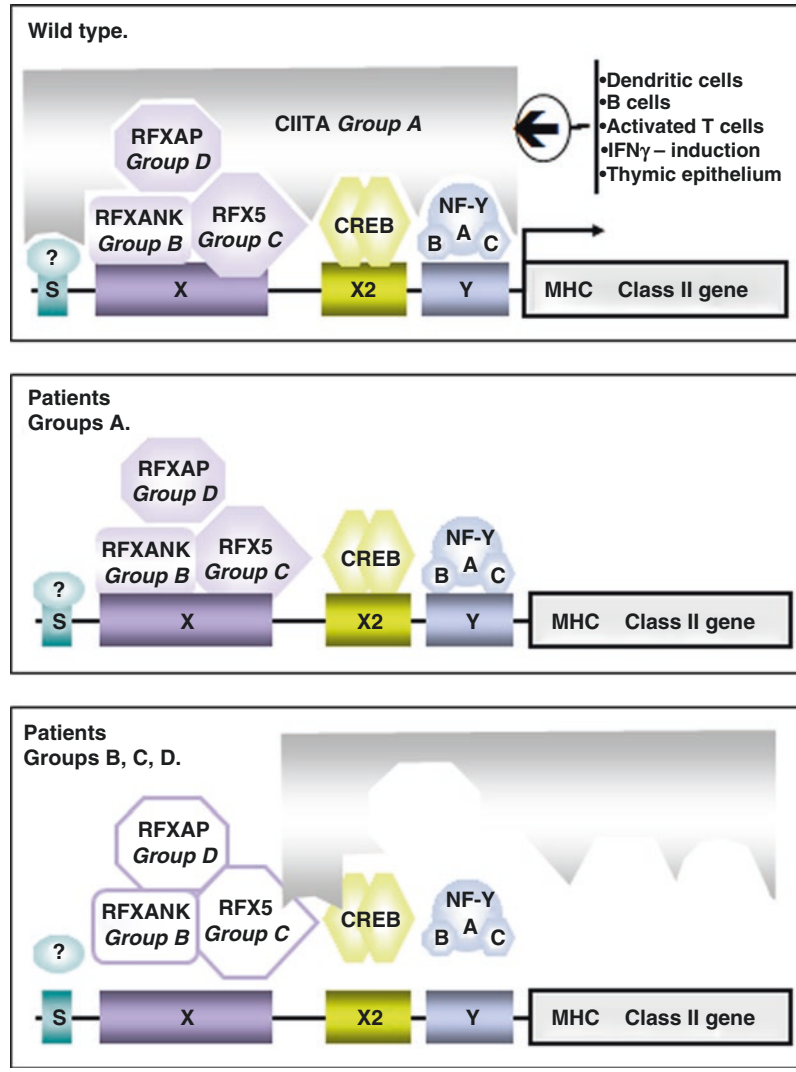

Fig. 2.2 Molecular defect and promoter occupation in MHC Class II deficiency. HLA Class II molecule expression is regulated by a proximal region promoter called S-Y comprised of S, X, X2 and Y boxes. The totality of factors that bind the S-Y module constitutes a complex called "enhanceosome". In case of a defective CIITA, the S-Y site is normally occupied. In case of a defect in one of the components of RFX (observed in patient groups B, C, and D) the S-Y site is unoccupied (Adapted from Villard et al. [682] and [351])

lymphocyte counts are reduced; whereas, the $CD3^+/CD8^+$ lymphocyte counts can be either low or normal [66, 584]. All SIOD patients show a reduced response to at least one T-cell specific mitogen [66]. Similarly they respond poorly to T-cell dependent B-cell mitogens (pokeweed mitogen), but normally to B-cell specific mitogen [66]. Absolute B-cell counts are normal in most patients while immunoglobulin levels might be reduced in some [584]. Delayed hypersensitivity skin tests were negative in one patient [584]. Adverse effects to vaccinations have not been reported yet. Interestingly, a high frequency of non-Hodgkin's lymphoma has been observed in patients and Smarcal 1-deficient are more sensitive to several genotoxic agents [46].

Arteriosclerosis is a common complication, leading to cerebral vascular accidents. Older patients frequently develop migraine-type headaches [337].The vascular disease is progressive and is not halted by renal transplantation, anticoagulants, or antimigraine medications. Large arteries including the aorta and carotids might be affected as well which is much in advance of their chronological age [125].

Recurrent fungal (oral thrush, candidal dermatitis), viral (*Herpes simplex*), or bacterial

infections (gingivitis, sinusitis, pneumonia, septicemia) are seen in almost 50 % of the patients [66, 584, 619]. The onset of infections usually follows growth failure and is preceded by ischemic events [66]. Opportunistic infections, including *Pneumocystis jiroveci*, fulminant viral infections (Cytomegalovirus and Epstein-Barr virus), and atypical mycobacterial infections have also been reported [66, 581, 583]. Recurrent infections are not associated with milder juvenile form of the disease [66].

Other findings in SIOD include microdontia with absence of dental pulp, microdontia, hypodontia, or malformed deciduous and permanent molars. Immunohistochemical analyses showed expression of SMARCAL1 in all developing teeth, raising the possibility that the malformations are cell-autonomous consequences of SMARCAL1 deficiency [143, 394, 448].

Eye refraction difficulties and optical neuropathy, testicular hypoplasia with azospermia, fatty infiltration of cardiac wall, pulmonary emphysema, and high pitch voice [125, 620].

Cartilage-hair Hypoplasia is equally distributed in both sexes and has been seen throughout the world [431]. The predominant feature in CHH is short-limb dwarfism which is evident at birth, metaphyseal flaring and irregularities. Globular epiphyses at the knees and ankles are also the typical radiographic signs. Other skeletal features can be variable which include incomplete extension at the elbow, anterolateral chest deformity with flaring of the ribs at the costochondral junction, Harrison grooves, genu varum, and excessively long fibula distally relative to the tibia [432]. Skeletal age can be reduced in some patients. Mild scoliosis has been observed in 25 % of the patients [403]. Bonafe et al. suggested that a diagnostic feature of CHH is cone-shaped epiphyses in the phalanges [68]. Anterior angulation of the entire sternum in CHH was described by Glass [255]. The mean adult height is 131.1 and 122.5 cm in males and females, respectively [403].

Skin manifestations of CHH are also variable. Most of these patients have hypopigmented skin. Finger nails are foreshortened and dysplastic. The hair is fine, sparse and light-colored. Under light microscopy, hair looks abnormally small caliber and hypoplastic with lack of the central pigmented column [401].

Involvement of the immune system in CHH was noted by the time it was first described as an unusual susceptibility to varicella infections [432]. Patient could be affected by severe herpes labialis. Markedly impaired function of T cells as well as lymphopenia and neutropenia have been described in CHH [401]. In spite of decreased $CD4^+$ cells, B lymphocyte count is usually normal while natural killer cell population is normal only in 40 % of patients. Lymphocyte stimulation studies with mitogens were subnormal in most patients. Humoral immunity may also be affected, with deficiencies in immunoglobulin A and G subclasses [402, 487]. Buckley et al. have considered a case of CHH in their series of 108 patients with SCID; however, CHH is not a common cause for SCID. Moreover, a generalized hematopoietic impairment has been described which involve all myeloid lineages in patients with CHH. Severe anemia and defective erythrogenesis requiring transfusion affect up to 79 % of patients, but can undergo spontaneous and permanent remission before adulthood in the majority of the patients [707]. Moreover, patients showing skeletal changes typical of (CHH) associated with some Omenn-like clinical signs, such as infections, erythroderma, lymphoadenopathy and hepatosplenomegaly have been reported to carry mutations in the ribonuclease mitochondrial RNA-processing [40, 551]. There is a statistically significant increased risk of cancer among CHH patients which is mainly attributable to non-Hodgkin lymphoma and basal cell carcinoma [401, 487]. The latter can be partly related to skin hypopigmentation. The prognosis of these patients after development of malignancies is poor.

Hirschprung disease was described in some of these patients, which may lead to aganglionic megacolon [635]. Splenomegaly with portal hypertension, dental abnormalities and defective spermatogenesis are other less known features.

2.12.4 Diagnosis

Skeletal abnormalities are manifest at birth and most of these children are born with evidence of intrauterine growth retardation and a short stature with a mean relative length of −3.0 SD [403]. Immunology tests could be impaired as discussed before. Other diagnostic features depend on the presentation and complications. Imaging studies can be diagnostic in some cases, but genetic testing is needed for confirmation. Thanks to recent advances, these conditions can be suspected and diagnosed in prenatal clinics [66, 394, 584].

2.12.5 Management

Severely affected SIOD patients usually present with growth failure in the neonatal period and die within the first decade of life. On the other hand, the milder juvenile form of the disease usually presents with growth failure and renal dysfunction between 8 and 13 years of age and progresses to renal failure over the next 6–12 years into adulthood. Patients with severe phenotype have at least one null allele. However, the severity and age of onset do not invariably predict survival [125, 288, 394].

There is no proven treatment for SIOD or CHH. Medical and supportive care may prolong survival of severely affected patients [394]. Combined renal and HSCT may treat the renal failure, bone marrow failure and immunodeficiency in SIOD, but not arteriosclerotic changes [512]. A study performed on five transplanted patients [47] showed a poor outcome likely due increased sensitivity to genotoxic agents. Of note, SIOD patients are prone to restrictive lung disease due to skeletal dysplasia [448] and conditioning regimens containing busulfan and cyclophosphamide associate with increased risk to develop pulmonary side effects. On this basis, reduced conditioning regimens should be considered although high incidence of acute GVHD is observed [46]. Patients usually die within the first two decades of life from infections (23 %), stroke (17 %), renal failure (15 %), complications of organ transplantation and lymphoproliferative disease (9 %), gastrointestinal bleeding, (6 %) bone marrow failure and unspecified lung diseases [46].Prophylactic and early administration of antibiotics reduces the severity and frequency of infections [66] and prolongs survival of early-onset patients [394]. Dislocated hips may warrant surgical treatment.

For CHH patients, management would similarly include treatment of complications. Acyclovir can be used for the treatment of severe varicella infections [187, 715]. These patients should not receive live attenuated vaccines like, however, varicella vaccine would be worthy of consideration [286, 289]. For CHH associated with severe immunodeficiency and or autoimmunity, HSCT should be considered before the development of severe infections and severe complications such as malignancies or organ damage that can influence the outcome of the disease [71, 707].

2.13 Combined Immunodeficiency with Intestinal Atresias (TTC7A Deficiency)

2.13.1 Definition

The association of hereditary multiple intestinal atresias (HMIA) and profound immunodeficiency has first been described in 1990. Recently, using whole exome sequencing, two teams of researchers identified *TTC7A* (OMIM*609332) as the causative gene of this disease (OMIM*243150) [116, 579].

2.13.2 Etiology

TTC7A mutations have been identified in 15 families. The same mutation was found homozygous in probands from seven French Canadian families. This reflects the founder effect often found in this population. This mutation consists in a 4-bp deletion that occurs at the 5′ splice donor site of exon 7, and leads to exon 7 skipping which generated a 158 bp deletion in the resulting

cDNA, predicted to cause a frameshift 281 amino acids through the gene with 49 new amino acids followed by a stop codon. This mutation was found in two other Canadian families in which the probands are compound heterozygous. The second mutation was a missense mutation L823P in one case and this mutation was also found in another family. The other patient had two deleterious missense mutations on the second allele (K606T and S672P) inherited from the mother. A founder effect was also suggested among Slavic population since a 4 bp deletion (exon 2 c.313ΔTATC) was shared by two families of this origin and was found homozygous in patients. Other mutations including deletion and missense mutations were also found.

Human TTC7A protein contains nine tetratricopeptide repeat (TPR) domains [149]. The TPR domains are degenerate 34-amino-acid repeat motifs that are found in many diverse proteins in all organisms and are thought to mediate protein–protein interaction, although in the vast majority of cases, the identity of a particular ligand has not yet been identified. TPR-containing proteins are involved in numerous cellular processes such as transcription, cell cycle, protein translocation, protein degradation and even host defense against invading pathogens. Spontaneously arising mutations in the mouse *TTC7A* ortholog, *Ttc7*, are known [703]. Between them, the spontaneous autosomal recessive mutation, the flaky skin (*fsn*) mutation, causes anemia, skin disorders (psoriasis) and gastric hyperplasia. It was mentioned that thymic histology of 8-week old fsn^{-}/fsn^{-} mice show a markedly reduced cortex cellularity (although data were not shown), and both neonate and adult fsn^{-}/fsn^{-} mice show a significant reduction on number of lymphocyte [52]. Papillomas in the stomach and increase apoptosis of cecal enterocyte were observed. Other *Ttc7* mutation in mouse, the autosomal recessive *hea* mutation, results in a lethal severe anemia with lymphopenia, for both CD4+ and CD8+ T cells [328]. The TTC7A is abundantly expressed in human thymus especially in thymic epithelial cells and in Hassall corpuscle. As the thymus in *hea/hea* mutant mice, TTC7A deficient patient thymus display lymphoid depletion without a clear corticomedullary demarcation. These observations suggest that Ttc7 and TTC7A play a crucial role in the thymocyte differentiation in mice as in human.

2.13.3 Clinical Manifestations

As intestinal atresia is the most common etiology of congenital small bowel obstruction accurate treatment needs to differentiate HMIA which is the rarest form of these diseases. The intestinal manifestations are present in fetal life since bowel distensions are often seen on fetal ultrasound performed as early as 17 weeks of gestation, which can also detect hydramnios and intraluminal calcifications, which seems to be specific of this condition [39, 77]. Prematurity and hypotrophy at birth with intrauterine growth retardation are often reported [60]. HMIA affects the entire gastrointestinal tract especially the small intestine and the colon, which differentiates it from non-hereditary MIA. Others anomalies are associated in sporadic cases as malrotation, septal ventricular defect, omphalocele and choanal atresias [60, 208].

The particularity of these atresias is to recur after surgical intervention which is consequently ineffective in restoring intestinal transit and which leads to short bowel syndrome.

The main infectious complications are peritonitis and bacterial sepsis, which are the cause of death, in most cases. The bacteria involved are often enteric bacteria as *Streptococcus faecalis*, *Enterococcus faecalis* and *Enterobacter cloacae*. However, one patient died from *Pneumocystis jirovicii* related pneumonia at 2 months of age.

2.13.4 Diagnosis

The sieve-like appearance of the atretic bowel section and the diffuse inflammation characterize the histological lesions of the bowel.

The sieve-like appearance consists of multiple small cysts with common muscularis, propria and submucosa but with own mucosa and muscularis mucosa. The inflammatory lesions are diffuse, of

variable stages, involve the mucosa and are associated with ulcerations. The lumen of the bowel contains mixed inflammatory cells and fibroblasts. Dense submucosal fibrosis is often noted as intraluminal and intramural calcifications [19, 368].

The immunodeficiency associated with the HMIA remained unidentified for a long time and consequently, only few immunological investigations are reported. This is probably due the death very early in the life. This association was first described in 1990. One patient reported here had a SCID phenotype with complete absence of T lymphocyte [446]. In contrast, B lymphocytes were detectable. The occurrence of a post-transfusion GVHd in two patients [446, 687] and of fatal *Pneumocystis jirovicii* pneumonia in another one [51] confirm that immunodeficiency is frequently associated, though often ignored. However, some reports mention hypogammaglobulinemia associated in some cases with lymphopenia. Recently, this lymphopenia has been more often characterized [19, 51, 130, 252, 445]. Severe hypogammaglobulinemia seems to be a constant feature. In contrast, T-cell lymphopenia is variable from one patient to another patient. Some patients had a profound lymphopenia similar to the one observed in SCID patients and others profound CD8 T lymphopenia whereas CD4 lymphocytes are normally present with a normal proportion of CD45RA+CD31+ naïve cells [51, 116] and personal data. In conclusion, the CD8 lymphopenia is probably a feature shared by most of the patients. The mitogen-induced proliferation is variable. B cell lymphopenia is also often observed.

2.13.5 Management

Surgery gives only poor results because the recurrence of atresias and the consequent short bowel syndrome justify the exclusive parenteral nutrition that constitutes a non-curative treatment, not without adverse events, especially liver alterations.

So, long as the precise function of TTC7A is not elucidated, it is difficult to propose a rational curative treatment. Indeed, two non-exclusive approaches can be proposed, i.e., HSCT and bowel transplantation.

HSCT was performed in at least three patients. Two of these patients died after HSCT, one of infection [116] and the other due to complications of the intestinal disease [579]. The only remaining patient after HSCT received a familial well-matched HSCT without any conditioning regimen. Twenty-two months after HSCT, the patient displays a nearly full chimerism, and a good immune reconstitution of T- and B-cell compartments with presence of naïve T-lymphocytes [116]. However, the patient is always dependent on parenteral nutrition because of a short bowel syndrome.

Bowel transplantation has been reported in one HMIA patient [252]. The patient had liver disease secondary to the parenteral nutrition and consequently received a 1 of 6 HLA matched liver-small bowel transplantation at 16 months of age. Two years after, liver and intestinal functions are normal without evidence of allograft rejection.

Surprisingly, an engraftment of T- and B-lymphocytes from donor was observed in this patient. The T-lymphocytes display a phenotype consistent with an intestine origin (CD3+CD4-CD8-TCRγ/δ and CD3+CD4-CD8αα+TCRγ/δ+). IgM and IgG levels were improved but without specific antibody production after immunization. However, after CMV and parainfluenza-3 infections, virus specific antibodies were produced.

Now, we know the causative gene of this complex disease and we can expect that the elucidation of the TTC7A function will allow an accurate curative treatment of patients in a short delay.

2.14 MHC Class II Deficiency

(CIITA deficiency, RFX5 deficiency, RFXAP deficiency, RFXANK deficiency)

2.14.1 Definition

MHC class II deficiency is a rare immunodeficiency (OMIM*209920) in autosomal recessive transmission. Most patients are of North African

origin (Tunisia, Morocco, Algeria). However, patients of various origins, including Europe, United States, and Middle-East have been described. This syndrome is also called «Bare lymphocyte syndrome». It is characterized by the absence of expression of HLA class II molecules. This absence of expression is the result of a mutation in the genes encoding one of the 4 trans-acting elements that regulate the expression of HLA class II molecules.

2.14.2 Etiology

This immunodeficiency was initially subdivided into four functional complementation groups: A, B, C, D. These four complementation groups were confirmed when the 4 genes involved were identified, that is, the genes encoding the Class II transactivator (*CTIIA* in group A, OMIM*600005) [623], the regulatory factor X associated protein containing ankyrin repeat (*RFXANK* also called *RFX-B* in group B, OMIM*603200) [416, 463], the fifth member of the regulatory factor X family (*RFX5* in group C, OMIM*601863) [622] and the regulatory factor associated protein (*RFXAP* in group D, OMIM*601861) [188]. Identification of the molecular origin of this immunodeficiency contributed to the clarification of the respective roles of these factors in the regulation of the transcription of HLA Class II molecules. HLA Class II molecules DR, DP, DQ are α/β heterodimers. In humans, the genes encoding these different chains are located on chromosome 6. The molecules are expressed constitutively by thymic epithelial cells, by the antigen presenting cells (B lymphocytes, dendritic cells and monocytes/macrophages) and by activated T lymphocytes. Aside from this constitutive expression, the expression of HLA class II molecules can be induced specifically by interferon γ. HLA Class II molecule expression is regulated by a proximal region promoter called S-Y comprised of 4 cis-acting DNA elements called the S, X, *X*2 and Y boxes [351, 533, 682]. The RFX ubiquitous complex composed of RFX5, RFXANK and RFXAP binds box X. CREB binds box *X*2, and NF-Y binds box Y. The totality of factors that bind the S-Y module constitute a complex called "enhanceosome". In case of a mutation in the gene encoding one of the components of RFX observed in patients presenting a MHC class II deficiency belonging to groups B C and D, the S-Y site is unoccupied [260, 324], proving that each of these components is indispensable for binding the enhanceosome on the S-Y site. Binding of the enhanceosome on the S-Y module is necessary for the transcription of molecule MHC class II genes, but it is not sufficient (Fig. 2.2). In fact, recruitment of the inducible CIITA coactivator, whose gene is mutated in patients with an MHC class II deficiency of group A, is indispensable.

In most patients (environ 60 %), the affected gene is *RFXANK* (group B) and mutations modify the Ankyrin repeat region, a region whose integrity is required for RFXANK function. The *RFXANK* mutation 752del G-25, linked with a founding effect, is observed in almost all North African patients [460, 495, 711]. Mutations in the *RFXAP* gene (group D) account for about 20 % of patients. These mutations result in synthesis of truncated proteins or the absence of transcription because a homozygous 75 bp insertion in the 5′-UTR, which impaired the activity of the RFXAP promoter.[668].The mutations observed in group A patients (about 15 %) involve the *CIITA* gene [416]. These mutations are diverse: missense mutations, non-sense mutations and splice site mutations. In the remaining patients (group C), mutations in the *RFX5* gene generally lead to synthesis of truncated proteins [417]. Punctual mutations in *RFX 5* or *CIITA* are associated with milder phenotypes [470, 712].

2.14.3 Clinical Manifestations

Despite the heterogeneity of molecular origins responsible for the different groups of patients presenting MHC Class II deficiency, clinical manifestations are similar [54, 195, 343, 575]. However, mild forms associated with certain mutations have been described [181, 290, 712].

Patients present recurrent infections characteristic of combined immunodeficiency. Susceptibility to bacteria, viruses and fungi testifies to the severity

of this immunodeficiency. The first infection occurs in infancy, at an average age of 4 months, and exceptionally after the age of 1 year. These recurrent infections essentially involve the gastrointestinal tract, the lungs, the upper respiratory tract and the urinary tract.

Digestive problems are common. They take the form of diarrhea starting most often during the first year of life, becoming chronic and associated with malabsorption leading to delayed height–weight development. Histology findings commonly include villous atrophy associated with intraepithelial infiltration by lymphocytes and macrophages. These types of diarrhea are very often associated with *Candida, Giardia lamblia* and *cryptosporidium* infections. However, viruses (*enterovirus* species or *adenoviruses)*, gram-negative bacteria (*E. coli, Salmonella* species*, Shigella, Pseudomonas*) and gram-positive bacteria (*Staphylococcus* and *enterococcus*) are also frequently involved.

Hepatic abnormalities take multiple forms. Sclerosing cholangitis secondary to chronic infection due to Cryptosporidium develops secondarily in over half the patients and constitutes a major factor in prognosis. Hepatitis cases are most often of viral origin. Cholangitis cases of bacterial origin (*pseudomonas, Enterococcus* and *streptococcus*) have also been observed.

Pulmonary infections occur in almost all patients. These can be interstitial affections caused by viral infections (adenovirus, CMV and RSV) or by *Pneumocystis jiroveci* which can cause major hypoxia leading to the death of the patient. Most patients present more than one episode of pulmonary infection of bacterial origin. The chronic nature of these pulmonary affections very frequently leads to bronchiectasies. Chronic upper respiratory tract infections such as sinusitis, rhinitis and otitis are common.

Meningitis and meningoencephalitis of viral origin can cause death in some cases. Enteroviruses including the polioviruses, the Herpes simplex virus, the coxsackievirus and the adenovirus have been reported. Infectious pyelonephritis and septicemias can also occur. Autoimmune cytopenias, particularly hemolytic anemias and neutropenias are described in about 10 % of patients.

Severity of clinical symptoms varies from one patient to another. In general, this variability cannot be clearly correlated with the mutated gene or the type of mutation. Specifically, this variability is observed among patients presenting an *RFXANK* mutation due to a founding effect.

2.14.4 Diagnosis

The immunological consequences of lack of MHC class II expression orient the diagnosis. These features can be accounted for by the lack of MHC Class II expression on Antigen Presenting Cells [195, 343]. The first characteristic is the inability to develop antigen specific humoral and cellular responses. Delayed–type hypersensitivy skin tests and *in vitro* Antigeng specific stimulation are negative in all patients. By contrast, responses to mitogens are normal. Humoral immunity is also always impaired. Hypogammaglobulinemia is variable from one patient to another, from agammaglobulinemia to a slight decrease in one immunoglobulin isotype (mainly IgA and IgG2). In all cases, specific antibody production is impaired. Patients display normal T cell count. However, most of them present CD4 lymphopenia. By analogy with MHC Class II -/- mice, the latter could reflect the abnormal selection and maturation of CD4 T lymphocytes in the absence of MHC class II expression on the thymus [271]. However, some MHC class II expression has been detected on medullary thymus cells from dead children and from aborted fetuses [269]. This finding suggests leakiness of the defect or the presence of an alternative regulation pattern of MHC class II gene transcription in thymic cells, that can account for partially preserved CD4 T cell differentiation and their normal repertoire building assessed by Vβ and Vα usage [367, 543].

The diagnosis is based on the lack of MHC Class II expression assessed by immunofluorescence. In most patients, MHC Class II molecules DR, DP, DQ are completely undetectable on

blood B lymphocytes and monocytes as well as on *in vitro* activated T cells. In some cases, residual expression of these molecules has been reported on various cell types. At least in some cases, this leaky expression, always lower than expression observed in controls, seems to be associated with a less severe clinical phenotype. In most patients low expression of MHC Class I molecules, around 10–30 % of controls, is also observed.

The final diagnosis requires mutation detection. The existence of the 4 different genes involved makes molecular analysis difficult. Different strategies can be proposed to direct the molecular analysis. First, in case of consanguinity, the study of polymorphic markers flanking the four genes involved can be useful. Second, according to the frequency of the mutation 752delG-25 in patients of North Afriqua origin, it is judicious to search for this mutation first in this population. In other cases, a functional identification of the gene affected could be helpful. Recently a functional test based on direct correction of the genetic defect by transduction of cells from patients with lentiviral vectors encoding CIITA, RFXANK, RFX5 or RFXAP has been proposed as a valuable tool for the diagnosis and classification of new MHCII-deficiency patients [419]. Molecular characterization is a crucial step for proposing an appropriate prenatal diagnosis at 8–10 weeks of gestation in at-risk families.

2.14.5 Management

MHC class II deficiency has a very poor prognosis. Supportive care associating symptomatic and prophylactic treatment of infection can reduce the frequency and the severity of clinical problems. Intravenous immunoglobulin injections are a part of this care. In some cases, parenteral nutrition is need. However, except in some patients who may survive for relatively long periods, this supportive care, as complete as possible, does not prevent progressive organ failure and death that occurs in most cases before 20 years of age [495].

The only radical treatment that can be proposed is HSCT for which some successful outcomes have been reported [30, 342, 575]. However, it appears that HSCT in MHC class II deficiency is associated with a lower survival rate than other immunodeficiencies because graft rejection, aGVHD and opportunistic infections. Indeed, the survival rates vary from 40 to 80 % in HLA matched situation and is <50 % in HLA mismatched one [14, 30, 219, 342, 495, 514, 534, 575, 607, 611]. In addition, in case of successful engraftment, the immune reconstitution is poor [14, 495] and the patients remain susceptible to infection [611]. The occurrence of aGVHd and the occurrence of lethal infection after transplantation are associated with viral infection status before stem cell transplantation [534]. These observations suggest that stem cell transplantation could be improved by performing the transplantation at the time of diagnosis that would minimize the risk of viral infection.

2.15 MHC Class I Deficiency

(TAP1/2 deficiency, Tapasin deficiency, β2- microglobulin deficiency)

2.15.1 Definition

MHC class I deficiency (OMIM*604571), is characterized by low expression of the MHC class I molecules. This is true whatever the molecular basis. In no case, a complete absence of MHC class I molecule expression has never been described. To date, less than 20 patients with elucidated MHC class I deficiency have been reported and only one presented tapasin deficiency [718] and two presented a β2- microglobulin deficiency. Others display a deficiency of either TAP 1 or TAP2 [155, 158, 232, 418, 442, 705, 718]. However, some asymptomatic subjects present non-elucidated low expression of MHC class I molecule [507]. Only elucidated MHC class I deficiency will be discussed in this section.

2.15.2 Etiology

MHC class I molecules are expressed ubiquitously and present endogenous peptides to CD8+ T cell. Consequently, MHC class I molecules are designated as the central agents of anti-viral immune response. The peptides, usually eight or nine amino-acids in length, and binding MHC class I molecules result from the degradation of newly synthesized protein carried out by the proteasome. They are further translocated in the endoplasmic reticulum by the two transporters associated with antigen processing proteins (TAP1 and TAP2), where they are loaded onto the MHC class I heavy chain/β2-microglobulin heterodimer. This loading is dependent on the peptide –loading complex that contains the heterodimer TAP1/TAP2, the thiooxido-reductase ERp57 and the glycoprotein chaperone calreticuline and tapasin (Fig. 2.3) [346, 717]. The role of tapasin seems to be multiple and complex. However, it is clear that tapasin stabilizes the TAP1/TAP2 complex, links it to MHC class I molecules and facilitates loading of peptides with progressively higher affinity [94, 717]. The peptide-loaded MHC class I molecules are further transported to the cell membrane where expression takes place. Membrane expression of MHC class I molecules is dependent on their association with high affinity peptides. MHC class I molecules that do not bind high affinity peptides do not travel through the Golgi apparatus and the empty MHC class I molecules expressed at the membrane level are unstable. Consequently, a defect in either TAP1/TAP2 complex or in tapasin leads to low MHC class I expression.

TAP1 and TAP2 molecules include a core domain, 10 and 9 transmembrane domains respectively and a catalytic nucleotide-binding domain. The genes encoding these two proteins, *TAP1* (OMIM*170260) and *TAP2* (OMIM*170261), are located in the HLA class II region [110, 369, 736]. So far, 12 families presenting a defect in TAP1/TAP2 complex have been reported. Homozygous TAP1 and TAP2 mutations have been found in seven and five families respectively [155, 158, 232, 418, 442, 705]. All

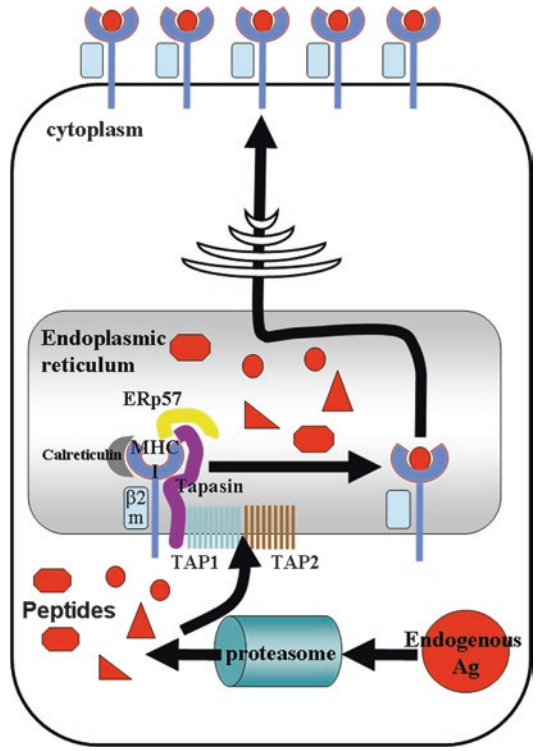

Fig. 2.3 Role of TAP1/TAP2 and TAPBP in the expression of MHC Class I expression. Peptides are translocated in the endoplasmic reticulum by TAP1 and TAP2, and the peptide –loading complex contains TAP1/TAP2, ERp57 and the chaperone molecules, calreticuline and TAPBP. TAPBP facilitates loading of peptides with high affinity (Adapted from Buckley [94] and Wright et al. [717])

theses mutations lead a premature stop codon and consequently to a truncated non functional protein.

Only one patient presenting a *tapasin* (*TAPBP*, OMIM*601962) mutation has been described [718]. The tapasin molecule contains a short cytoplasmic tail, a transmembran region and an N terminal intraluminal region. The mutation described consists in a large deletion of 7.4 kb leading to a putative frame shifted and truncated protein that is not detectable.

Homozygous mutation of Beta-2 microglobulin encoding gene (*B2M*; OMIM*109700) has been found associated with a familial hypercatabolic hypoproteinemia in two siblings born from consanguineous parents [691]. This mutation leads to a substitution of a very conserved alanine

to a proline which would affect the secondary structure of the protein and consequently its entry in the endoplasmic reticulum.

2.15.3 Clinical Manifestations

The clinical consequences of TAP1/TAP2 deficiency are variable from one subject to another. Some patients are asymptomatic [157, 500]. In most cases, symptoms, when they exist, occur late in childhood, at about 4–7 years of age. Despite the few patients described, no difference in clinical manifestation can be detected between TAP1 and TAP2 deficiency. Two typical features have been reported [110, 154, 233, 736]. The first consists in chronic infections affecting the respiratory tract and the second in skin granulomatous lesions.

In most cases, the respiratory tract is involved. Chronic infections of the upper respiratory tract are often the first manifestation and are responsible for purulent rhinitis, pansinusitis and otitis media. Frequent association with nasal polyposis has to be noted. Secondly, the infections extend to the lower respiratory tract and a to a chronic inflammatory lung disease that progressively degrade the lung tissues, including bronchiolitis, bronchiectasis, and emphysema. These lesions inevitably evolve into a respiratory insufficiency. Death may be secondary to this degradation but may also occur during an acute infection. The pathogen most often involved in respiratory alteration is *Haemophilus influenza*, but others can be detected such as *Streptococcus pneumonia*, *Klebsiella*, *Pseudomonas aeruginosa* and *Toxoplasma gondii.* Altogether, respiratory manifestations can mimic cystic fibrosis.

Skin lesions are present in half the patients and can be the only manifestation in patients without respiratory involvement [442]. They start with local inflammation that progressively extends, ulcerates, and evolves into chronic necrotizing granulomatous lesions mimicking Wegener disease [442, 518, 705]. In most cases, they are localized on the legs. However, some such lesions have been described on the face, around the mouth and the nose, and in some cases are very mutilating, associated with perforation and destruction of the nasal cartilage. In some cases, these granulomatous lesions are related to vasculitis [442, 518, 705] associated with infiltration by NK cells and, to a lesser extent, TCRγ/δ T lymphocytes [442]. More recently, such skin lesions have been reported in association with *Toxoplasma gondii* infection [176]. Moreover, such granulamotous lesions can involve the upper respiratory tract, but have never been found in patient lung biopsies.

Recently, necrotizing retinocchoroiditis related to *Toxoplasma gondii* has been reported as the only clinical manifestation in a 14 year-old patient [500].

In spite of the role of the MHC class I in the peptide presentation to CD8 T lymphocytes, it is noticeable that no patient presents severe viral infection and there is no evidence of a higher incidence of neoplasm in these subjects. This observation suggests that either other effectors such as NK cells and TCR γ/δ T lymphocytes could be efficient enough to eliminate virus infected cells in this situation, or independent TAP peptide presentation is sufficient to trigger TCR α/β CD8 lymphocytes. NK cells and TCR γ/δ T lymphocytes, beneficial in virus clearance, could however generate granulomatous and epithelial lesions, the lack of MHC class I dependent inhibition of their cytotoxic activity allowing the killing of uninfected cells [233, 739]. Epithelial lesions could favor bacterial colonization. Moreover, the TAP dependent MHC class I presentation of exogenous peptides of bacterial origin could play a more important role in the antibacterial defense than previously thought [154, 736].

Clearly, there is no correlation between mutation and clinical severity. The environmental context and/or genetic background could constitute determinant factors in the development of clinical manifestations.

The only patient presenting tapasin deficiency suffered from primary chronic glomerulonephritis for 10 years at time of diagnosis. This 54 year-old woman does not present any manifestation that can be related to an immunodeficiency, except Herpes Zoster virus infection [718].

The two siblings with β2-microglobulin deficiency presented with forearm deformity including shortened ulna and bowed radius. Except these symptoms, the patients were healthy until adulthood. After a miscarriage in the 7th month of pregnancy at 21 years of age, the first patient developed skin ulcerations on the legs related to granulomatous lesions and subsequently severe idiopathic thrombocytopenic purpura. Her affected younger brother did not present any clinical manifestations. However, the chest x-ray detected a granulomatous lesion in the lung [686].

2.15.4 Diagnosis

With the exception of two patients who present T cell lymphopenia, most TAP1/2 deficient patients have normal T cell count. However, most of them present a slight CD8 TCRα/β lymphopenia in contrast with the TAP-/- mouse model [670]. However, it seems that a more severe CD8 TCRα/β lymphopenia could exist early in life and be partially corrected later [154]. CD8 T lymphocytes display a diversified α/β repertoire [154] and cytotoxic activity, at least against EBV [156, 157]. In most patients, TCRγ/δ T lymphocyte count is increased, especially T lymphocytes bearing Vδ1 chain, and these lymphocytes can kill autologous cells [157, 442]. NK cells, that are present in the normal range show poor spontaneous cytotoxic activity against MHC class I deficient targets, that is corrected after cytokine-mediated activation. Moreover, activated NK cells can kill autologous cells [418, 683, 737, 738]. The killing of autologous cells by TCRγ/δ T lymphocytes and activated NK cells could play a role in the pathogenesis of epithelial lesions.

In most cases, hypergammaglobulinemia involving different isotypes is observed. However, some patients present a hypogammagloblinemia involving one or more isotypes [418, 518]. Antibodies to common viruses are present even in case of hypogammaglobulinemia, and often at high titer [177].

In contrast, the two β2-microglobulin deficient patients presented a hypo IgG contrasting with normal levels of IgA and IgM. The association with a low level of albumin is characteristic of a hypercatabolic hypoproteinemia due to the lack of neonatal Fc Receptor (nFcR). Indeed, nFcR is a heterodimer composed of a β2-microglobulin and a non-classical MHC class I α-chain and it protects its ligands i.e IgG and albumin from the degradation [26].

The diagnosis is based on low MHC class I expression assessed by immunofluorescence. In case of TAP1/2 or TAPBP deficiency, residual expression is 30–100 fold less than in controls [155, 158, 442]. The consequence of β2-microglobulin on the MHC Class I expression has not been directly studied, but the transfection of the mutant cDNA did not restore the MHC Class I expression of the β2-microglobulin deficient cell line Daudi [31, 691]. Final diagnosis requires mutation detection. The involvement of TAP1/TAP2 or tapasin can be assessed by HLA typing in consanguineous families that confirms the linkage to the chromosome 6. In contrast, B2M gene is on the chromosome 15. A functional test based on direct correction of the genetic defect by infection of patient cell line with recombinant vaccinia virus expressing TAP1, TAP2 or both subunits could assist genetic diagnosis [154, 567].

2.15.5 Management

Chronic lung colonization evolves to respiratory failure which may lead to the patient's death. Based on the similarity of these respiratory manifestations with those observed in cystic fibrosis, it is legitimate to propose to symptomatic patients with TAP deficiency management analogous with that recommended in cystic fibrosis, including prophylactic antibiotherapy in association with physiotherapy [233]. In spite of the absence of humoral immunodeficiency, treatment using intravenous immunoglobulin has been reported useful in patients with severe pneumonia.

The lesions of the upper respiratory tract may require local medical treatment (local washing and topical steroids) or surgical (polypectomy)

treatment. However, surgery has to be carefully considered because, in one patient, surgical intervention for chronic sinusitis has been reported to accelerate the nasal disease [233].

Treatment of skin granulomatous lesions is based only on optimal antiseptic topical care [233]. Immunosuppressive treatment including steroids in combination with either cyclophosphamide, methotrexate, azathioprine or cyclosporin, has worsened skin lesions as well as lung manifestations and has to be avoided. In the same way, immunomodulatory intervention based on the use of Interferon α or γ is also disappointing, since it is associated with lesion progression [705].

A curative treatment has not been reported so far. Lung transplantation could be considered if the hypothesis concerning the role played by NK and TCR γ/δ cells in lesion pathogenesis is confirmed. The immunoglobulin substitution in the β2-microglobulin deficient patients has not been proposed but we can speculate that it would be challenging as in other pathologies associated with IgG loss as nephrotic syndrome and protein-losing enteropathy. The rationale of HSCT that would provide MHC class I positive hematopoietic cells could be debated.

2.16 CD8 Deficiency

(ZAP-70 deficiency, CD8α chain defect)

2.16.1 Definition

Two immunodeficiencies characterized by the isolated absence of CD8+ T cells have been identified, caused by a defect in either ZAP70 (OMIM*269840) [112, 193] or CD8α chain (OMIM*608957) [152]. In spite of this shared feature, the clinical and biological consequences are very different. The ZAP-70 deficiency constitutes a SCID, while the CD8 α defect is considered non–severe and compatible with life. Both are inherited as an autosomal recessive trait.

2.16.2 Etiology

The differentiation and activation of T lymphocytes require TCR-dependent signal transduction including tyrosine phosphorylation of many substrates. The tyrosine kinase *ZAP70* (Zeta associated protein-70) (OMIM*176947), belonging to the tyrosine kinase Syk family, plays a major role in this biochemical pathway. The antigen recognition is assured by the TCR, while the CD3 complex consisting of the γ, δ, ε_2, ζ_2 chains transmits an intracytoplasmic signal by recruiting tyrosine kinases from the Src and Syk families. The CD3 complex contains, in its intracytoplasmic portion, a total of ten ITAM motifs (Immunoreceptor Tyrosine-based Activation Motif), targeted for phosphorylation. Three of these motifs are carried by CD3ζ, and one by each of the other chains, CD3γ, CD3δ and CD3ε. Phosphorylation of these motifs by protein kinases of the Src family leads to recruitment by the ζ chain of ZAP-70, which is then phosphorylated and activated by the tyrosine kinase p56lck [111, 699]. ZAP-70 phosphorylates different substrates and consequently induces a calcium signal and MAPK activation leading to immune response [256] (Fig. 2.4). The normal thymic differentiation of CD4 positive T lymphocytes in ZAP-70 deficient patients proves that in humans, in contrast with the ZAP-/- mouse model, CD4 differentiation can occur in the absence of this tyrosine kinase [34, 467, 549, 552]. Syk, highly expressed in patient thymocytes, may compensate for the loss of ZAP-70 in CD4, but not in CD8 thymic selection [239, 479]. ZAP-70 is also expressed in NK cells.

To date, around twelve different *ZAP70* mutations have been reported in the literature, but we can suppose that some ZAP-70 deficient patients are not reported. Most patients are born of related parents and present a homozygous mutation [34, 112, 192–194, 239, 325, 420, 435, 473, 479, 513, 549, 660, 664]. The mutations described include missense mutations, splice site mutations and deletions. Most mutations involve the catalytic domain but in fact affect protein stability. Two missense mutations found in a compound heterozygote patient, one affecting the

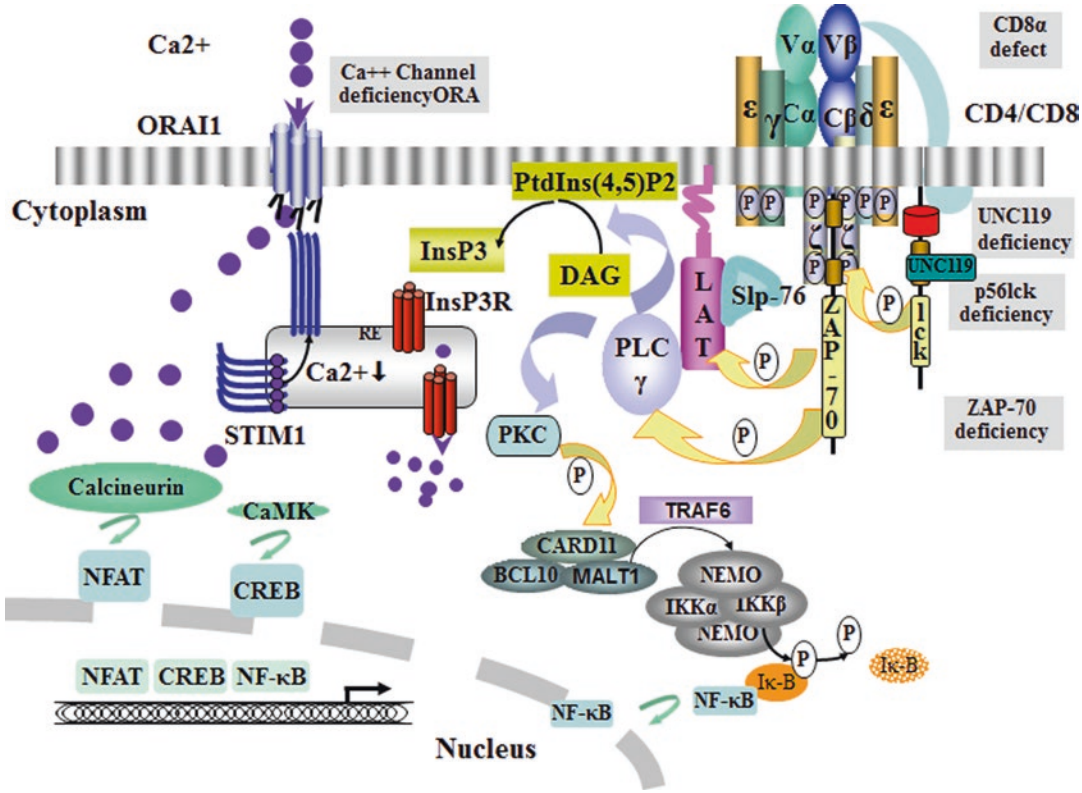

Fig. 2.4 T cell activation and immunodeficiencies. T cell activation defect are localized on a simplified schema resuming the main steps of T cell activation (Adapted from Feske [209])

first SH2 domain and the other affecting the kinase domain, are associated with a temperature-dependent instability of ZAP-70 [420]. A hypomorphic mutation, a single G-to-A substitution in a non-coding intron, which allows residual expression of normal protein, was observed in a patient with a moderate clinical and immunological phenotype [513].

CD8 molecules are expressed on the cell surface either as a αα homodimer in NK cells and TCRγ/δ T lymphocytes, or as an αβ heterodimer in TCRα/β T lymphocytes. However, surface expression of CD8β is dependent on expression of CD8α because CD8β polypeptides are otherwise retained in the endoplasmic reticulum and degraded. CD8 constitutes a coreceptor for TCR recognition of MHC class I–binding peptides and is necessary for the maturation, positive selection and activation of class I MHC restricted cytotoxic T lymphocytes. To date, two cases of CD8α deficiency (*CD8A*, OMIM*186910) have been reported in two families [152, 407]. Both are Spanish gypsy patients and present the same homozygous mutation. It is a missense mutation, Gly111Ser, affecting a very conserved position. This mutation is restricted to the Spanish Gypsy population and a study of microsatellite markers has shown that it is derived from a common founder and that it is detected at a 0.4% rate in this population [407].

2.16.3 Clinical Manifestations

Patients with ZAP-70 deficiency present infections indistinguishable from these observed in other severe combined immunodeficiencies. They occur in most cases within the first year of life and involve bacterial, viral and fungal pathogens. In some cases, opportunistic infections

such as *Pneumocystis jiroveci* related pneumonia or a CMV uncontrolled infection are the first manifestations of the disease. Frequently, *Candida* is responsible for cutaneous and oral infections and even for septicemia. Other infections due to various virus including varicella zoster virus, Rotavirus and parainfluenza have been reported, as well as lower and upper respiratory tract bacterial infections. These infections are often associated with a failure to thrive. Moreover, the patient presenting mutations associated with a thermo- sensitive ZAP-70 was affected by infiltrative erythematous skin lesions on his face and extremities [420]. In contrast with other SCID patients, some ZAP70 deficient patients display palpable lymph node and a normal sized thymus detected by chest radiology. Some patients presented with erythrodermia, eosinophilia and increased IgE level as observed in Omenn's syndrome [664]. However, in the case of a partial ZAP-70 deficiency due to the hypomorphic mutation, the patient displayed an attenuated and late onset form of the disease without autoimmunity [513].

The severity of this later immunodeficiency contrasts with the late onset of clinical manifestations in both CD8α deficient patients described so far. The age at diagnosis in the latter is 25 and 16 years [152, 407]. However, both patients suffered from recurrent respiratory infections very close to those observed in TAP deficiency since the childhood. In the first patient described the pulmonary lesions led to death at 33 years of age. The main pathogens reported are *Pseudomonas aeruginosa* and *Haemophilus influenza*. Similarities with TAP deficiency are numerous. Some subjects who present the same CD8 deficiency are as healthy as the siblings of the first case described, and patients do not present high incidence of viral infection.

2.16.4 Diagnosis

ZAP-70 and CD8α deficiencies share a common feature: the lack of blood CD8 T lymphocytes. However, other biological findings are very different and are going to be described sequentially.

ZAP-70 deficient patients have a normal or high blood lymphocytes count. Except for the absence of CD8 TCR α/β T lymphocytes (in most cases, less than 3 % of blood lymphocytes), other lymphocyte populations, including CD4 T lymphocytes, and TCRγ/δ T lymphocytes, are normally present. NK cell count usually normal cells are reported slightly decreased in one case [325]. CD4 lymphocytes display a normal Vβ repertoire [552], suggesting that ZAP-70 is not indispensable for CD4 lymphocyte selection. However, peripheral CD4 lymphocytes function poorly. *In vitro* proliferation assays are useful to orient the final diagnosis. The proliferative as well as the IL-2 secretive responses to PHA and anti-CD3 antibody are absent and restored in part by exogenous IL2. Antigen-induced proliferations are also poor. In contrast, the association of a phorbol ester (PMA) with a calcium ionophore (ionomycin) that bypasses proximal TCR/CD3 signaling induces normal T cell proliferation. The lack of calcium mobilization and poor protein tyrosine phosphorylation after CD3 triggering confirm a defect in a proximal signal step [34, 239]. These functional abnormalities were also observed in the case of the partial deficiency whereas the patient displayed a T cell lymphopenia including CD4 lymphocytes [513].

Humoral immunity is variably altered. Hypogammaglobulinemia involving all isotypes associated with a complete absence of specific antibodies observed in most patients contrasts with the normal or high level of immunoglobulins reported in others [596]. Some of these patients display normal antibody response after tetanus immunization. In any case, the hypogammaglobulinemia does not constitute an absolute diagnostic criterion.

Final diagnosis requires DNA sequencing in order to confirm and to characterize the *ZAP70* mutation.

Blood T lymphocyte phenotype is characteristic of patients with CD8α deficiency. The patients present normal TCRα/β CD3, TCRγ/δ CD3 and CD4 T lymphocyte counts. Surprisingly, the lack of CD8 T cells is associated with an increased T cell population that expresses CD3 and TCRα/β, but expresses neither CD4 nor CD8 [152, 407].

This population is polyclonal and displays a normal Vβ repertoire. It probably represents a population with CD8 cytotoxic T lymphocytes, since it expresses a phenotype associated with effector cytotoxic T lymphocytes (CD11b+, CD57+ and CD28-) and transcripts for CD8α and CD8β [152].

In contrast with the ZAP-deficient CD4 T lymphocytes, CD4 lymphocytes from CD8α patients are normally functional. Proliferative responses are normal whatever the mitogen or antigen tested. NK cells are normally present and are functional towards the K562 line as target. Humoral immunity is completely spared. The final diagnosis will be established by the detection of a *CD8α* mutation; to date, only one mutation has been described.

2.16.5 Management

Because of the very different severity of the clinical manifestations of the two types of immunodeficiency, ZAP-70 deficiency and CD8α deficiency, prognosis and consequently management will be different as well.

By analogy with the other forms of SCID, the only treatment of ZAP-70 deficiency is HSCT. Matched and mismatched transplantations were successful in most of the transplanted patients [194, 610, 660].

In contrast, the management of patients with CD8α deficiency consists of treatment of respiratory infections and prevention of bronchiectasis. One patient died when lung transplantation was planned, after improvement with intravenous antibiotherapy [152]. We can suppose that early recognition allowing treatment at the time of the first clinical manifestations would lead to the best prognosis.

2.17 Lck Deficiency

2.17.1 Definition

In 1998, a low expression of p56lck associated with an alternatively spliced lck transcript lacking the exon 7 has been reported in a SCID patient with a predominant CD4 lymphopenia [257]. This aberrant splicing is associated with a low expression of p56lck. However, no mutation responsible for this exon skipping, which has also been reported in a patient who has a common variable immunodeficiency associated with CD4 lymphopenia, was found [586]. More recently, a patient with an identified genetic cause of p56lck deficiency has been reported with mutation in *LCK* gene (OMIM*153390) [291].

2.17.2 Etiology

P56lck is a tyrosine kinase constitutively associated to CD4 or CD8 which is activated upon CD3-TCR triggering by the HLA-peptide complex. This activation results from a conformational change due to the binding of SH3 and SH2 to their ligands (including UNC119) and dephosphorylation of a tyrosine residue (Y505) by the phosphatase CD45. When phosphorylated, Y505 binds the SH2 domain of p56lck and this conformation inhibits its kinase activity [577]. Active p56lck phosphorylates ITAM of the CD3 complex and of the ζ chain and consequently allows the recruitment of ZAP-70 and the downstream signals responsible of T cell activation. *(See* Sect. 2.15 *for more details)* In the only patient who displays an identified cause of p56lck, a homozygous mutation in exon 9 was found and led to an amino acid substitution (L341P) which is predicted to destabilize the protein.

2.17.3 Clinical Manifestations

The patient who had the identified p56lck deficiency had symptoms associating infections with inflammatory and autoimmune manifestations. The infections mainly involved the respiratory tract with pneumonia and pneumatocele. The inflammatory manifestations included daily fever, skin lesions that consisted in non-infectious nodular lesions, inflammation of interphalangeal joints and serositis. Autoimmunity was responsible of cytopenia. One patient with a low

expression of p56lck had a combined immunodeficiency picture including chronic diarrhea, oral candidiasis and failure to thrive at 2 months of age [257]. In contrast, the other was described as a CVID [586].

2.17.4 Diagnosis

The common biological feature of these patients is CD4 lymphopenia. In contrast, CD8 T lymphocytes, B lymphocytes, and NK cells are normally represented. In the patient with the identified cause of p56Lck deficiency, the CD4 lymphocytes display a memory phenotype (CD45RA-CD45RO+ CD27+) and the CD8 an EMRA phenotype(CD45RO-CD45RA+CD62L-CD27-). The repertoire of TCRα/β and TCRγ/δ) T lymphocytes is restricted. The more specific feature is the low surface expression of CD4 and CD8 antigens. The IgG and IgA levels were normal and IgM level was high but no specific antibodies was detected. In contrast, autoantibodies (ANA, anti-dsDNA and rheumatoid factor) were present. The p56lck expression was low in patient's T lymphocytes and this protein had no kinase activity. As expected, the downstream activation events, including phosphorylation of p56lck substrates, calcium mobilization, and T-cell proliferation were not induced after CD3 triggering.

2.17.5 Management

In light of the severity of the clinical manifestations, both patients received a HSCT and one died shortly after [291].

2.18 Idiopathic CD4 Lymphopenia

2.18.1 Definition

In 1993, the Centers for Disease Control (CDC) defined the condition of decreased $CD4^+$ T-cell count without HIV as idiopathic $CD4^+$ T lymphocytopenia (ICL). This entity is characterized by (i) $CD4^+$ T-cell count $<0.3 \times 10^9$/l in adults and <1000 cells/μL in children above 23 months of age or <20 % of the total T-cell count on two occasions; (ii) the absence of HIV-1, HIV-2 or human T-cell lymphotrophic virus infection (HTLV); and (iii) the absence of any known immunodeficiency disorder or therapy associated with reduced $CD4^+$ T-cell count. Most cases are adults but some ICL/SUHIS have been described in children. ICL has to be distinguished from secondary forms of CD4 lymphocytopenia. These secondary forms include infections (mycobacteria, viruses such as CMV, EBV, HBV) malignancies, and autoimmune diseases [8, 688, 740].

2.18.2 Etiology

It is unlikely that a single pathophysiology will be operative in ICL. Some potential pathogenic mechanisms of ICL have been proposed. Defective cytokine related decreased bone marrow clonogenic capability has been involved in *de novo* T cell generation [309]. A disturbed thymic T-cell maturation process may account for the decrease in naive T cells [229]. Enhanced expression of Fas and Fas ligand in unstimulated cell populations might lead to spontaneous apoptosis of T lymphocytes [370, 548]. Some features argue for a disrupted cytokine dependent CD4 T cell homeostasis; i- the decreased response of CD4 lymphocytes to IL-7 and IL-2 contrasting with an increased response to TSLP [89, 527]. ii- High levels of plasma IL-7 were found and inversely correlate with CD4+ T-cell counts [405] and with CD4+ lymphocyte response to IL-7 [527]. In addition, the impaired expression of CXCR4 on CD4 lymphocytes which can be restored by IL-2 therapy, suggests that alteration in T cell homing may contribute to the immunodeficiency [593].

Impaired early biochemical events of the CD3-TCR pathway have been detected with reduction of T-cell proliferation [304] and are related to low activity of p56lck in at least four cases [262, 303]. Recently, in one of these patients, a heterozygous polymorphism of the

UNC119 gene has been found (OMIM*615518) [261, 262]. UNC119 is a crucial adaptor for the activation of p56lck [109].

It has also been suggested that cytotoxic anti-CD4+ antibodies are involved in the pathogenesis of ICL in some patients [576].

2.18.3 Clinical Manifestations

In most cases, a diagnosis of ICL is made at the time of opportunistic infections such as *Cryptococcus* infection [355, 471, 488, 724], *Pneumocystis jiroveci* pneumonia [377, 609] or mycobacterium infection [310, 472, 613, 672]. These infections occur in patients without particular history and often constitute the first manifestation of the disease [613]. The most common pathogen involved is *Cryptococcus neoformans* with a central nervous system (CNS) localization in most cases [742]. Manifestations outside the CNS may be isolated or not [355, 724]. Other fungal infections are also frequent and they include histoplasmosis, Candidiasis (oral vaginal and esophageal), cerebral toxoplasmosis. Mycobacterial infections are also frequent. Typical [310] and atypical mycobacteria [472] are involved, with pulmonary and extra pulmonary localizations [672]. Viral infections are also frequent. The most frequently observed virus is the Zoster virus that may lead to multi-dermatotomal localization. Oral or genital herpes simplex, human papillomavirus, molluscum contagiosum and CMV infections and HHV8 related Kaposi's sarcoma are also reported, as well as bacterial infections such as nocardiosis and salmonellosis [186, 298, 408, 505, 526, 613, 618, 673, 692].

Some non-infectious clinical manifestations associated with ICL have been described [613]. They include autoimmune diseases such as Behcet syndrome [673], Sjogren syndrome [340], psoriasis [285], vasculitis [70] and thrombotic thrombocytopenic purpura [613].

Some patients already known to present CD4 lymphopenia have developed secondary malignancies. This observation suggests that idiopathic CD4 lymphopenia could favorise malignancy occurrence. As in other immunodeficiencies, lymphomas, especially B-cell non-Hodgkin's lymphomas, are often reported [91, 97, 274], as well as HHV8 related Kaposi's sarcoma [214, 308, 539].

However, such CD4 lymphopenia has been reported in healthy subjects.

2.18.4 Diagnosis

Idiopathic CD4 lymphocytopenia is probably a heterogeneous disorder. Non transient CD4 lymphopenia is the biological feature that defines this disease. $CD4^+$ T cell counts are stable over time in contrast to the progressive loss of this subpopulation observed in the course of HIV disease. Naïve CD4 CD45RA T cells are more affected than the memory CD4 CD45R0 T cells and the Vβ repertoire has been reported restricted [229].

In addition to $CD4^+$ lymphocytopenia, several patients also display $CD8^+$ lymphocytopenia [613]. Low CD8 T-cell counts at diagnosis are associated with a worse prognosis and increase risk for infection related-death [741]. Low memory CD27 + B or NK cell counts have also been reported in others [186, 298, 405, 613, 618].

A slight hypogammaglobulinemia involving IgG and IgA is often associated [298, 618].

Finally, the diagnosis is based upon the exclusion of known causes of CD4 lymphopenia, especially HIV infection. Moreover, secondary CD4 lymphopenia has also to be excluded before concluding to idiopathic CD4 lymphocytopenia.

2.18.5 Management

Because the similarity with the clinical manifestations observed in HIV patients, management can be based on the guidelines for these latter. However, because of the great clinical variability observed among patients, the clinical course of an individual patient has to be taken into account. Prophylactic treatment against *Pneumocystis jiroveci* can be proposed. The need for lifelong prophylaxis against Cryptococcus is debated. Some authors recommend it. However, the absence of relapse associated with a better

outcome of cryptococcosis in ICL than initially described, reported in a recent series, brings this prophylaxis into question [740, 742]. Anti-viral and anti-fungal prophylaxis may be proposed depending on the clinical history of the patient. Infection management has to include early diagnosis and appropriate treatment. Treatment by interferon γ, in association with antifungal treatment, has been useful in a patient who presented cryptococcosis [471].

Some treatments intended to increase CD4 lymphocytes have been reported. IL-2 treatment has improved CD4 count in some patients treated [142, 629, 661, 692, 704, 723]. However, one of them developed gastric aplastic large cell lymphoma more than 1 year after treatment initiation, without a clear relationship between the treatment and the occurrence of malignancy [688].

Allogenic HSCT performed in a patient who had developed aplastic anemia has led to complete immune reconstitution [511].

2.19 TCRα Deficiency

2.19.1 Definition

TCR alpha deficiency represents a severe immunodeficiency recently described in two unrelated patients from Pakistani origin [447] carrying mutations in the gene encoding the TCRα subunit constant gene, mapping on the chromosomal region 14q11.2. The mutation was identified by genetic linkage studies using polymorphic microsatellite markers and genome-wide SNP genotyping.

2.19.2 Etiology

Mutations identified in the two patients at homozygous level (c.*1G>A substitution) impairs TRAC splicing transcript. The mutation was located in the consensus 5' splice site of TRAC gene and causes an exon skipping of the last coding exon 3, resulting in the direct joining of exon 2 to the untranslated exon 4. The mutated protein lacks the transmembrane and cytoplasmic domains of the TCRα subunit constant gene.

2.19.3 Clinical Manifestations

Infections represent the main clinical signs of this rare immunodeficiency. TRAC patients suffer from recurrent respiratory tract infection, otitis, candidias, diarrhea and failure to thrive. Viral infections, herpes, chronic EBV infections have been reported in the two affected children described in literature. In particular, one patient showed an increased susceptibility to develop severe herpes virus infection.

Patients also suffer from lymphoadenopathy and organomegaly. Skin manifestations, such as eczema, have been reported and alopecia can be present. Autoimmune hemolytic anemia, autoantibodies (anti-TTG, anti-ANA) have been reported in affected patients. One patient showed increased susceptibility to severe herpes virus infection.

2.19.4 Diagnosis

The diagnosis is done on the basis of the profound reduction of TCRαβ surface expression evaluated by flow cytometric analysis. In the two affected patients, conventional $CD3^+$ T cells expressing TCR γδ were present along with an abnormal population of $CD3^{low}$ cells expressing TCR αβ at very low level. Thymic emigrants ($CD45RA^+$ $CD27^+$) are present within the $CD3^{hi}$ subset, although T cells are present, they poorly proliferate in response to phytohemagglutinin and OKT3. B cells and immunoglobulin levels in peripheral blood were detected within the normal range. Humoral immunity against vaccine antigens was maintained.

2.19.5 Management

Regular antibiotic prophylaxis is required to prevent infections; however, HSCT could be considered the treatment of choice. HSCT has been

performed with success in both patients reported in literature at the age of 6 and 7 years, upon reduced intensity conditioning.

2.20 CRAC Channelopathy

(ORAI-1 deficiency, STIM-1 deficiency)

2.20.1 Definition

This immunodeficiency identified in 1994 is characterized by the lack of intracytoplasmic calcium increase after immunoreceptor engagement [210, 212, 213, 371, 503]. While the functional characteristics are similar in all patients, two genetic causes, responsible for this immunodeficiency, have been identified, a mutation in *ORAI1* (OMIM*610277) and a mutation in *STIM1* (OMIM*605921) [363]. To date patients from only 6 families having such an immunodeficiency have been reported, 3 had the *ORAI1* mutation and 3 the *STIM1* one.

2.20.2 Etiology

Calcium signals are second messengers that play a crucial role in immune and in non-immune cells. For example, in T lymphocytes, TCR/CD3 triggering leads to the kinase activation described in the Sect. 2.15, and subsequently to ZAP-70 dependent phosphorylation and activation of the phospholipase Cγ (PLCγ) which then hydrolyses phosphatidylinositol- 4,5 biphosphate (PtdIns(4,5)P2) to diacylglycerol (DAG) and Inositol-1,4,5- triphosphate (InsP3). The binding of InsP3 to the Ca2+ permeable ion channel, the InsP3 receptor at the endoplasmic reticulum (ER) membrane level, induces Ca2+ release from ER stores. Ca2+ depletion of ER stores results in store operated Ca2+ entry (SOCE) mainly mediated by the Calcium 2+ release activated channel (CRAC) in plasma membrane [168, 209].

The structure of the CRAC channel was an enigma for a long time. Two independent genetic analyses, that are genome-wide SNP analyses of two patients presenting a Ca++ Channel deficiency and their relatives, and genome-wide RNA interference screen in Drosophila, allowed the identification of ORAI1, a component of the CRAC channel [212, 676, 728]. ORAI1 is a ubiquitous transmembrane protein with four membrane domains and its tetramer constitutes the pore-forming subunits of the CRAC channel [276]. The role of the two homologues of ORAI1, ORAI2 and ORAI3, in human lymphocytes is unknown [599].

The mechanism of CRAC channel activation by the Ca2+ depletion of ER stores has been elucidated by the identification of STIM 1 and STIM2 by two independent approaches [389, 560]. STIM1 and STIM2 are calcium sensors of ER. However, in humans the role of the each protein seems different: STIM1 controls calcium entry after ER store depletion and STIM2 is the sensor of basal ER calcium [546].

The ubiquitous protein STIM1 is located in the ER and cytoplasmic membrane. Ca2+ depletion of ER results in Ca2+ dissociation from STIM1 and then successively to the multimerization of STIM1and its binding to ORAI1 that provides a physical basis for the activation of Ca2+ influx [397, 599].

To date, mutations of *ORAI1* have been identified in six patients from three families (OMIM:612782) [212, 426]. In one family, the non-sense mutation (A88fsX25) has been found to be homozygous in patients. This mutation leads to an absence of protein expression. In contrast, in another family, the mutation R91W leads to an amino acid substitution in the first transmembrane domain and the normally expressed protein exerts a transdominant negative effect as judged by the partial SOCE defect observed in cell form heterozygous parents. Two other missense mutations, A103E and L194P, which, respectively, involved the second and the third transmembrane domains, are found in double compound patients of the third family. The altered proteins are not expressed in these patients' cells in spite of a normal mRNA level suggesting that these mutations lead to protein instability.

Three STIM1 mutations have been reported in three families (OMIM:612783). The patients

were homozygous for these mutations. The first mutation was an insertion (380insA) which leads to a stop codon at position 136 E136X) and to the absence of the protein. In second family, the mutation found by whole exome sequencing was a splice site mutation which led to an abnormal mRNA and to the absence of the protein. In contrast, in the third family, the Arg429Cys mutation led to the normal expression of an abnormal protein. The amino acid 429 is located in the cytoplasmic domain of STIM1 that binds to ORAI1. Thus, the altered protein seems to exert a dominant negative effect.

2.20.3 Clinical Manifestations

Twelve patients with CRAC deficiency were analyzed if we consider patients with identified mutations and siblings with clinical manifestations compatible with immunodeficiency. The infectious manifestations occurred before 3 months of age in all patients except in one patient who suffered from a Kaposi Syndrome at 2 years. [92, 210, 212, 213, 230, 371, 426, 503, 515]. The clinical manifestations, including BCGitis, viral (EBV, CMV and HSV) dissemination, toxoplasmosis encephalitis and candidiasis, are very close to those observed in severe combined immunodeficiencies. Only one ORAI1 mutated patient had neutropenia and thrombocytopenia as autoimmune manifestations. In contrast, all the patients with STIM1 mutations had autoimmune manifestations and lymphoproliferative syndrome (splenomegaly, hepatomegaly and adenopathies) which can be considered to be fully part of STIM1 deficiency. The most observed autoimmune manifestations are cytopenias (mainly anemia and thrombocytopenia) but one patient had a joint effusion related to the presence of anti-nuclear antibodies. Moreover, some of them had a more or less severe eczema. The hallmark of SOCE deficiencies is the association with extrahematopoietic manifestations, ectodermal dysplasia and congenital myopathy. Ectodermal dysplasia consists in a defect in dental enamel formation associated in some patients with anhydrosis and nails defect. The myopathy results from type 2 muscle atrophy and leads to a global hypotony with delayed walking and later to respiratory failure due to respiratory musculature involvement. In addition, patients with STIM1 deficiency had a partial iris hypoplasia. The presence of ectodermal dysplasia and of myopathy in patients with SOCE deficiency, as the muscular defect observed in mice stim1-/- or Orai1-/-, suggest that STIM1- and ORAI1-dependent SOCE is crucial for the development and/or function of skeletal muscle and of ameloblast. The anhydrosis observed in ORAI1 deficiency illustrates that secretion by the epithelial cells of the sweat glands is SOCE-dependent [344]. Only one ORAI1 deficient patient presented facial dysmorphy and two an encephalopathy. Thus, it is improbable that theses manifestations are related to SOCE deficiency.

2.20.4 Diagnosis

In all patients, activation-induced extracellular Ca2+ influx is absent, contrasting with normal Ca2+ release from ER stores. This calcium influx defect is seen after receptor triggering, but also when thapsigargin, an inhibitor of the SERCA (sarcoplasmic endoplasmic reticulum calcium ATPase) which pumps calcium from the cytoplasm into the ER, is used to deplete internal Ca^{2+} stores. All these observations point to a defect in SOCE. This SOCE defect is found in T, B and NK cells as well as in non hematopoietic cells such as fibroblast [211, 371, 422, 503]. The SOCE deficient T lymphocytes display an activation defect including inability to activate the transcription factor NF-AT and consequently to produce cytokines (Fig. 2.4) [213, 371]. Neutrophils and platelets display the same defect without detectable functional consequences [371].

In these patients, T-cell differentiation is unaffected. All blood lymphocyte populations including CD4, CD8, TCR α/β and TCRγ/δ T cells, B lymphocytes and NK cells are normally present. Some patients presented hyperlymphocytosis. The distribution of T lymphocytes between

memory and naïve is variable from one patient to another one. Some patients had nearly normal a proportion of naïve (CD45RA) T-cells. In contrast, another patient had very few naïve T-cells with an excess of terminally differentiated CD8 T cells. [213, 230, 371, 426]. These phenotypic abnormalities could not be related to SOCE deficiency itself, but more probably to chronic infectious complications. In contrast, in the patients tested, the NK-T cell population defined as CD3+Va24+Vb11+ is absent. The presence of TREG has been studied only in two STIM1 deficiency patients and was found low in one [515] and normal and functional in the other one [230].

The diagnosis is based on poor proliferative response to mitogens including PHA and anti-CD3 monoclonal antibody, that is partially restored by exogenous IL2 [213, 371]. The expression of cytokines by T lymphocytes such as IL2, IL4, IL10, IFNγ TNFα and IL-17is also altered. In some patients, proliferation induced by the association of PMA and Ionomycin is also low [213]. Paradoxically, in one patient, specific antigen-induced proliferation is detectable [371] as anti-viral cytotoxicity in another one.

Hypergammaglobulinemia is often observed and involves IgG, IgA and IgM. In one patient, IgG displayed restricted heterogeneity. The antibody response to immunization is absent in most cases. However, some patients are able to mount antigen specific antibodies in response to either immunization or infection [230].

2.20.5 Management

The severity of the clinical manifestations justifies HSCT, which has been successfully performed in four patients [213, 371].In at least some cases, partial donor chimerism is sufficient to correct the immunodeficiency. However, the patients have developed extra hematopoietic manifestations such as muscular dysplasia and hypohydrotic ectodermal dysplasia after transplantation. It is notable that all untransplanted patients died before 1 year of age.

2.21 STK4 Deficiency (MST1 Deficiency)

2.21.1 Definition

STK4 deficiency (OMIM*614868) represents a very rare combined immunodeficiency characterized by progressive loss of naïve T cells, intermittent neutropenia, recurrent bacterial and viral infections, disseminated warts and skin abscesses [1, 469]. Heart atrial septal defects can also be present [1]. Patients carrying biallelic defect in *STK4* gene (OMIM*604965) located on chromosome 20q13.12 and encoding a serine threonine kinase 4.

2.21.2 Etiology

The molecular defect of this novel immunodeficiency has been identified in mutations in STK4 gene (previously named MST1) encoding a serine threonine kinase with homology to yeast Ste20 [136, 647] and to the highly conserved HIPPO [729], which plays a role in controlling apoptosis, tumorigenesis. Indeed STK4 acts as proapoptotic factor by promoting Fas-mediated apoptosis [492] and upon apoptotic stimuli, it is cleaved by caspases and translocate into the nucleus [117, 701]. Of note it also plays anti-apoptotic function by protecting cells against death caused by oxidative stress [376]. The gene contains at the N-terminal a catalytic domain and C-terminal coiled-coil SARAH domain mediating hetero and homodimerization [374].

Null mice have been generated and show progressive T and B cell lymphopenia due to increased apoptosis and severe reduction in thymic egression and impaired ability to home peripheral lymph nodes [178, 730]. Similarly, patients carrying mutations in MST1 gene have immunophenotype resembling the mouse model. STK4 deficient cells have a higher degree of apoptosis and show rapid death upon mitogens and antigens stimulation. Interestingly, the analysis of mitochondrial transmembrane

potential in T cells and neutrophils granulocytes from the patients showed an increased dissipation leading to increased apoptosis [1].

The mutations reported so far in literature are spread over the gene and lead to a truncated protein. In particular, de Saint Basile' group described four patients from two unrelated Turkish families carrying a homozygous stop mutation (R117X) at the kinase domain of the gene, while three individuals from a second family of Iranian origin showing a single nucleotide deletion (1103delT) causing a frameshift at residue 369X [469]. In parallel, a homozygous premature termination mutation (W250X) in exon 7 was reported in other three patients [1]. More recently, a stop mutation (R115X) has been described in the kinase domain in a patient with profound T-cell deficiency and recurrent infections and epidermodysplasia bullosa [137].

2.21.3 Clinical Manifestations

Patients with MST1 deficiency usually present during the first years of life with recurrent and/or severe infections, such as oral candidiasis and pneumonias often caused by *Streptococcus pneumonia*, *Haemophilus influenzae* or viral agents (e.g. Varicella zoster virus, HPV, HSV). Epstein Barr virus infections are frequently observed, and of note EBV B-cell-lymphoproliferative syndrome can develop. Mucocutaneous candidiasis and skin manifestations are frequent and range from erythematous lesions to disseminated flat warts caused by EV-HPV infections. Skin infections caused by Molluscum contagiosum are also observed. Recently, epidermodysplasia verruciformis caused by a specific group of related human papillomavirus genotypes, has been described in a 19-year-patient with T-cell deficiency [137]. Finally, three patients reported by Klein's group showed structural cardiac abnormalities including atrial septal defect [1] likely caused by the impact of modifier genes.

2.21.4 Diagnosis

Clinical history indicates recurrent bacterial and viral infections. Laboratory findings indicate a progressive reduction in naïve T cells and memory T cells, while effector memory T cells are less affected. Gaussian distribution of Vbeta subclasses may be altered. B cells are also decreased with a relative increased frequency in transitional B cells. Hypergammaglobulinemia and elevated IgE have been reported. Interestingly, patients develop autoantibodies. Continuously or intermittent neutropenia has been reported [1] in the absence of defect of neutrophil maturation.

2.21.5 Management

Treatment depends on the severity of the disease, Immunoglobulin replacement and anti-infective prophylaxis are indicated. Anti-CD20 Abs along with HSCT has been used to cure autoimmune hemolytic anemia [469]. However, HSCT represents the treatment of choice to cure the disease.

2.22 CARD11/BCL10/MALT1 (CBM) Complex Deficiencies

2.22.1 Definition

Recently, two families with CARD11 (also called CARMA1) deficiency have been reported [268, 625] as well as two families with a MALT1 deficiency [313, 430]. The consequences observed are related to the crucial role played by the CARD11/BCL10/MALT1 complex (CBM) in the NF-kB pathway.

2.22.2 Etiology

Following the stimulation of antigen receptor (TCR and BCR), the transcription factor NF-kB is activated and translocated in the nucleus. This family of transcription factors plays a crucial role in the control of activation, proliferation and

survival. In basal situation, cytoplasmic NF-kB is inhibited by Ik-B, which masks its nuclear localization domain. After activation, Ik-B is phosphorylated by the Ik-B kinase (IKK) complex made of NEMO, IKKα and IKKβ. This phosphorylation allows the ubiquitination of Ik-B and therefore the translocation of NF-kB to the nucleus. However, it has been shown that CARD11 (also called CARM1) is essential for a complete NF-kB activation in mature T and B cells. The proteins of the CARMA family contain a N-terminal CARD (Caspase Recruitment Domain), a coiled-coil domain, and a MAGUK domain including a PDZ, a SH3 and a C-terminal Guanylate Kinase-like domain. Each protein has distinct and non-overlapping tissue distribution and CARD11 is expressed in hematopoietic tissues. Upon TCR or BCR triggering, CARD11 is phosphorylated by several kinases including at least protein kinase C (PCK θ in T cells and PKCβ in B cells) in its linker domain. The phosphorylation-induced conformational changes of CARD11 enable it to associate with its downstream signaling components especially the preformed BCL10-MALT1 complex. MALT1 (Mucosa-associated Lymphoid Tissue Lymphoma Translocation Gene 1) is a caspase-like cysteine protease. It contains an N terminal Death domain followed by two immunoglobulin-like domains capable of interacting with the CARD domain of BCL10 and a C terminal caspase-like domain.

This newly formed CBM complex is crucial for IKK activation, probably due to a direct interaction between CARD11 and NEMO [63, 565, 653, 654]. However, MALT1 does not seem to be essential for BCR activated canonical NF-kB pathway in contrast to the non-canonical NF-kB-pathway activated downstream BAFF-R. Especially, it has been shown that this pathway is of importance for the BAFF-induced survival of marginal zone B, but not of follicular B lymphocytes [386, 566, 665].

In both families, the *CARD11* mutations were found to be homozygous (OMIM*607210). In the first family, the mutation consists in a large deletion (1377 bp) encompassing exon 21, and the protein is not detectable. The second mutation (2833C>T) introduces a premature stop codon at position 945 and the abnormal protein is deprived of the gaunylate kinase domain.

Homozygous missense mutations of *MALT1* were found in 2 families (OMIM*604860). The two mutations result in an amino acid substitution, the first one (266G>T) at position 89 (serine to isoleucine) in the CARD domain of the protein and the other (1739 G>C) at position 580 (tryptophan to serine) in the C-terminal domain. These proteins are probably instable since they are only few or not detected. When detectable, the protein is not able to bind to BCL10 to form the CBM [430].

2.22.3 Clinical Manifestations

In the first family with CARD11 mutation, two siblings had clinical symptoms of SCID before the diagnosis in the index case. Only one case is reported in the second family. The age at presentation was between 3 and 6 months. Two patients had pneumonia due to *P. Jiroveci*. Two patients died respectively at 3 and 15 months of age because of respiratory failure, one had meningitis and recurrent pneumonias before. The clinical phenotype is very close to that observed in the SCID patient.

The three patients with the *MALT1* mutation had recurrent pulmonary infections, which began at an early stage (4 months of age in one patient), and which can lead to respiratory failure. Several bacteria were found in the bronchoalveolar liquid including *Pseudomonas, Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae* and *Staphylococcus aureus. Streptococcus pneumoniae* and *Haemophilus influenzae* were also responsible for meningitis in one patient. CMV has been found in one patient. In all patients, the oral mucosa is involved and gingivitis, cheilitis and aphtous ulcers with oral inflammation can be observe. Inflammatory digestive manifestations such as esophagitis, gastritis and duodenitis were present associated with villous atrophy in one patient and T cell lymphocytic infiltration in another one [430]. In addition, one patient had dermatitis complicated by infections (*Staphylococcus aureus*, VZV and HSV).

One patient had dysmorphic facial features. The severity of the lung lesions is illustrated by the death of two patients, at 13.5 and 7 years of age, respectively, because of respiratory failure.

2.22.4 Diagnosis

The immunological investigations are available for two CARD11-deficient patients. Blood cell, including lymphocyte, count was normal. CD4 and CD8 T lymphocytes, like NK-T cells, were normally represented and displayed a nearly normal phenotype regarding the naïve and memory T cells. T cell repertoire was normal. In contrast, TREG were absent. Total B cells were normally present. However, the B cells are predominantly naïve (IgD+, CD27-) with a transitional B-lymphocyte phenotype (CD38+CD10+). The TREC and KREC analysis were normal, mirroring the normal presence of T and B lymphocytes. NK cell count was normal in one patient and low in the other one.

Normal B cell presence contrasted with the panhypogammaglobulinemia found in the three patients tested.

Anti-CD3 induced T cell proliferations were profoundly impaired whereas PHA can promote a residual proliferation. In parallel, the CARD11 deficient CD4 T lymphocytes failed to secrete IL-2, IL-17 and IFNγ after activation with PMA and Ionomycn and to upregulate OX40, CD25 and ICOS expression after CD3 triggering, contrasting with a normal upregulation of CD40L and CD69.

The consequences of CARD11 deficiency have also been studied on B lymphocyte functions. Anti-IgM and PMA failed to induce Ik-B degradation whereas CD40L did. In the same way, the absence of BCR dependent upregulation of CD25 and ICAM expression on B cells contrasts with the normal induced expression of these molecules after CD40L stimulation. In all activation situations, CD69 and CD86 expression is upregulated. Altogether, these data confirm the crucial role of CARD11 in NF-kB activation driven by TCR and BCR, but not by CD40 [63, 565, 653, 654].

In conclusion, the diagnosis of CARD11 deficiency has to be evoked in patients with clinical manifestations close to those observed in SCID patients and who have panhypogammaglobulinemia with normal T and B cell counts.

As expected, the characteristics of MALT1-deficient T lymphocytes are similar to those of CARD11-deficient T lymphocytes: 1- Normal lymphocyte counts including T (CD4 and CD8), 2- Normal distribution of naïve CD45RA and memory CD45R0 among CD4 lymphocytes, 3- Absence of anti-CD3-induced T cell proliferation, 4- A residual or an absence of PHA- and ConA-induced proliferation, and 5- Failure of IkBα degradation and NF-kB p65 phosphorylation after T cell activation.

However, the B cell compartment is very different. Serum immunoglobulin levels are normal in all patients and elevated serum IgE was found in one patient. Two patients display no production of antibody to T-independent antigens such pneumococcal polysaccharides after vaccination, and of natural isohemagglutinins and a poor production of anti-tetanus antibody in spite of a normal number of blood B lymphocytes. However, the third patient who had no anomaly of antibody production displayed a low number of B lymphocytes which are mainly naïve B cell. The marginal B lymphocytes are absent and switched memory B cells are reduced. These observations confirm that the integrity of the CBM complex is crucial for the TCR-driven activation and that MALT1 is important for the survival of marginal zone B lymphocytes dependent of the BAFF-R pathway.

2.22.5 Management

According the severity of the clinical symptoms including *P. jirovicii* infections, the only appropriate treatment is HSCT. Moreover, the two patients who did not receive this treatment died before the age of 15 months. The other two, who received such a treatment, are well. In one case, the donor was an HLA identical brother and the chimerism was complete 5 months after the transplant. The other patient received transplantation with a

matched unrelated donor after a toxicity reduced conditioning regimen and 12 months after, the chimerism was mixed.

Although the MALT1-deficient patients received intravenous immunoglobulins from infancy, they both died because of pulmonary failure. By analogy with the CAR11 deficiency and the profound alteration of T-cell functions, HSCT could be proposed as curative treatment.

2.23 RHOH Deficiency

2.23.1 Definition

Ras homolog gene family member H gene (RHOH) deficiency is a recently described CID that predisposes patients to human papillomavirus (HPV) infection.

2.23.2 Etiology

Ras homolog gene family member H gene (*RHOH*; OMIM*602037) is expressed mainly in hematopoietic cells [272], and its activity is regulated at the transcriptional and posttranslational levels. On TCR stimulation, RhoH undergoes tyrosine phosphorylation and mediates recruitment of Zap70 and Lck to the TCR/linker of activation in T cells (LAT) signalosome [179]. The gene was first identified as part of a fusion transcript with Bcl-6 as a result of a t(3;4) (q27;p11) translocation in diffuse large B cell lymphoma [147]. Using next generation exome sequencing technology, a homozygous nonsense mutation (Y38X) in the Ras RHOH gene has recently been found to cause immunodeficiency in two young adult siblings born to consanguineous French parents [138].

2.23.3 Clinical Manifestations

Both patients manifested with persistent cutaneous HPV infection resembling epidermodysplasia verruciformis and psoriatic lesions. One of them developed Burkitt's lymphoma in childhood and granulomatous lung disease, whereas the younger one had molluscum contagiosum, and gingivostomatitis.

2.23.4 Diagnosis

Both patients showed no major abnormalities in the total T cell counts, frequencies of B cell subsets, NK cells, and in antibody production. However, the patients had low naïve T cells and recent thymic T cell emigrants with an increased proportion of effector memory T cells and TEMRA cells. The patients also showed restricted T cell repertoire and impaired T cells proliferative responses using anti-CD3 but variable responses using mitogens and recall antigens simulation.

2.23.5 Management

No curative immunologic treatment was used for both patients. However, standard therapeutic protocols should be used to treat disease complications like Burkitt's lymphoma, lung granulomas or viral infections.

2.24 OX40 Deficiency

2.24.1 Definition

Kaposi sarcoma (KS) is a rare human herpes virus 8 (HHV-8))–induced endothelial tumor. It was recently linked to OX40 deficiency.

2.24.2 Etiology

Using both genome-wide linkage analysis by homozygosity mapping and whole-exome sequencing, a homozygous mutation in *TNFRSF4* (OMIM*600315) which encodes OX40 was found in a young Turkish women [93, 572]. OX40 is a co-stimulatory molecule, which has been implicated in long-term T cell immunity [140].

2.24.3 Clinical Manifestations

The patient presented with childhood-onset classic KS and visceral leishmaniasis.

2.24.4 Diagnosis

Immunologic testing showed normal proportions of T, B, and NK, in PBMCs. However, the patient had a low proportion of effector memory CD4+ T cells in the peripheral blood and PBMCs showed impaired IFNγ production in response to antigenic stimuli (BCG, tetanus, CMV, EBV, VZV and HSV-1) and the CD4+ T cells showed weak proliferation in response to the same antigens. The serum immunoglobulins and antibody responses to previous vaccines were normal. In contrast, the frequencies of in vitro–generated total IgG-secreting B cells and the circulating memory B cells were low compared to healthy controls. Furthermore, OX40 levels were lower, but not abolished, on the surface of activated T cells from the patient.

2.24.5 Management

The patient was treated initially with IFN-α2a therapy. Due to bad response, vinblastine was started and then switched to etoposide which resulted in regression of the lesions.

2.25 IL21/IL21R Deficiency

2.25.1 Definition

Recently, six distinct homozygous mutations in the *IL21R* gene (OMIM*605383) and only one homozygous mutation in the *IL21* gene (OMIM*605384) have been described [202, 349, 350, 578, 624].

2.25.2 Etiology

Interleukin-21 regulates proliferation and activation of T- and B- cells and promotes cytotoxicity of NK- cells [329, 502]. Interleukin-21 receptor gene (IL21R) binds to the common γ chain (*IL2RG*, γc) to transmit signals via JAK–signal transducer and activator of transcription (STAT) pathways. IL-21 has been shown to play an important role in the immune response by regulating proliferation of T lymphocytes, B cell differentiation and cytotoxicity of NK cells [228, 329, 502, 529]. Homozygous loss-of-function mutations in the IL21R gene has recently been found to cause and autosomal recessive combined primary immunodeficiency [350].

2.25.3 Clinical Manifestations

The patients with IL21R deficiency showed increased susceptibility to cryptosporidia and cholangitis, sinopulmonary infections, and both candida and *Pneumocystis jiroveci* infections. Meanwhile, the case with IL21 deficiency presented with early-onset inflammatory bowel disease and common variable immunodeficiency-like disease.

2.25.4 Diagnosis

Immunologic testing of IL21R deficiency showed normal T and B lymphocytes counts, but abnormal T cell proliferation to specific stimuli. The serum immunoglobulin levels were normal except for high total IgE and the patients had impaired specific antibody responses. They also showed impaired IL-21-induced proliferation and immunoglobulin class-switching in B cells, abnormal T cell cytokine production, and poor NK cell cytotoxicity. IL21 deficiency led to decreased number of B cells.

2.25.5 Management

Liver and stem cell transplants were performed in one patient each and both patients died due to serious infections. The other two patients were too sick to undergo any transplant. This demonstrates the importance of early identification of such cases to reach good outcome.

2.26 IKAROS Deficiency

2.26.1 Definition

IKAROS deficiency is a rare immunodeficiency, which belongs to the complex group of combined T and B cell immunodeficiency. The gene is located on chromosome 7 (p13) and codes a zinc finger protein playing a crucial role in regulating the functional properties of the remodeling complexes recruited to gene loci during lymphocyte differentiation. Mutation has been reported in individual with severe pancytopenia, absence of B and NK cells.

2.26.2 Etiology

The *IKAROS* gene encodes for a C2H2 zinc finger protein originally isolated from a screen for transcriptional regulators controlling T cell differentiation and regulating gene expression via chromatin remodeling [79, 247]. It is specifically expressed during lymphocyte development and outside the hematopoietic system, Ikaros mRNA has been found in a small area of the developing corpus striatum. Interestingly, when this nuclear factor is expressed ectopically in non-lymphoid cells, it acts as a transcriptional activator. Four isoforms differentially expressed during T-cell ontogeny have been isolated [443] and show a diverse transcriptional and cellular localization. In B cells, distinct activities of Ikaros mediate V(D)J rearrangement downstream FoxO1 and cooperate with Pax5 in the rearrangement of distal V(H) genes [20]. Recently, it has been demonstrated that Ikaros regulates the genomic distribution of the Mi-2b nucleosome-remodeling and histone deacetylase (NuRD) [725] complex during T cell differentiation in a DNA site-specific and independent manner.

The gene contains four Kruppel type zinc fingers organized in two domains [638]. Deletion of the N-terminal zinc finger domains leads to early and complete arrest in lymphocyte differentiation, while mutations in the C-terminal zinc fingers, which ablate Ikaros protein interactions have a dramatic effect on the ability of these proteins to bind DNA and activate transcription. In particular, it has been demonstrated that transcriptionally inactive, but not transcriptionally active genes associate with Ikaros-heterochromatin foci [79]. Accordingly, Ikaros binds to the DNA control elements of target genes thus allowing their recruitment to centromeric foci where they are transcriptionally silenced.

Mice lacking Ikaros DNA binding domain are devoid of T and B-lymphocytes and natural killer cells and their earliest defined progenitors [246]; thus highlighting its role in the differentiation of pluripotential hematopoietic stem cells into the lymphocyte pathways. Additionally, mice carrying a hypomorphic mutation show defects in early neutrophil differentiation, while it is dispensable in mature neutrophils [184]. More recently, Schjerven and coworkers generated trasgenice mice lacking different zinc finger domains demonstrating the different role played by each ZNFG region in B, NK and plasmacytoid cells development [589].

In humans, deletions in Ikaros have been identified in acute lymphoblastic leukemia [331, 457] and genetic lesions resulting in the loss of Ikaros function have been demonstrated to be an important event in the development of BCR-ABL1 ALL [458]. Overexpression of the dominant negative isoform of Ikaros gene Ik-6 was observed in human B-cell malignancies [464], in acute myelomonocytic and monocytic leukemias [720]. Furthermore, decreases in Ikaros activity have been reported in blast crisis in chronic myeloid leukemia thus suggesting that mutations that alter Ikaros expression may contribute to human hematological malignancies [465]..

More recently, a case of combined immunodeficiency syndrome characterized by thymic hyperplasia and impaired system function has been described [474].

2.26.3 Clinical Manifestations

The first patient described to carry mutations in *IKAROS* gene [474] started to show signs of severe immunodeficiency at the age of 16 years, when she developed disseminated

varicella-zoster infection. Over time, severe sinopulmonary infections have been also observed. Hypogammaglobulinemia, severe defect in IgA production and profound B cells and NK cells deficiencies have been reported. Computed tomography revealed the presence of important thymic hyperplasia resembling the phenotype observed in the Ikaros-null mouse in which thymoma was present likely caused by aberrant regulated T cell receptor signaling leading to T cell hyperproliferation [689]. More recently a severe bone marrow aplasia, selective lymphopenia caused by low B cell number (<1 %) and near absent NK cells (<1 %) was reported in a premature male infant of Caucasian origin carrying a missense at position 629 in the coding mRNA of Ikaros in only one allele [258]. T cells were normal in frequency, however further immunophenotype showed absence of CD45RO, and the vast majority of T cells expressed TCR αβ. T cells did not respond to mitogens and anti-CD3.

2.26.4 Diagnosis

Congenital pancytopenia associated with severe aplastic anemia has been observed in patients with Ikaros deficiency. Severe immunodeficiency caused by absent B and NK cells leads to increased susceptibility to develop infections. Infections from *Pseudomonas aeroginosa* and cellulitis have been reported [258]. Pulmonary failure has been reported as a consequence of repeated lung infections, and renal dysfunction can occur. All these immunological features resemble the immunophenotype of Ikaros null mice.

2.26.5 Management

The treatment of choice for Ikaros deficiency is allogeneic HSCT. Reduced intensity myeloablative preparative conditioning regimen associated with horse anti-thymocyte globulin was used [258]. Antibiotics, IVIG and nutritional support were used prior to HSCT.

2.27 IKK2 Deficiency

2.27.1 Definition

IKK2 deficiency (OMIM #615592) is an autosomal recessive combined immunodeficiency, characterized by early onset life-threatening bacterial, fungal, and viral infections and failure to thrive. Only five cases have already been reported [475, 497, 612].

2.27.2 Etiology

IKK2 deficiency is caused by homozygous mutation in the *IKBKB* gene (OMIM*603258). Pannicke et al. performed genetic studies in four patients with clinical characteristics of SCID, but normal B- and T- cell numbers. The patients carried a homozygous mutation of *IKBKB*, leading to loss of expression of IkB kinase 2 (IKK2), a component of the IKK-nuclear factor kB (NF-kB) pathway [497].

2.27.3 Clinical Manifestations

Patients with IKK2 deficiency suffer from SCID clinical characteristics, including early onset of severe viral, bacterial, and fungal infections [497]. The second report showed pneumonia with *Pneumocystis jiroveci* and systemic infection with Mycobacterium bovis, which led to her death [475].

2.27.4 Diagnosis

The patients with IKBKB deficiency have hypo- or agammaglobulinemia, with relatively normal number of B- and T- cell numbers. Regulatory T cells and γδ T cells were absent. Functional studies show impaired differentiation and activation of immune cells [497]. Hyper IgM phenotype has also been reported [475].

2.27.5 Management

While only a few cases have already been reported, therapeutic options should be tried. HSCT should be the treatment of choice in this group of patients.

2.28 NIK Deficiency

2.28.1 Definition

NIK deficiency is an autosomal recessive disorder that has recently been described in a large consanguineous family with two patients suffering from combined immunodeficiency phenotype [709].

2.28.2 Etiology

NIK (NF-kB- Induced Kinase) deficiency is caused by mutation in the *MAP3K14* (OMIM*604655) gene encoding NIK. Loss of kinase activity of mutant NIK leads to defective activation of NF-kB signaling. Hypogammaglobulinemia could be occurred due to impaired survival of B-cells and impaired expression of ICOSL [709].

2.28.3 Clinical Manifestations

Recurrent and severe bacterial and viral infections, candidiasis, and *Cryptosporidium* infection have been reported in patients with NIK deficiency. Granulomatous hepatitis and tuberculosis osteomyelitis due to BCG dissemination was reported in a case with NIK deficiency [709].

2.28.4 Diagnosis

Patients with NIK deficiency have decreased B- and NK- cell numbers, decreased immunoglobulin levels, and decreased class-switched memory B-cells [709].

2.28.5 Management

Allogeneic HSCT after reduced toxicity conditioning was successfully performed in a case with NIK deficiency. However, allogeneic HSCT without conditioning was unsuccessful in the second patient [709].

2.29 CTPS1 Deficiency

2.29.1 Definition

CTPS1 deficiency (OMIM*615897) is an autosomal recessive combined immunodeficiency, which has recently been described in five families with one or two affected children [415].

2.29.2 Etiology

CTPS1 deficiency is caused by mutations in the *CTPS1* gene (OMIM*123860), encoding CTP synthase 1, which is essential for lymphocyte proliferation.

2.29.3 Clinical Manifestations

Early onset recurrent encapsulated bacterial infections as well as severe chronic viral infections, including EBV and VZV have been reported in CTPS1 deficiency. Two patients suffered from EBV-driven B-cell non-Hodgkin's lymphoma [415].

2.29.4 Diagnosis

CTPS1 deficiency is characterized by variable lymphopenia and impaired proliferation of activated T- and B- cells in response to antigen receptor-mediated activation [415].

2.29.5 Management

Six of 8 reported patients with CTPS1 deficiency underwent HSCT [415].

2.30 Other Combined Immunodeficiencies

(DOCK8 deficiency, ITK deficiency, MAGT1 deficiency, CD25 deficiency, STAT5b deficiency, MTHFD1 deficiency, ICOS deficiency, LRBA deficiency)

2.30.1 Definition

There are some other combined immunodeficiency diseases, which have not been explained in other sections of this chapter; some of them are fully explained in other chapters.

Deficiency of dedicator of cytokinesis 8 (DOCK8) was found in 2009 to cause combined immunodeficiency disease (OMIM*243700) [200, 727]. *(See* Sect. 9.13 *for more details)*

IL-2-inducible T-cell kinase (ITK) deficiency is a recently described primary immunodeficiency (OMIM*613011) that is characterized by severe EVB-associated lymphoproliferative disease [305]. *(See* Sect. 5.9 *for more details)*

Mutations in the X-linked *MAGT1* gene have been recently reported to cause combined immunodeficiency now named X-linked immunodeficiency with Mg2+ defect, EBV infection and neoplasia (XMEN) (OMIM*300715) [382]. *(See* Sect. 5.8 *for more details)*

Human IL-2 receptor α chain deficiency (CD25 deficiency, OMIM*606367), caused by mutation in the *IL2RA* gene (OMIM*147730), is a combined immunodeficiency characterized by invasive viral and bacterial sinopulmonary infections, as well as lymphoproliferation and severe multi organ autoimmune disorders. *(See* Sect. 5.11 *for more details)*

Human STAT5B deficiency, a rare autosomal recessive primary immunodeficiency, caused by mutation in the *STAT5B* gene (OMIM*604260) [102, 461]. *(See* Sect. 5.12 *for more details)*

Methylene-tetrahydrofolate dehydrogenase 1 (MTHFD1) deficiency, a defect of vitamin B12 and folate metabolism, is due to mutation in the *MTHFD1* gene (OMIM*172460). *(See* Sect. 9.21 *for more details)*

Hypogammaglobulinemia associated with LRBA deficiency (OMIM*614700) and ICOS deficiency (OMIM*607594) is explained in details in Sects. 3.7 and 3.10, respectively.

2.30.2 Etiology

DOCK8 deficiency is caused by biallelic loss-of-function mutations in the DOCK8 gene, most of which lead to absent or trace amounts of expressed DOCK8 protein [726].

MAGT1 encodes for a membrane associated transporter that is highly selective for Mg2+ [263]. Two MAGT1 isoforms have been described: a 335–amino acid form that contains four transmembrane domains, and a longer (367 amino acids) form with five transmembrane domains and an intracytoplasmic tail that may be involved in signaling [78, 731].

The high affinity receptor for IL-2 is composed of three subunits: α (CD25), β (CD122) and γ (common γ) [438]. Whereas the β and γ chains are constitutively expressed on T cells, α chain expression is restricted to the early stages of thymocyte differentiation and to activated mature T cells. Although the β and γ chains together can form an IL-2 receptor of low affinity, the α chain cannot form a functional receptor in the absence of both the other chains [378]. The presence of the high affinity receptor on activated T cells is necessary for optimal proliferative responses to IL-2 after stimulation of the T-cell receptor. CD25 is also highly expressed on CD4+, naturally occurring T regulatory cells [224, 300, 335]. These specialized cells play an important role in a complex regulatory system which maintains tolerance to self [573], controls lymphocyte homeostasis [29] and regulates immune responses to various pathogens [55]. Naturally occurring T regulatory cells express FOXP3, a transcription factor which is essential for the development of these cells. Genetic abnormalities in FOXP3 result in a low number of T regulatory cells which leads to Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) [115].

The transcriptional activating factor STAT5b is required for efficient signaling through the growth hormone receptor, receptors which use IL-2 receptor common γ chain, γc (IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-21) and the receptors for erythropoietin (EPO), thrombopoietin (TPO), and granulocyte colony-stimulating factor (G-CSF) [37]. STAT5B homozygous deficient patients have typically moderate T and NK cell lymphopenia associated with high T cell activation, hypergammaglobulinemia, high IgE levels

and marked deficiency in insulin-like growth factor (IGF)-1 production [234, 306]. Since signaling from IL-2 is essential for sustaining FOXP3 expression in natural Tregs, patients with STAT5b deficiency were found to have markedly decreased FOXP3 expression in CD4+ T cells and defective Treg function [461].

Details on etiology of LRBA deficiency, ICOS deficiency, and MTHFD1 deficiency are presented in Sects. 3.7, 3.10, and 9.21, respectively.

2.30.3 Clinical Manifestations

Patients with DOCK8 deficiency are susceptible to viral infections, recurrent sinopulmonary infections, atopy, early onset malignancies and autoimmunity [13, 22, 227, 580, 634].

The clinical presentation of ITK deficiency resembles X-linked lymphoproliferative disease (XLP). Patients are also at risk of developing cytopenias, varicella and CMV infections, *pneumonitis jiroveci* pneumonia and an increased risk of lymphoma [388, 409, 626].

The clinical presentation of MAGT1 deficiency is characterized by chronic viral infections, EBV in particular, which led one patient to develop EBV-associated lymphoma. Other clinical features include recurrent upper respiratory tract infections, viral pneumonia, herpes simplex virus 1 infections, and chronic diarrhea.

The patients with CD25 deficiency showed a combination of both immunodeficiency and autoimmune manifestations. Severe viral infections such as CMV pneumonitis were part of the initial presentation and later on suffered persistent CMV disease and EBV infection. Lymphoproliferation was markedly evident in patients with lymphadenopathy and hepatosplenomegaly, while autoimmune manifestations were also strikingly apparent. The patient described by Caudy et al. [103] showed type I diabetes mellitus, hypothyroidism, and autoimmune hemolytic anemia and neutropenia.

STAT5B deficiency is characterized by growth failure, chronic lung disease caused by lymphocytic interstitial pneumonitits (LIP), and autoimmunity [102, 461].

Details on clinical phenotypes of LRBA deficiency, ICOS deficiency, and MTHFD1 deficiency are presented in Sects. 3.7, 3.10, and 9.21, respectively.

2.30.4 Diagnosis

Reported immunologic abnormalities in DOCK8 deficiency include T-cell lymphopenia that appears to be progressive, defective T-cell proliferation, decreased IgM, elevated IgE, eosinophilia and a variable IgG antibody response [633]. Patients were also found to have deficiency of CD27+ memory B cells and impaired CpG-driven B cell proliferation and immunoglobulin production [312], selective TH2 bias which may explain several features of the disease phenotype [13] and impaired NK cell functions [135, 440].

Most cases with ITK deficiency have shown progressive hypogammaglobulinemia, T-cell lymphopenia, and lack of circulating NKT cells which might contribute to EBV associated lymphoproliferation.

Immunologic defects of MAGT1 deficiency include CD4 lymphopenia, reduced numbers of recent thymic emigrants, and impaired T-cell proliferation in response to CD3 stimulation. By contrast, the T-cell response to phorbol 12-myristate 13-acetate and ionomycin is intact, which is consistent with a role for Mg2 in proximal intracellular signaling. This is associated with normal B cell activation and serum immunoglobulin levels.

The diagnosis of CD25 deficiency should be considered in patients who present with autoimmunity and immunodeficiency. The combination of recurrent infections and chronic candidiasis with enteropathy, end crinopathies, lymphadenopathy and other autoimmune manifestations may be suggestive of this deficiency. CD25 deficient patients share similar clinical features with other immunodeficiency such as IPEX (FOXP3 deficiency) and the Autoimmune Polyendocrinopathy Ectodermal Dystrophy (AIRE deficiency). Serology studies may also be of value in this condition. Assessment of

hormones levels as well as auto antibodies such as ANA, anti-mitochondrial antibodies, ANCA may help to better define the various autoimmune manifestations which associate with CD25 deficiency.

STAT5b deficiency should be considered in the differential diagnosis of a patient who is born with a normal birth length, but then acquires significant short stature and recurrent infections, particularly pulmonary, although clinical evidence of immunodeficiency may not necessarily be present.

Details on diagnosis of LRBA deficiency, ICOS deficiency, and MTHFD1 deficiency are presented in Sects. 3.7, 3.10, and 9.21, respectively.

2.30.5 Management

Early diagnosis and treatment is very important in all combined immunodeficiencies. Most patients with DOCK8 deficiency die prematurely of malignancies or infections, if they do not undergo HSCT. In CD25 deficiency, symptomatic and supportive treatment with total parenteral nutrition may be required. Prompt antibiotic, antiviral and antifungal therapy should be administered when required and hormonal replacement should be instituted and monitored. Immunosuppressive treatment with corticosteroids or cyclosporin A may provide temporal relief from some autoimmune manifestations. The only known cure for this condition is a bone marrow transplant. Engraftment is facilitated by myeloablative conditioning. Long term survival and robust immune reconstitution has been observed in one patient [597]. Treatments for STAT5b deficient patients consist mainly on symptomatic therapy and prophylaxis against infections in addition to immune suppression to control LIP and autoimmunity. Treatment of MTHFD1 deficiency is mentioned in Sect. 9.21. Intravenous immunoglobulin therapy is also the treatment of choice in hypogammaglobulinemia. Details on treatment of LRBA deficiency and ICOS deficiency are presented in Sects. 3.7 and 3.10, respectively.

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Predominantly Antibody Deficiencies

3

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3.1 Introduction

Primary antibody deficiencies (PADs) are the most common types of primary immunodeficiency diseases (PIDs), accounting for approximately half of the diseases [15, 160, 219, 253, 291, 292, 333]. The spectrum of PADs is broad, ranging from patients with a severe reduction of all serum immunoglobulin classes (Ig) and totally absent B cells to patients who have a selective antibody deficiency with normal serum immunoglobulin (Fig. 3.1) [292]. Many of these disorders share a clinical phenotype with common features such as chronic and recurrent infections, chronic inflammation, and autoimmunity [292]. Hypogammaglobulinemia is the major hallmark of patients with PADs, and the main manifestation is recurrent bacterial infections, predominantly occurring in the respiratory and gastrointestinal traces [12, 110, 241]. *(See* Table 1.2 *and* Fig. 1.9 *for updated classification of predominantly antibody deficiencies)*

The infections are usually caused by pyogenic bacteria with *Haemophilus influenza, Moraxella catharrhalis, Streptococcus pneumonia, Staphylococcus aureus, and Pseudomonas aureginosa* being the most common species. Unlike patients with T-cell deficiencies who have increased susceptibility to opportunist infections, patients with antibody deficiencies do not have

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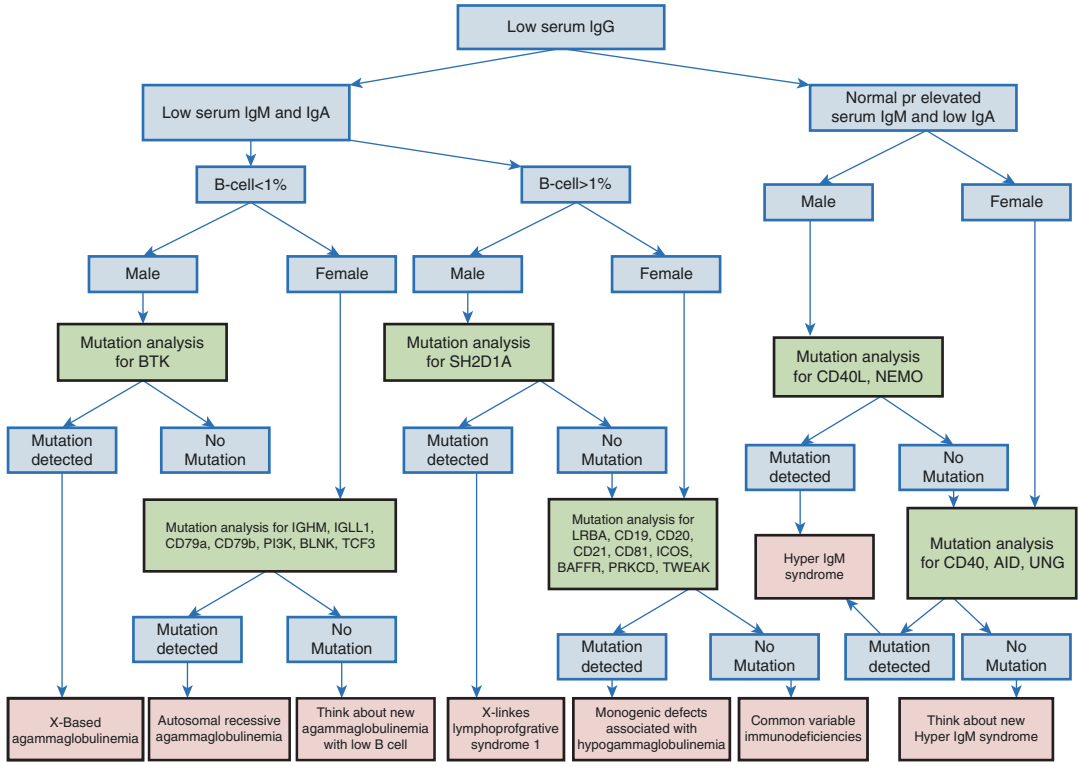

Fig. 3.1 Approach to a patient with hypogammaglobulinemia. †Exclude thymoma, if peripheral blood B cells low. If the patient has findings of clear T-cell deficiency or features like structural defects, abnormal facies or need for remedial education, remember that certain combined immunodeficiencies (e.g., ataxia-telangiectasia, IPEX, ICF, NBS, CARD11, STAT1/GOF), genetic or syndromic immunodeficiencies (e.g., Kabuki, Cornelia de Lange, Roifman) and chromosomal syndromes (Di George/22q11, Jacobsen/11qter, Chromosome 18q sdr, Turner, Down, Wolf-Hirschhorn, Mohr-Traenebjaerg/X22q, OLEDAID/X28q, trisomy 8, monosomy 22, various translocations) may present with immunoglobulin deficiency (Adapted from Seppanen et al. [363])

problems with fungal or viral pathogens, except patients with X-linked agammaglobulinemia (XLA), who are susceptible to enteroviruses and may develop chronic enteroviral encephalomyelitis [267, 339].

Patients are usually free of infection until the latter part of the first year of life, as passively acquired IgG from the mother decreases to below protective levels. Most patients with antibody deficiency can lead normal lives if given replacement gammaglobulin therapy and prophylactic antibiotics. Delays in diagnosis and/or inadequate management may lead to permanent organ damage (*e.g.,* bronchiectasis or bronchiolitis obliterans) or death from overwhelming infection [54, 364].

PADs often arise as a result of defects in early B cell development, class switch recombination or terminal B cell differentiation [1, 307]. B cell development begins in the bone marrow where several defined genes are responsible for the early development and continues in secondary lymphoid organs

The genes involved include Bruton's tyrosine kinase (BTK), Igα, Igβ, λ5, μ heavy chain, B cell linker protein (BLNK), the p85a subunit of phosphoinositide 3-kinase (PIK3R1) and the E47 transcription factor. Mutations in genes involved in early B cell development result in severe forms of PADs, characterized by a block in B cell differentiation before the production of surface Igs, markedly reduced number of mature

B cells in the peripheral circulation, profound hypogammaglobulinemia and early onset of recurrent bacterial infections in affected children [6, 100, 276].

In secondary lymphoid organs, two mechanisms, class switch recombination (CSR) and somatic hypermutation (SHM), are essential for the generation of high affinity IgG, Ig A, and IgE antibodies secreted by plasma cells. Known genes important for CSR and SHM include CD40Ligand (CD40L), CD40, Inhibitor of k light polypeptide gene enhancer in B-cells, kinase gamma (IKBKG), activation induced cytidine deaminase (AID) and Uracil N glycosylase (UNG). Defects in CSR are characterized by low serum levels of IgG, IgA, and IgE leading to recurrent bacterial infections but normal or elevated serum IgM [41].

Terminal stages of B cell development are controlled by a variety of different genes including state of TNF receptor superfamily members (TACI, BAFF-R and potentially TWEAK), the MutS protein homolog 5 (MSH5), the CD19-B cell receptor (BCR) complex (CD19, CD21 and CD 81) and the B cell differentiation antigen, CD20 [180]. The serum level of antibodies is related to expression of LPS-responsive beige-like anchor (LRBA) protein in mature B cells which is necessary for inhibition of early apoptosis plasma cells [243].

Recent advances in the understanding of the genetic basis of B lymphocyte differentiation and identification of the genes involved in primary antibody deficiencies have led to a significant increase in our understanding of the pathogenesis of this group of disorders. Differential diagnosis is important, since some of them have a different prognosis and required a different type of treatment [237].

Immunoglobulin replacement therapy in association with prophylactic antibiotics, is essential to prevent bacterial and viral infections [17, 81, 193]. The purpose of this chapter is to provide current knowledge on the pathophysiology, diagnosis and management of different forms of PADs.

3.2 X-Linked Agammaglobulinemia

(BTK deficiency)

3.2.1 Definition

X-linked agammaglobulinemia (XLA; OMIM*300755) is a rare PID, characterized by absence of circulating B cells with severe reduction in all serum immunoglobulin levels due to mutations in the *BTK* gene (OMIM*300300). Affected patients present an early onset of recurrent bacterial infections. The incidence of the disease varies from 1:100,000 to 1:200,000, depending on ethnicity.

3.2.2 Etiology

XLA represents the prototype for PIDs and was described for the first time by Colonnel Bruton in 1952 [72]; however, the underlying genetic defect was only identified in the early 1990s by two different groups [406, 417]. Bruton's tyrosine kinase (Btk), a member of the Tec family of kinases, was found to be mutated in the majority of male patients with agammaglobulinemia [8, 241, 299, 319, 418]. The animal model deficient for Btk (xid mouse) [327] showed remarkable similarities with the human phenotype and helped to elucidate the pathogenic mechanism responsible for the B cell defect in XLA. B cell development takes place in the bone marrow and depends on the sequential expression of specific gene products that regulate B cell maturation [43, 258, 264]. B cell maturation follows specific steps starting from pro-B to pre-B to immature and then mature B cells that exit the bone marrow and enter the periphery [83]. Pre-B cells express the pre-BCR receptor complex that requires Btk for the initiation of the downstream signalling cascade, necessary for further maturation (Fig. 3.2) [97, 446, 453]. Mutations in *BTK* result in a developmental arrest of B cell

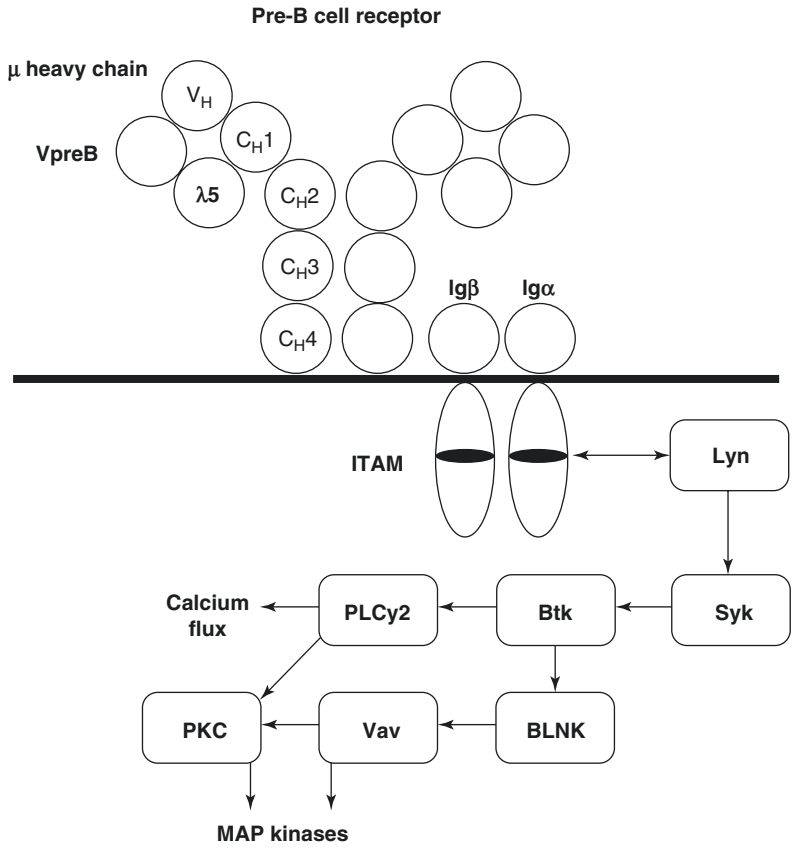

Fig. 3.2 A schematic diagram summarizing the relationships of several molecules whose absence is associated with agammaglobulinemia. Pre- B cells express the pre-BCR, a receptor complex formed by the μ heavy chain, Igα, Igβ, VpreB and λ5, that initiates downstream signalling necessary for B cell differentiation through kinases such as Btk. Mutations in the Btk (BTK), μ heavy chain (IGHM), Igα (CD79A), Igβ (CD79B), λ5 (IGLL1), and B-cell linker protein (BLNK) genes have been described in the patients with agammaglobulinemia

development in the bone marrow at the pro-B to pre-B stage [405]. Studies performed both on patients and animal models have underscored the importance of this check point for B cell maturation in the bone marrow evidencing an accumulation of B cells in the pro to pre-B stage in XLA patients when compared with healthy controls [100]. Since the block in B cell development takes place early in the bone marrow [99], less than 1 % of B cells are detectable in the periphery of these patients. Immunoglobulin levels are very low for all classes and there is virtually no humoral response to recall antigens. BTK deficiency specifically affects the B cell lineage, resulting in reduced size of lymph nodes and tonsils, tissues normally highly populated by B cells. On the other hand, both number and function of T cells are conserved, with the former being slightly increased.

Btk maps on the X-chromosome and mutations can be both familiar and de novo ones; in the first case, mothers of affected individuals are healthy carriers. One case of a female patient with agammaglobulinemia due to *BTK* mutation has been reported so far, due to skewed X-chromosome inactivation.

3.2.3 Clinical Manifestations

The protective role of maternal IgG transferred through the placenta is underscored in XLA: clinical symptoms in affected patients initiate typically between the ages of 6–12 months, when the maternal IgGs are catabolized. Recurrent bacterial respiratory and/or gastrointestinal infections are the hallmark of this disorder. Many patients may remain asymptomatic for the first year of life. Rare cases of young adolescents or even adults affected with XLA, but without symptoms until that age have been reported [181, 223, 383, 408].

Typically, XLA patients suffer from recurrent otitis media, sinusitis, bronchitis, pneumonia and gastrointestinal infections [102]. Frequency of these manifestations is variable based on the different cohorts of patients investigated, however the upper and lower respiratory tract appear to be the mostly affected [241, 280, 319, 382].

Bacterial infections are the hallmark of XLA, both as presenting symptoms and as complications once immunoglobulin replacement therapy, either intravenous (IVIG) or subcutaneous (SCIG) therapy is initiated [7, 332]. Such infections are mainly caused by encapsulated pyogenic bacteria, namely *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* and others. Pseudomonas species has been reported to be the most frequently isolated pathogen in septicemia, followed by *H. infuenzae*, *S. pneumoniae* and *S. aureus*. Septic arthritis in these patients is mainly caused by *H. infuenzae* and *S. pneumoniae* before IVIG therapy, whereas a viral cause is mainly responsible after IVIG therapy. Bacterial meningitis can also complicate the history of these patients, especially before appropriate treatment and is caused by the above-mentioned pathogens as well.

Typically, XLA patients suffer from recurrent infections of the upper and lower respiratory tract. Chronic sinusitis is present in more than 65 % of patients. Recurrent bronchitis and/or pneumonia continue to occur even when IVIG therapy is regularly established, leading to the development of bronchiectasis [241, 280, 319].

Infections of the gastrointestinal tract are also frequent in XLA patients. Giardia lamblia is frequently isolated from stool samples from these patients and unfortunately, its eradication appears unsuccessful, resulting in chronic diarrhea and malabsorption. Similar clinical findings are caused by *Campylobacter jejuni* infections, that can however be accompanied by skin manifestations and fever. The diarrhea may persist for weeks, although some patients may remain asymptomatic. It appears that antibodies are an important line of defense against Campylobacter, explaining the increased susceptibility to this pathogen in XLA patients. Salmonella has also been described as cause of g-i infection in XLA patients [241, 280, 319].

Mycoplasma species are also frequently cause infections in XLA patients, mainly interesting the respiratory and urogenital tract, and in some cases joints. Since the isolation of these microorganisms is often difficult, the course of the infection may be prolonged with consequently severe symptoms at presentation. Frequently, combined infections with Mycoplasma species and other bacteria can increase disease severity. Recurrent bacterial conjunctivitis is also rather frequent (5–8 %), and pathogens involved are the ones so far described.

Besides bacterial infections, viral infections may complicate the natural history of XLA. Affected patients are particularly susceptible to enterovirus, namely poliovirus, echovirus and coxsackie virus. Vaccine associated poliomyelitis after live attenuated oral vaccine (Sabin) has been reported and is complicated by a high mortality rate.

Progressive neurological symptoms in XLA patients, such as ataxia, paresthesias, loss of cognitive skills, neurosensorial hearing loss should always raise the suspicion of enteroviral infection. Enteroviral meningoencephalitis in XLA patients tends to manifest slowly throughout the years, although fulminating infection with fever, headache and seizures has also been reported [175, 278, 349, 442]. The difficulty in isolating the enterovirus from the CSF was thought to be overcome by using PCR techniques; however such method does not always identify the enterovirus. CSF characteristics are usually suggestive (associated with clinical findings) of a viral infection: pleocytosis, elevated protein content and in some cases hypoglycorrhachia. Unfortunately, patients with symptoms of encephalitis may have normal or near-normal CSF findings. Chronic enteroviral infections were more frequent before the initiation of IVIG therapy; however, such infections do still occur. High dose IVIG treatment has been shown to be efficient in controlling the infection and limiting the CNS involvement, however, the limited number of patients studied does not allow statistical conclusions [323]. Intrathecal delivery of IVIG has also been used in some cases for a more prompt and

direct effect. An anti-inflammatory effect of high dose IVIG has been proposed, although it is difficult to demonstrate. MRI or CT scan is usually normal at the onset of symptoms, and has therefore limited diagnostic value. Chronic enteroviral infection eventually results in cerebral edema, diffuse inflammation and progressive cerebral atrophy [175, 278, 349, 442]. Chronic leptomeningitis has been reported in some cases instead of the "classic" findings of encephalitis.

CNS enteroviral infection may also present with peripheral edema and erythematous rash mimicking a dermatomyositis-like syndrome [40]. Biopsy specimens from skin and muscle evidence inflammation. Such manifestations follow the CNS involvement and demonstrate a disseminated enteroviral infection. Involvement of the liver, with an enteroviral hepatitis, ALT increase and hepatomegaly has also been reported, usually associated with rash and fever. Hepatitis C infection from contaminated IVIG preparations has been reported in the early 90s. XLA patients seem to tolerate better the HCV infection when compared with CVID patients. More than a third of the reported patients cleared the infection or remained asymptomatic, whereas only one patient developed hepatic failure, but was co-infected with hepatitis B virus. *Pneumocystis jiroveci* has been documented as a rare cause of pneumonia in XLA patients, mainly debilitated ones [24, 131, 350]. Recurrent pyoderma was recently shown to be the only clinical manifestation of an XLA patient. Chronic gingivitis has also been reported as the only clinical finding in an XLA patient. *Helicobacter cinaedi* bacteremia with macules and no fever was recently reported in an adult patient with XLA.

Arthritis has been reported in almost 20 % of XLA patients [241, 280, 319, 382]. Clinical findings are indistinguishable from RA, including motion limitation, effusion, pain and destructive pannus formation. In some cases, a pyogenic cause has been isolated, although in the majority of the cases no isolates are found. These manifestations tend to respond to IVIG therapy, sometimes at increased doses indicating a potential infectious cause. Antibiotics are usually associated with the IVIG treatment. In many reported cases, an enteroviral or Mycoplasma infection was associated with the rheumatic manifestations. Interestingly, although B cells have been proposed to be involved in RA pathogenesis, no B cell infiltrates were found in the synovium of an XLA patient with RA.

Neutropenia has also been reported in XLA [78, 92, 149, 208]. A Japanese nationwide study showed that 18 % of XLA patients presented neutropenia before IVIG treatment was initiated. In different studies, neutropenia has been reported in a percentage variable form 10–25 %, although the clear involvement of Btk in neutrophil development has not been elucidated yet. Other rare manifestations include glomerulonephritis, alopecia, amyloidosis, von Recklinghausen disease. Conjunctivitis is rather frequent mainly in adult patients, and some report a benefit from IVIG treatment.

3.2.4 Diagnosis

The typical laboratory findings of XLA consist in low to undetectable immunoglobulin serum levels in the almost complete absence of peripheral B cells (>2 %), reflecting the early block in B cell development [22, 103]. Rare cases of patients with peripheral B cells and/or near normal Ig levels have been reported; in such cases specific antibody response to specific antigens is used for further characterization. Once the clinical suspicious is made by the clinical findings, Btk expression levels may be helpful in confirming the clinical suspicion of XLA; molecular analysis of the *BTK* gene should always be performed in order to define the mutation, if any, causing the disease. Once the mutation is defined, carrier diagnosis and prenatal diagnosis can be performed where necessary.

3.2.5 Management

Immunoglobulin replacement therapy is essential in XLA as in all humoral immunodeficiencies. In the past, intramuscular administration was used; current protocols are based on IVIG or

subcutaneous immunoglobulins. It is widely accepted, based on different international studies, that maintaining pre-infusion IgG levels >500 mg/dL assures a notable reduction in the number of infections, reducing the necessity for hospitalizations. Using a dose of 400 mg/kg/dose every 3–4 weeks is usually sufficient to maintain such levels. Several studies have argued on the cut-off level that should be considered protective. Currently, the subcutaneous administration appears very promising for different reasons: First of all, it is well tolerated and is indicated in particular for patients with previous severe adverse reactions to the intravenous preparations. In second place, it is as efficient as the intravenous one and in addition the subcutaneous therapy offers better quality of life, since the administration takes place at the patients' home.

However, the immunoglobulin replacement therapy presents certain limitations. From one hand, it contains only IgG that are not selected on antigen specificity. Secreted antibody deficiency is not replicable. In addition, different studies have shown that after almost two decades of follow-up, patients regularly on IVIG therapy may develop lung complications (chronic lung disease). Therefore, the optimal therapy is still to be determined; on the other hand the role of respiratory physiotherapy is becoming very important as the main strategy in order to maintain and even ameliorate lung function.

Any infectious episode in XLA should be immediately treated with antibiotics. In XLA, patients require frequent therapies with antibiotics, many of which for long periods. In addition, the infectious agent is not always eradicated even though antibiotics may be used for months. Frequently, antibiotic prophylaxis is necessary in order to control the number of infections even when IVIG therapy is performed regularly.

Considering the specificity of the defect in XLA, where Btk is defective in the B cell lineage, the gene therapy approach has been strongly considered. After the complications (leukemia) in two SCID patients treated with gene therapy, a lot of discussions have aroused on the risks involved with such approach. However, recent advances in the field have demonstrated that gene therapy is possible for XLA in the murine model and will probably soon becomes a therapeutic option for affected patients as well.

The introduction of antibiotics and IVIG has completely changed the prognosis of XLA patients. Before the introduction of appropriate therapy, patients would die before the age of 10. Nowadays, the prompt use of antibiotics, regular replacement therapy and an early diagnosis can assure a longer life span with less complications. However, the situation is still rather dramatic. After a follow-up of 17 years, almost 70 % of an Italian group of XLA patients had developed chronic lung disease, either obstructive, restrictive or both [319]. The progressive damage of the lung structure and the consequent functional deterioration result in important limitations for these patients. Recently, lung transplant was performed in a limited number of XLA patients with very good results, a positive follow-up for the first year and significant improvement of the respiratory function.

Malignancy has been reported in XLA as well [39, 140, 241, 280, 319, 382, 409]. The percentage is variable in the different studies. Colorectal cancer has been reported in several patients, although the underlying association with XLA is not well defined yet. Gastric adenocarcinoma has been observed in XLA patients with underlying chronic gastritis. Lymphoid malignancies have been reported but percentages vary in the different cohorts of patients.

3.3 AR-Agammaglobulinemia

(μ heavy chain deficiency, λ5 deficiency, Igα deficiency, Igβ deficiency, BLNK deficiency)

3.3.1 Definition

Autosomal recessive agammaglobulinemia (AR-agammaglobulinemia) is rare form of PID, characterized by severe reduction of all of immunoglobulin classes and absence of peripheral B cells, in the absence of *BTK* mutations [22, 100]. It affects both males and females. However, the

underlying genetic defect is currently known only in a limited number of patients.

3.3.2 Etiology

B cell development takes place in the bone marrow where the sequential expression of specific gene products promotes B cell differentiation from the pro-B to pre-B to immature B to mature B cell that enters the periphery [43, 147, 174, 239, 247, 340]. Pre- B cells express the pre-BCR, a receptor complex formed by the μ heavy chain (*IGHM*; OMIM*147020), Igα (CD79A; OMIM*112205), Igβ (CD79B; OMIM*147245), VpreB and λ5 (*IGLL1*; OMIM*146770), that initiates downstream signalling necessary for B cell differentiation through kinases such as Btk and *BLNK* (OMIM*604615) [97]. Animal models and *in vitro* studies have elucidated the importance of each of the pre-BCR components and associated transcription factors for the transition from pro-B to pre-B stage of maturation and consequently became candidates for the cases of agammaglobulinemia of unknown genetic origin [218, 247, 295, 441, 454].

The first patients with mutations in the mu heavy chain were described in 1996 [448]. A more extensive investigation including large numbers of agammaglobulinemic patients was undertaken in the United States and in Italy in order to define the exact incidence of mu heavy chain mutations within the cohort of patients with agammaglobulinemia of non-defined genetic origin. Approximately 40–50 % of these patients presented mutations in the mu heavy chain locus.

λ5/14.1 together with VpreB comprise the surrogate light chains that are part of the pre-BCR receptor complex, which is essential for early B cell development. Conley et al. reported on the first male patient with mutations in the λ5/14.1 gene causing autosomal recessive agammaglobulinemia [275].

Igα and Igβ form the signalling transducing elements that associate with the pre-BCR and allow the initiation of the downstream signalling cascade, rendering both valid candidates for this disease. In fact, Minegishi et al. reported on the first patient with a mutation in the Igα gene, resulting in alternative exon splicing of the gene product which abolishes the expression of the protein on the cell surface [99]. The second reported male patient had a homozygous alteration at an invariant splice donor site of intron 2, which presumably resulted in the truncation of the protein [431].

Igβ is essential for the downstream signalling cascade after pre-BCR cross-linking both in mice and humans. Recently, two different groups identified patients affected with agammaglobulinemia and mutations in Igβ. Dobbs et al. [132] reported recently on a 15 year old female patient with a hypomorphic mutation in Igβ and a leaky defect in B cell development. Ferrari et al. [154] on the other hand, recently reported on a 20 year old male patient with a homozygous nonsense mutation in Igβ, resulting in a stop codon. Bone marrow analysis of this patient evidenced a complete block of B cell development at the pro-B to pre-B cell transition, closely resembling the one observed in the animal model. In addition, in vitro studies showed that the nonsense Igβ mutation abrogates the expression of the pre-BCR on the B cell surface.

BLNK (also called SLP-65) is activated after BCR cross-linking and initiates the downstream signaling cascade. Since mutations in pre-BCR components have been found to cause agammaglobulinemia and BLNK acts downstream of this complex, it was evaluated as a candidate gene. In fact, Minegishi et al. [277] reported on the first male patient with mutations in BLNK resulting in agammaglobulinemia. Bone marrow analysis showed a specific block at the pro-B to pre-B stage, and additional experiment concluded that BLNK is essential for B cell development once the pre-BCR is expressed.

3.3.3 Clinical Manifestations

Clinical symptoms in patients with μ heavy chain deficiency reminds those of XLA, although apparently in a more sever manner [99, 448]. In fact, age at diagnosis appears younger for this disorder when compared to XLA. Chronic enteroviral encephalitis, recurrent bronchitis, pneumonia,

Pseudomonas aeruginosa sepsis, otitis media and others characterized the onset of the disease. Clinical history ameliorated after regular immunoglobulin replacement therapy was initiated at a regular basis. Chronic infection by Giardia lamblia, resistant to therapy, resulting in anemia and malabsorption is present in one female patient with mu heavy chain deficiency *(*Plebani, personal communication, 2015*)*. Neutropenia has also been reported in almost a third of patients with this disorder. Bone marrow analysis from mu heavy chain deficient patients evidenced an early arrest of B cell development, even earlier to that seen in Btk deficient ones, with almost complete absence of peripheral B cells.

On the other hand, the clinical history of the patient affected with λ5/14.1 deficiency started at the age of 2 months with recurrent otitis media and was found to be hypogammaglobulinemic with absence of peripheral B cells at the age of 5 years, when he was hospitalized for Haemophilus meningitis [275]. Peripheral B cell analysis evidenced less than 0.06 % of B cells. Bone marrow studies showed a specific block at the pre-B to pre-B stage of differentiation.

The first female patient affected with Igα deficiency presented chronic diarrhea with failure to thrive within the first month of life [99]. At 1 year of age, she was hospitalized for bronchitis and neutropenia. Immunological work-up showed severely reduced levels of all immunoglobulin classes and absence of peripheral B cells. Bone marrow analysis evidenced a specific block at the transition from pro-B to pre-B cell. Interestingly, no lymph nodes were detectable during clinical examination. The second patient was a male with a history of respiratory infections, diarrhea and a dermatomyositis-like phenotype [431]. Unfortunately he died of a pulmonary infection.

The patient with the hypomorphic mutation in Igβ presented recurrent lower respiratory tract infections from the age of 5 months [132]. After initiation of the IVIG therapy at the age of 15 months, her clinical history presented a significant amelioration. The patient carrying the nonsense mutation in the Igβ gene was first admitted at the age of 8 months for pneumonia and Salmonella-caused enteritis [154]; his immunological workup evidenced a complete absence of peripheral B cells (CD19 < 1 %) and panhypogammaglobulinemia. IVIG therapy was initiated immediately but the patient's clinical history was complicated by recurrent bronchitis, sinusitis, otitis media and bacterial conjunctivitis.

Clinical history of the single reported patient affected with BLNK deficiency [277], includes recurrent otitis from the age of 8 months and two episodes of pneumonia before the age of 6 months. The first immunological workup evidenced undetectable serum IgG, IgA and IgM levels in the absence of peripheral B cells. Once on regular IVIG therapy and during an 18 year period of follow-up, his clinical history was complicated with chronic otitis and sinusitis, hepatitis C from immunoglobulin reparation, and a protein-losing enteropathy during adolescence.

3.3.4 Diagnosis

The typical laboratory findings of AR-Agammaglobulinemia consist in low to undetectable immunoglobulin serum levels in the almost complete absence of peripheral B cells, as defined by CD19 and CD20 expression (<2 %), reflecting the early block in B cell development [22, 100]. When *BTK* mutation analysis results negative and/or when female patients are identified, sequencing analysis of the other known genes (μ heavy chain, Igα, Igβ, λ5, BLNK) should be performed.

3.3.5 Management

Immunoglobulin replacement therapy is essential in AR-Agammaglobulinemia as in all humoral immunodeficiencies. In the past, intramuscular administration was used; current protocols are based on IVIG or subcutaneous immunoglobulins. It is widely accepted, based on different international studies, that maintaining pre-infusion IgG levels >500 mg/dL assures a notable reduction in the number of infections, reducing the necessity for hospitalizations. Using a dose of 400 mg/kg/dose every 3–4 weeks is usually sufficient to maintain such levels. Several studies have argued on the cut-off level that should be

considered protective. Currently, the subcutaneous administration appears very promising for different reasons: First of all, it is well tolerated and is indicated in particular for patients with previous severe adverse reactions to the intravenous preparations. In second place, it is as efficient as the intravenous one and in addition the subcutaneous therapy offers better quality of life, since the administration takes place at the patients' home.

Any infectious episode in AR-Agammaglobulinemia should be immediately treated with antibiotics. In XLA and AAR, patients require frequent therapies with antibiotics, many of which for long periods. In addition, the infectious agent is not always eradicated even though antibiotics may be used for months. Frequently, antibiotic prophylaxis is necessary in order to control the number of infections even when IVIG therapy is performed regularly.

The introduction of antibiotics and IVIG has completely changed the prognosis of patients affected with AR-Agammaglobulinemia. However, the identification of genetic defects causing autosomal recessive agammaglobulinemia has been accomplished in a limited number of patients and frequently interests single patients; on the other hand, not enough follow-up and observation time is available in order to define specific complications present in these forms, although so far, the prognosis appears similar to that of XLA.

3.4 Other Forms of Agammaglobulinemia with Absent B-Cells

(TCF3 deficiency, LRRC8 deficiency, Thymoma with immunodeficiency)

3.4.1 Definition

The condition of agammaglobulinemia with absent B-cells may be observed in other conditions besides the ones described so far. E47/TCF3 deficiency (*TCF3*; OMIM*147141) was recently described in four patients with agammaglobulinemia and reduced peripheral B cells that expressed CD19, but lacked BCR expression on the cell surface [56]. The leucine-rich repeat-containing 8 (*LRRC8*) is another gene (OMIM*608360) implicated in the pathogenesis of agammaglobulinemia: it was identified in a female patient with agammaglobulinemia and minor dysmorphic features [351].

Thymoma with immunodeficiency or Good's Syndrome (GS) is a rare association of thymoma and combined immunodeficiency [155] classified as "predominantly antibody deficiency", included in the "profoundly decreased or absent B cells" group [22, 103]. It has similar characteristics with common variable immunodeficiency (CVID); nevertheless, GS is associated with a poorer prognosis. Its presentation, usually after the fourth decade of life, can be related with recurrent infections or a casual finding of an anterior mediastinal mass (thymoma). The major immunological defects are hypogammaglobulinemia, few or absent B cells, an abnormal CD4/CD8 T-cell ratio and impaired T-cell mitogenic responses. Hematological disorders and associated autoimmune diseases are also common.

Primary myelodysplastic syndromes (MDS) are heterogeneous clonal hemopoietic stem cell disorders clinically presenting with a varying degree of peripheral cytopenias and an increased probability of leukemic evolution [141]. Hypogammaglobulinemia may be found in a limited number of patients affected with MDS.

3.4.2 Etiology

The broadly expressed transcription factor E47 resulted mutated in the four patients with TCF3 deficiency. The recurrent mutation E555K has a dominant negative effect and results in an autosomal dominant form of agammaglobulinemia. Animal models have underlined the role of transcription factors such as E47 in B cell development [61]. Affected patients carrying the E555K

mutation presented an unusual peripheral B cell phenotype: enhanced CD19 expression with absent expression of BCR. Bone marrow analysis in 2 out of 4 affected patients showed a reduction both in pro-B and pre-B cells, suggesting an earlier developmental arrest than that seen in other forms of agammaglobulinemia [56].

The leucine-rich repeat-containing 8 (LRRC8) is a novel family of proteins with unknown function and consists of four transmembrane helixes with one isolated and eight sequentially located leucine-rich repeats (LRRs). The protein consists of 810 amino acids and shows a higher expression in the bone marrow than in peripheral blood. LRRC8 is expressed on a variety of tissues and cell types. The reported patient presented a chromosomal translocation t(9;20)(q33.2;q12) resulting in the deletion of the eighth, ninth and half of the seventh LLR domains located close to the C-terminal. The patients' parents showed no chromosomal abnormalities. The deletion in almost three LRRs in the C-terminal of the protein, led to the expression of two isoforms, wild type and mutant, in the patient. Experiments with retroviral overexpression of wild type and mutant LRRC8 in mice showed that LRRC8 plays an important role in the early stages of B cell development, especially at the pro-B to pre-B transition, explaining therefore the causative link between mutations in LRRC8 and the agammaglobulinemia found in the patient. The wide expression of LRRC8 in diverse tissues such as brain, heart, liver, kidney, may explain, at least partially, the dysmorphic features described in the reported female patient [351].

Good's syndrome is a rare condition and is typically diagnosed after the fourth decade. The pathogenesis of Good's syndrome remains unclear, although some hypotheses have been proposed. Bone marrow stromal stem cells have been suggested to secrete interferon-like cytokines which alter the growth and differentiation of B cell and thymocyte precursors [232, 397]. Further, autoantibodies or activated T-cells have been proposed to inhibit the production of immunoglobulins by B cells through a similar mechanism to that found in paraneoplastic syndromes associated with thymoma [187, 203]. The decrease in CD8 or CD4 memory T-cells may explain the increased susceptibility to viral infections and predisposition to tumours as described by some authors [155, 214, 215].

It is generally accepted that MDS arise from a hematopoietic stem cell harboring irreversible DNA damage. Despite a plethora of demonstrable progenitor cell anomalies, a definitive, archetypal molecular aberration in MDS clonal hematopoietors, remains elusive. Mutational activity of oncogenes, genetic or epigenetic tumor suppressor gene inactivation, defective ribososmal biogenesis and aberrant cytokine signaling in hematopoietic and bone marrow stromal cells have all been well documented. The concept of an immune-mediated response against normal hematopoietic cells in MDS bone marrow has crystallized because hematopoietic cytopenias of these patients were associated with clinical autoimmune phenomena, T-cell mediated myelosuppression, and cytokine turmoil in bone marrow milieu [144, 161, 162, 176, 427].

3.4.3 Clinical Manifestations

Patients affected with TCF3 deficiency presented a clinical history suggestive of agammaglobulinemia: pneumococcal meningitis, recurrent otitis, vaccine-associated polyomyelitis and arthritis. Associated clinical features included eosinophilic dermatitis and hepatomegaly. Low peripheral B cells and severe hypogammaglobulinemia was observed in all patients [56].

The reported patient with mutations in LRRC8 is a female patient with agammaglobulinemia and 0.6 % of CD20+ B cells in the periphery. She presented with epicantic folds, mild hypertelorism, a high-arched palate and low set ears [351].

Good's syndrome is a rare condition and is diagnosed after the fourth decade [155, 187, 214, 282]. The clinical presentation consists of recurrent infections or it may be a casual finding of an anterior mediastinal mass (thymoma). The major immunological defects are hypogammaglobulinaemia, few or absent B cells, an abnormal

CD4/CD8 T-cell ratio and impaired T-cell mitogenic responses. Hematological disorders and associated autoimmune diseases are also common.

The clinical presentation of MDS is variable [53, 141, 144, 161, 162, 427]. Typically, affected patients present symptoms related to low red and/or white blood cell count such as: fatigue, shortness of breath, pale skin, weakness, malaise, unexplained bleeding, fever and infections that won't resolve. Serological immunological abnormalities like hyper- or hypogammaglobulinemia, positivities of antinuclear antibody, positivities of direct Coombs test, or inverted CD4/8 ratios are found in 18–65 % of patients with MDS. Furthermore, the presence of autoimmune manifestations is a recognized feature of MDS clinical spectrum, with an estimated incidence of 10 %. Such phenomena usually include acute systemic vasculitic syndromes, skin vasculitis with or without fever, arthritis, peripheral neuropathy, glomerulonephritis and relapsing polychondritis.

3.4.4 Diagnosis

The typical laboratory findings of autosomal recessive agammaglobulinemia consist of low to undetectable immunoglobulin serum levels and the almost complete absence of peripheral B cells (<1 %), reflecting the early block in B cell development [22, 100]. In the case of TCF3 deficiency, low peripheral B cells with the typical finding of enhanced CD19 expression in the absence of BCR expression on the cell surface, are rather suggestive. Bone marrow evaluation where available will show an earlier block at the pro-B cell stage. Genetic analysis of the TCF3 gene will lead to definite diagnosis. Regarding LRRC8, its involvement in the pathogenesis of agammaglobulinemia resulted from a chromosomal translocation involving part of the LRRC8 gene in a syndromic patient. The clinical suspicion of LRRC8 should therefore emerge in the case of syndromic patients with agammaglobulinemia and absent B cells. Cytogenetic studies aiming to identify the translocation involving the *LRRC8* gene followed by genetic studies of the gene encoding for LRRC8 will identify the exact genetic alteration.

Good's syndrome is typically diagnosed by means of CT scan showing an anterior mediastinal mass. Surgical removal and histologic analysis confirm the diagnosis. Immunological work-up of affected patients (immunoglobulin serum levels, lymphocyte subset characterization, proliferative responses to mitogens) allow defining the immunological defect in affected patients.

The diagnostic approach for myelodysplasia is based on complete differential blood cell count (CBC), peripheral blood smear and bone marrow aspirate/biopsy. Further investigations include cytogenetic studies on bone marrow aspirates.

3.4.5 Management

The introduction of antibiotics and immunoglobulin replacement therapy has completely changed the prognosis of agammaglobulinemic patients. Nowadays, the prompt use of antibiotics, regular replacement therapy and an early diagnosis can assure a longer life span with less complications. The clinical history of affected patients may include diverse complications such as chronic lung disease and malabsorption due to gastrointestinal infections. However, considered the limited number of patients affected with TCF3 and LRRC8 deficiency, and the limited follow-up period, it is not feasible, at least for the moment, to provide comparative data for known complications in XLA such as incidence of tumours, autoimmune phenomena and similar complications. Regarding Good's syndrome, treatment consists in immunoglobulin replacement therapy, control of infectious episodes, frequently opportunistic ones considering the associated T cell defect, and intense clinical follow-up. According to some reports, affected patients have a worse prognosis when compared with patients affected with

CVID. Myelodysplasia is an incurable disease with non-transplantation therapy, but highly variable in its natural history. Supportive treatments in case for hypogammaglobulinemia, lymphopenia, neutropenia or other cell type alterations follow the general guidelines applicable in such conditions. Treatment options are variable depending on stadiation, clinical features, genetic characterization and other parameters. The only curative approach is represented by stem cell transplantation, with known associated risks for the patients.

3.5 PI3KD Syndrome

3.5.1 Definition

Mutations in class I PI(3)K molecules have now been described to be responsible for primary immunodeficiency with variable clinical presentation ranging from agammaglobulinemia (p85α, p110δ) to hyper-IgM syndrome and combined immunodeficiency with bronchiectasis (p110δ).

3.5.2 Etiology

PI3Ks are a broadly expressed group of enzymes that respond to a variety of extracellular signals to influence cell cycle progression, cell growth and survival, cell migration and metabolic control. Multiple isoforms of PI3K have been described, all of which function as heterodimers. Class I PI(3)K molecules play an important role in cells of the immune system and are composed of a catalytic subunit p100 and a regulatory p85 subunit that regulates stability and activity of p110. The p110 subunit's expression is restricted to leucocytes. Upon cell activation, p85, that normally inhibits p110, releases p110 and allows for p110 to induce the generation of phosphatidylinositol-(3,4,5)-triphosphate (PtdIns(3,4,5)P3), leading to the recruitment of pleckstrin homology domain-containing signaling proteins to the plasma membrane. PtdIns(3,4,5)P3 generation leads also to increased phosphorylation of the AKT kinase and activation of the mTOR complex 1. The first patient reported to be mutated in one of the PI3K subunits carried a heterozygous mutation in p110δ (E1021K) and was affected with primary B cell deficiency [202]. No functional studies aimed to explain the pathogenic role of this mutation were performed at that time [202]. Recently, two independent groups [30, 252] reported on the identification of dominant-activating germline mutations in p110δ leading to combined immunodeficiency with lymphopenia, elevated IgM serum levels (most patients), altered T and B cell distribution, bronchiectasis, lymphoadenopathy and increased predisposition to lymphomagenesis. The most frequently reported mutation in p110δ is the E1021K [30, 252], while one patient was reported to carry the heterozygous mutations N334K, seven patients were reported to carry the heterozygous E525K in p110d [252] and two patients were reported to carry the C416R mutation [105]. While the presence of these heterozygous mutations did not alter the protein expression of p110δ, Akt phosphorylation was increased upon activation when compared to wild type healthy controls. T cell senescence was observed in affected patients with reduction of the naïve T cell subsets and expansion of the later subsets such as T cell effector memory. The reported mutations lead to hyperactivation of the PI(3)K-Akt-mTOR pathway which results in enhanced glycolysis (normally controlled by mTOR), explaining therefore the T cell senescence observed. Increased susceptibility to activation induced cell death (AICD) further explains the T cell lymphopenia observed in affected patients [30]. On the other hand, almost all reported patients share the lack of switched memory B cells and the prevalence of naïve/transitional B cells. Experimental data demonstrated that B cells were able to secrete IgM *in vitro*, but were defective in class switching, confirming the immunological phenotype of affected patients. Inhibition of the PI(3)K-Akt-mTOR cascade either with p110δ inhibitors such as GS-1101 or

mTOR inhibitors (rapamycin) resulted in partial recovery of the observed T cell alterations.

Regarding the regulatory subunit, p85a, the first case of p85α deficiency was recently reported. The single reported patient, identified by whole exome sequencing, harbored a homozygous nonsense mutation leading to the substitution of a tryptophan with a premature stop codon in exon 6 of p85α [101]. This mutation led to the abrogation of p85α expression in patient's T cells, neutrophils or dendritic cells. The amount of p50α (an alternative product of the gene encoding for p85α) was normal/slightly increased in T cells, normal in dendritic cells and reduced in neutrophils. Expression levels of p110δ were decreased in patient's T cells, neutrophils and dendritic cells. A B cell defect similar to that seen in Btk deficient mice was observed in mice that are deficient in the p85α or p110δ subunit of class I PI3K. The reported patient's bone marrow analysis revealed an earlier block in B cell development than that observed in other forms of agammaglobulinemia due to mutations in btk or components of the pre-BCR and the presence of minimal VDJ rearrangement. Surprisingly, although PI3K is widely expressed, the immunological phenotype of the patient is restricted to the B cell compartment with minor additional alterations in PI3K deficient DC responses to LPS stimulation [101]. T cells did not exhibit any alterations in terms of maturation or activation.

3.5.3 Clinical Manifestations

The clinical phenotype of dominant-activating p110δ mutations is complex. Typically, affected patients present an early onset of disease, characterized by recurrent upper and lower respiratory tract infections. Initial immunological work-up shows elevated IgM serum levels while IgG and IgA levels may be normal, elevated or low. Reduction of naïve T cell subsets, expansion of terminally differentiated T cells (such as effector memory CD8 T cells), reduction of switched memory B cells and expansion of naïve and transitional B cells, are immunological hallmarks of the disease [30, 252]. Even upon replacement therapy, affected patients continue to present recurrent respiratory infections leading to the development of bronchiectasis. Affected patients present lymphadenopathy and splenomegaly. Infections by herpes group viruses such as CMV, EBV HASV and VZV, are typical for almost all reported patients. The underlying pathogenic mechanisms render patients' CD8 T cells incapable of eliminating chronic viral infections. Formation of abscesses is also frequent among affected patients, mainly involving skin and glands. A single patient with the E1021K mutation presented with the immunological phenotype of agammaglobulinemia, although clinical details are not available [202]. Finally, patients with p110d mutations present an increased frequency of B cell lymphomas of different types [105, 227]. Regarding p85α deficiency, the single female patient reported, born to consanguineous parents, was evaluated at the age of 3.5 months for neutropenia, interstitial pneumonia and gastroenteritis [101]. Her initial immunological work-up showed lack of peripheral B cells (<1 %) and agammaglobulinemia. She was put on immunoglobulin replacement therapy with progressive resolution of the neutropenia and the clinical manifestations. However, her clinical history resulted rather complicated. At the age of 12 she developed erythema nodosum. At the age of 15, she was treated with TNF antagonists and methotrexate for juvenile idiopathic arthritis. At 17 years of age, the patient was diagnosed with Campylobacter bacteremia and inflammatory bowel disease. No alteration in growth or insulin metabolism was noted, even though the mutated gene is involved in cell growth and metabolic control.

3.5.4 Diagnosis

The laboratory findings for patients affected with p110δ mutations may vary including elevated IgM, variable IgG and IgA serum levels, reduced naïve T cells, expansion of terminally differentiated T cells, reduced switched memory B cells and expansion of naïve and transitional B cells.

Typically affected patients present with lymphopenia. Additional clinical features such as chronic viral infections (CMV, EBV, VZV), lymphadenopathy and bronchiectasis may be of help in the diagnostic process. Definite diagnosis can however only be achieved through genetic analysis of the gene encoding for p110δ.

Regarding p85α deficiency, the typical laboratory findings of AR-Agammaglobulinemia consist in low to undetectable immunoglobulin serum levels in the almost complete absence of peripheral B cells, as defined by CD19 and CD20 expression (<2 %), reflecting the early block in B cell development [22, 101]. When *BTK* mutation analysis results negative and/or when female patients are identified, and sequencing analysis of the other known genes (heavy chain, Igα, Igβ, λ5, BLNK) results negative, p85α genetic analysis should be undertaken.

3.5.5 Management

The limited number of patients affected with p110δ mutations does not offer yet sufficient information on the natural history of this disorder. Clinical management of affected patients may include immunoglobulin replacement therapy, respiratory physiotherapy (due to bronchiectasis) and antibiotic prophylaxis (considering the lymphopenia). The experimental data so far published suggest that specific p110δ inhibitors such as GS-1101 or mTOR inhibitors (rapamycin) may be of help in this disorder since they allow partial T cell recovery in vitro. One patient was treated with rapamycin in vivo with reduction of lymphadenopathy and significant clinical benefits [252]. In addition, one patient underwent HSCT due to severe disease with good clinical response [30, 417]; HSCT may therefore be a long term treatment option for young patients. The high risk of B cell lymphomas in patients with p110δ mutations should always be taken into consideration during clinical management [105, 227].

Regarding p85α deficiency, as in other forms of AR-agammaglobulinemia, treatment consists of immunoglobulin replacement therapy using either the intravenous or the subcutaneous route. Antibiotic treatment is mandatory in case of infectious episodes and frequently prolonged periods of treatment are required. Not enough data on long-term follow-up are available to better define complications.

3.6 Common Variable Immunodeficiency

3.6.1 Definition

Hypogammaglobulinemia with normal or low number of B-cells is the prototype of common variable immunodeficiency (CVID). CVID (OMIM*240500) is a heterogeneous group of disorders characterized by hypogammaglobulinemia, defective specific antibody production and an increased susceptibility to recurrent and chronic infections [12, 110]. Patients with CVID also have an increased incidence of autoimmunity, lymphoproliferative disorders and cancers [116, 220].

CVID affects males and females equally. It has an estimated prevalence ranging from 1:10,000 to 1:50,000 [121, 151, 177] and is the most prevalent human PIDs requiring medical attention. The clinical spectrum of CVID is broad, and it may present at any age, but peaks of presentation is in childhood and early adult life have been noted [253, 292] with an average delay of 4–6 years between the onset of symptoms and diagnosis [12, 109, 110].

In spite of several years of investigation into the nature of this defect since it was first recognized in 1953 [198], the basic molecular defect in CVID is still unknown. As there is no single diagnostic immunological or genetic test for CVID, its diagnosis requires a decrease of immunoglobulins of at least two isotypes (serum IgG, IgA, and/or IgM) reduced by two or more standard deviations from the normal mean and genetic exclusion of other antibody deficiencies associated with well-defined single gene defects [12, 110].

3.6.2 Etiology

Genetics Although the most CVID cases are sporadic, it has been estimated that 10–20 % of the cases are familial presenting in childhood, in which 80 % present with autosomal dominant inheritance presenting in adulthood [34, 177, 288]. In multiple-case families, CVID is often present in one parent, accompanied by IgA deficiency (IgAD) in the descendants [425] and it has been estimated that about 15 % of the patients with CVID have a first degree relative with either IgAD or CVID [80, 426]. Some cases of IgAD, who progress to CVID, have also been reported [370]. All these data support the involvement of hereditary factors and a genetic association between CVID and IgAD, suggesting that the two disorders may represent an allelic condition reflecting a variable expression of a common defect.

In order to identify the genes responsible for CVID, several HLA association studies, as well as linkage analyses, have focused on the HLA region on chromosome 6 [106, 126, 229, 300, 355, 359, 370, 424]. Genetic linkage analysis of families with IgAD and CVID has identified the presence of susceptibility loci near the class II and III MHC regions. The DR/DQ locus has been reported to be the strongest predisposing locus. MHC class II genes play a fundamental role in antigen presentation to T helper cells that in turn provide help to B cells for a proficient Ig production. Therefore, particular MHC class II alleles might contribute to the Ig deficiency and to the associated autoimmune manifestations.

The HLA class III region genes encode components of the complement system and cytokines involved in inflammation, such as tumor necrosis factor (TNF)-α and -β. There is also evidence that IgAD and CVID share susceptibility loci at 4p, 5p, 12p and 14q [67, 229, 424].

Attempts to identify the genes responsible for CVID have resulted in finding new monogenic defects during the past few years, including mutations in Inducible costimulator (*ICOS*, OMIM*604558) causing ICOS deficiency (OMIM*607594) [166, 345], CD19 (OMIM*613493) [353, 413], CD21 (OMIM*120650) [400], CD81 (OMIM*186845) [414], CD20 (OMIM*613495) [231], lipopolysaccharide-responsive, beige-like anchor protein or LRBA (OMIM*606453) [251], TWEAK (OMIM*602695) [429], NFkB (OMIM*615578) [95] and PRKCD (OMIM*615559) [344]; however, these genes account for less than 3 % of patients with CVID [346].

These new monogenic defects which share clinical phenotypes of CVID actually represent a different entity and may occasionally be misdiagnosed as CVID. In addition, alterations in Tumor necrosis factor receptor superfamily member 13b (*TNFRSF13B* or *TACI*, OMIM*604907), Tumor necrosis factor receptor superfamily member 13c (*TNFRSF13C* or *BAFFR*, OMIM*606269) and MutS, the *E. coli*, homolog of, 5 (MSH5*603382) sequences may represent disease-modifying alterations [160].

B cell development and differentiation is critically dependent upon signal transduction through the B cell antigen receptor (BCR). Co-receptors associated with the BCR can modulate BCR signal transduction positively or negatively. Mutations in CD19 lead to relatively normal B cell development but the lack of CD19 signal transduction results in a poor response to antigenic stimuli and an inability to mount an effective humoral response.

There are also other diseases which may present with hypogammaglobulinemia: X-Linked Lymphoproliferative syndrome 1 (OMIM*308240), which is characterized by fulminant infectious mononucleosis, dysgammaglobulinemia and lymphoma, and is caused by mutations in SH2 domain protein 1A *SH2D1A* gene (OMIM*300490). *(See* Sect. 5.4 *for more details)*

Hepatic veno-oclussive disease with immunodeficiency syndrome (OMIM*235550), which is characterized by severe hypogammaglobulinemia, combined T- and B-cell immunodeficiency, absent lymph node germinal centers and tissue plasma cells and hepatic veno-occlusive disease, is caused by mutations in the Nuclear body protein sp110 (*SP110*, OMIM*604457) gene. *(See* Sect. 9.19 *for more details)*

Disturbances in B-cells There is no definite explanation for the molecular basis of CVID. Based on current knowledge, the core defect is in late B cell differentiation, although the nature is unknown. Other components of the immune system such as T cells or dendritic cells could also be involved.

Although most CVID patients have normal numbers of B cells, their B cells fail to differentiate into immunoglobulin-secreting plasma cells. Consequently, CVID patients have reduced levels of serum immunoglobulin, isohemagglutinins and respond abnormally to immunization with protein and polysaccharide antigens.

The level of IgG at time of diagnosis shows a direct association with switched memory B cell, and autoimmune cytopenia and a reverse association with chronic lung disease and efficiency of therapy [94, 330]. Patients with decreased level of antibodies also suffer from pulmonary complications especially bronchiectasis, whereas those with an increased level of serum IgA mainly suffer from infections only [205, 324]. Lymphoproliferation, reduced survival, and lymphoid malignancy are also observed a higher frequency in patients with increased IgM. Elevated serum levels of BAFFR and APRIL have been documented in CVID cases with Polyclonal lymphocytic infiltration and autoimmunity [220].

Moreover, evaluation of the total count of B cells (correlating with increased pulmonary morbidity and mortality), IgD-IgM-CD27+ switched memory B cells, $Tr^{hi}CD38^{hi}IgM^{hi}$ transitional B cells and CD21 low B cells (linked to lymphoproliferative disorders) are in line with the clinical manifestation of CVID patients [94, 438].

However, some CVID patients can produce normal post-vaccination titers of antibodies [334, 335]. B cell activation and differentiation depend on the interaction between populations of T cells and B cells. Inadequate help from HLA class-II-restricted CD4+ T cells in T cell- dependent B cell responses can be the reason for the low serum immunoglobulin concentration of switched immunoglobulin isotypes and impaired specific-antibody production in patients with CVID [50].

The reduced number of switched CD27+ memory B cells in CVID patients has been considered as a basis for sub classification of CVID [9, 69, 317, 420, 434]. Based on this classification, CVID patients with more than 0.4 % of class switched memory B cells (group II) are potentially able to respond to immunization with a polyvalent pneumococcal polysaccharide vaccine [221]. Furthermore, the severe reduction of class switched memory B cells in the peripheral blood is an indicator of a disturbed germinal center reaction in CVID [165].

Ig CSR deficiencies seem to be closely related to CVID, as they also lack switched isotypes, which is one of the clinical hallmarks of CVID. Many patients diagnosed with Ig CSR deficiencies have serum IgM levels in the normal range for their age, making it difficult to distinguish them from patients with CVID. For a diagnosis of CVID, selected molecular genetic defects should be ruled out in patients who meet the diagnostic criteria for CVID, whenever possible [5, 343].

The severe decline in the production of high affinity antibodies, due to a failure in somatic hypermutation (SHM), is another sign of impaired terminal B cell differentiation in CVID patients [58]. Impaired SHM has been detected in 77 % of patients with CVID who are susceptible to frequent severe respiratory-tract infections [29]. In addition, light-chain mutation levels are directly related to the percentage of memory B cells in CVID patients [49, 165] and may be considered as a prognostic factor for respiratory complications.

Recently, two TNF family members, B-cell activating factor of the TNF family (BAFF) and a proliferation inducing ligand (APRIL), were identified on the surface of antigen presenting cells (APC). APRIL and BAFF both bind to receptors of the TNF-R family, called B-cell maturation antigen (BCMA) and TACI [254]. Interaction between APRIL and BAFF with their receptors induces isotope switching in naive human B cells which is a mechanism independent of formal T cell regulated isotype switching [91]. A third receptor, BAFF-R, unique for BAFF, is expressed on B cells but also on resting T cells [255]. Although BAFF enhances B-cell survival [167, 356], APRIL has no detectable effect on

B-cell survival and is known mainly as an oncogenic factor, with expression in different tumor lines [130].

Disturbances in T-cells Approximately half of the patients with CVID may have reduced T-cell numbers and diminished lymphocyte proliferative responses to mitogens and antigens. Several defects have been demonstrated in the T-cell function of CVID patients. Of all patients with CVID, 25–30% have increased numbers of CD8+ T cells and a reduced CD4/CD8 ratio (<1). This subtype of patients often has splenomegaly and autoimmune manifestation [188]. Two studies evaluating thymopoiesis have yielded different results [129, 193]. One group found a significantly increased level of T-cell receptor excision circles (TRECs) as a marker for increased thymopoiesis [129], while the other group showed a decrease in thymopoiesis, subsequent to a reduction of CD31+ recent thymic emigrants [193]. Over 70% of CVID patients have decreased numbers of CD4+ T cells, suggesting a decreased thymopoiesis and the difference between the above studies could potentially be explained by the heterogeneous character of the patient populations [165].

Alteration in the production of IL-7 has been investigated in different studies [188, 193]. Isgro et al. demonstrated that a possible pro-inflammatory cytokine state (low level of IL-7) impairs growth and differentiation of several CFC progenitors in the bone marrow of the patients [193]. In contrast, Holm et al. showed an elevated plasma level of circulating IL-7 in a subgroup of CVID [188]. These patients show increased numbers of circulating CD8+ T cells with decreased rate of apoptosis and a predominance of (CCR7−) effector-memory T cells [49, 189]. It was also suggested that a relative deficiency of transforming growth factor (TGF)-1, as a regulator of IL-7 secretion by bone-marrow stromal cells, could be a reason for the high IL-7 level in this subgroup of patients [49]. Defects in IL-7 synthesis in a subgroup of patients with CVID suffering from splenomegaly, autoimmune disorders and an increase in circulating CD8+lymphocytes have also been described [188].

In addition, based on an in vitro study, increased expression of interleukin-12R and interleukin-18R was noted in a subset of patients with CVID [268]. Collectively, these findings favor the hypothesis of a Th1 immune response polarization in CVID patients [49]. Decreased expression of the co-stimulatory molecules and defects in IL-12 production, result in reduction of T-cell activation and proliferation and this may be due to the association of CVID with specific HLA alleles [49]. Although in some cases of CVID, alterations in the production of IL-12 [114, 259] have been reported, no notable Th2>Th1 shift has been verified [165].

Considering the T cell receptor signaling pathways, failure to recruit ZAP70 [57] and/or reduced Vav expression [169] have been demonstrated in a subgroup of patients with impaired proliferative T cell responses. However, as no mutation in the Vav gene or its promoter has been shown, it remains obscure whether the defective expression of Vav results in an impaired recruitment of ZAP70 or whether both are subsequent to another defect upstream [165].

Cellular immunity biomarkers also correlate with clinical consequence of CVID including naive CD4+ T cells (diminished in cases with autoimmune cytopenia and lymphoproliferation) [163, 302] and regulatory T cells (reduced in autoimmunity and granulomas) [31, 271].

Disturbances in NK-cells The NK gene complex, essential for NK-cell function is located on the short arm of chromosome 12. According to linkage studies, this locus may be one of the major non-HLA susceptibility loci for CVID [67]. This finding may be interesting, as decreased absolute numbers of peripheral blood NK cells have been observed in a subgroup of CVID patients [35].

Disturbances in the innate immune system Some studies have demonstrated abnormalities in the innate immune system including dendritic cells (DC), in CVID [28, 50, 82, 114, 293, 294, 362]. However, these abnormalities may involve some, but not all, CVID patients. Most of the described abnormalities in dendritic cells are related to the

monocyte derived DC [50, 362]. DCs have a well-known role in both innate and adaptive immunity in initiation and persistence of the primary immune response. Thus, a failure of DCs to mature into fully stimulatory cells might be an explanation for the failure to support antigen-specific immune responses in CVID [49].

Recently, it has been realized that CVID patients have broad TLR9 activation defects, which would prevent CpG-DNA-initiated innate immune responses. These defects may lead to impaired responses of plasmacytoid dendritic cells and loss of B cell function [115]. Involvement of Toll-like receptor pathways in the pathogenesis of CVID is supported by the fact that genetic defects in TLR signaling are associated with impaired antibody responses and an increased susceptibility to bacterial infections [123, 316].

3.6.3 Clinical Manifestations

The main clinical symptoms associated with CVID patients are recurrent infections, autoimmune manifestations, lymphoproliferation, lymphoma and other selected cancers. The age at onset of symptoms is variable, ranging from childhood to late adult life, with some evidence of a bimodal distribution [12, 110]. In contrast to patients with XLA, patients with CVID have normal sized or enlarged tonsils and lymph nodes and approximately 25 % of patients have splenomegaly [188].

Four distinct clinical phenotypes have been described for categorizing patients which can assist the prognosis of disorder including infections only, cytopenias, lymphoproliferation, and enteropathy [47, 93].

Acute sino-pulmonary infections Almost all patients with CVID have a history of acute, chronic, or recurrent infections; particularly pneumonia, sinusitis, and otitis mainly by encapsulated bacteria [12, 110, 184]. Approximately 89 % of patients with CVID have had at least one episode of chronic sinusitis and 70 % have had recurrent otitis media before diagnosis [14, 260]. Between 75 and 84 % of CVID patients have experienced at least one episode of pneumonia before diagnosis and many have suffered multiple episodes [81, 320, 388].

Chronic pulmonary disease Bronchiectasis, an irreversible lung complication, has been reported in 37.5–73 % of CVID patients [204, 310, 398]. It has been documented that a subgroup of CVID patients who have low numbers of IgM memory B cells and reduced levels of anti-pneumococcal polysaccharide IgM antibodies are at an increased risk of developing recurrent bacterial pneumonia and bronchiectasis [85, 420]. Measurement of these parameters may guide the physician and result in a more aggressive treatment in patients susceptible to infections and lung disease.

Asthma is an obstructive lung complication, which has been observed in 9–15 % of patients with CVID [284]. The etiology of asthma in patients with CVID is unknown.

Non-caseating, granulomatous infiltrations have been reported in 5.4–22 % of patients with CVID [150, 269]. These lesions are not clearly distinguishable from sarcoidosis. Non-caseating granulomas are occasionally also found in lymphoid tissues or the liver [269].

Lymphoid interstitial pneumonitis (LIP) may also develop in the airways of patients with CVID [76, 122]. LIP can be suspected based on findings on high resolution CT (HRCT) scans. Presence of granulomatous lung disease and lymphoid interstitial pneumonia are associated with a worse prognosis and a higher rate of lymphoproliferative disease [48, 225].

Gastrointestinal disease There is a high prevalence of inflammatory and infectious gastrointestinal disorders in patients with CVID [436]. Mild, watery diarrhea is common and occurs periodically in about 20 % of patients, with 10 % having a more severe enteropathy resulting in malabsorption and weight loss [392]. Gastrointestinal pathology in these patients includes nodular lymphoid hyperplasia, inflammatory bowel disease (ulcerative colitis, ulcerative proctitis, or Crohn's disease), sprue-like illness with flat villi, giardiasis and nonspecific malabsorption. Defects in cellular immunity, rather than antibody deficiency

alone, appear to predispose patients to such symptoms [436]. *Helicobacter pylori* is an important pathogen in CVID resulting in chronic active gastritis involving both the antrum and corpus [455].

Approximately 10 % of CVID patients have significant liver dysfunction, with hepatitis B and C virus infection, primary biliary cirrhosis, and granulomatous disease.

Autoimmune diseases Approximately 20–25 % of subjects with CVID have, at the time of diagnosis or later, developed one or more autoimmune conditions such as autoimmune cytopenia, rheumatoid arthritis, or pernicious anemia [38, 113, 184].

The mechanism underlying the increased susceptibility to autoimmunity in CVID patients is unknown. Most CVID patients with idiopathic thrombocytopenia purpura (ITP) or autoimmune hemolytic anemia (AIHA) have been successfully treated with infusions of high doses of intravenous immunoglobulin (IVIG), coupled with a short course of corticosteroids. However, due to a higher incidence of medical complications associated with use of immunosuppressive treatment in patients with CVID, this type of therapy should be used with caution [110].

Lymphoma and cancers Individuals with CVID are susceptible to malignancy, particularly lymphoma. The incidence of malignancy is increased (11–13 %) in CVID patients during the fifth and sixth decades of life [184]. The majority of these malignancies involve the gastrointestinal tract and the lymphoid tissues [113, 156, 217, 222, 270, 347]. Patients with lymphoma usually have a childhood onset, while those with gastric cancer were in their fourth decade of life when the cancer was diagnosed [4].

An association between Non-Hodgkin Lymphoma (NHL) and congenital immunodeficiency is well established and most of the NHL cases associated with immunodeficiency appear in patients with T cell defects. In a survey of malignancy in CVID patients, a 438-fold increased likelihood of developing NHL was reported for females compared to the age-adjusted expected incidence [116]. A 1.8 to 5-fold increase in all types of cancers has also been described in CVID patients [217, 270] including a 47-fold increase for stomach cancer and a 30-fold increase for lymphoma [217]. Benign manifestations, including nodular lymphoid hyperplasia, splenomegaly and generalized lymphadenopathy, have also been reported [217, 222].

Mucosa-associated lymphoid tissue (MALT) lymphoma, which represents a subset of low-grade B-cell non-Hodgkin lymphomas, is a rare lung complication in CVID patients [19, 329].

Selected CVID patients show evidence of radiosensitivity [18]. Unnecessary radiographic diagnostic tests should thus be avoided or replaced by alternative tests, and minimum radiation doses should be ensured in all cases. There is also controversy surrounding the use of radiotherapy in CVID patients with cancer. The toxic effects of radiation in CVID patients, however, are dose-dependent and it would be interesting to establish a threshold for radiation-induced aberrations in CVID patients as this would help to ensure the use of safe doses for diagnostic and therapeutic procedures [4].

3.6.4 Diagnosis

The most important laboratory criterion for establishing the diagnosis of CVID (International Classification of Diseases 10: D83) is a low serum IgG concentration, ranging from profoundly reduced (<100 mg/dL) to just 2 SDs below the normal values for age [2, 103]. Most patients have low levels of IgA, and approximately half show reduced IgM levels.

Isohemagglutinins are naturally occurring IgM antibodies against the ABO blood group antigens. By 1 year of age, 70 % of infants have positive isohemagglutinin titers, depending, on their blood group. The measurement of specific antibodies after immunization with protein (tetanus, diphtheria) and polysaccharide (pneumococcal vaccines) antigens is important to evaluate the ability of patients to produce specific antibodies. Documenting impaired production of specific

antibodies (isohemagglutinins and/or poor responses to one or more vaccines) is thus potentially valuable for the diagnosis of CVID.

Flow cytometry is important in evaluating numbers of peripheral B cells in patients with profound hypogammaglobulinemia. Numbers of B cells in the peripheral blood may be normal or reduced and approximately 13 % of patients will have a B-cell count of less than 3 % in peripheral blood [110].

Patients with a definite diagnosis of CVID should be more than 4 years of age (excluding transient hypogammaglobulinemia of infancy) and should present clinical symptoms directly attributable to immune dysfunction [363].

Many disorders with hypogammaglobulinemia present with recurrent bacterial infections. As there is no single diagnostic immunological or genetic test for CVID, it is important that patients are investigated to exclude other well-defined causes of hypogammaglobulinemia. Secondary causes of hypogammaglobulinemia should be ruled out including medication, protein loss, B cell lymphomas and bone marrow failure.

In male CVID patients, X-linked agammaglobulinemia (XLA), X-linked lymphoproliferative (XLP) syndrome and X-linked immunoglobulin class switch recombination (CSR) deficiency should be excluded [13, 209]. The onset of XLA and XLP is usually shortly after birth, whereas CVID is most often manifested after the age of 2. XLA can be distinguished from CVID by agammaglobulinemia and the nearly complete lack of B cells (<1 % of lymphocytes). Patients with less than 2 % B cells (CD19+) will need further molecular evaluation for XLA, or abnormalities in the pre-B-cell receptor complex (resulting in autosomal recessive agammaglobulinemia). XLP can be distinguished from CVID by a very low number of natural killer T-cells [311] and a history of EBV infections.

Although there is no screening test for CVID, evaluation of calculated globulin during liver function testing using the bromocresol green methodology (a cutoff value of <18 g/L) were explained recently[201].

3.6.5 Management

The mainstay of treatment for CVID is immunoglobulin replacement therapy [79, 297, 303]. Intravenous (IVIG) [303] or subcutaneous (SCIG) [152, 298] immunoglobulin prophylaxis can be used on a regular basis to maintain a trough level of at least 400–500 mg/dL. A dose of 400–600 mg/kg every 3–4 weeks is usually required. It has been shown that doses of 600 mg/kg every 4 weeks achieved serum IgG trough levels of greater than 500 mg/dL [338]. In patients with lung damage, a trough level of 700–800 mg/dL is required. Higher doses of immunoglobulin may be necessary for patients with severe chronic sino-pulmonary infections and to prevent bronchiectasis [322]. Trough levels should be measured periodically and the dose adjusted, as endogenous production or clearance of immunoglobulin in individuals may change over time.

Adverse reactions to immunoglobulin administration should be monitored during therapy. The most common reactions include backache, nausea, vomiting, chills, low-grade fever, myalgias and fatigue. Adverse effects occur within 30 min of the infusion and usually last for several hours. Slowing the rate of infusion or interrupting the infusion for a few minutes helps in preventing symptoms. These reactions may be minimized by pre-medication with anti-inflammatory drugs including corticosteroids.

In addition to use of the IVIG or SCIG, other forms of supportive care, such use of prophylactic antibiotics are important as bacterial infections may become chronic even with appropriate immunoglobulin replacement [81, 110].

Long-term antibiotic therapy may be added to immunoglobulin replacement therapy. There are no controlled studies that compare the effectiveness of any regimen of antibiotic prophylaxis in patients with established immunodeficiency. Regimens derived from studies of preventing otitis media in children include: sulfisoxazole 50 mg/kg daily; amoxicillin 20 mg/kg daily or divided bid; trimethoprim-sulfamethoxazole 3–5 mg/kg as trimethoprim once daily or divided into twice-daily dosages; and azithromycin, 10 mg/kg weekly [119, 124, 396].

Table 3.1 Abstracted guideline for management of common variable immunodeficiency complications

Type of clinical Complication	Prevention	Screening	Treatment
Infectious	Ig replacement; prophylactic antibiotics; vaccination	Patients' awareness; sputum monitoring; routine visits	High dose Ig; therapeutic antibiotics
Pulmonary	Control of infection; high dose Ig	Spirometry; HRCT; routine visits	Endoscopic sinus surgery; inhaled corticosteroids; anti-inflammatory antibiotics; IL-2 therapy; B2 agonists; leukotriene receptor antagonists; lung transplantation
Lymphoproliferative		Lymph nodes biopsy; spirometry; imaging; routine visits	Systemic corticosteroids; hydroxychloroquine; immunosuppressive agents
Autoimmune	Ig replacement?	CBC, diff, PBS; thyroid examination and thyroid function; routine visits	Corticosteroids; anti-CD20 monoclonal antibodies; TNF-α Inhibitors
Gastrointestinal	Control of infection, autoimmunity and lymphoproliferative complications	Upper and/or lower endoscopy and yearly ultrasonography; routine visits	Immunomodulators; TNF-α inhibitors
Neoplasia	*Helicobacter pylori* eradication; decreasing unnecessary irradiation	Routine cancer screening; screening by endoscopy; bone marrow examinations	Routine chemotherapy; rituximab protocols; surgical modalities; allogeneic stem cell transplantation

Adapted from Salehi Sadaghiani et al. [342]
CBC complete blood count, diff differentiation of cell blood count, HRCT high-resolution computed tomography, Ig immunoglobulin, *PBS* peripheral blood smear

The prognosis for patients with CVID depends on the frequency of infections, structural lung damage and concomitant presence of autoimmune disease. Other major factors in determining the prognosis is the extent of end-organ damage and the success of prophylaxis against infections. Patients and their families should thus be educated about early signs of infection in order not to delay treatment. Prevention, screening and treatment of different CVID complications were given in Table 3.1 [342].

3.7 LRBA Deficiency

3.7.1 Definition

Childhood onset hypogammaglobulinemia, caused by homozygous mutations in *LRBA* gene (OMIM*606453) (lipopolysaccharide-responsive, beige-like anchor protein) with autosomal recessive inheritance have recently been described. LRBA deficiency (OMIM*614700) is characterized by impaired antibody production, infections, autoimmunity and immune dysregulation. Affected patients show an early-childhood onset of recurrent infections, particularly respiratory infections, variable autoimmune disorders, including ITP, AIHA as well as gastrointestinal symptoms, including IBD.

3.7.2 Etiology

The *LRBA* gene is located on the long arm of chromosome 4 at 4q31.3. In humans, it encodes the lipopolysaccharide-responsive and beige-like anchor protein, which is a protein involved in autophagy or self-digestion, leading to deficient antigen presentation [3]. *LRBA* interacts with the

signaling enzymes (PKA and PKC) with an A-kinase anchoring protein (AKAP) motif to compartmentalize these signaling molecules in organelles and membranes [3]. It has been suggested that *LRBA* plays a role in apoptosis, and increased apoptosis has been observed in LRBA-deficient EBV-immortalized B-cell lines [139]. Phosphorylation of BAD, a key apoptosis regulator, is diminished in LRBA-deficient cells [3]. Reduced areas of autophagy in the Golgi apparatus and accumulation of autophagosomes have been observed in response to cellular stress, raising the hypothesis that antibody producing plasma cells are undergoing apoptosis in LRBA deficient patients [312].

Moreover, it has been proposed that there is an autophagy-dependent regulation of the mucosal tissues which could explain the gastrointestinal manifestations in LRBA deficient patients [243].

3.7.3 Clinical Manifestations

The clinical manifestations are not well known but recently 13 autosomal recessive LRBA-deficient patients with childhood-onset humoral immune deficiency (ranging from IgA deficiency to total hypogammaglobulinemia) have been diagnosed [3, 23].

Autoimmunity (especially ITP), bronchiectasis due to lymphoid interstitial pneumonia, chronic inflammatory bowel disease, growth retardation, and CNS granuloma formation are other associated complications in this disease and all patients with LRBA deficiency have shown reduced counts of switched memory B cells.

3.7.4 Diagnosis

The laboratory findings of LRBA deficiency include hypogammaglobulinemia (low serum IgG and IgA and normal or reduced IgM level) and normal number of B cells in peripheral blood.

Flow cytometry has shown reduced counts of switched memory B cells. Once the clinical suspicion is supported by laboratory findings, molecular analysis of the *LRBA* gene should be performed in order to identify the mutation.

3.7.5 Management

Similar to CVID, the mainstay of treatment for patients with LRBA deficiency is immunoglobulin replacement therapy. Intravenous or subcutaneous immunoglobulin prophylaxis can be used on a regular basis to maintain plasma levels at trough level of at least 500–600 mg/dL.

3.8 CD19 Complex Deficiencies

(CD19 deficiency, CD21 deficiency, CD81 deficiency)

3.8.1 Definition

During last two decades, multiple genetic defects have been found, resulting in different antibody deficiency syndromes [6]. One group encompassed genes of the CD19 complex, which encode B cell surface proteins, including CD19, CD21, CD81 (TAPA-1), and CD225 [66, 261]. This complex functions as a B cell co-receptor to reduce threshold for B cell antigen receptor (BCR) activation following antigen binding [86, 262]. Different components of this complex are involved in B cell development and differentiation as well as in innate and adaptive immune responses [153]. To date, humoral immunodeficiencies due to genetic defects in 3 out of the 4 components of CD19 complex have been reported in humans [33, 207, 400, 412–415]. Whereas CD19 and CD21 are specifically expressed on B cells, CD81 and CD225 are widely expressed on immune cells (T, B, and NK lymphocytes, monocytes, and eosinophils), hepatocytes and most stromal and epithelial cells [419].

3.8.2 Etiology

CD19, a member of the Ig family, is encoded by the *CD19* gene (OMIM*107265), which is located on 16p11.2 [128]. This B cell surface protein is involved in B cell development, differentiation and activation. As a part of the CD19 complex, it functions in reducing the activation

threshold of the B cell receptor as well as in immune responses [128, 153]. Furthermore, CD19 appears to influence the differentiation of the B1 B-cell subset. CD19-deficient mice have decreased numbers of natural antibody-producing B1 B cells and are susceptible to infections with *Streptococcus pneumoniae* [173].

Different types of CD19 mutation are found to be responsible for CD19 deficiency. All of these deletions or insertions with subsequent frame shifting, create premature stop codons, leading to a truncated CD19 protein. Presumably, early degradation of the truncated CD19 protein leads to lack of CD19 expression, though the remaining truncated protein is likely to be non-functional.

CD21 is encoded by the *CD21* gene (OMIM*120650), located on 1q32 [6]. Heterozygous mutation in the *CD21* gene is responsible for a form of specific antibody deficiency. Substitution at the splice donor site of exon 6 in one allele (c.122511G>C) causes in-frame skipping of the exon. Whereas mutations at exon 13 (c.2297G>A) causes a frame shift, leading to a premature stop codon. These mutations lead to lack of CD21 expression which, together with a low frequency of memory B cells, is responsible for the hypogammaglobulinemia [400].

CD81, another component of the CD19 complex, is encoded by the *CD81* gene (OMIM*186845), located on 11p15.5 [6]. Studies using animal models have identified the role of CD81 in regulating CD19 expression [256, 279, 403]. In humans, a homozygous substitution mutation (c.561+1G>A), directly downstream of exon 6, disrupts the normal splice donor site with subsequent activation of a cryptic splice site. Alternative splicing of CD81 transcript creates a premature stop codon, presumably leading to truncated protein product. In the absence of the CD81 protein and in the context of normal CD19 alleles, CD19 protein products are sequestered within the ER/pre-Golgi and prevented from translocation to the cell membrane. The resulting $CD81^{-}CD19^{-}$ B cells fail to respond to BCR stimulation by antigens, leading to hypogammaglobulinemia [414]. The genetic pattern in CD19 complex deficiency is thus autosomal recessive.

3.8.3 Clinical Manifestations

The increased threshold of BCR activation and the decreased count of memory B cells lead to diminished antibody responses by B cells. The resulting hypogammaglobulinemia and defective vaccine-driven antibody production predisposes affected individuals to recurrent infections, mostly involving the upper respiratory tract, and gastrointestinal systems [33, 207, 413, 419]. Therefore, mutations in the CD19 complex cause CVID [413].

Patients with CD19 deficiency experience a late onset immunodeficiency, usually in the second decade of life, with autoimmune nephritis, marked decrement in CD19+ B lymphocytes, selective IgG1 deficiency, decreased IgM levels, autoimmune cytopenia, increased IgD-CD27- naïve B cells and a decreased frequency of CD5+ B and CD27+ memory B cells 1.

The only CD21 deficient patient described to date was a 6 year old boy, born to non-consanguineous parents, who was tonsillectomized due to episodic infections in the upper respiratory tract. Protected from infections up to 26 years of age, he subsequently developed persistent myalgias, fevers, sore throat, chronic diarrhea with weight loss, frequent infections in the respiratory tract and splenomegaly, leading to continuous administration of IVIG. Hypogammaglobulinemia, lack of IgG4, lower than normal levels of IgG1, and a very low frequency of $IgD^{-}CD27^{+}$ memory B cells was demonstrated. The patient was devoid of CD21 expression both on the B cell surface and intracellularly which was shown to be due to compound heterozygous mutations in *CD21* [400].

The CD81 deficiency patient showed progressive glomerulonephritis, a normal absolute B cell count and a lack of CD19+ B cells, decreased frequency of memory and transitional B lymphocytes and normal transcriptional levels of *CD19* [414].

3.8.4 Diagnosis

The clinical symptoms resemble CVID and include an increased susceptibility to recurrent infections, especially those caused by bacteria in

the respiratory and gastrointestinal tracts. In some cases, patients develop nephritis. Characteristic laboratory findings include hypogammaglobulinemia accompanied by decreased levels of IgA and/or IgM, and an absence of B cell responses to antigens. Flow-cytometric analyses show a decline in $CD19^+$ B cells as well as in $CD27^+$ memory and $CD5^+$ B lymphocytes. Following affirmative laboratory findings, *CD19* sequencing confirms the diagnosis. In the case of chromosomal deletions, fluorescence *in situ* hybridization analysis may verify this [33, 207, 413, 419].

The flow-cytometric analyses of the patient with CD21 deficiency revealed a lack of $CD21^+$ B cells and a reduced frequency of IgD^-CD27^+ class-switched memory B lymphocytes and the disease was confirmed by DNA sequencing of the *CD21* gene. Furthermore, the high levels of in-frame skipped CD21 transcripts lacking exon 6 and the lack of the transcripts containing the mutated exon 13 sequence were affirmative [400].

Lack of normally spliced CD81 transcripts and increased levels of alternatively spliced transcripts is characteristic for CD81 deficient patients. Sequencing of the *CD81* gene confirms the diagnosis [414].

3.8.5 Management

Antibiotic management of infections as well as prophylactic antibiotics is administered similar to other CVID patients. Treatment of choice for hypogammaglobulinemia is usually immunoglobulin replacement therapy [342].

3.9 CD20 Deficiency

3.9.1 Definition

CD20 has been identified as one of the first B cell–specific discrimination antigens [378] and is related to the MS4A (membrane-spanning 4-domains, subfamily A, member 1) family of molecules with several membrane spanning domains [244, 245]. Despite being expressed on pre-B and mature B cells, it is lost during differentiation into plasma cells [394]. It has been shown that CD20 can regulate B cell activation and proliferation [393, 395] as well as regulating of Ca^{2+} transport across the cell membrane [73, 211]. It has recently been reported that CD20 deficiency causes a new type of humoral immunodeficiency with a normal development of antigen independent B cells, along with a reduced capacity to develop proper antibody responses and production of class-switched memory B cells [231].

3.9.2 Etiology

A homozygous mutation of the *CD20* gene (OMIM*112210), located at 11q12.2 leading to CD20 deficiency has previously been described [231]. CD20 is involved in B cell signaling associated with B cell survival, proliferation, activation, differentiation, development and immunoglobulin secretion [96]. Absence of CD20 expressing B cells with a diminished formation of germinal centers leads to a reduced frequency of memory B cells and subsequent decrease in IgG levels. Lack of B cells "counter selection for long V_H-CDR3" explains the defective antibody responses against polysaccharide vaccines [231]. Despite that the majority of lymphocyte subpopulations was normal, there was either reduced or nearly absent numbers of marginal zone and class switched memory B cells. Ca^{2+} responses elicited by triggering IgG or IgM and B-cell proliferation were normal while somatic hypermutation was affected. There were a small number of memory B cells in the presented patient.

3.9.3 Clinical Manifestation

The immunological and clinical findings in CD20 deficiency are early onset, but mild, perhaps reflecting more an IgG subclass deficiency than a CVID-like antibody deficiency. However, a history of frequently respiratory infections and recurrent bronchopneumonia has been

reported. During 5 years observation IgG levels were persistently low in this patient whereas IgA and IgM serum levels were normal. This patient has diminished frequency of somatic hypermutation in IgG heavy chain genes, and very low number of memory B cells. T-dependent responses against tetanus toxoid were normal, whereas T-independent responses after vaccination with pneumococcal polysaccharides were reduced [231].

3.9.4 Diagnosis

With clinical symptoms somewhat resembling a mild form of CVID, the patient shows recurrent respiratory infections, hypogammaglobulinemia and defective antibody responses to polysaccharide vaccine. CD20 deficiency is defined as consistently low IgG levels but normal IgM and IgA levels. Also, the number of CD19+ B cells was normal, but CD20 expression was noticeably absent. Therefore, patients suspected of having CD20 deficiency should be evaluated for expression of CD20 on B cells and investigation genomic and transcript sequences of CD20 verify the diagnosis.

3.9.5 Management

The primary treatment of CD20 should be replacement of antibody [231], achieved by either the intravenous or subcutaneous route of Ig, usually in doses same as CVID patients for treatment of hypogammaglobulinemia [109]. Antibiotic prophylaxis, including co-trimoxazole, may be considered [231].

3.10 Other Monogenic Defects Associated with Hypogammaglobulinemia

(ICOS deficiency, TACI deficiency, BAFF receptor deficiency, TWEAK deficiency, NFKB2 deficiency, MOGS deficiency, TRNT1 deficiency, TTC37 deficiency)

3.10.1 Definition

There are several new monogenic defects leading to partial antibody deficiency, presenting with recurrent respiratory infections, lack of antibody responses to vaccines, hypogammaglobulinemia or IgG subclasses deficiency, thus resembling CVID [6].

3.10.2 Etiology

Defects in the following genes *ICOS* (OMIM*604558), *TACI* (*TNFRSF13B*; OMIM*604907), *BAFF receptor* (*TNFRSF13C*; OMIM*), *TWEAK* (*TNFSF12*; OMIM*602695), *NFKB2* (OMIM*164012), *MOGS* (OMIM*601336), *TRNT1* (OMIM*612907), and *TTC37* (OMIM*614589) have recently been described to be associated with hypogammaglobulinemia.

The ICOS gene is located at 2q33.2 and the product of this gene is the inducible T-cell costimulator, which belongs to the CD28 and CTLA-4 Ig-like costimulatory receptor family [368]. This molecule is constitutively expressed on naive B cells and involved in signaling pathways related to T-dependent antibody responses [233, 449]. Experimental studies have shown that the ICOS protein is involved both in the regulation of T-cell proliferation (secretion of IL-2, TNF-α, and IFN-γ) and humoral immune responses (secretion of IL-4, IL-5, IL-6) and it is pivotal for super-induction of IL-10 [166, 345]. The former mechanism may lead to dysregulation of terminal B-cell differentiation into memory and plasma cells. Selective impairment of IL-17 production has also been observed in ICOS deficient helper T cells stimulated by anti-CD3/anti-ICOS, which play a key role in the regulation of inflammatory processes in the tissues [233].

TACI is a highly polymorphic gene, located at position 17p11.2. This gene produces the transmembrane activator and calcium-modulator and cyclophilin ligand interactor, which is known as the lymphocyte-specific member 13B from the tumor necrosis factor receptor superfamily with a

high degree of amino acid substitutions [357]. TACI interacts with the calcium-modulator and cyclophilin ligand (CAML), B-cell activating factor (BAFF), a proliferation-inducing ligand (APRIL) and TWEPRIL [182]. Signaling through this protein activates several transcription factors in B cells via binding to TRAFs, including calcineurin NFAT, AP-1 and NF-kappa-B [42]. Together with BAFF-R and the B-cell maturation antigen (BCMA), TACI constitutes a complex signaling network that modulates CSR, plasma cell formation, and negatively regulates B-cell homeostasis [421]. This network shows partly overlapping expression patterns and redundant functions [88]. TACI is also found on a subset of T cells, is highly expressed by human marginal zone B cells and switched memory B cells, but low to absent on mature naive and transitional B cells [89]. Additional molecular studies will be required to determine exactly how *TACI* mutations influence the clinical phenotype of antibody deficiency [325].

The *BAFF-R* gene, which is located on the long arm of chromosome 22 (22q13.2) encodes a homotrimeric protein that serves as a receptor for the tumor necrosis factor receptor family [337, 445]. As described above, this receptor forms a complex receptor network of TACI/BCMA/BAFF-R together with the BCR and is required for BAFF-mediated proliferation and differentiation of transitional and mature B cells [265, 404]. By activation of BAFF-R, a survival signal is followed by BclXL and Mcl1 (via NF-kappa-B induced by NIK and TRAF 3) and mTOR (via AKT induced by PI3K) which is necessary for terminal B cell development [178, 444]. BAFF-R expression increases when transitional B cells differentiate into MZ and follicular B cells. However, BAFF-R is not found on long-lived plasma cells in the BM, which rather express BCMA, whereas TACI is expressed by B cells of the MZ and switched memory B cells [435].

TWEAK (TNF-like weak inducer of apoptosis), a cytokine belonging to tumor necrosis factor (TNF) superfamily, is encoded by the *TWEAK* gene located on 17p13 [429]. Upon binding to its receptor, Fn14 in immune cells, it induces apoptosis, possibly via the MAPK and NF-kB pathways, and promotes immune functions [52, 212, 213, 287]. A heterozygous loss of function mutation in exon 6 of *TWEAK* was previously reported in the conserved TNF-homology domain and when introduced into selected cell lines, the mutant TWEAK failed to elicit apoptosis. Defective TWEAK, via the formation of TWAEK-BAFF complexes, also reduces BAFF-induced B cell proliferation, survival, and immunoglobulin isotype switching. These dysfunctions explain the abnormalities observed in lymphocyte survival and immune function in TWEAK deficiency [429].

The role for PKCδ in promoting apoptosis and subsequent regulation of B-cell survival and tolerance was previously documented [389]. Analyses revealed that a homozygous mutation in *PRKCD* with a recessive inheritance impaired expression of PKCδ at the protein level and diminished its nuclear translocation which otherwise is required for its pre-apoptotic function, especially in B cells [45, 309] PMA (phorbol-12-myristate-13-acetate) induces apoptosis in normal B-cells, whereas, PKCδ deficient B lymphocytes showed inhibition of cell death. This inhibition was observed in the case of PMA induction but not recorded in FAS and thapsigargin treated cells [290, 309]. The aberrant survival of immature B cells leads to hyperproliferation. Increased secretion of IL-10 by the affected B cells and may be responsible for observed autoimmunity [281]. Defects in caspase-3 activation may also be involved in the etiology of the disease. The observed failure in NK cell function possibly involves chronic EBV infection [45].

NF-kB2 is a member of NF-kB transcription factor family encoded by the *NFKB2* gene located on 10q24 with roles in immune system development and function [60]. Different members of the TNFR superfamily, including BAFF-R, RANKL, CD40, and LTβR are involved in NF-kB2 activation [328]. Following stimulating signals upon binding of the cognate ligands to these receptors, inactive NF-kB2 (p100) is phosphorylated by IKKα dimers at specific serine residues in the C terminus (Ser866, Ser870), which allows for ubiquitination of Lys855. The subsequent proteasomal processing leaves a p52 subunit which is

translocated to the cell nucleus as a p52/RelB dimer that initiates transcription of target genes involved in lymphoid organ development, B and T cell maturation and adaptive immune responses [60, 170, 386]. NF-kB2 also prevents hyper-responsiveness of naïve $CD4^+$ T cells, thus avoiding autoimmune responses [194].

3.10.3 Clinical Manifestations

ICOS deficiency was first reported in 2003 [242] in a CVID patient with an autosomal recessive pattern with a late onset. This case was followed by reports on 8 patients living along the River Danube who had a common ancestry owing to a founder mutation [336, 345, 391, 433, 435]. Major clinical features of ICOS deficiency include diminished Ig levels, autoimmunity, lymphocyte infiltration, malignancy, reduced class-switched and memory B-cell counts and defective IgG1 and IgE antibody production in response to immunization, suggesting a reduced germinal center formation [336, 451]. Histopathology revealed severely aberrant and vestigial germinal centers in the patients' lymph nodes [104, 450].

In the TACI-mutated patient cohort, autoimmunity was present in 40 % and signs of lymphoproliferation were present in 60 % of the patients and the frequency of malignant B-cell lymphomas was higher than in patients with other monogenic defects associated with a partial antibody deficiency. From 2005 to now, TACI deficiency has been described in up to 10 % of CVID patients and also in individuals with a diagnosis of IgG subclass and IgAD deficiency in CVID/IgAD families with marked differences both in the type of immunodeficiency and immunodysregulation [137]. Complex pattern of heritage (homozygous, heterozygous, and compound heterozygous), mostly in the hotspot extracellular portion (C104R and A181E) of the molecule, and phenotypic diversity/incomplete penetrance in clinical manifestations of these cases suggest that modifying factors may play a role in these cases. Screening for mutations for *TACI* to predict prognosis or help in genetic counseling has not as yet proven to be useful [127].

Mutations in the *BAFFR* gene have been reported to cause lymphopenia and a late onset antibody deficiency (CVID) in humans leading to respiratory and gut infections, and autoimmunity, cancer and granuloma are prevalent in patients [137]. BAFFR deficient patients suffer from a defect of the long-term humoral memory (except of IgA+ memory), short-lived plasma cells (except IgA secreting plasma cells from mucosal tissues), a relative increase of transitional B cells and reduced specific antibody responses, especially to polysaccharide antigens [127].

Patients with TWEAK deficiency show an autosomal dominant pattern of inheritance and patients manifest with numerous warts, B cell lymphopenia, chronic thrombocytopenia and intermittent neutropenia, decreased IgA and IgM levels, increased frequencies of double-negative and CD8+ T cells, with a majority of B cells having a naïve phenotype and lack of antibody production in response to T cell-dependent and T cell-independent vaccines [429].

To date, two different heterozygous mutations in the *NFKB2* gene were reported to cause antibody deficiency. Both of these mutations are heterozygous alterations with a dominant pattern of inheritance. Regarding the role of NF-kB2 in development and function of lymphoid organs and of T and B cells, lack of this transcription factor leads to decreased frequency of memory B cells, reduced immunoglobulin levels, defective responses to vaccination, atopy or asthma and autoimmunity.

In PKCδ deficiency, in addition to common bacterial infections including sinusitis and episodes of otitis, the patients suffer from intermittent fever and chronic EBV infection. Autoimmune-driven hepatosplenomegaly as well as persistent generalized lymphadenopathy have been observed without any microbial deposits in lymph node biopsies. Progression of autoimmunity with elevated levels of different autoantibodies with subsequent "intermittent lupus-like rash" and confluent erythematosus macules over the trunk and extremities has also been noted.

3.10.4 Diagnosis

The patients affected by all above novel monogenic defects, manifest CVID-like symptoms. Serum immunoglobulin analysis reveals diminished IgA and IgM levels as well as IgG deficiency or IgG subclass deficiency. Affected individuals are unable to respond to both T-dependent and T-independent vaccinations. However, special features may provide important clues as to the diagnosis including: Increment in double-negative and CD8+ T cell subsets (in CD19 deficiency), B cell lymphopenia with normal IgA serum levels and IgA1 plasma cells (BAFF-R deficiency), severe autoimmune adrenal insufficiency (NF-kB2 deficiency), lymphoproliferative disorders (TACI deficiency) and increased levels of inflammatory markers, defective FAS activity and proliferation of double-negative T cells reminiscent of ALPS (PKCδ deficiency). Next generation sequencing of patients with CVID presentation may help identification of the mutation, leading to a correct diagnosis. Western blot analysis, looking for truncated proteins, also may lead to a timely diagnosis.

3.10.5 Management

Antibiotic prophylaxis as well as antimicrobial management of infections is recommended. Immunoglobulin replacement therapy, either by the intravenous or subcutaneous route, is used to correct the antibody deficiency. For management of autoimmunity, lymphoproliferation and endocrinopathy of these patients, specific therapy should be considered by consultation of specialists [342].

3.11 Immunoglobulin Class Switch Recombination Deficiencies Affecting B Cells

(AICDA deficiency, UNG deficiency, MMR deficiency, INO80 deficiency)

3.11.1 Definition

Immunoglobulin class switch recombination deficiencies (CSR-Ds) are a consequence of various defects impairing the CSR machinery. They selectively result from an intrinsic B-cell defect, and are caused by mutations in genes encoding molecules essential for CSR, such as Activation-Induced Cytidine Deaminase (*AICDA* or *AID*; OMIM*605257), Uracyl-DNA Glycosylase (*UNG*; OMIM*191525), Post meiotic segregation 2 (*PMS2*; OMIM*600259), INO80 complex subunit (*INO80*; OMIM*610169), MutS E. coli homolog of 6 (*MSH6*; OMIM*600678), and others still undefined genes [137, 191, 313, 331]. They are defined by the presence of elevated or normal serum IgM levels contrasting with low or null serum levels of the so-called "switched isotypes" (IgG, IgA and IgE), hence this condition's former name "hyper-IgM syndrome" They are clinically characterized by recurrent and chronic bacterial infections (not opportunistic infections), lymphoid hyperplasia and autoimmune disorders. As compared to CSR-D due to defects in the CD40-mediated signaling, they have a much better prognosis since most of bacterial infections can be controlled by IgG substitution. However, some of them could be associated with malignancies [137].

3.11.2 Etiology

CSR-Ds caused by an intrinsic B cell defect result from a defective maturation of the antibody repertoire, a process required for production of diverse antibody isotypes with high affinity for antigen. Antibody maturation takes place within the secondary lymphoid organs (the spleen, lymph nodes and tonsils) in an antigen- and T-cell-dependent manner. When mature but naive B cells emigrating from the bone-marrow (or fetal liver) encounter antigens that they specifically recognize through their BCR of the IgM isotype and through a close interaction with the T follicular helper T cells (T_{FH}), they proliferate vigorously and give rise to a peculiar lymphoid

formation, the germinal center (GC), in which B cells undergo the two major events required for antibody maturation, CSR and generation of somatic hypermutation (SHM) (Fig. 3.3).

CSR is achieved through a recombination process between two different switch (S) regions (each of which located upstream of a constant (C) region in the Ig locus), with deletion of the intervening DNA [197, 263, 422]. Replacement of the Cμ region by a downstream Cx region (Cα, Cγ or Cε region, coding respectively for IgA, IgG or IgE) results in the production of switched isotypes with the same variable (V) region and thus the same antigen specificity and affinity. The first step of this process is the transcription of S-regions' DNA, which is induced by cytokines. Interestingly, each cytokine targets a specific S region, leading to the production of the corresponding isotype (as an example, IL4 targets the Sε region and induces CSR towards the IgE isotype). As a result of this transcription step, RNA/DNA hybrids are formed on the template DNA strand, leaving DNA strands accessible to the activity of a B cell specific molecule, the Activation-induced cytidine deaminase (AID) [286]. This enzyme introduces a lesion on DNA by selectively changing cytosine (C) residues into uracil (U) residues [46, 68, 315]. The U:G mismatch lesion is subsequently recognized and processed by the uracil N-glycosylase (UNG), which removes the U residues and produces an abasic site that is eventually cleaved by apurinic/apyrimidinic endonucleases (APE) [168, 326]. The single strand DNA breaks are then processed into DNA double strand breaks (DSBs) required for the inter-switch regions' recombination process. DSBs can also be generated through the endonuclease activity of the postmeiotic segregation 2 (PMS2) enzyme (a component of the mismatch repair (MMR) machinery in a PMS2/MLH1 complex) [411]. CSR-induced DSBs are sensed by different components such as Ataxia-telangiectasia mutated (ATM), the MRE11/RAD50/NBS1 complex, phosphorylated histone γH2AX and the repair protein p53 binding protein 1 (53BP1) and repaired mostly through the Non Homologous End Joining (NHEJ) pathway.

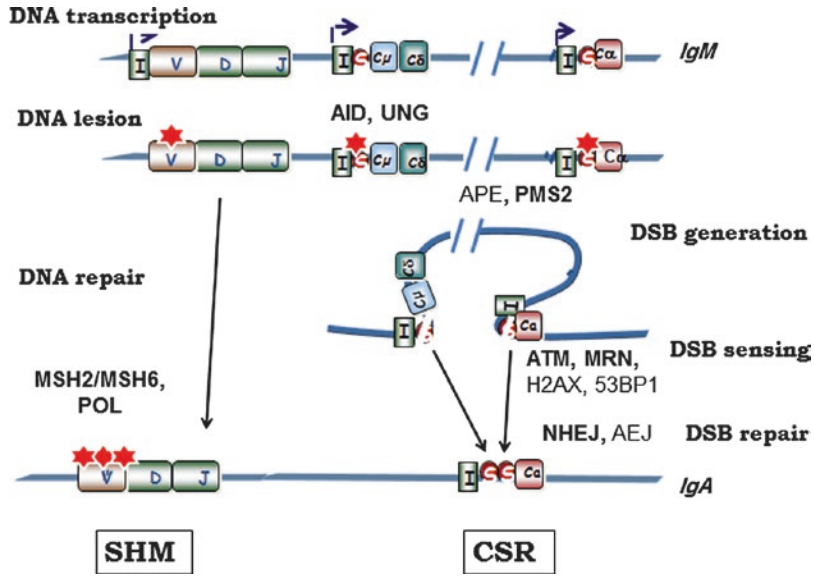

Fig. 3.3 Schematic representation of class switch recombination and somatic hypermutation. *CSR* class switch recombination, *SHM* somatic hypermutation, *DSB* double strand DNA breaks, *AID* activation induced cytidine deaminase, *UNG* Uracil N glycosylase, *APE* endonuclease, *PMS2* post meiotic segregation 2, *ATM* Ataxia Telangiectasia mutated, *MRN* MRE11/RAD50/NBS1 complex, *NHEJ* non homologous end joining, *AEJ* alternative end joining, *MSH2/6* MutS homologous 2/6, *POL* error prone polymerases. In *bold* known human defects (Defect in POLɧ leads to Xeroderma Pigmentosum variant, but not to antibody deficiency)

Somatic hypermutation stochastically introduces missense mutations (or, much more rarely, deletions or insertions) into Ig V regions and their proximal flanking regions at a very high rate (around 1 mutation for 1×10^{-3} bases), without changing the C region, thus the Ig isotype [384]. This process leads to the selection and proliferation of B cells expressing a BCR with high affinity for antigen, through an interaction with follicular dendritic cells in the GC. As in CSR, the first step in SHM is the introduction of uracil residues by AID during the transcription of V region's DNA, followed by the UNG's activity and creation of an abasic site [315]. However, this lesion's repair differs from that of CSR since no DSBs are needed. The UNG-induced abasic sites are repaired by several error prone polymerases. AID-induced U:G mismatches, not processed by UNG, can also be repaired during DNA replication or by the MutS homologous 2/6 (MSH2/MSH6) complex, another component of the MMR machinery and the error prone polymerase η [384].

Although CSR and SHM occur simultaneously in B cells in GCs following CD40/BCR activation, each is not a prerequisite for the other; since IgM may be mutated and IgG or IgA unmutated. Although SHM defects have never yet been reported as being causative of an immunodeficiency, CSR defects always cause a pathological condition characterized by a susceptibility to recurrent and severe bacterial infections.

Autosomal recessive AID deficiency It is the most frequent of CSR-D caused by an intrinsic B cell defect (around 40 % of these conditions). It is characterized by a drastic defect in both CSR and SHM since AID is absolutely required for both processes [138, 285, 331]. Mutations are scattered all along the gene, with no peculiar hotspot; most of them (but not all) lead to an absence of protein expression. However, few mutations located in the C terminal part of AID (AID C^{ter}), that do not affect protein expression, lead to defective CSR but normal SHM [138]. This observation strongly suggests that AID is not only a cytidine deaminase but plays a further role in CSR, likely by recruiting CSR-specific cofactors, still unknown [390].

Autosomal dominant AID deficiency Interestingly, two different nonsense mutations located in the nuclear export signal located in the C terminal part of AID lead to a CSR-D transmitted as an AD disease, an observation likely related to the fact that AID acts in CSR as a multimeric component [192].

Autosomal recessive UNG deficiency This condition is very rare (<1 % of CSR-Ds) and characterized by a profound impairment in CSR but normal frequency of SHM. However in the absence of UNG, SHM which are introduced only during replication or through MMR repair present a strikingly abnormal pattern of nucleotide substitution with an excess of transitions. The four mutations reported in the three patients lead to lack of protein expression [191].

Autosomal recessive PMS2 deficiency Although the main symptom of AR PMS2 deficiency is the early onset occurrence of cancers, as others defects in the MMR pathway, some patients can firstly present with a CSR-D with normal SHM, pinpointing the role of this molecule in human CSR [313]. In the 13 patients observed, all present drastic mutations in PMS2 gene, leading to lack of protein expression.

Autosomal recessive INO80 deficiency This appears as a very rare CSR6D, while only two patients have been reported so far. The three observed mutations are missense mutations that led to normal expression of protein [228].

Other CSR-D As much as 60 % of patients affected by a CSR-D caused by an intrinsic B cell defect remain not molecularly defined. In these conditions, the clinical and biological phenotype can be very close to that caused by AID C^{ter} mutations with drastic CSR defect and normal SHM. A possible defect in the putative cofactor(s) of AID is suspected. Other patients are likely sufferings from a DNA repair defect with occurrence of malignancies [314].

3.11.3 Clinical Manifestations

Most of clinical manifestations are shared these different forms of CSR-Ds caused by an intrinsic B cell defect. Patients present recurrent bacterial infections that predominantly affect the respiratory tracts (leading to the severe complications of sinusitis and bronchiectasis, if left untreated). *Streptococcus pneumonia* is the most prevalent microorganisms causing these infections. Gastrointestinal infections may occur. They are vulnerable to intestinal tract infections (sometimes in relation to persistent *Giardia* infections) leading to malabsorption and failure to thrive, especially in cases of inadequate treatment. Symptom onset generally occurs during early childhood, although some patients are only diagnosed in adulthood. In contrast to patients with CD40L or CD40 deficiency, susceptibility to opportunistic infections (which is characteristic of abnormal T cell responses) and neutropenia are not observed in these patients. Unlike agammaglobulinemic patients, these CSR deficient patients do not appear to develop severe enteroviral infections – suggesting that IgM (even when lacking mutations) acts as an initial barrier against enteroviruses and perhaps other viruses. Interestingly, IgM has been shown to protect efficiently against some bacteria, such as non typable *Haemophilus influenzae* [273]. Other complications are frequent such as lymphadenopathies and auto-immune/inflammatory disorders. The clinical features characteristic of the different molecular defects is described below:

Autosomal recessive AID-deficiency In all of the 72 patients we observed, the CSR-defect appears dramatic, with a very high susceptibility to bacterial infections, most of them being diagnosed in childhood [321, 331]. Besides the high susceptibility to infections, a hallmark of the disease is the occurrence of impressive lymphadenopathies affecting as much as 75 % of patients, and often requiring tonsillectomy or lymph node biopsy/resection. They affect cervical, mediastinal and mesenteric lymph nodes. Histological examination reveals the presence of characteristic giant GCs, (between 5 and 10 times larger than normal), which leads to reduction/disappearance of mantle zone and inter-follicular areas (Fig. 3.4). The GCs are filled with proliferating B cells that express CD38, surface IgM and surface IgD – all markers of GC founder cells [321]. One possible explanation is that, in the absence of functional AID, antigens continuously induce B cells' proliferation, since no successful antibody maturation and selection can occur or that AID plays a direct role in GC B cells' apoptosis [240] Lymphadenopathies are not obviously linked to infections since they can occur in patients receiving adequate Ig substitution [321].

Autoimmunity is a frequent complication (affecting 31 % of patients) with the presence of IgM auto-antibodies against blood cells (causing hemolytic anemia, thrombocytopenia and (more rarely) neutropenia) or other tissue types (causing hepatitis and systemic lupus erythematous, for example). Auto-inflammatory manifestations are also described, as uveitis, non-infectious arthritis or Crohn's disease [135, 321]. There is no correlation between the presence of autoimmunity/auto-inflammatory diseases and the occurrence of infections, since AID-deficient patients receiving optimal Ig replacement therapy may still develop these complications. A defect in central and peripheral tolerance has been described with surprisingly, a defect in the T reg cells' counts [272].

Interestingly, the very few patients carrying AID C^{ter} mutations that allow normal SHM generation present with the very same susceptibility to infections as other AR AID-deficient patients. However, auto-immune manifestations have not been reported in these four patients and, more strikingly, lymphadenopathies occur but are much less impressive. In the one patient who had two successive biopsies of an enlarged cervical lymph node, a feature of follicular hyperplasia without the presence of giant GCs was noted.

Autosomal dominant AID deficiency Patients with AD AID deficiency present with a milder phenotype as compared with the AR condition and most of them are diagnosed at adulthood [192]. The phenotype is very close to that observed in common variable immunodeficiency

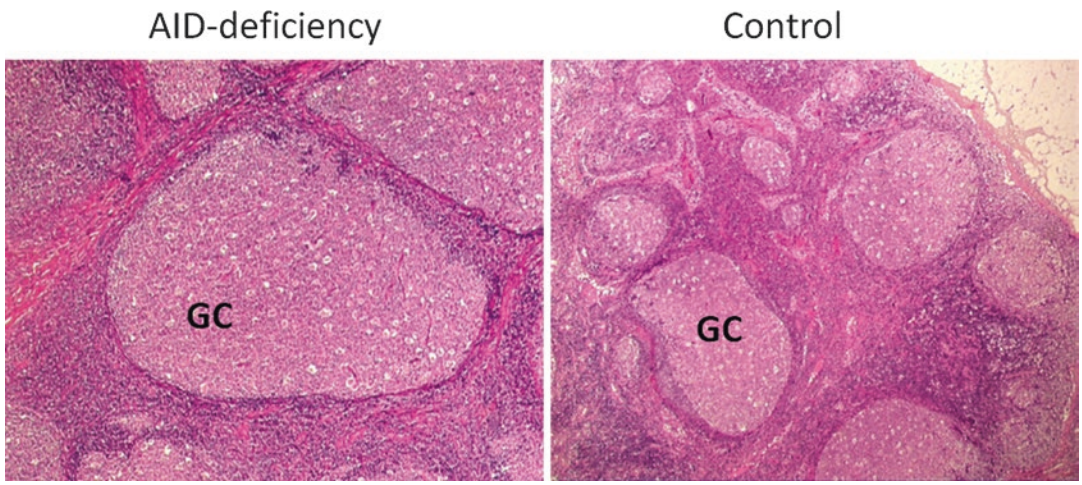

Fig. 3.4 Biopsy of a cervical lymph node from an AID-deficient patient and a control. *GC* germinal center

(CVID), characterized by recurrent bacterial infections affecting mainly the respiratory tract. In contrast to the AR form of AID-deficiency, .no lymphadenopathies, no auto-immune manifestations have been reported (but only 15 patients have been observed so far).

Autosomal recessive UNG deficiency Uracil-N glycosylase deficiency is a very rare AR disease and only three patients have been described to date. All three patients had a history of frequent bacterial respiratory infections from early childhood onwards. One patient developed chronic epididymitis in adulthood [191]. Neither opportunistic infections nor abnormally severe viral infections are reported. Two of the three patients presented with lymphadenopathy, with enlargement of mediastinal or cervical lymph nodes. The only one performed biopsy revealed lymphoid hyperplasia but with no giant GC typical of AID deficiency. In adulthood, the eldest of the patients developed autoimmune manifestations, hemolytic anemia and Sjögren syndrome. Clinically UNG deficiency is indistinguishable from AID deficiency. As UNG belongs to the base excision repair pathway involved in the repair of spontaneously occurring DNA lesions, it appears as an important anti-mutagenesis mechanism. Although not observed in patients, UNG defect could however predispose to tumourigenesis as reported in elderly UNG-deficient mice [289]. Although UNG is expressed in mitochondria, no mitochondrial abnormalities have been observed in patients, suggesting the presence of efficient compensatory mechanisms. However, in UNG-deficient mice, post-ischemic brain injury is more severe than in control animals likely because of defective mitochondrial DNA repair [143]. Hence, this type of complication might also occur in patients.

Autosomal recessive PMS2 deficiency The hallmark of this disease is the early onset of malignancies (mean: 9 years of age), especially colorectal cancers, supratentorial primitive neuro-ectodermal tumors, medulloblastoma and hematological malignancies, which strongly worsens the prognosis [443]. However, before occurrence of cancers, patients can present during years with symptoms evocative of a CSR-D, with recurrent and severe sino-pulmonary bacterial infections, that require IgG replacement therapy [313]. A frequent (11/13 patients observed) characteristic (but not specific) feature is the presence of *café au lait* skin spots or hypopigmented skin areas.

Autosomal recessive INO80 deficiency The two described patients present with a CVID-like phenotype with recurrent bacterial pulmonary infections from childhood [228].

Other CSR-D These pathological conditions, which are not molecularly defined, are certainly a

heterogeneous entity. Some patients present with a phenotype very close to that of AR AID deficiency, although the CSR-D can be milder with residual IgG and/or IgA levels. Recurrent bacterial infections affecting mostly the respiratory tract are the main symptom of the disease. Lymphadenopathies can occur with features of follicular hyperplasia (with no giant GC) at histological examination. Auto-immunity is also reported in 25 % of patients. Some of these forms are associated to a higher frequency of hematopoietic malignancies [190, 314].

3.11.4 Diagnosis

The most important laboratory criteria for establishing the diagnosis of CSR-D is a low serum IgG, IgA, and IgE concentration and normal or elevated serum IgM levels. Antibody responses are restricted to the IgM isotype with the presence of antibodies to isohemagglutinins and polysaccharide antigens and non-typable *Haemophilus influenzae* [273, 321]. In contrast, the IgG response to protein infectious or vaccinal antigens is impaired. Although circulating B cell counts are found normal, analysis of subpopulations reveals an absence of switched B cells (IgM(−), IgD(−)). B cells, although normally able to proliferate upon *in vitro* activation, cannot undergo CSR, pinpointing to a defect in the CSR machinery [136]. In all cases, a T cell immunodeficiency has to be excluded since T cell functions' impairment leads to a secondary CSR defect (4). Phenotyping of T cells and T cell subsets and study of T cell functions, including expression of CD40L on activated T cells, are required before making the diagnosis of CSR-D caused by an intrinsic B cell defect.

Some signs are essential to orientate properly the genetic study which remains, however, the only way for a definitive diagnosis (Table 3.2).

Autosomal recessive AID deficiency Consanguinity (which is reported in 70 % of cases) and/or episodes of massive lymphadenopathies/and or autoimmune manifestations are evocative of AID-deficiency. The diagnosis is confirmed by the Ig dosages since the CSR-D is drastic, with neither IgG nor IgA produced. Very high IgM levels (up to tenfold above normal values) are not uncommon. Although there is no switched B cells as in other CSR-Ds, the proportion of B cells expressing CD27 is normal, suggesting that CD27 is a marker of proliferation in GC rather than a marker of mutated B cells.

Autosomal dominant AID deficiency There is no peculiar sign evocative of this disease but this diagnosis should be checked for in adult patients with a phenotype of CVID, especially, in familial cases.

Autosomal recessive UNG deficiency UNG-deficiency appears as very rare and two out of the three reported patients were born from a consanguineous family. The CSR–D is drastic although very low residual levels of IgG and IgA can be detected. The proportion of B cells expressing the CD27 marker is variable, observed in low range in the youngest of the three patients.

Autosomal recessive PMS2 deficiency Although the main symptom is the occurrence of early onset cancers, some of the patients present firstly with a CSR-D for years. The CSR-D is mild, affecting especially IgG2 and IgA production and tending to ameliorate with age, likely by accumulation of long-lived plasma cells. CD27+ B cell counts are always found decreased. Diagnosis can be suspected when anamnesis reports familial history of non polyposis colic carcinoma, a frequent complication in adult heterozygous subjects (Lynch syndrome). Moreover, detection of café-au-lait skin spots or depigmentated skin areas (highly suggesting of an MMR defect) can orientate the gene investigation. As *PMS2* gene is difficult to sequence because of the presence of a pseudogene, a biochemical approach studying PMS2 protein expression in EBV B cell lines appears as an easier tool for diagnosis.

Of note, defect in MSH6, a component of the MSH2/MSH6 complex of the MMR pathway, leads to subtle CSR-D defect with decreased serum IgG2 levels, decreased numbers of CD27+ cells, and a strong bias in nucleotide substitution

Table 3.2 Diagnosis of CSR-Ds caused by an intrinsic B cell defect

Gene defect	transmission	Main clinical features[a]	Main biological features	Differential diagnosis
AID	AR	Massive lymphadenopathies Auto-immunity	Drastic CSR-D Normal counts of CD27+ B cells	
AID C^{ter}	AR	Lymphadenopathies	Drastic CSR-D Normal counts of CD27 + B cells	
AID ^{NES}	AD		Mild CSR-D Normal counts of CD27 + B cells	CVID
UNG	AR	Lymphadenopathies Auto-immunity	Drastic CSR-D Variable counts of CD27+ B cells	AID deficiency
PMS2	AR	Café au lait skin spots cancers	IgG (especially IgG2) and IgA mild defect Decreased counts of CD27+ B cells	
INO80	AR		Decreased counts of CD27+ B cells	CVID
unknown	? ?	Lymphadenopathies Auto-immunity Susceptibility to malignancies	Variable CSR-D Normal counts of CD27+ B cells Variable CSR-D Decreased counts of CD27+ B cells	Ataxia Telangiectasia DNA repair defects

AR autosomal recessive, *AD* autosomal dominant, C^{ter} C terminal part of AID, *NES* nuclear export signal of AID, *CVID* common variable immunodeficiency

[a]Besides the susceptibility to bacterial infections shared by all CSR-Ds

of SHM, but without obvious clinical consequences [159]. This observation pinpoints to the peculiar role of PMS2 in human CSR, likely through its endonucleasic activity [411].

Autosomal recessive INO80 deficiency Both described patients present with decreased IgG and IgA serum levels with normal IgM. Interestingly, in the youngest patient, switched Ig levels tend to increase with age, likely by accumulation of long lived plasma cells. SHM are found normal, however on a reduced CD27+ B cell population [228].

Other CSR-D This condition characterized by a variable CSR-D with normal SHM, lymphadenopathies and auto-immune manifestations is not easily diagnosed. The CSR-D is variable as well as the numbers of CD27+ B cells. Some of these patients present with a drastic CSR, normal SHM, a phenotype very similar to that induced by AID C^{ter} mutations. Strikingly, physicians should be aware that Ataxia Telangiectasia patients can present with the very same phenotype [148]. Therefore, this disease, which is much more frequent than CSR-D, has to be excluded by simple tests such as careful clinical examination looking for specific signs, even still discrete (telangiectasia, neurological disabilities) and/or by dosage of α-fetoprotein in serum.

3.11.5 Management

The mainstay of treatment for CSR-Ds is immunoglobulin replacement therapy that effectively reduces the incidence and severity of complications in this group of patients. IVIG can be used

on a regular basis to maintain a trough level of 400–500 mg/dL in patients. Subcutaneous Ig replacement is certainly a treatment for the future. However, Ig substitution does not prevent lymphoid hyperplasia, which can require surgical resection in case of impressive enlargement, as observed in AR AID deficiency. IgG substitution does not prevent either auto-immunity which can be life threatening and require treatments with steroids, anti-CD20 antibodies or immunosuppressive therapies. Antibiotics are generally administrated during infectious episodes rather than a prophylactic treatment.

An accurate diagnosis based on clinical, biological and especially genetic data is essential to set-up an adequate follow-up and prevent complications. Moreover, it allows a prenatal diagnosis in severe forms of CSR-Ds (especially PMS2-deficiency). New genetic approaches, such as whole exome/genome sequencing, will very likely allow the delineation of the molecularly undefined CSR-Ds in the near future.

3.12 Selective IgA Deficiency

3.12.1 Definition

Selective IgA deficiency (IgAD, OMIM*137100) is the most common primary antibody deficiency [2, 177]. It is defined as a serum IgA level of less than 0.07 g/l and normal serum IgG and IgM levels in a patient older than 4 years [27, 59, 77, 80]. Partial IgA deficiency is defined as a decreased IgA levels that are more than two standard deviations below the normal age-adjusted means [118].

IgA deficiency was first described in patients with ataxia-telangiectasia in 1961 [399]. IgAD affects both males and females equally. Based on different ethnic groups, the frequency of IgAD varies, ranging from 1:142 to 1:18,000 [21, 210, 354].

The defect is presumed to result from impaired switching to IgA or a maturational failure of IgA-producing lymphocytes, but the nature of basic defect is unknown. Many affected individuals are asymptomatic whereas selected patients suffer from recurrent mucosal infections, allergies, and autoimmune diseases [80, 179].

3.12.2 Etiology

IgAD and CVID often coexist in members of the same family, and some individuals initially present with IgAD subsequently then develop CVID [87, 146, 172, 177, 195, 200, 248, 370, 372, 373].

These data support the involvement of hereditary factors and a genetic association between IgAD and CVID. Genetic linkage analysis of families with IgAD and CVID had identified susceptibility loci on chromosome 6 within the MHC locus near the class I, II, and III regions [358–360]. The DR/DQ locus has been reported to be the strongest predisposing locus. Studies on multiply-affected families with IgAD and CVID have shown an increased allele sharing in the proximal region of the MHC at chromosome 6p21 [425]. A more detailed genetic analysis in 101 multiple-case families and 110 single-case families also localized the defect to the HLA-DQ and HLA-DR loci [229].

Although it has been found that a fundamental defect in IgAD is the failure of IgA-bearing B lymphocytes to mature into IgA secreting plasma cells, the reason of this defect is still not understood. Isotype switching and terminal differentiation into IgA-secreting plasma cells using transforming growth factor beta (TGF-ß) [380] or IL21 [62] may indicate a key role of cytokine in this process.

Genetic defects of a tumor-necrosis factor receptor family member termed TACI have been identified in a few patients with IgAD and CVID, possibly causing defects in isotype switching [90]. Although the former point has been questioned, molecular studies have demonstrated impaired mu switch (S) to S alpha rearrangements in peripheral B cells in some IgA deficient subjects [196, 432]. IgAD can be a component of other forms of PIDs, such as ataxia-telangiectasia, mucocutaneous candidiasis [206, 399] and IgG2 subclass deficiency [306].

Transient or permanent IgAD may develop after therapy with certain drugs including phenytoin, carbamazepine, valproic acid, zonisamide, sulfasalazine, gold, penicillamine, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs [206, 304]. IgAD has also been reported in

patients with chromosome 18 abnormalities [423]. In addition, congenital rubella and Epstein-Barr virus infections have been implicated in a few cases of acquired IgAD [108].

A subgroup of patients with IgAD exhibit IgG subclass deficiency and defective specific antibody production and have higher rates of recurrent infections and bronchiectasis, which require more effective monitoring [11]. Moreover, severe clinical manifestation, including infectious complications and autoimmune diseases may be present in IgAD patients with a low count of switched memory B cells [10, 249] . Diminished number of regulatory T cells in the former group has been demonstrated and correlates with autoimmunity.

Selected IgAD patients may develop into CVID and familial aggregation of these two disorders suggesting a common genetic background (associated with the HLA A1-B8- DR3-DQ2 haplotype) and a similarity of the underlying B cell defect. In line with this reasoning IgAD patients with autoimmune disorders (defective switched memory B cells or regulatory T cells) and severe infections (IgG subclass deficiency or specific antibody deficiency) are at higher risk for development of CVID [16, 87, 146, 305, 360]

3.12.3 Clinical Manifestations

Approximately two thirds of patients with IgAD remain asymptomatic [107]. Association of concomitant defects in individuals with IgA deficiency may predispose affected individuals to recurrent infections. These concomitant immune defects may include deficiency of IgG subclasses, defects in specific antibody production against protein and polysaccharide antigens and defects in mannan-binding lectin (MBL) [20, 63, 142, 157].

In symptomatic IgA deficient patients, infections include recurrent viral infections, recurrent otitis media, frequent sinopulmonary infections, and gastrointestinal infections [142, 177].

Invasive infections such as septicemia and meningitis are not generally features of IgAD. Patients with IgA deficiency are also have a higher frequency of autoimmune diseases [430], and, potentially, malignancy [270].

Lack of severe infection in patients with IgAD may, in some cases, be attributed to a compensatory increase in secretory IgM [2, 177].

Sinopulmonary infections Recurrent sinopulmonary infections are the most frequent symptom associated with IgAD. These are caused by extracellular encapsulated bacteria (e.g. *Haemophilus influenza* and *Streptococcus pneumoniae*). Frequent, recurrent episodes of otitis media and sinopulmonary infections are most commonly observed in patients with IgAD and decreased IgG subclass levels (especially IgG2 in children) [376, 440].

Patients with IgAD who have a combination of IgA deficiency and a deficiency of one or more IgG subclasses or impaired antibody responses to protein and polysaccharide antigens are at risk for chronic lung complication such as impaired lung function and bronchiectasis [55, 381, 416].

In our unpublished study, among 40 patients with bronchiectasis of unknown etiology, we found 3 (7.5 %) patients with IgAD with an associated IgG subclass deficiency and/or defects in specific antibody production against polysaccharide antigens. This finding is similar to previous studies in which the rate of IgAD among patients with bronchiectasis varied between 5.3 and 14 % [381, 416].

Some authors have indicated a need to assess antibody responses to polysaccharide vaccines in patients with bronchiectasis of unknown etiology [410]. This is may be indicated for patients with IgAD and a history of recurrent or chronic otitis media and/or sinusitis, IgG2 subclass deficiency, or low levels of baseline specific antibodies [416]. Therefore, a search for IgAD should be performed in patients with bronchiectasis of unknown etiology and in patients with a history of recurrent otitis media and sinopulmonary infections.

Gastrointestinal diseases Patients with IgAD are more susceptible to gastrointestinal diseases including giardiasis, nodular lymphoid hyperplasia, celiac disease, and inflammatory bowel disease [183]. Up to 50 % of IgA deficient individuals have precipitins to cow's milk [111, 112] and

most of IgA deficient patients develop circulating immune complexes in their serum 15–60 min after drinking milk [112].

Autoimmune disorders A variety of autoimmune diseases including immune thrombocytopenic purpura, autoimmune hemolytic anemia, type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, Graves' disease, celiac disease and vitiligo are associated with IgAD [108].

It has been postulated that absence of IgA in the serum permits cross reactive antigens to enter the circulation and subsequently initiate autoimmune reactions.

Patients with IgAD often have autoantibodies against thyroglobulin, red blood cells, thyroid microsomal antigens, basement membrane, smooth muscle cells, pancreatic cells, nuclear proteins, cardiolipin, human collagen, and adrenal cells [236, 348]. A significant number of patients with IgAD have anti-IgA antibodies that may result in transfusion reactions [236, 348]. Anti-IgA antibodies occur in some IgA deficient individuals with undetectable IgA but may occasionally be seen in patients lacking in one of the two IgA subclasses [387]. Thus, blood products should be carefully considered before use in patients with IgAD.

Allergy IgA deficiency may be associated with allergy and the most common allergic disorders reported in IgA deficient individuals are asthma, allergic rhinitis, allergic conjunctivitis, urticaria, atopic eczema and food allergy [177, 354, 369, 385].

Malignancies IgA deficient patients have been reported to be at a higher risk for gastrointestinal and lymphoid malignancies [117, 246]. However, more recent studies suggest no marked over representation of tumors in IgA deficient patients [270].

3.12.4 Diagnosis

IgAD is defined as serum IgA level (less than 7 mg/dL) in a patient older than 4 years with normal serum levels of IgG and IgM and exclusion of other causes of hypogammaglobulinemia. Low serum IgA levels in children aged 6 months to 4 years should be confirmed to be persistently low at age 4 years before making a diagnosis of IgAD. Patients with IgAD, especially patients with absent secretory IgA, which is associated with one or more IgG subclass deficiencies or an impaired polysaccharide responsiveness, may develop recurrent sinopulmonary infections and GI tract infections. Therefore, IgA deficient patients may be evaluated for specific antibody production against protein and polysaccharide antigens. Measurement of IgG subclass and secretory IgA should also be performed to determine if there is a concomitant functional antibody deficiency and if these patients would benefit from administration of immunoglobulin.

Some patients with IgAD may progress to CVID. Therefore, long-term follow-up and repeat immunoglobulins determinations at regular intervals (bi-annually) is indicated, especially in symptomatic IgA deficient patients.

The presence of auto-antibodies such as ANA and thyroid antibodies should be investigated in patients with IgA deficiency. Allergy tests and measurement of anti-gluten antibodies of the IgG class should be performed, if there is evidence of food intolerance or malabsorption. IgA deficient patients with concomitant functional antibody deficiency, who are selected for IVIG therapy, should be assessed for the presence of anti-IgA antibodies.

3.12.5 Management

For individuals with asymptomatic IgAD, no therapy is recommended. The use of prophylactic antibiotics can be considered in IgA deficient patients with a history of infections and some patients may benefit from long-term prophylactic antibiotics [246]. Aggressive antimicrobial therapy is indicated in all IgA deficient patients at the time of infections. Routine active immunization is not contraindicated in patients with IgAD. The use of immunoglobulin replacement therapy for patients without a

demonstrable impairment of specific antibody formation is controversial [142, 171, 246]. If there is inadequate response to antimicrobial therapy and patients have a concomitant specific antibody defect, a trial of gammaglobulin should be considered [27]. Gammaglobulin should be given with a product low in IgA and with caution and potentially providing premedication. The anti-IgA antibodies are not a contraindication, if the gammaglobulin is given subcutaneously [171, 387].

If patient with IgAD who are on a medication known to cause IgA deficiency, the drugs should be changed or discontinued. The prognosis of patients with IgA deficiency depends on the presence of a concomitant specific antibody defect, allergy and autoimmune diseases.

3.13 Other Immunoglobulin Isotypes or Light Chain Deficiencies

(Isolated IgG subclass deficiency, IgA with IgG subclass deficiency, Ig heavy chain mutations/deletions, k light chain deficiency)

3.13.1 Definition

IgG subclass deficiency was first reported in 1970 [361]. It is defined as a deficiency of one or more IgG subclasses, (less than 2SD below the mean normal level for their age) in the presence of a normal level of total IgG [257]. Most such patients show a normal IgM level. In some patients, abnormal IgG subclasses are associated with a low level of IgA [157]. Therefore, IgG subclass deficiency could be seen with or without IgA deficiency. The clinical significance of IgG subclass deficiency in patients with recurrent infections remains unclear because approximately 2 % of normal individuals have an IgG subclass deficiency of one or more IgG subclasses [75, 257]. A low level of one or more IgG subclasses without clinical manifestations is generally not considered sufficient for a diagnosis of immunodeficiency.

3.13.2 Etiology

Human IgG is subdivided into four subclasses, IgG1, IgG2, IgG3 and IgG4. IgG1 is the major component of total IgG (66 %), followed by IgG2 (24 %), IgG3 (7 %) and IgG4 (3 %). IgG1 and IgG3 appear early in ontogeny [257, 361], are efficient activators of the classical complement pathway [70, 120] and are directed mainly against protein antigens. IgG2 includes a preponderance of antibodies to polysaccharide antigens of encapsulated bacteria. The IgG2 subclass reaches the adult level at 5–10 years of age.

The basic pathogenesis of IgG subclass deficiencies remains unknown. In a few cases, lack of expression of Ig isotypes has been shown to be due to homozygous deletions of corresponding constant region genes [64, 274, 301, 308, 371]. Most IgG subclass deficiencies are due to dysregulation of the expression of the γ genes.

The most common type of IgG subclass deficiency is IgG4 deficiency (40 %), followed by those of IgG2 (28 %), IgG3 (17 %) and IgG1 (14 %). Isolated IgG1 deficiency is rare because it usually results in a major deficiency of total IgG.

IgG subclass deficiency is sometimes associated with IgA deficiency. IgG subclass deficiency is also observed in association with other primary immunodeficiency diseases including ataxia telangiectasia [37], Wiskott-Aldrich syndrome [296] and secondary immunodeficiencies such as HIV infection or AIDS [44], as well as following hematopoietic stem cell transplantation [230].

Immunoglobulin heavy chain deletion is an autosomal recessive disease, which is caused by chromosomal deletion of a cluster of genes, the IgG heavy chain locus at 14q32.32 (*IGHG1*, OMIM *147100). One or more IgG and/or IgA subclasses as well as IgE may be absent, but the affected cases may be asymptomatic [71].

klight chain deficiency is an autosomal recessive disease, which is caused by mutations in the immunoglobulin kappa constant region gene located on chromosome 2p11.2 (*IGKC*, OMIM*147200). Although this disease can be associated with other conditions, it can also be asymptomatic. The pathogenesis of the disease involves a failure to express kappa chains, but

the reason for this remains unknown [51, 250, 379, 452].

3.13.3 Clinical Manifestations

The most frequent symptom observed in patients with IgG subclass deficiencies is recurrent respiratory infections such as otitis media, sinusitis and bronchitis caused predominantly by encapsulated organisms [318, 365, 366, 407]. Severe systemic infections including sepsis, pneumonia, meningitis and cellulitis are less common. Some patients also present frequent viral infections. Allergic disease is also frequently encountered in patients with IgG subclass deficiency [234] and many patients are atopic; asthmatic bronchitis is also associated with the respiratory infections.

IgG2 deficiency is the most common subclass deficiency associated with recurrent infection, and may be accompanied by IgA and/or IgG4 deficiencies. Most of these patients have impaired polysaccharide responsiveness. IgG4 deficiency is the most common form of IgG subclass deficiency, but is not usually of clinical significance. However, recurrent pneumonia and bronchiectasis have been described in IgG4 deficiency.

3.13.4 Diagnosis

In patients with recurrent respiratory infections and normal IgG levels, IgG subclass should be evaluated. IgG subclass levels must be compared with those of age-matched controls. In some cases, the total IgG level may be low, and care should be taken to determine whether a diagnosis of common variable immunodeficiency (CVID) might be more appropriate.

Impaired responses to polysaccharide are observed commonly in young patients with IgG2 subclass deficiency [407]. A clinically significant IgG subclass deficiency must be established by measuring the antibody response to vaccine antigen, especially pneumococcal polysaccharide vaccine. In individuals with recurrent infections and low levels of one or more IgG subclasses, an impaired antibody response to vaccination is considered the most important determinant of disease [75]. Susceptibility to infection may wane over time, although immunologic abnormalities may persist [185].

Tests for cellular immunity, complement activity and phagocytic function should be performed to rule out other primary immunodeficiency diseases. Chest X-ray, sinus imaging and pulmonary function tests should be considered. A search for associated illnesses should be undertaken.

3.13.5 Management

Asymptomatic patients with IgG subclass deficiency and normal antibody responses to polysaccharide antigens require no therapy. Many patients do well with prompt medical management and immediate use of antibiotics in the course of an infectious episode.

Some patients with recurrent infections or chronic respiratory infections need to be treated with prophylactic antibiotics, especially in winter. Immunoglobulin replacement therapy is occasionally required in cases with a failure of prolonged antibiotics, severe symptoms and persistent radiographic abnormalities. IgG subclass deficiency without symptoms are not an indication for immunoglobulin replacement therapy.

Some children may recover from IgG subclass deficiency spontaneously, particularly if there is not a complete absence of a subclass. In contrast, symptomatic patients may progress to CVID. Therefore, a repeat of subclass determination yearly or half-yearly is required in patients with IgG subclass deficiency.

3.14 Specific Antibody Deficiency with Normal Immunoglobulin Concentrations

3.14.1 Definition

Specific antibody deficiency (SAD) is characterized by abnormal IgG antibody responses to a majority of polysaccharide antigens and increased

susceptibility to recurrent bacterial infections in subjects over the age of 2 years, but who show normal concentrations of immunoglobulins and IgG subclasses [376, 377, 437]. SAD may be the most common immunodeficiency observed among children with increased susceptibility to infection [145, 186, 199].

3.14.2 Etiology

Although the basic origin of SAD remains unclear, there is some evidence of genetic involvement in certain families and an association with certain Gm and Km IgG allotypes [125]. Studies also suggested a defect in the B-cell repertoire[25] and marginal zone of the spleen [402]. A strong association between SAD and allergic disease suggests that this disorder may be caused by immune dysregulation, with impaired response to polysaccharide antigens [65]. This may help in defining the molecular basis of SAD.

3.14.3 Clinical Manifestations

Patients with SAD usually develop recurrent bacterial respiratory infections such as sinusitis, otitis media and bronchitis. Systemic infections such as pneumonia, sepsis or meningitis are less common. Affected individuals frequently show asthma-like symptoms caused by chronic sinusitis. Almost all children with SAD have at least one form of allergic disease, most commonly allergic rhinitis [65]. Patients usually exhibit normal growth and development.

3.14.4 Diagnosis

The diagnosis of SAD should be considered in patients older than 2 years with recurrent upper and/or lower respiratory tract infections. SAD with normal immunoglobulin levels is a primary immunodeficiency of unknown origin [25, 26, 158, 352, 374, 375]. The prevalence of this disorder is unknown, but it may be a frequent finding in patients evaluated for recurrent respiratory tract infections [145, 186, 199].

Methods that measure IgG and IgM antibodies simultaneously may give falsely normal antibody concentrations due to short-lived increases in IgM antibodies. IgG specific for serotypes included in currently used pneumococcal vaccines may be determined by a standardized ELISA method and expressed in micrograms per milliliter [374].

The most accurate type-specific determinations are made using a reference standard serum (Food and Drug Administration SF89) and preadsorption with C polysaccharide common to all types and the 22 F polysaccharide, which is cross-reactive [98]. (Laboratories that meet these standards include Louisiana State University Children's Hospital, New Orleans, LA; ARUP Laboratories, University of Utah, Salt Lake City, UT; and IBT Reference Laboratory, Progene Biomedical Inc, Lenexa, KS.)

Protection against infection and colonization is associated with antibody concentrations of 1.3 μg/mL or higher or 200–300 ng of antibody nitrogen per milliliter (N/mL) per serotype. The conversion factor is 160 ng of antibody N/mL to 1 μg/mL [235, 238].

The interpretation of antipneumococcal antibody concentration results is based on antibody increases over preimmunization concentrations (immune response) and on final concentrations following immunization. High pre-immunization antibody concentrations to a specific serotype are less likely to rise after immunization [375].

Adequate responses to individual pneumococcal serotypes are defined as a postimmunization antibody concentration of 1.3 μg/mL or higher or at least fourfold over baseline [26, 375]. In patients immunized with heptavalent pneumococcal conjugate vaccine, it is important to measure antibody responses against at least 6 serotypes present only in the polysaccharide vaccine.

Age also plays a significant role in the interpretation of responses to polysaccharide immunization. Well-validated age-adjusted criteria that define normal responsiveness to pure polysaccharides are yet to be developed. In general, responses to pure polysaccharide antigens are

unreliable in patients younger than 2 years [375]. Between the ages of 2 and 5 years, individuals should respond to approximately half or more of the pneumococcal type-specific polysaccharides.

Although controversy exists regarding the actual number of pneumococcal serotypes needed to determine a normal response, the consensus recommends that for patients older than 5 years, individuals should respond to at least approximately 70% of pneumococcal serotypes. Pneumococcal conjugate vaccines stimulate antibody responses as would other protein immunogens. Criteria regarding the magnitude and number of serotypes in response to conjugate pneumococcal vaccines with respect to the diagnosis of primary immunodeficiency have not been established.

3.14.5 Management

Patients with SAD may benefit from additional immunization with conjugate pneumococcal vaccines. Patients who fail to respond to the polysaccharide vaccine when immunized after 2 years of age usually respond to the conjugate vaccine [374]. If there are no responses to vaccines and the patient remains symptomatic, immunoglobulin therapy should be considered to control and prevent infections.

3.15 Transient Hypogammaglobulinemia of Infancy

3.15.1 Definition

Transient hypogammaglobulinemia of infancy (THI) was first reported in 1956 [164]. It is defined as hypogammaglobulinemia due to abnormal and prolonged delay in IgG production by infants that extends to the 2 or 3 years of age [133, 266]. THI is defined as a low level of IgG (less than 2SD below the mean for their age), with or without reduction of IgA and/or IgM, in an infant beyond 6 months of age in whom other primary immunodeficiencies have been ruled out. Despite the low level of IgG, most infants can respond to vaccine antigens. The true incidence of THI has not been estimated because it is rarely associated with severe infection and cases are not referred to immunologists.

3.15.2 Etiology

There is no known genetic basis for THI, although an increased incidence is reported in families with other immunodeficient individuals. Twelve patients with THI were described to have an increased incidence of atopic diseases [428]. Transiently elevated $CD4^+$ $CD25^{high}$ $FOXP3^+$ T-cell numbers, reduced CD19 expression and decreased memory B-cell numbers were also observed in patients with THI [32, 341]. Some studies suggested that THI was caused by T-helper deficiency [367] or a cytokine imbalance [226].

3.15.3 Clinical Manifestations

Some infants with THI are asymptomatic, have a normal response to vaccine antigen and grow out of their hypogammaglobulinemia. However, clinical manifestations of THI include bacterial sinopulmonary infections and other respiratory tract infections [74]. THI is rarely associated with sepsis, meningitis, or invasive infections [74, 216]. Case reports have documented these more severe infections [74, 224], but studies of larger cohorts indicate that they are uncommon [216]. Sixty percent of patients are male. Some children may have asymptomatic hypogammaglobulinemia, and others may have allergies or autoimmune diseases [283]. Patients may be associated with hematologic abnormalities, most commonly mild neutropenia and less commonly thrombocytopenia. Infants with THI have normal growth and development.

3.15.4 Diagnosis

The clinical presentation of transient hypogammaglobulinemia of infancy (THI) occurs in infants and young children with recurrent

bacterial sinopulmonary infections and frequent viral illnesses. Infants are normally protected by transplacentally acquired maternal IgG for the first 3–6 months of life, until the natural degradation of the maternal antibodies (half-life of approximately 21 days). In some infants, production of IgG (and in some cases IgA and IgM) does not reach normal levels until early childhood (as late as 36 months). This delay in antibody production may be associated with recurrent infections. In THI, IgG levels spontaneously correct to normal at a mean age of 27 months, with all patients reaching normal levels by 59 months [134].

The definitive diagnosis of THI can only be made after IgG (and in some cases IgA and/or IgM) levels have corrected; before that, infants with a decreased IgG concentration have hypogammaglobulinemia of infancy that may become THI. Although most children with THI spontaneously recover their IgG values and have a benign clinical course, some of them do not recover and develop selective IgA deficiency, common variable immunodeficiency or other forms of dysgammaglobulinemia [266].

In THI, IgG concentrations were repeatedly below the age-specific normal range for a period of time during infancy and early childhood. IgM and or IgA may also be transiently low. Specific antibody production is usually preserved, and cellular immunity is intact. Isolated, transient deficiencies of IgA, IgG2 [36] and specific antibody deficiencies are sometimes associated with THI.

Laboratory evaluation in THI reveals IgG levels below the fifth percentile for their age [447]. Some authors stipulate that measurements be repeated to eliminate misdiagnosis due to laboratory error [401]; however, this is not universally applied. A decreased IgG level is sometimes associated with a decreased IgA level and, less often, with a decreased IgM level [216]. Evaluation also includes measurement of specific antibody production to protein and polysaccharide antigens and enumeration of lymphocyte subsets by flow cytometry. Most children have normal booster responses to protein vaccines and normal isohemagglutinin concentrations. Transient impairment of antibody responses to viral infections was noted in one report, but measurement of antiviral antibody titers is not usually part of the evaluation [84]. Rare individuals have transient suppression of vaccine responses, which recovers by the age of 3–4 years [118]. Decreased numbers of circulating T cells were noted in some patients with THI, but this is also not a prominent feature in most patients [367].

3.15.5 Management

Prediction of the eventual outcome of hypogammaglobulinemia towards THI as opposed to a persistent form of immunodeficiency is based on the clinical severity [439] and the ability to respond to specific antigens despite low IgG concentrations. Recently, evaluation of memory B cells has been used to predict the evolution of hypogammaglobulinemia of infancy with patients with low IgM and/or class-switched memory B cells being more likely to have a permanent form of immunodeficiency [283].

THI is a self-limited disease, with recovery by 3 years of age. Therefore, asymptomatic patients with THI require no treatment, and immunoglobulin levels should be monitored at least every 12 months if infections begin to occur, to document their therapy.

Preventive antibiotic therapy may be indicated for some patients with THI. A period of IVIG replacement may be considered. Antibiotic prophylaxis should be the initial mode of preventive therapy. If this fails or is not tolerated, some patients may benefit from immunoglobulin administration, particularly during seasons when respiratory illnesses are more frequent. An increase in the patient's own IgG production can be monitored by keeping the IgG dose and infusion intervals constant; IgG production is clearly reflected by increasing IgG trough levels. When IgA and/or IgM are also low at the start of IgG replacement, their levels should also be monitored regularly. An increase into the normal range is a clear sign of improvement and may allow discontinuation

of IgG replacement therapy based on objective data. Immunoglobulin replacement therapy should be stopped after 3–6 months to reassess the status of the patient's humoral immune function [118].

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Phagocytes Defects

4

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4.1 Introduction

Our understanding of primary immunodeficiency diseases (PID) in general is changing, shifting from the simple towards the more complex, often including more than exclusively the immune system [41]. As with other PIDs, the recent progress in molecular biology over the last decade has facilitated better understanding of the nature of phagocytes defects (Table 4.1). *(See* Table 1.3 *and* Fig. 1.10 *for updated classification of phagocytes defects)*

Fifty years after the description by Kostmann, a gene mutation has been identified in patients with the syndrome bearing his name [38, 40]. Long-term follow-up of relatively large patient groups with known gene mutation(s) (thanks to international multi-center studies) [162] will give

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Table 4.1 Characteristics of phagocytes defects [206]

Diseases	Genetic defects	Inheritance	Associated features
Chronic granulomatous disease	*CYBB*	XL	Infections, McLeod syndrome (in patients with deletions extending into the contiguous Kell locus); Discoid lupus and oral ulcers (in female carriers)
	CYBA	AR	Infections, autoinflammatory phenotype
	NCF1	AR	Infections, autoinflammatory phenotype
	NCF2	AR	Infections, autoinflammatory phenotype
	NCF4	AR	Infections, autoinflammatory phenotype
Leukocyte adhesion deficiency	*ITGB2*	AR	Delayed umbilical cord separation, periodontitis, omphalitis, skin ulcers, leukocytosis
	FUCT1	AR	Skin ulcers, periodontitis, mental and growth retardation; hh blood group
	FERMT3	AR	Skin ulcers, periodontitis, bleeding tendency
RAC-2 deficiency	*RAC2*	AD	Poor wound healing, leukocytosis
β-Actin deficiency	*ACTB*	AD	Mental retardation, short stature
Localized juvenile periodontitis	*FRP1*	AR	Aggressive periodontitis
Papillon-Lefèvre syndrome	*CTSC*	AR	Periodontitis, palmoplantar hyperkeratosis
Specific granule deficiency	*CEBPE*	AR	Bilobed nuclei of the neutrophils
Shwachman-Diamond syndrome	*SBDS*	AR	Exocrine pancreatic insufficiency; chondrodysplasia
Severe congenital neutropenias	*ELANE*	AD	Susceptibility to myelodysplasia/leukemia
	GFI1	AD	B/T lymphopenia
	HAX1	AR	Susceptibility to myelodysplasia/leukemia, neurological problems
	G6PC3	AR	Structural heart defects, urogenital abnormalities, deafness, venous angiectasias
	VPS45A	AR	Extrameduallary hematopoiesis, bone marrow fibrosis, nephromegaly
	WASP	XL	Monocytopenia, myelodysplasia
	LAMTOR2	AR	Hypogammaglobulinemia, partial oculocutaneous hypopigmentation, growth failure
	JAGN1	AR	Bone phenotype
	CSF3R	AR	Poor response to GCSF
Cyclic neutropenia	*ELANE*	AD	Oscillations in production of all types of blood cells
Glycogen storage disease type 1b	*G6PT1*	AR	Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly
3-Methylglutaconic Aciduria	*TAZ*	XL	Cardiomyopathy, growth retardation
	CLPB	AR	Microcephaly, hypoglycemia, cataracts, neurological problems, hypotonia
Cohen syndrome	*COH1*	AR	Retinopathy, developmental delay, facial dysmorphisms
Poikiloderma with neutropenia	*C16ORF57*	AR	Poikiloderma, myelodysplasia
Myeloperoxidase deficiency	*MPO*	AR	Asymptomatic, candidiasis

us more insight into the natural course of these diseases and will influence our treatment approaches in the future. The clinical identification and careful description of individual patients will continue to add to our better understanding of these disease processes. The ESID/PAGID diagnostic criteria for severe congenital neutropenia (SCN) from 2006 are an example: as commonly perceived, SCN is an isolated condition due to several gene mutations, but it is also part of many complex syndromes [75].

Another half-century mark worth mentioning is the 'coming of age' of hematopoietic stem cell transplantation (HSCT) [10], still the main curative procedure for most immunodeficiencies. The future looks even better for these patients as the era of gene therapy has arrived, albeit still evolving, with (un)expected complications keeping it from being 'the perfect treatment' [207].

4.2 Chronic Granulomatous Disease

(gp91 phox deficiency, p22 phox deficiency, p47 phox deficiency, p67 phox deficiency, p40 phox deficiency)

4.2.1 Definition

Chronic granulomatous disease (CGD) is a genetically heterogeneous disease characterized by recurrent life-threatening infections with bacteria and fungi and dysregulated granuloma formation. CGD is caused by defects in the NADPH oxidase, the enzyme complex responsible for the phagocyte respiratory burst which leads to the generation of superoxide and other reactive oxygen species (ROS). There are five related genetic defects mapping to different chromosomes that result in this phenotype. The disease was first described by Janeway et al. in 1954 [110], but was not well characterized until 1959 by Bridges et al. [33]. It was initially termed fatal granulomatous disease of childhood, but with early diagnosis and better treatment, the prognosis no longer warrants this pessimistic name.

4.2.2 Etiology

The fully assembled NADPH oxidase is a six-protein complex. In the basal state, it exists as two components: a membrane-bound complex embedded in the walls of secondary granules, and proteins in the cytosol [236]. The secondary granule membrane contains the heme and flavin binding cytochrome b_{558}, composed of a 91-kd glycosylated β chain ($gp91^{phox}$) and a 22-kd nonglycosylated α chain ($p22^{phox}$). The cytosolic components are $p47^{phox}$, $p67^{phox}$, $p40^{phox}$ and RAC2.

After cellular activation, such as that initiated by the phagocytosis of microbes, the cytosolic components $p47^{phox}$ and $p67^{phox}$ are phosphorylated and bind tightly together. In association with $p40^{phox}$ and RAC2, these proteins combine with the cytochrome complex ($gp91^{phox}$ and $p22^{phox}$) to form the intact NADPH oxidase. Following assembly, an electron is taken from NADPH and donated to molecular oxygen, leading to the formation of superoxide (O_2^-). In the presence of superoxide dismutase, this is converted to hydrogen peroxide (H_2O_2), which, in the presence of myeloperoxidase and chlorine in the neutrophil phagosome, is converted to hypohalous acid (OHCl), or bleach [3]. The rapid consumption of oxygen and production of superoxide and its metabolites is referred to as the respiratory burst.

Mutations in five members ($gp91^{phox}$, $p47^{phox}$, $p22^{phox}$, $p67^{phox}$, and $p40^{phox}$) of the NADPH oxidase complex account for all known cases of CGD. The majority of the identified mutations in these genes result in complete or nearly complete absence of the NADPH oxidase activity [236]. The gene for $gp91^{phox}$, *CYBB*, (OMIM*300481) maps to Xp21.1 and causes X-linked CGD (OMIM*306400), accounting for about 65–70 % of cases in Western countries or places with low rates of consanguinity. Its partner in the

membrane, p22^{phox}, encoded by *CYBA*, (OMIM*608508) maps to chromosome 16q24 and causes one of the four forms of autosomal recessive CGD (OMIM*233690), accounting for less than 5 % of cases. The cytosolic factor p47^{phox} is encoded by *NCF1,* located at 7q11.23 (OMIM*608512), accounting for about 25 % of cases. The other cytosolic factor, p67^{phox}, encoded by *NCF2*, is located at chromosome 1q25 (OMIM*608515), and accounts for less than 5 % of cases [12, 209, 220, 221, 283]. The cytosolic factor p40^{phox} is encoded by the gene *NCF4*, located at 22a13.1 (OMIM*601488). To date, defects in *NCF4* have been described in a single child suffering from severe inflammatory bowel disease with mildly impaired respiratory burst activity [166].

The nomenclature for various levels of protein expression of gp91^{phox} has been confusing [236]: when gp91^{phox} was absent, such as due to a stop codon or a deletion, it has been referred to as X91^{0}; when reduced amounts of a hypofunctional protein are present, such as due to a splicing or promoter defect, X91^{-}; and when normal amounts of a nonfunctional protein are present, such as due to a missense mutation, X91^{+}. Similar nomenclature has been used for recessive forms of CGD [222]. However, more recent work has shown that the critical issues surrounding NADPH oxidase characterization are not protein presence or absence, but function. Specifically, mutations in *CYBB* fall into functional and nonfunctional categories regardless of protein expression, with important clinical consequences [131]. In fact, function can be largely predicted from the mutation: stop codons or deletions obviously are null and have no function and more severe clinical presentations with higher mortality. A bit more surprising is the finding that essentially all missense changes beyond amino acid 310 in CYBB lead to a complete loss of function, while missense changes up to amino acid 309 may have residual function with better survival than those with absent function. That is, those gp91^{phox} -deficient patients with residual function have clinical courses similar to those with p47^{phox} deficiency. Similarly, those patients with recessive disease who have complete loss of function have clinical courses similar to gp91^{phox} -deficient patients with no residual function. This tight genotype-phenotype correlation in CGD indicates that very small increments in residual superoxide production have major effects on survival and disease severity. However, surprisingly enough, these features have no correlation with the frequency or severity of gastrointestinal manifestations in CGD [131].

In general, X-linked CGD tends to have an earlier onset and be more severe than p47^{phox} deficiency [283]. A single case of a dominant negative mutation in *RAC2* presented with an impaired neutrophil respiratory burst due to rac's critical role in NADPH oxidase function, as well as impaired chemotaxis and adhesion, due to RAC's critical role in linking surface adhesion molecules to the cytoskeleton [136]. The frequency of CGD in the general population is close to 1:200,000 live births, and likely higher than that. The rates appear about the same across ethnic and racial groups, with about one third of the X-linked mutations representing de novo mutations [16, 102, 270, 283], but in regions with high rates of consanguinity the relative rates of recessive CGD are much higher [285].

The X-linked carrier state for gp91^{phox} is not entirely silent. Lyonization of the X chromosome leads to two populations of phagocytes in X-CGD carriers: one displays normal respiratory burst function, whereas the other population, which has inactivated the normal X chromosome and left the defective one active, has impaired respiratory burst activity. Therefore, X-CGD carriers have a characteristic mosaic pattern on respiratory burst testing of peripheral blood. As few as 10 % of cells having normal respiratory burst activity is usually sufficient to prevent severe bacterial and fungal infections. However, other manifestations of heterozygous carriage of X-CGD mutations include discoid lupus erythematosus–like lesions, aphthous ulcers, and photosensitivity and are not clearly related to the degree of skewing of X-chromosome inactivation [31, 129]. The ratio of neutrophil Lyonization in peripheral blood is apparently not fixed and may change over time, allowing carrier women and girls to develop a CGD infection diathesis over time.

4.2.3 Clinical Manifestations

Infectious manifestations CGD can present any time from infancy to late adulthood, but the majority of patients are diagnosed as toddlers and children. However, a growing number of patients are diagnosed in later childhood or adulthood [283].

The frequent sites of infection are lung, skin, lymph nodes, and liver. Osteomyelitis, perianal abscesses, and gingivitis are also common [236, 283] (Table 4.2). Pulmonary infection is typically pneumonia, but hilar lymphadenopathy, empyema, and lung abscesses also occur (Fig. 4.1). The microbiology of infections in CGD is remarkable for its relative specificity. The overwhelming majority of infections in CGD are due to only a limited number of organisms*: Staphylococcus aureus, Burkholderia (Pseudomonas) cepacia* complex*, Klebsiella pnuemoniae, Salmonella* species*, Serratia marcescens, Nocardia* species*,* and *Aspergillus* species. In the pre-prophylaxis era, most lung, skin, and bone infections were staphylococcal. With trimethoprim-sulfamethoxazole prophylaxis, the frequency of bacterial infections in general has diminished. Staphylococcal infections in particular are essentially confined to the liver and lymph nodes [283]. Whereas the typical liver abscess in the immunocompetent patient involves enteric organisms, is liquid and easily drainable, the liver abscesses encountered in CGD are dense, caseous, and staphylococcal and have required excisional surgery [147]. More recent experience is that the simultaneous use of steroids and antibiotics allows cure of these liver abscesses [141]. Bacteremia is uncommon, but when it occurs, it is usually due to *B. cepacia, S. marcescens*, or *Chromobacterium violaceum,* one of the gram-negative rods that inhabits soil and warm brackish water. Bacterial and *Nocardia* infections in CGD tend to be symptomatic and associated with elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and fever [67]. In contrast, fungal infections are much less symptomatic in terms of leukocytosis or fever, and are often detected at asymptomatic stages. Unlike in neutropenic patients, fungal pneumonias do not generally cavitate in CGD, whereas *Nocardia* infections do.

Table 4.2 Percentage prevalence of frequent infections by site in CGD patients

Type of Infection	USA (n=368) [283]	Japan (n=221) [102]	Iran (n=41) [177]	Germany (n=39) [145]
Pneumonia	79 %	88 %	65 %	67 %
Abscess	68 %	77 %	53 %	41 %
Lymphadenitis	53 %	85 %	75 %	72 %
Osteomyelitis	25 %	22 %	21 %	15 %
Sepsis	18 %	28 %	ND	23 %

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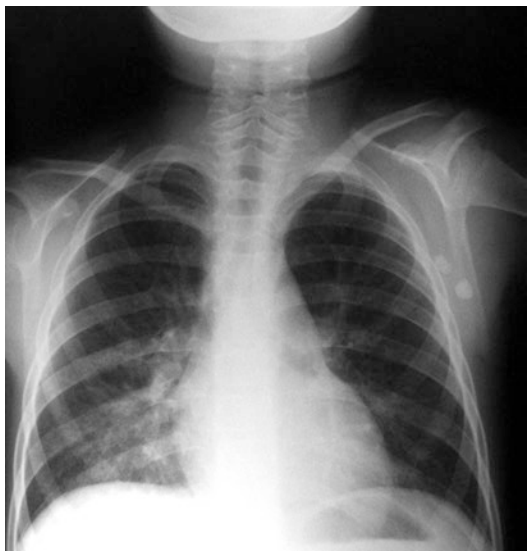

Fig. 4.1 Pneumonia and localized regional BCGitis in a 9 year-old X-linked CGD patient. Chest X-ray showing a right basal pneumonia and 2 calcified lymph nodes on the left axillae sequel to neonatal BCG vaccination

Fungal infections have been the leading cause of mortality in CGD [283]. However, the advent of itraconazole prophylaxis and the newer agents for treatment of filamentous fungal infections, such as voriconazole and posaconazole, have markedly reduced the frequency and mortality of fungal infections in CGD. Bony involvement by fungi typically occurs by direct extension from the lung (Fig. 4.2). *Aspergillus nidulans* is an organism virtually exclusive to CGD. It causes a much higher rate of osteomyelitis than other fungi, and has had a much higher rate of mortality than *Aspergillus fumigatus* or other fungi [235, 254].

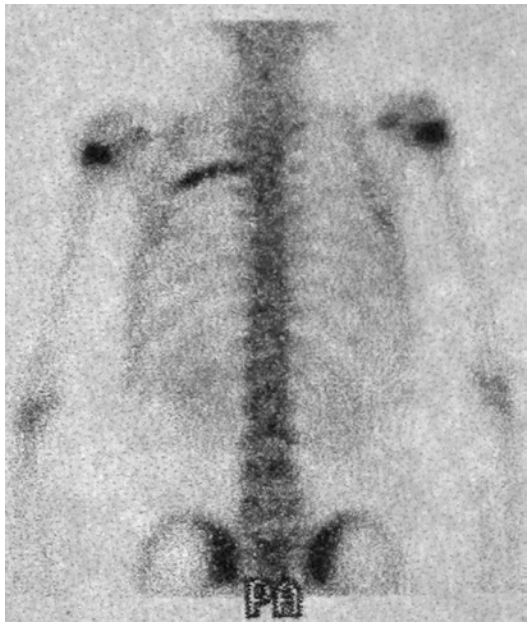

Fig. 4.2 Osteomyelitis in a 7 year-old X-linked CGD patient. Total body scintigram showing a posterior arch left rib fungal oeteomyelitis in a CGD patient. His only manifestation was increased erythrocyte sedimentation rate in a routine follow up laboratory control. No fever, pain or discomfort was reported at presentation

Besides *A. nidulans and C. violaceum*, other microorganisms should also encourage physicians to suspect CGD. *Granulibacter bethesdensis* is a novel gram-negative rod isolated from necrotizing lymph nodes and meninges in CGD [94]. *Penicillium piceum* is a relatively nonpathogenic fungus that produced lung nodules and osteomyelitis in a CGD patient [227].

BCG vaccine, given to almost 90 % of newborns around the world, is usually the first important infectious challenge CGD patients will face (typically 3.75×10^4 to 3.2×10^6 live organisms/dose). Different BCG strains are used around the world, some of them defined as "Strong" (e.g., Pasteur 1173, Danish 1221) and others as "Weak" (e.g., Glaxo 1077, Tokyo 172) based on their immunogenicity potential, degree of cutaneous hypersensitivity or granuloma formation, and incidence of side effects [17, 250]. BCG complications range from none to self-limited localized BCGitis to fatal disseminated BCGosis (Fig. 4.2). Although all BCG strains appear to be equally aggressive in severe combined immunodeficiency (SCID) patients [158], the type of BCG vaccine may have a role in CGD, where "Strong" strains have a higher and more severe complications (SDR, personal observation). In some CGD surveys, some pneumonias were reported to be mycobacterial, but BCG and tuberculosis infections are clearly increased [34, 49, 137, 283].

Table 4.3 Percentage prevalence of frequent granulomatous complications by site in CGD patients

Site of granulomatous complication	Percent of affected patients (patients in the study)
Gastrointestinal tract	32 % (140) [159]
Genitourinary tract	18 % (60) [276]
Choreoretinal lesions	24 % (38) [92]

Inflammatory manifestations Patients with CGD are prone to excessive granulation tissue and granulomata (Table 4.3). These can affect any hollow viscus, but are especially problematic in the gastrointestinal (GI) and the genitourinary tracts (GU). Marciano et al. (2004), analyzed 140 CGD patients and found 43 % of the X-linked and 11 % of the AR-CGD patients had symptomatic, biopsy proven inflammatory bowel disease. Abdominal pain was the most frequent symptom [159]. Walther and colleagues found 38 % of patients had some kind of urologic event, including bladder granulomata, ureteral obstruction, and urinary tract infection. All patients with granulomata of the bladder or stricture of the ureter had defects of the membrane component of the NADPH oxidase: 8 had gp91^{phox} defects and 1 had a p22^{phox} defect [26]. Steroid therapy is quite effective and surprisingly well tolerated for resolution of obstructive lesions of both the GI and GU tracts. Several reports and many anecdotes confirm the benefit of steroids given at about 1 mg/kg for a brief initial period and then tapered to a low dose on alternate days [45, 181, 208, 253]. Prolonged low-dose maintenance may be necessary and does not appear to be associated with an increased rate of serious infections. There are anecdotal reports of the successful use of infliximab in severe cases of inflammatory

bowel disease in CGD patients, but several of these have been accompanied by severe infections and death from typical CGD pathogens [267]. Therefore, we advise against their use in CGD, but if needed, intensified vigilance and prophylaxis for intercurrent infections seem prudent.

Chorioretinal lesions could be seen in up to one fourth of X-linked CGD patients. They are mostly asymptomatic retinal scars associated with pigment clumping. Interestingly, these same lesions can also be detected in gp91^{phox} female carriers [92]. Bacterial DNA has been isolated from these lesions, which typically do not progress even during profound immunosuppression, making the role of infection in CGD-associated chrorioretinal lesions unclear [278].

Hepatic abnormalities are frequently described in CGD patients. Liver enzymes were reported to be elevated at least once in 73 % of a CGD cohort followed at the NIH (n = 194), 25 % had persistent elevations of alkaline phosphatase and drug-induced hepatitis was reported in at least 15 % of these patients. One-half had splenomegaly that was usually associated with portal vein venopathy; in cases with abnormal liver enzymes who underwent biopsy liver histology, 75 % had granulomata and 90 % had lobular hepatitis [108].

Autoimmune disorders are more common in CGD. Both discoid and systemic lupus erythematosus have been described in CGD patients, and in X-linked female CGD carriers [36, 156] (Fig. 4.3). Idiopathic thrombocytopenic purpura (ITP) and juvenile idiopathic arthritis (JIA) are also more frequent in CGD than in the general population [283].

The gene coding for the Kell blood cell antigen system (XK) maps to Xp21, immediately adjacent to *CYBB*, the gene for gp91^{phox}. Patients with deletions in the X-chromosome may delete portions of both genes (contiguous gene disorder) and thereby present with CGD and McLeod syndrome. McLeod syndrome is a form of acanthocytosis that may result in anemia, elevated creatine phosphokinase, and late-onset peripheral and central nervous system manifestations. Special care has to be taken when transfusing X-linked CGD patients to avoid Kell(+) transfusions into Kell(−) patients [84, 165]. All X-linked CGD patients should be tested for Kell antigens. Consideration should be given to blood storage for CGD patients with McLeod syndrome if bone marrow transplantation is even remotely contemplated.

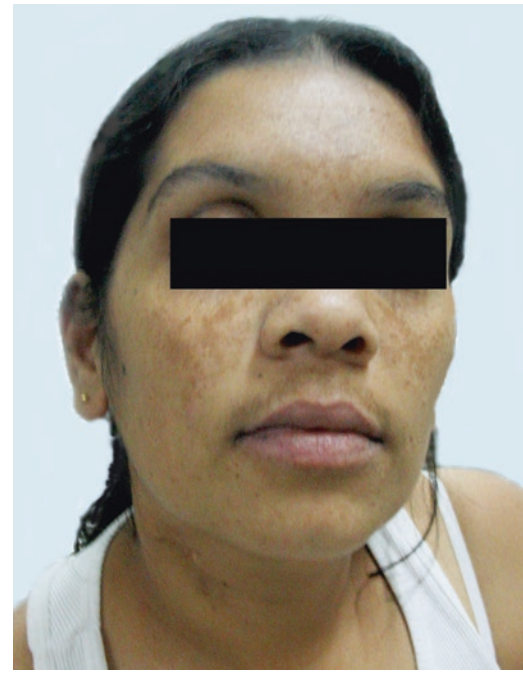

Fig. 4.3 Cutaneous manifestations in a female CGD carrier. Photosensitive discoid lupus-like lesions involving the cheeks of a 36 years-old X-linked CGD female carrier. A scar on the right side of her neck, secondary to lymphadenitis drainage, can also be seen

Unlike many of the immunodeficiencies affecting lymphocytes, CGD patients are not more prone to develop neoplasia. Sporadic cases of acute lymphoblastic leukemia, Hodgkin lymphoma and squamous cell carcinomata due to voriconazole photosensitivity have been reported [148, 167, 284].

4.2.4 Diagnosis

A history of recurrent and/or unusually severe infections, particularly abscesses or those caused by the pathogens commonly associated with CGD (see above), should prompt testing for this disorder. Although CGD has no pathognomonic clinical findings, the diagnosis should be particularly considered in the patient with a constellation of

characteristic pathologies coupled with characteristic microbiology. Consistent clinical findings include splenomegaly, hepatomegaly, growth retardation, diarrhea, and abnormal wound healing with dehiscence, but these are neither necessary nor sufficient for the diagnosis. CGD patients may have minimal clinical signs and symptoms despite significant infectious involvement. Leukocyte counts are not consistently elevated during infection, whereas elevations of the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) are sensitive indicators of infection. Similar to other primary immunodeficiencies, diagnosis and treatment of infections in CGD must be aggressive. Invasive procedures oriented towards direct microbiological diagnosis should be considered as first-line diagnostic tests and should not be left until after the failure of empirical therapy. The reduction in mortality and morbidity in recent years is largely attributable to prophylaxis and aggressive recognition and treatment of infections in these patients [1, 85, 161, 246].

Diagnostic tests for CGD rely on various measures of superoxide production. These include direct measurement of superoxide production, ferricytochrome c reduction, chemiluminescence, nitroblue tetrazolium (NBT) reduction, and dihydrorhodamine 123 (DHR) oxidation. Currently, we prefer the flow cytometry-based DHR oxidation assay because of its objectivity, its relative ease of use, its ability to distinguish between X-linked and autosomal forms of CGD, and the ability to detect gp91^{phox} carriers [274, 275]. However, myeloperoxidase deficiency gives an abnormal DHR, even when not completely deficient, but can be distinguished by a normal NBT test or other measures of superoxide production directly. It can also be confirmed by myeloperoxidase staining of neutrophils.

The other mentioned techniques are highly effective and provide reliable diagnoses of CGD, but suffer either from an inability to distinguish individual populations or the need for significant operator experience and interpretation.

Several other conditions may affect the neutrophil respiratory burst. Glucose 6-phosphate dehydrogenase (G6PD) deficiency and glutathione synthetase (GS) deficiency may mimic certain aspects of neutrophil dysfunction of CGD, such as the decreased respiratory burst and increased susceptibility to bacterial infections [218, 223, 281]. However, G6PD deficiency is most often associated with some degree of nonsferocytic hemolytic anemia, whereas CGD is not; on the other hand, severe GS deficiency is associated with 5-oxoprolinuria, acidosis and mental retardation, in addition to hemolytic anemia. Diverse pathogens, including *Legionella pneumophila, Toxoplasma gondii, Chlamydia, Entamoeba histolytica,* and *Ehrlichia risticii*, have been shown to inhibit the respiratory burst *in vitro*. Human granulocytic ehrlichiosis infection depresses the respiratory burst by downregulating gp91^{phox} [14].

Techniques such as immunoblotting can be used to confirm the diagnosis of CGD. Failure to detect p47^{phox} or p67 ^{phox} proteins indicates autosomal recessive mutations in the corresponding genes. A limitation of immunoblotting is that it cannot distinguish between the X-linked gp91^{phox} defect and the p22 ^{phox} autosomal recessive defect, since expression of these two proteins is mutually co-dependent. That is, if there is a deficiency of either one of them, the other is also absent in the membrane [236]. Sequencing of the CGD genes to determine the exact molecular defect is recommended but not necessary. Genetic testing is available through specialized commercial laboratories and selected tertiary referral centers.

Genetic testing may help with risk profiling of X-linked CGD. X-CGD mutations are usually either missense or nonsense. Nonsense mutations generally lead to more severe CGD with diminished survival. Missense mutations that affect amino acids 1–309 are associated with slight DHR positivity, residual superoxide formation and better survival. In contrast, any mutations affecting amino acids 310 and beyond usually alter critical protein functional domains leading to complete loss of DHR activity, more severe CGD, and diminished survival [131].

4.2.5 Management

The cornerstones of CGD management are: (a) Early diagnosis, (b) Antimicrobial prophylaxis with

trimethoprim-sulfamethoxazole (TMP-SMX), itraconazole, and interferon-γ (IFNγ), and (c) Aggressive management of infectious complications, which usually include invasive diagnostic procedures and parenteral/prolonged anti-infectious medication. In this section, curative options for CGD are also discussed.

Antimicrobial prophylaxis CGD is the only primary immunodeficiency in which prospective, randomized, placebo-controlled studies of prophylaxis of infection have been performed [1, 85, 161] Antimicrobial prophylaxis in CGD relies on a triad of antibacterial (TMP-SMX or cotrimoxazole), antifungal (itraconazole) and immunomodulator therapies (IFNγ). Altogether this scheme dramatically reduces the morbidity rates for severe infections from 1 per patient-year to almost 1 every 10 patient-years [1, 85, 160, 161].

The first prophylactic agents shown to be effective in CGD patients were nafcillin and TMP-SMX [124, 204]. With time, TMP-SMX became the standard of care for CGD patients. In a retrospective study, TMP-SMX (5 mg/kg/day) lowered the incidence of bacterial infections from 15.8/100 patient-months to 6.9/100 patient-months in X-linked patients; and from 7.1 to 2.4/100 patient-months in autosomal recessive CGD [161]. No increase in fungal infections has been noted due to the use of TMP-SMX prophylaxis.

Prophylactic TMP-SMX is usually prescribed at 5 mg/kg/day divided twice daily, although several centers use single-day doses to enhance treatment adherence. For patients allergic to sulfonamide drugs, alternatives include trimethoprim as a single agent, oral beta-lactamase stable penicillins such as dicloxacillin, and fluoroquinolones.

Itraconazole is highly effective antifungal prophylaxis in CGD [35, 85, 176, 203]. In the only prospective, randomized, double-blind placebo-controlled antifungal trial in CGD, Gallin and coworkers reported 7 serious fungal infections in patients receiving placebo, compared to only 1 serious fungal infection in those receiving itraconazole (100 mg/day in patients aged 5–12 years; 200 mg/day in patients ≥ 13 years or ≥ 50 kg). The 39 patients in this study were randomized to receive placebo or itraconazole for a year and were then crossed-over to the other arm of the protocol; all patients were on antibacterial prophylaxis and most were receiving prophylactic IFNγ [85]. Itraconazole-resistant fungal infections do occur, but most have been responsive to voriconazole or posaconazole [6, 234]. The advent of the azole antifungal drugs has dramatically altered the clinical consequences of fungal infections in CGD. Azole serum levels are strongly influenced by individual metabolic rates and other medications; therefore, azole blood level monitoring is critical when evaluating fungal treatment response [105]. It is also important to be aware of steroid-azole interaction leading to impaired steroid metabolism in some patients, as this can cause iatrogenic hypercortisolism during therapy and iatrogenic adrenal insufficiency on steroid withdrawal.

Immunomodulatory therapy An international, multi-center, randomized, double-blind, placebo-controlled trial, showed that IFNγ (50 mcg/m^2 subcutaneously three times weekly) reduced the number and severity of infections in CGD patients, regardless of their age, CGD genotype, or concomitant use of other prophylactic agents [1]. This study included 128 CGD patients (4–24 years-old) from 13 centers (10 US, 3 European) and found that IFNγ was well tolerated. Marciano et al. confirmed the tolerability and long-term efficacy of IFNγ in a study of 76 CGD patients followed for up to 9 years [160]. Based on 328 patient-years of observation, the incidence of serious infections was 0.30/ patient-year, and the mortality rate was 1.5 %/patient-year.

For patients over 0.5 m^2, IFNγ 50 mcg/m^2 three times weekly is recommended, while in children less than 0.5 m^2, 1.5 mcg/kg subcutaneously three times weekly is the suggested dose. Fever and myalgias are the most common IFNγ adverse events, but can be minimized by administration before bedtime and concomitant use of acetaminophen.

The need for administration by injection, cost, continuing improvement in prognosis based on better antifungals, and lack of general familiarity

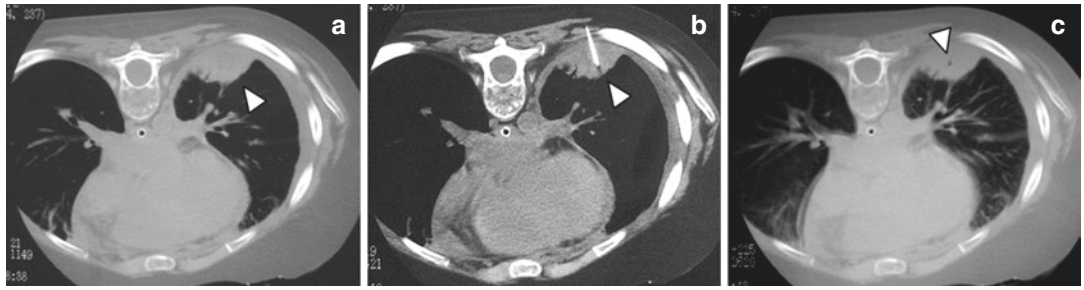

Fig. 4.4 Pre, intra and post CT scan-guided FNA in a 7 year-old X-linked CGD patient. (**a**) A thorax CT scan showing a pleural-based nodular lesion in the basal portion of the left lung (*white arrowhead*; the patient was placed on prone position for the procedure). (**b**) Pulmonary fine needle aspiration biopsy performed with a 21G needle (*white arrowhead*). (**c**) Post- biopsy control CT scan where no complications are detected (e.g., bleeding, pneumothorax) and a small intralesional scar can be seen (*white arrowhead*)

with cytokine therapies have contributed to the less than universal use of IFNγ in CGD patients around the world [35, 145, 176]. Despite the strong evidence for IFNγ's prophylactic benefit in CGD, it has not been shown to help in the treatment of acute infections.

Acute infection management Life-threatening infections may occur at any time in patients with CGD, even in those who have been free of infections for months or years. Serious infections, particularly those caused by fungi, may be asymptomatic or minimally symptomatic at presentation. Significant increases in ESR or CRP should prompt a search for occult infection. Imaging with plain radiographs, ultrasound, CT, or MR are extremely important for the detection of and determination of extent of infections. Because the differential diagnosis for any specific infection includes bacteria, *Nocardia*, mycobacteria, and fungi, a definitive microbiologic diagnosis is essential for directing therapy. Biopsies to obtain microbiological specimens should be insisted upon before the initiation of therapy and not after empirical therapy has failed (Fig. 4.4).

While definitive management of infections depends on their etiology, initial empiric therapies are necessary and some general approaches can be outlined. For pneumonias, after diagnostic specimens have been obtained, empirical initiation of TMP-SMX, and/or a carbapenem, and/or fluoroquinolone, along with voriconazole is appropriate. Most *Burkholderia*, *Serratia* and *Nocardia* infections are sensitive to TMP-SMX. The use of TMP-SMX as therapy for infections that have occurred on prophylaxis remains highly effective, and may reflect either the effect of high dose exposure, a failure of patients to actually take their prophylaxis, or both.

Staphylococcal pneumonias are extremely rare after the initiation of prophylaxis, although they may still cause lymph node or liver infections. Lymphadenitis is usually staphylococcal and often necrotic. These infections respond faster to excision along with antimicrobials. *Chromobacterium violaceum,* a Gram-negative rod that lives in warm brackish water and produces a deep purple pigment, can cause bacteremia and sepsis in CGD. It typically responds to TMP-SMX, quinolones or carbapenems. *Granulibacter bethesdensis* is a newly identified Gram-negative rod that causes necrotizing lymphadenitis and meningitis in CGD. It grows slowly on Legionella or tuberculosis media and responds best to ceftriaxone [94].

Staphylococcal liver abscess in CGD is a special case, as it responds best to a combined therapy with intravenous antibiotics and steroids (1 mg/kg/d for about 2 weeks followed by slow taper) and allows for avoidance of drainage or liver surgery [141]. Further, liver surgery appears to be associated with more long-term morbidity than steroid treatment of liver abscesses.

In general, fungal infections in CGD are more indolent while bacterial infections are more acute

in clinical presentation. However, Siddiqui et al. have described an acute fulminant pneumonitis with hypoxia due to inhalation of mulch or compost [245]. This presentation appears pathognomonic to CGD and requires urgent institution of antifungals and steroids to control the severe pulmonary inflammation.

Granulocyte transfusions have been used in CGD, especially in the setting of refractory fungal infections [109, 194, 273, 288]. However, with the remarkable improvement in antifungals over the last few years, the clinical reasons to use them are very few. Further, granulocyte transfusions often lead to alloimmunization, which may significantly impair the likelihood of successful bone marrow transplantation. Therefore, we view granulocyte transfusions as a useful last resort.

Although bone marrow transplantation is usually contraindicated in the setting of active infection, it has been used repeatedly and successfully for refractory chronic infections in CGD. Ozsahin et al. controlled infections and achieved full immune reconstitution in an 8-year-old boy with *Aspergillus nidulans* infection [194]. Bielorai et al. reported a similar case [21]. The recent series or Gungor et al. showed rates of success >90 % in CGD patients with active inflammatory or infectious complications [97].

Curative treatments Successful hematopoietic stem cell transplantation (HSCT) is a definitive cure for CGD [115, 237]. While outcomes may be better in younger patients with less CGD sequelae, HSCT is also useful and successful in patients with recurrent serious infections despite prophylaxis and/or severe, difficult to treat, inflammatory disease [97]. In their European series of 56 patients (mean age 12.7 years, range 0–40), Gungor et al. gave reduced intensity conditioning (high dose fludarabine, low dose or targeted busulfan, and serotherapy with antithymocyte globulin, thymoglobulin, or alemtuzumab) prior to HSCT with unmanipulated bone marrow or peripheral blood stem cells from HLA-matched related donors or HLA-matched unrelated donors [97]. Forty-two patients had intractable infections and/or active inflammation. Overall survival was 93 % at a median follow up of 21 months and the 2-year probability of survival was 96 %, including those patients transplanted in the setting of ongoing infection and/or inflammation. All surviving patients had stable myeloid donor chimerism of at least 90 % and had resolution of all infectious and inflammation. All six cases of acute graft versus host disease (GVHD) ≥ grade II and all four cases of chronic GVHD occurred in patients with HLA-matched unrelated donors. Three patients died from GVHD-related complications. One additional patient, who had an HLA-matched related donor, had secondary graft failure at 9 months and died from hemorrhagic shock 10 days after the second HSCT. Two of the surviving patients have fathered children. These data are very encouraging for the value and safety of HSCT for CGD, even in the setting of active disease.

CGD appears well suited for gene therapy since it results from single-gene defects that almost exclusively affect the hematopoietic system. Retroviral and lentiviral vectors that provide normal gp91^{phox}, p47 ^{phox}, or p67 ^{phox} genes can reconstitute NADPH oxidase activity in deficient cells, establishing the proof-of-principle for gene therapy in CGD [63, 153, 279]. Peripheral blood stem cells from five adult patients with p47^{phox} deficient CGD were transduced ex vivo with a recombinant retrovirus containing a normal p47^{phox} gene and then reinfused without myeloablative conditioning [153]. Functionally corrected granulocytes were detectable in peripheral blood following this procedure at a peak frequency of 0.004–0.05 % of granulocytes, a level well below that needed for protection.

Subsequently, two adults with X-linked CGD were treated with retrovirus-based gene therapy and non-myeloablative bone marrow conditioning [192]. Clinical response was observed after gene transfer, but both patients had insertional activation of ecotropic viral integration site 1 (EVI1) and developed monosomy 7 [193]. One patient died of infection 27 months after gene therapy. In another study, three adults with X-linked CGD underwent gene therapy and achieved early marking (26 %, 5 %, and 4 %, respectively) [114]. However,

over time all had marked diminution or loss of their corrected cells. The long-term risks and effectiveness of gene therapy remain to be determined [114, 193, 252]. New gene therapy trials are underway using lentiviral vectors to reduce the risks of insertional myelodysplasia and more aggressive bone marrow preparative regimens to make room for corrected cells [58, 138, 247].

Prognosis. When the first 92 patients with "fatal granulomatosis of childhood" were reported, 45 had already died, 34 of them before the age of 7 years. Today, survival is dramatically improved [270]. In the United States CGD registry in 2000, more than 25 % of all living CGD patients (and 42 % of those with autosomal recessive CGD) were 20 years or older [283]. In a German cohort of 39 patients observed over a 22-year period, the survival rate was 50 % through the fourth decade of life [145]. In a British cohort, aggressive antibacterial and antifungal prophylaxis greatly diminished the risk of serious infections compared to historic controls [35].

The quantity and quality of the lives of CGD patients have improved dramatically since its initial description. Life-threatening infections continue to occur, but diagnostic and treatment opportunities have improved as well, making CGD a disease that is eminently survivable. Efforts to focus on the other significant complications of CGD, such as inflammatory bowel disease, are sorely needed. Hematopoietic stem cell transplantation offers definitive correction, and gene therapy should eventually improve and become a therapeutic option. In the interim, antimicrobial prophylaxis with TMP-SMX, itraconazole and IFNγ; early diagnosis of infections and aggressive treatment of them; and aggressive management of CGD-associated colitis will keep patients well.

4.3 Leukocyte Adhesion Deficiency

(ITGB2 or CD18 deficiency, SCL35C1 or CDG-IIc deficiency, FERMT3 or Kindlin3 deficiency)

4.3.1 Definition

During inflammation, white blood cells or leukocytes play a key role in maintaining tissue homeostasis by elimination of pathogens and removal of damaged tissue. Leukocytes migrate to the site of inflammation following a gradient of chemokines, which originates from the source of infection. Upon recruitment to a local vessel, the cells slow down due to transient interactions between selectins and their ligands, which are upregulated on leukocytes and endothelial cells during inflammation. Subsequently, stable adhesion by leukocytic integrins to ligands on the endothelium results in leukocyte arrest, after which the cells extravasate and migrate into the affected tissue.

Leukocyte adhesion deficiencies [*i.e.*, LAD-I (OMIM*116920), -II (OMIM*266265) and -III (OMIM*612840, the latter is also known as LAD-1/v) are caused by defects in the adhesion of leukocytes to the blood vessel wall, resulting in severe immunodeficiency [144]. Patients suffer from recurrent bacterial infections and neutrophilia, but fail to make pus; those with severe disease have delayed separation of the umbilical cord. In LAD-I, mutations are found in *ITGB2* (OMIM*600065), the gene that encodes the β subunit of the β_2 integrins. In the rare LAD-II disease, the fucosylation of selectin ligands is disturbed, caused by mutations in *SLC35C1* (OMIM*605881), the gene that encodes a GDP-fucose transporter of the Golgi system. Fucosylation is important in several cell types, demonstrated by mental retardation and short stature of LAD-II patients. LAD-III is characterized by an additional Glanzmann-like bleeding tendency due to a well-characterized platelet dysfunction. The mutations in LAD-III are found in *FERMT3* (OMIM*607901), encoding kindlin-3, a protein involved in the regulation of β integrin conformation in blood cells [269].

LAD-I is an autosomal recessive disorder caused by decreased expression or functioning of CD18, the β subunit of the leukocyte β_2 integrins. LAD-I was first described in 1980 and since then several hundred patients have been reported. Mutations are found in *ITGB2* (integrin β_2, CD18), located at 21q22.3, encoding the β_2

integrin. So far, more than 80 different mutations have been reported [269]. Usually, this leads to the absence or decreased expression of the β_2 integrins on the leukocyte surface, but sometimes a normal expression of nonfunctional β_2 integrins is found. Decreased expression of the common β_2 subunit leads to a similar decrease in the expression of all four α subunits on the leukocyte surface (CD11a/CD18 or LFA-1; CD11b/CD18, CR3 or Mac-1; CD11c/CD18 or gp150,95; and CD11d/CD18).

LAD-II was first reported in 1992 in two unrelated boys. So far, fewer than 10 patients have been reported, most of them from the Middle East [79, 269]. Patients with LAD-II have a defect in the fucosylation of various cell surface glycoproteins, some of which function as selectin ligands, such as sialyl Lewis X carbohydrate groups (sLeX, CD15a). As a result, the initial "rolling" of leukocytes over the endothelial vessel wall in areas of inflammation, which is mediated by reversible contact between L-selectins on the leukocytes and E- or P-selectins on the endothelial cells with their respective sialated fucosyl ligands on the opposite cells, is disturbed [205]. Without rolling, the leukocytes cannot slow down and stably adhere, and in this way LAD-II leads to decreased leukocyte extravasation and recruitment at the site of infection. Fucosylation is important as well for several unrelated functions, and LAD-II patients present as a result with additional symptoms, including mental and growth retardation and the Bombay (Hh) blood type [79, 163].

The molecular defect in LAD-II has been identified as a deficiency in a Golgi GDP-fucose transport protein (GFTP) [146, 150]. This protein is encoded by *SLC35C1* (Solute carrier family 35 member C1), or *FUCT1* (GDP-fucose transporter 1) at 11p11.2. Only seven different mutations have been reported so far [269]. Since the genetic cause reveals that the defect involves glycosylation, LAD-II has now been categorized as one of the group of the congenital disorders of glycosylation (CDG), being reclassified as CDG-IIc [146, 150].

In 1997, for the first time a syndrome affecting a 5-years old boy was reported who was hospitalized with a history of nonpussing inflammatory lesions, leukocytosis and an overt bleeding tendency [135]. Apart from the platelet aggregation defect, similar leukocyte defects are seen in the classical LAD-I syndrome, hence designated the novel combination of leukocyte and platelet defects Leukocyte Adhesion Deficiency type-1/variant (LAD-1/v), which was later termed LAD-III. In LAD-III, all integrins are normally present but fail to be activated during leukocyte or platelet activation [135].

LAD-III has now been identified in more than 25 families worldwide. In addition to recurrent non-purulent infections, LAD-III patients exhibit a severe Glanzmann Thrombasthenia-like bleeding disorder. Families have often lost newborns within weeks after birth, demonstrating the high mortality rate of LAD-III patients [133]. The bleeding disorder originates from a platelet defect, indicating that the signaling defect also affects the β_3 integrin fibrinogen receptor $\alpha_{IIb}\beta_3$ on blood platelets [135, 268].

The molecular defect in LAD-III is in *FERMT3* (fermitin family homolog 3) at 11q13.1 [134, 155, 258], encoding kindlin-3, a protein involved in inside-out signaling to all blood cell-expressed β integrins (β_1, β_2 and β_3). So far, 9 different mutations in *FERMT3* have been reported [269].

The kindlin family consists of fibroblast-specific kindlin-1, ubiquitously expressed kindlin-2 and hematopoietic kindlin-3, with high homology between them [154]. Loss of kindlin-1 leads to the Kindler syndrome, a hereditary genodermatosis characterized by skin blistering and cutaneous atrophy. Absence of kindlin-2 is embryonically lethal in mice, corresponding to its ubiquitous expression. Kindlin-3$^{-/-}$ mice were first described in 2008 [175] and characterized by a severe bleeding tendency, anemia and defective leukocyte function. The phenocopy of some of the major LAD-III symptoms in the kindlin-3$^{-/-}$ mice contributed to the discovery of kindlin-3-deficiency as the cause of LAD-III.

A discussion has taken place in the literature about the importance of a genetic variation in the gene encoding CalDAG-GEF1 (a guanine nucleotide exchange factor for Rap1, involved in integrin activation) in some patients with LAD-III [199]. Since the functional defect in such

patients can only be corrected by reconstitution with kindlin-3 and not by reconstitution with CalDAG-GEF1, this variation in CalDAG-GEF1 is of no importance for the functional defect in LAD-III patients [258]. Recently, a pedigree was identified with homozygous mutations in the *RASGRP2* gene encoding an inactive CalDAG-GEF1. The defect resulted in a moderate platelet defect in aggregation and spreading but no leukocyte defect [37].

The small guanosine triphosphatases (GTPases) Rho proteins are members of the Ras-like superfamily. Similar to Ras, most Rho GTPases cycle between active GTP-bound, and inactive GDP-bound conformations and act as molecular switches that control multiple cellular functions.

4.3.2 Etiology

Circulating leukocytes normally migrate to the site of infection following a gradient of chemoattractants in a process called chemotaxis. These chemotactic factors or chemoattractants may be derived either from the infected tissue or local complement activation, or directly from the pathogens themselves, and diffuse within the tissue into the local vasculature. These gradients of chemoattractants recruit the leukocytes in interplay with factors expressed locally on the luminal side of blood vessel endothelial cells. Neutrophils are short-living leukocytes that are recruited early in the inflammatory response (Fig. 4.5).

Leukocytes following the chemotactic gradient towards the site of infection have to leave the blood stream, in a process called extravasation. Extravasation is a multi-step process involving adhesion molecules, in which chemoattractants function as activating agents or (pro-) inflammatory mediators. The first step of extravasation consists of initial contact between endothelial cells and leukocytes marginated by the fluid flow of the blood. L-selectin (CD62L) on leukocytes plays a role herein, contacting several cell adhesion molecules on endothelial cells. Within the local environment of an inflammatory tissue reaction, the endothelium begins to express the adhesion molecules P-selectin (CD62P) and later on E-selectin (CD62E). The low-avidity interaction of these selectins with their fucosylated ligands on the opposite cells forces the leukocytes to slow down and start a rolling movement along the vessel wall [290].

In contrast to the low-avidity binding of leukocytes to selectins, the final step of firm adhesion and subsequent migration depends on stable interaction between integrins on the leukocytes and their ligands on the endothelial cells upon leukocyte activation by endothelial factors [132, 242, 255].

Integrins are ubiquitously expressed transmembrane receptors consisting of an α and a β chain. They represent the major class of adhesion receptors on hematopoietic cells. In mammals, 18 α and 8 β subunits form 24 known combinations, each of which can bind to a specific repertoire of cell-surface, extracellular matrix, or soluble ligands. Different hematopoietic cell types and tissues express different integrins. On leukocytes, $\alpha_4\beta_1$ (VLA-4), $\alpha_5\beta_1$ (VLA-5), $\alpha_L\beta_2$ (LFA-1; CD11a/CD18), $\alpha_M\beta_2$ (CR3; CD11b/CD18), $\alpha_X\beta_2$ (gp150,95; CD11c/CD18) and $\alpha_D\beta_2$ (CD11d/CD18), the latter only being expressed on macrophages, are the most prominent family members, whereas $\alpha_{IIb}\beta_3$ and $\alpha_2\beta_1$ are the predominant integrins expressed on platelets [2, 151].

Integrins are type I transmembrane glycoproteins that form heterodimers via non-covalent association of their α and β subunits, with sizes of 120–170 kDa and 90–130 kDa, respectively [151]. The β_2 integrin receptor subfamily is selectively expressed on leukocytes and bind to adhesion molecules on endothelial cells (intercellular adhesion molecule [ICAM]-1 and ICAM-2) and tissue cells (ICAM-1), as well as to several extracellular proteins and plasma opsonins, such as complement factors. The main β_2 integrin on neutrophils is CR3.

Once leukocytes are slowly rolling along the endothelial cells, these leukocytes are able to recognize concentration differences in a gradient of chemoattractants and to direct their movement towards the source of these agents. Although the details of this process remain unknown, the gradient most likely causes a difference in the number of ligand-bound chemoattractant receptors on either side of the cell, thereby inducing the cytoskeletal rearrangements needed for

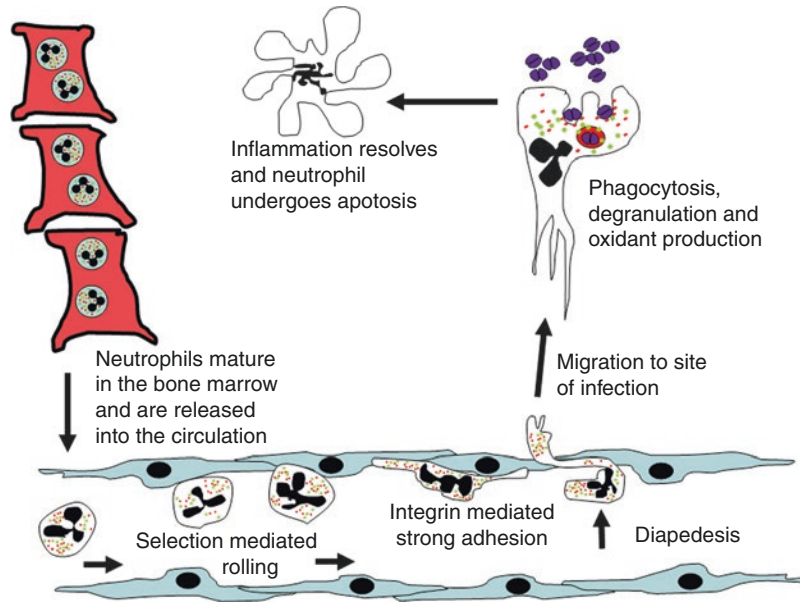

Fig. 4.5 The life cycle of the neutrophil is shown, including the phases of migration of neutrophils to sites of infection or inflamed tissues. Neutrophils develop in the bone marrow (*upper left*) and are released into the circulation. Neutrophils sense infection or inflammation in the post capillary venule (*bottom* of figure) where bacterial factors and inflammatory chemoattractants and chemokines act on both the neutrophils and endothelial cells to increase adhesion. The initial phase of increased adhesion engages selectins which mediate short-lived weak binding encounters between neutrophils and endothelium (rolling). This is followed by activation of integrins, triggering strong adhesive forces that mediate spreading of neutrophils onto the endothelium. This is followed by additional conformational changes that weaken integin adhesion, allowing chemotactic migration of the neutrophil between endothelial cells (*lower right*), though the basement membrane, and into the tissues to the site of infection. At the site of infection neutrophils phagocytose bacteria (*upper right*) or other pathogens, triggering the process of degranulation, production of reactive oxygen species, and activation of proteases. Over hours to days, neutrophils proceed into an apoptotic phase (*upper middle*), triggering engulfment by macrophages in a process that minimizes tissue damage and leads to resolution of inflammation

movement [242]. Since adhesion molecules such as the β_2 integrins are essential for the connections with the tissue cells or with the extracellular matrix proteins, these connections must be formed at the front of the moving leukocytes and broken at the rear end [83]. For continued sensing of the chemoattractant gradient, the chemoattractants must dissociate from their respective receptors for repeated usage. This occurs through internalization of the ligand-receptor complex, intracellular disruption of the connection, and transport of the free receptor to the front of the cell, followed by reappearance of the free receptor on the leukocyte surface. Within the infected tissue, the chemoattractant gradient persists and leukocyte migration is maintained.

The ligand specificity of integrins is determined by their large extracellular ligand-binding head domain, which is composed of several domains of both the α and β subunit. The head domain is attached to the membrane via two flexible legs (one from each subunit), which terminate intracellularly as short cytoplasmic tails. This domain architecture of integrins underlies their ability to transduce bidirectional signals across the plasma membrane: "inside-out" and "outside-in" [242]. Leukocyte activation, *e.g.* as a result of chemokine binding to chemokine receptors, ligand binding to selectins, or antigen binding to the T-cell receptor, and subsequent intracellular signaling induces conformational changes in the extracellular regions of the β_2 integrins, leading to an enhanced affinity for their ligands ("inside-out" signaling). In addition, integrins cluster in larger complexes, which increases their ligand avidity. Binding to extra-

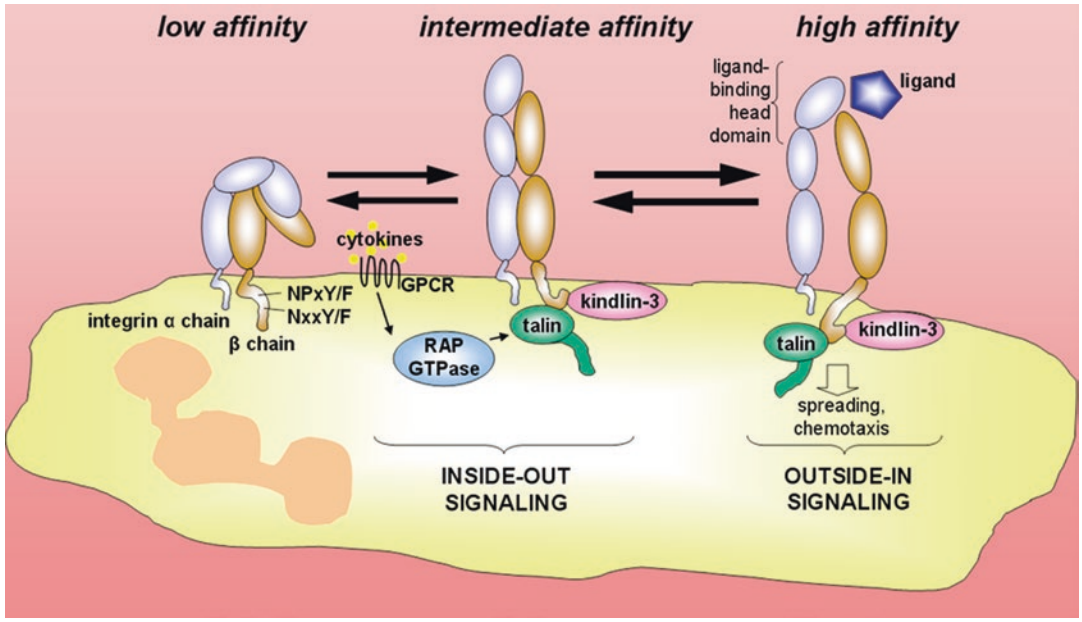

Fig. 4.6 Leukocyte integrin activation. Upon cell stimulation via e.g. G-protein-coupled receptors (GPCR) for chemoattactants, inside-out signaling results in recruitment of talin-1 and kindlin-3, which act in concert to induce conformational changes in integrins from a low ligand-binding affinity towards an intermediate and subsequent high-affinity state. Talin-1 binds to a membrane-proximal NPxY/F motif whereas kindlin-3 binds to a membrane-distal NxxY/F motif of the β integrin cytoplasmic tails

cellular ligands leads to further conformational changes of the β_2 integrins, resulting in high ligand affinity and subsequent recruitment of cytosolic proteins and the initiation of downstream signaling cascades that regulate cell spreading and alter gene expression, cell proliferation, differentiation and apoptosis ("outside-in" signaling) [104, 242].

The common activator of most, if not all, integrins is talin, a large cytoskeletal protein that acts as an allosteric activator of integrins by inducing their ligand-binding affinity [242]. The head domain of talin contains a so-called FERM (4.1 protein, ezrin, radixin, moesin) domain, consisting of three subdomains, F1, F2 and F3. The latter, the F3 subdomain, contains a phosphotyrosine-binding (PTB)-like domain that binds to the NPxY/F motif found in the membrane-proximal cytoplasmic region of several β integrins. The head domain is connected to a long cytoplasmic rod which can interact with the cytoskeleton.

The kindlin proteins have been identified as additional relevant players in the activation of integrins on blood cells. Kindlins comprise a family of integrin-binding proteins [154]. In man, the family consists of three members – kindlin-1, 2 and 3 – that share a high degree of homology. Kindlin-3 is only expressed in hematopoietic cell types, where it plays an important role in a variety of functions depending on integrin-mediated adhesion, such as platelet clot formation and leukocyte extravasation. Biochemical studies have confirmed that all kindlins directly bind synthetically generated cytoplasmic tails of β_1, β_2 and β_3 integrins [100]. Although kindlins possess a FERM domain that is homologous to that of talin, recent studies have demonstrated that the kindlin-binding site of β integrins is distinct from the talin-binding site, *i.e.* at a membrane-distal NxxY/F motif in the cytoplasmic integrin tail. Biochemical studies with mutants of kindlin-2 have shown that the PTB domain in F3 is, in analogy to talin, essential for integrin binding, in addition to a requirement of the N-terminus of the protein for interaction with β_3 [78, 87, 100] (Fig. 4.6).

In sum, leukocyte adhesion deficiencies (*i.e.*, LAD-I, –II and -III, the latter also known as LAD-1/variant) are immunodeficiencies caused by defects in the adhesion of leukocytes (especially neutrophils) to the blood vessel wall. As a result, patients with any LAD subtype suffer from severe bacterial infections and neutrophilia, often preceded by delayed separation of the umbilical cord. LAD-II is characterized by additional developmental problems, whereas in LAD-III, the immune defects are supplemented with a Glanzmann-like bleeding tendency.

The talin and kindlin-3 mediated outside-in affinity regulation of the integrins is essential for the leukocyte and platelet adhesion to their respective substrates. Whereas kindlin-3 defects have been demonstrated to cause LAD-III (or LAD-1variant), any inherited defect in talin-1 has not yet been reported – if compatible with life at all. The regulation of adhesion depends on a signaling cascade that may result in similar adhesion defects.

4.3.3 Clinical Manifestations

LAD-I manifests as recurrent, life-threatening bacterial infections, primarily localized to skin and mucosal surfaces. Infections are usually apparent from birth onward, together with severe septicemia in some patients, and a common presenting feature is omphalitis with delayed separation of the umbilical cord in severe cases (Fig. 4.7). Later on patients develop non-purulent, necrotizing infections of the skin and mucus membranes, resulting in a high mortality rate at early age. Absence of pus formation at the sites of infection is a hallmark and the infections have a high tendency for recurrence; secondary bacteremias may also occur. Among patients who survive infancy, severe gingivitis and chronic peridontitis are major features. Fungal infections may present in individual cases [83].

The clinical course of LAD-II with respect to infectious complications is milder than LAD-I, and correlates with lower leukocyte counts. While rolling is defective in LAD-II patients, the adhesion and transmigration via β_2 integrin is intact, thereby apparently permitting some neutrophil mobilization to sites of inflammation, and allowing some level of neutrophil defense in tissues. In addition, the mechanisms of β_2-integrin activation are still intact [205]. Although recurrent bacterial infections occur in almost all patients, they often are not very severe and do not result in overt wound healing defects or necrotic lesions as in LAD-I. Most infections occur in the first years of life, although periodontitis has been reported at later ages [79, 163].

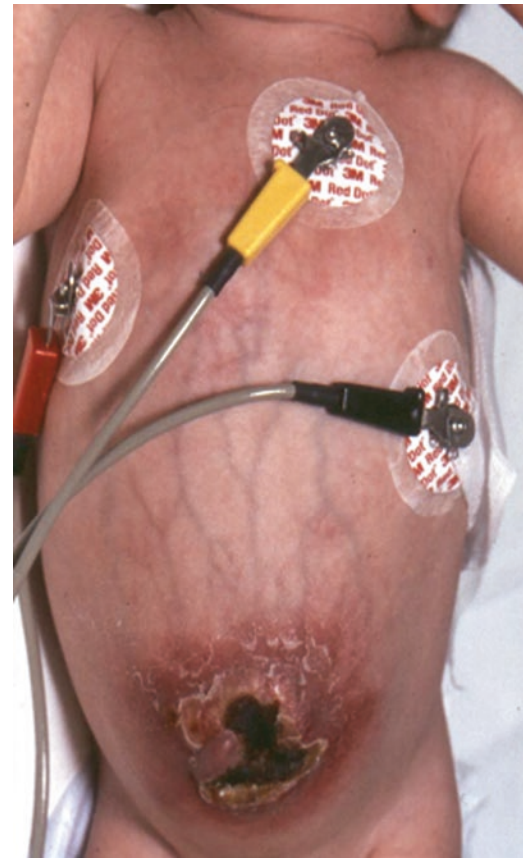

Fig. 4.7 Severe omphalitis in a child with LAD-1

However, LAD-II patients present with other abnormal features, such as short stature, mental retardation and facial dysmorphisms. Patients are born at term, with no apparent dysmorphism, but severely impaired postnatal weight gain and microcephaly were reported in most patients. In some families intrauterine growth retardation was sufficient to

screen for LAD-II prenatally. In addition, convulsions, cerebral atrophy and autistic features were reported for more than half of the patients [89].

It should be mentioned that the early and late features of LAD-II, namely, moderate immunodeficiency accompanied by neutrophilia in the first few years of life and severe mental retardation and short stature in childhood, are also prominent features of other congenital disorders of glycosylation (CDGs).

LAD-III patients suffer from severe recurrent non-purulent infections [135]. In addition, LAD-III patients are affected by a bleeding tendency, similar or more severe than exhibited by Glanzmann thrombasthenia patients [133, 135].

Some patients suffering from LAD-III may also present with an osteopetrosis-like bone defect in addition to the increased bleeding tendency and recurrent infections. A prominent osteopetrosis phenotype was also observed in the kindlin-3 knockout mice. The cause of this osteopetrosis might lie within the osteoclasts, which represent macrophage-like hematopoietic cells critical for bone resorption. Bone resorption requires the formation of a so called 'sealing zone' that depends on $\alpha_v\beta_3$ integrin-mediated adhesion to the bone, thereby explaining the skeletal defect [175, 233]. However, the prevalence and manifestations of osteopetrosis in the patients differ, as unaffected bone formation is also found in LAD-III. The reason for this heterogeneity remains unclear.

4.3.4 Diagnosis

LAD-I patients exhibit mild to moderate leukocytosis, especially granulocytosis, with neutrophil counts reaching levels above 100,000/μL during acute infection [83]. Due to the lack of adhesive capacity only few, if any, leukocytes are present at the sites of infection, which are most often caused by *Staphylococcus aureus,* streptococci or Gram-negative enteric organisms.

Definitive diagnosis of LAD-I is based on genetic analysis, revealing mutations in *ITGB2*. Flow cytometry with antibodies to detect CD18 allows discrimination of two forms of LAD-I, *i.e.* a severe form with less than 2% CD18 expression and a moderate form with 2–30%. However, using CD18 alone for diagnosis is problematic: protein positive mutations that are hypofunctional can be misleading. Therefore, assessment of both CD18 and CD11a is suggested, which increases sensitivity of diagnosis of LAD-I [143]. The severity of clinical presentation and complications in LAD-I correlates with the percentage of leukocytes demonstrating normal CR3 cell surface expression and/or the degree of CD18 molecule deficiency. Patients with severe LAD-I exhibit earlier, more frequent, and more serious episodes of infection, often leading to death in infancy, whereas patients with a moderate to mild phenotype manifest with fewer serious infectious episodes and survive into adulthood.

Extensive *in vitro* studies on neutrophil functions have demonstrated a marked defect in random migration as well as chemotaxis to various chemoattractants. Adhesion to and transmigration across endothelial cell layers were found to be severely impaired. Neutrophils fail to mobilize to skin sites in the *in vivo* Rebuck skin-window test [83].

The biochemical hallmark of LAD-II is a lack of expression of fucosylated glycoconjugates, such as the Lewis antigens Lewis X (LeX) and sialyl Lewis X (sLeX) on leukocyte proteins, α1,6-core fucosylated N-glycans on fibroblast proteins and blood group antigen H on erythrocytes, the latter known as the rare Bombay blood group phenotype. Expression of L-selectin (CD62L) and CR3 (CD11b/CD18) on LAD-II neutrophils is normal [79, 163].

Neutrophil values range from 5000 to >50,000/μL in absence of infection up to 150,000/μL during infectious episodes. With intravital microscopy, it was observed that LAD-II neutrophils roll poorly, i.e. 15% of the rolling fraction of control and LAD-I neutrophils [205]. The neutrophil counts remain high during childhood and then drop at adolescence; this finding might be explained by an improvement in adaptive immunity with age, providing better defense against infections and reducing the stimuli for neutrophilia.

Final proof of LAD-II arises from genetic analysis of the *SLC35C1* gene. The mutation seems to determine the severity of LAD-II: whereas GFTP is improperly located in the ER in some patients, it is directed to the Golgi but still

dysfunctional in others, the latter correlated with a milder immunological phenotype.

LAD-III should also be confirmed by genetic analysis, which should identify mutations in *FERMT3*. Expression of integrins on neutrophils and platelets (*i.e.* $\alpha_{IIb}\beta_3$, $\alpha_2\beta_1$) is normal or slightly increased, and integrin activation can be induced by artificial stimulation with mAbs or cations. Based on the persistent leukocytosis, many of the patients were suspected to suffer from juvenile myelomonocytic leukemia (JMML) [133]. However, the increased sensitivity of bone marrow (BM) or blood cells to GM-CSF as the hallmark for JMML, is negative in LAD-III.

Many tests have been performed on LAD-III neutrophils. One example of an assay to discriminate between LAD-I and LAD-III neutrophils is the NADPH oxidase screening test with unopsonized zymosan [133]. Zymosan is used to induce uptake and NADPH oxidase activity in purified neutrophils based on the requirement for kindlin-3-dependent CR3 activation before uptake of the zymosan. The response is absent in both types of LAD, but activation and subsequent zymosan uptake can be induced by high Mg^{2+} concentrations only in case of LAD-III. Similarly, neutrophil adhesion to CR3 ligands is absent in response to several chemoattractants, but can be induced with Mn^{2+} upon artificial integrin activation.

In addition to the recurrent infections, LAD-III patients suffer from a bleeding tendency. Platelets from Glanzmann patients are still capable of forming small aggregates upon collagen stimulation, whereas platelets from LAD-III patients are not [268]. These aggregates require functional GPIa/IIa (integrin $\alpha_2\beta_1$), thus explaining the clinically more severe bleeding manifestations in LAD-III patients, in which all platelet integrins are functionally defective.

Rac2$^{-/-}$ mice have a phenotype similar to the human diseases of LAD and chronic granulomatous disease (CGD), including increased susceptibility to *Aspergillus* infection [219]. The mice show a prominent leukocytosis likely due to reduced shear-dependent endothelial capture via L-selectin (CD62L) and defective neutrophil chemotaxis in response to multiple agonists.

Neutrophils have reduced F-actin assembly, reduced phagocytosis and reduced superoxide production by the NADPH oxidase complex in response to the chemoattractant fMLP.

4.3.5 Management

The only curative treatment for LAD-I and LAD-III is HSCT. In case of LAD-II, oral fucose supplementation may moderate the immune defect, but the mental condition is hardly if at all improved by this treatment.

Antibiotics are commonly used to prevent and treat acute or recurrent infections, and patients affected with the moderate form may survive to adulthood with antibiotics only. As a curative treatment, HSCT is the only approach, and is most often the treatment of choice for patients suffering from the severe form of LAD-I.

Both reduced-intensity and myeloablative conditioning regimens are currently being used in HSCT of LAD-I patients. With myeloablative conditioning, more complete depletion of host marrow can be achieved, thereby decreasing the possibility of mixed chimerism and the risk of rejection. However, pre-transplant infections in immunodeficient patients lead to a high rise in mortality rate with this regimen, especially in patients suffering from co-morbid complications. According to studies by the group of Hamidieh et al., use of the less toxic reduced-intensity conditioning (RIC) regimen is found to be a more safe and feasible therapeutic approach in the treatment of LAD-I patients [99]. Recipients of RIC transplant, those with either full or mixed chimerism, had a long-term survival rate with no manifestation of LAD-I symptoms.

Further, granulocyte transfusions have been reported as a successful supplementation to LAD-I treatment. A patient who was suffering for more than a year from an ecthyma gangrenosum lesion, despite treatment with targeted antibiotics and anti-fungal therapy, has been cured by massive granulocyte transfusions [170]. Overall, the role of granulocyte transfusion in acute infectious episodes is debatable owing to its side effects.

In contrast to the severe form of LAD-I, the moderate form of LAD-I can often be controlled with prompt use of antibiotics during acute infectious episodes and, sometimes, prophylactic antibiotics, but frequent use of antibiotics may result in resistance of the bacteria. HSCT on the other hand can be unsuccessful especially in case of an incompletely matched donor. Survival of HSCT treatment is lower than average for immunocompromised patients, presumably owing to the risk of pre-transplant infections.

Infections are commonly treated with antibiotics. In addition, high-dose oral supplementation of fucose had strong beneficial effects in some, but not all patients [103, 149, 164]. During 9 months of treatment with fucose of the first patients, infections and fever disappeared, elevated neutrophil counts returned to normal, and in one of the patients even psychomotor capabilities improved. However, treatment of the original two Israeli Arab patients did not exhibit a similar beneficial response. In one of the patients treatment led to an autoimmune neutropenia upon refucosylation of the surface antigens [103]. Upon discontinuation of the therapy, selectin ligands were lost and neutrophil counts increased again within a week [149].

The metabolic pathways causing the severe psychomotor and growth retardation are still unclear. Oral fucose supplementation may cure immunological symptoms in some cases, but developmental delay hardly improves.

Patients with LAD-III need prophylactic antibiotics as well as repeated blood transfusions, but the only curative therapy is HSCT. While untransplanted, the need for transfusion differs per patient and can rise to more than 20 and 50 transfusions per year for erythrocytes and platelets, respectively [133]. In addition, granulocyte transfusions have been used and are believed to have improved pathogen clearance.

The survival of untransplanted LAD-III patients is low, and the high mortality is further demonstrated by the incidence of deceased siblings who were not diagnosed but suffered from similar symptoms. Less than four patients have so far survived childhood without HSCT, and the oldest reported patient is a young adult now, though the need for platelet transfusions has increased to 1–2 transfusions per week (unpublished data). Upon successful HSCT, patients may continue to live without further symptoms [73].

Whereas the success rate of HSCT has improved over the last years, pre-transplant infections and the bleeding disorder pose major complications in the treatment of LAD-III patients.

4.4 RAC-2 Deficiency

4.4.1 Definition

RAC-2 deficiency or neutrophil immunodeficiency syndrome (OMIM*608203) is also a leukocyte migration disease. As in patients with LADs (Sect. 4.3) and β-actin deficiency (Sect. 4.5), there is lack of pus formation at the site of infection [7]. Ambruso et al. reported an infant with recurrent infections and poor wound healing, suggesting a neutrophil defect, in whom they found a missense mutation in the *RAC2* gene [7].

While most Rho GTPases are expressed widely, the expression of Rac2 is restricted to hematopoietic cells. Of the various Rac isoforms, Rac2 predominates in the human neutrophil. Studies using mutant mice have identified several Rac2 GEFs, including DOCK2, GIT2, and P-Rex1, required for neutrophil function. Whereas DOCK2 and GIT2 regulate both Rac1 and Rac2 activities, genetic data suggest that P-Rex1 functions as a predominant Rac2 GEF in mouse neutrophils [66]. P-Rex1-deficient neutrophils demonstrate a selective defect in Rac2 activation following fMLP stimulation, and P-Rex1$^{-/-}$ neutrophils phenocopy many of the functional defects observed in Rac2$^{-/-}$ cells [66, 219].

Interestingly, the phenotype was predicted by a mouse knock-out of Rac_2 and resembles leukocyte adhesion deficiency (LAD) in many aspects [195].

4.4.2 Etiology

Ras-related C3 botulinum toxin substrate 2 or *RAC2* (OMIM*602049) is a Rho-GTPase

important for the expression of L-selectin, F-actin assembly, chemotaxis and superoxide generation and regulation of actin polymerisation. In activated neutrophils the cytosolic RAC2 comigrates with p67^{phox} (RAC-1 in macrophages) to attach to p47 ^{phox} to form the NADPH oxidase complex (Fig. 4.8) [13]. Besides p47 ^{phox} inducible Nitric oxid (iNos) has been suggested to play a role in neutrophils of iNOS-knockout mice [113]. The mutant RAC2 does not bind to its physiological ligand GTP, thus activation of superoxide production via phagocyte oxidase is inhibited [188]. Neutrophils from mice deficient in RAC-2 have defects in rolling on endothelium, chemotaxis and phagocytosis [219]. In humans neutrophils show also defects in chemotaxis, decreased release of enzymes of azurophilic granules after activation with fMLP or PMA and a deficient polarization and actin polymerisation in response to fMLP as well as a deficient production of reactive oxygen radicals (ROS) to fMLP. Interestingly, the syndrome combines feature seen in LAD, chronic granulomatous disease (CGD), specific granule deficiency (SGD) and β-actin deficiency. The *RAC2* gene is located on chromosome 22q13 and has a size of 18 kb. In a zebra fish model Rac2 signaling is necessary for both neutrophil 3D motility and CXCR4-mediated neutrophil retention in hematopoietic tissue [59]. In a recent study in Rac2$^{-/-}$ mice an impaired response to *Citrobacter rhodentium* infection with clinical signs of severe colitis suggests that impaired Rac2 function may promote the development of inflammatory bowel disease [81], which may be linked in humans to rare p67 ^{phox} variants with a reduced binding to RAC2 [178].

The G-protein-coupled receptors (GPCR) for chemoattractants that allow increases in integrin avidity and actin-polymerization are disturbed upon cellular activation in the setting of RAC2 deficiency [7].

4.4.3 Clinical Manifestations

Mutations in the hematopoietic-specific GTPase, *RAC2*, have been found to cause a severe phagocytic immunodeficiency in humans, characterized by life-threatening infections and poor wound healing starting at infancy [7, 195].

Patients with RAC2 deficiency suffer from delayed separation of the umbilical cord, poor pus formation, non-healing perirectal/periumbilical abscesses, and peripheral blood leukocytosis similar to LAD-1. Reduced binding of RAC2 to a genetic variant of p67 ^{phox} may be associated with inflammatory bowel disease.

Both children were found to have a heterozygous dominant negative c.169G>A, p.Asp57Asn (D57N) mutation. This mutation corresponds to mutations in the GTP binding pocket of other Rho GTPases and Ras superfamily members, such as p21Ras D57A, that result in dominant negative activity. The second case was identified by newborn screening for SCID by current TREC analysis.

Why the TRECs are disproportionately low in this case of a relatively mild lymphopenia remains unclear. Overall the lymphocyte phenotype of the human mutation is less severe than that seen in the Rac2-deficient mouse, which may reflect the differences between a murine null and the dominant-negative human mutants.

There is also a recent interesting report of common variable immunodeficiency in two siblings with homozygous complete RAC2 deficiency in consanguineous Iranian siblings [5].

4.4.4 Diagnosis

Many tests have been performed on RAC2-deficient neutrophils. One example of an assay to discriminate between LAD-I, LAD-III and RAC2-deficient neutrophils is the NADPH oxidase screening test with zymosan and the F-actin polymerization test [7, 135]. Adhesion may be affected to a certain degree, but spreading and chemotaxis are defective in RAC2-deficiency.

Wound biopsies show appropriate number of neutrophils and normal CD18 expression, differentiating this disease from LAD-1. Chemotaxis toward C5a, fMLP, and IL-8 is impaired. Moreover, neutrophil polarization in response to fMLP is also deficient. NADPH oxidase activity is normal after PMA, but decreased after fMLP stimulation [190],

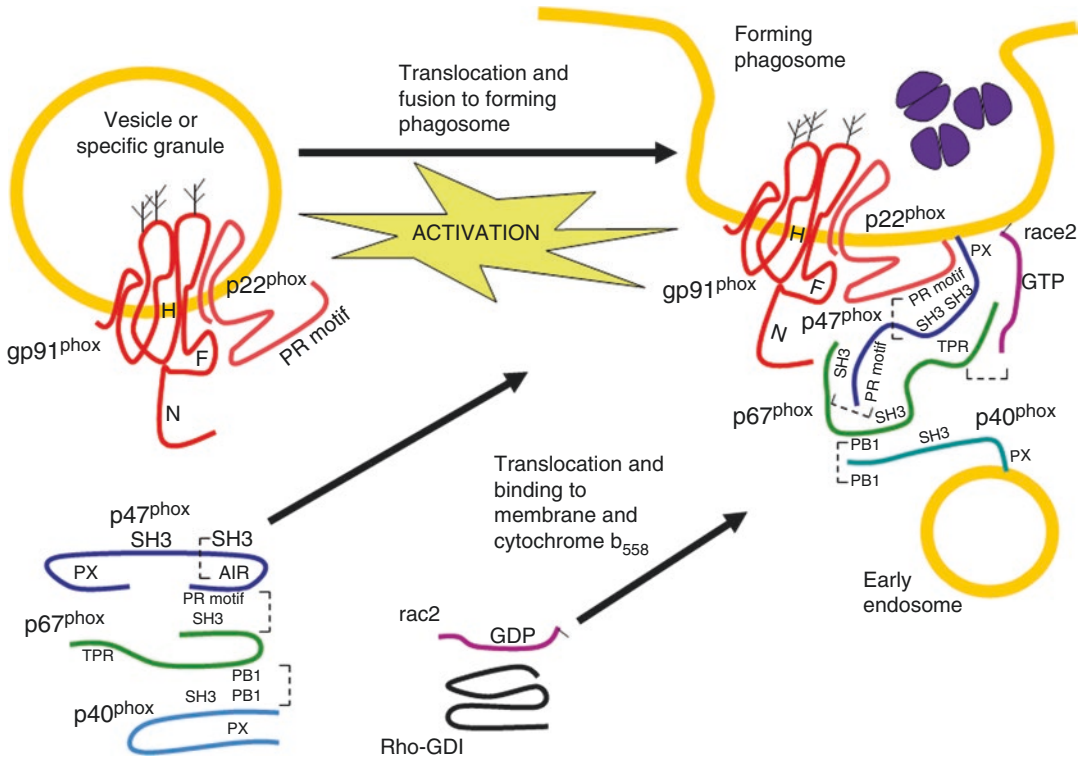

Fig. 4.8 Molecular features of activation mediated assembly of the phagocyte NADPH oxidase from subunit components are shown. The cartoon images of the subunits are highly schematized and not drawn to scale in order to emphasize some of the known structural features each subunit and some of the intra- and intermolecular binding affinities in the resting state (*left side* of figure) and upon assembly of the fully activated oxidase (*right side* of figure). Some known or suspected binding interactions between specific domain motifs are indicated by dotted lines. In the resting neutrophil the cytochrome b_{558} heterodimers consisting of gp91^{phox} and p22^{phox} are predominantly present in small vesicles and specific granules (*upper left*). "N", "F", and "H" labels on the gp91^{phox} subunit indicate, respectively, the NADPH binding pocket and the Flavin binding site in the cytoplasmic C-terminal region, plus the two Heme moieties within the transmembrane region. Three n-glycosylation sites on two of the intravesicular (topologically extracellular) domains of gp91^{phox} are indicated by the small tree-like stick figures. Indicated in the C-terminal tail of the p22^{phox} subunit is a basic proline-arginine rich region (PR motif) capable of binding with a SH3 domain. In the resting neutrophil the p47^{phox}, p67^{phox} and p40^{phox} subunits exist in the cytoplasm predominantly as a heterotrimer, and the rac2 (rac1 in monocytes) exists separately in its unactivated inhibited GDP charged state bound to Rho-Guanine Nucleotide Dissociation Inhibitor (Rho-GDI). Both p47^{phox} and p40^{phox} have PX domains at the N-terminal portion of the molecule that are protected by intramolecular interactions in the resting state, but which engage specific species of membrane lipid inositides in the activated cell. Of importance in the resting state is that a very basic autoinhibitory region (AIR) of p47^{phox} interacts with one of its own SH3 regions while a PR motif in a nearby domain binds to the C-terminal SH3 domain of p67^{phox}. Both p67^{phox} and p40^{phox} contain PB1 motifs that mediate binding between these two subunits, an interaction that also appears to stabilize and protect p67^{phox} from proteolysis. There is also some evidence to suggest that in the resting state, there is an additional intramolecular interaction between the PX domain and PB1 domain of p40^{phox} that inhibits and protects that PX group. Upon activation of the neutrophil, vesicles and specific granules containing membrane cytochrome b_{558} fuse with the forming phagosome (*upper right*), with early endosomes and/or at the plasma membrane. Phosphorylation of the AIR region of p47^{phox} disengages and unfolds it from the SH3 domain, leaving that SH3 domain free to interact with the PR motif of p22^{phox}. Other phosphorylation events induce additional conformational changes in p47^{phox} and p40^{phox} that enhance binding of PX domains to newly generated forms of membrane inositides. There is some evidence to suggest a distinct binding predilection of p47^{phox} or p40^{phox} PX domains, for the types of inositides appearing on activation in phagosome membranes and early endosome membranes, respectively (indicated schematically). Neutrophil activation also triggers disengagement of rac2 from the Rho-GDI with exchange of GDP for GTP allowing binding of rac2 to the TPR region of p67^{phox} and interaction of the rac2 myristoylated C-terminus with the membrane. The fully assembled oxidase shown schematically on the right side of the figure allows electrons to flow from NADPH through the flavin and heme moities to molecular oxygen to form superoxide in the phagosome

which in itself already demonstrates the uniqueness of RAC2-deficient neutrophil reactivity.

4.4.5 Management

Patients with mutations in RAC2 need prophylactic antibiotics as well as repeated blood transfusions, followed by the only curative therapy of HSCT. Survival of untransplanted RAC2 deficient patients is unknown. Only 2 patients with dominant negative RAC2 mutations have so far survived childhood with HSCT (the oldest reported patient has become a teenager, unpublished data). Of the 2 patients with complete deficiency of the protein due to autosomal recessive defects in *RAC2*, one died at 21 after a renal transplant rejection, while the other was alive at 28 years of age without HSCT [5]. No neutrophil defect was observed in the complete RAC2 deficiency, in contrast to the two *de novo* autosomal dominant-negative D57N mutated cases reported to date. Upon successful HSCT, dominant-negative RAC2-defective patients may continue to live without further symptoms. It remains to be seen whether the CVID-like complete RAC2-deeficient individuals have a similar life-threatening risk to the more severely affected patients with a heterozygous *de-novo* dominant-negative mutation.

4.5 β-Actin Deficiency

4.5.1 Definition

β-actin deficiency (OMIM*243310) is a leukocyte migration disease. As in patients with LAD syndromes, there is no pus formation at the site of infection.

4.5.2 Etiology

β-actin deficiency is an autosomal dominant deficiency of the actin polymerisation of neutrophils. A heterozygous negative dominant mutation of non-muscle β-actin (*ACTB*) (OMIM*102630) impairs the binding of profilin, which is an actin regulatory protein [189].

4.5.3 Clinical Manifestations

The patients suffer from recurrent bacterial and fungal infections without pus formation, mental retardation and photosensitivity. One patient developed recurrent stomatitis, cardiomegaly, hepatomegaly and hypothyroidism [188].

4.5.4 Diagnosis

Wound biopsies show reduced numbers of neutrophils. Chemotaxis and phagocytosis is markedly impaired as well as polymerisation of actin monomeres after activation. LAD-1 (CD18) and LAD-2 (CD15s) should be excluded. Definitive diagnosis can be achieved by mutational analysis of the ACTB (cytoplasmic actin) gene.

4.5.5 Management

HSCT is the therapy of choice to correct the immunodeficiency, but likely would not correct the associated non-hematologic/immune abnormalities. Until transplant or if transplant is not possible then management with long-term prophylactic antibiotics should be instituted.

4.6 Localized Juvenile Periodontitis

4.6.1 Definition

Localised juvenile (prepubertal) periodontitis (LJP) (OMIM*170650) is a form of aggressive periodontitis that occurs in the primary dentition of children. In the absence of systemic disease it is thought to be a special form of the more frequently occurring localised aggressive periodontitis in adolescences and adults. Neutrophils show impaired chemotaxis.

4.6.2 Etiology

The disease is thought to be caused by reduced chemotaxis by the challenge with fMLP due to a

reduction of high affinity formylpeptide receptors [98, 201]. Whereas specific single nucleotide polymorphisms (SNPs) were found in patients with chronic periodontitis no such differences were observed in patients with aggressive periodontitis. It is therefore unlikely, that these SNPs occur in LJP [111]. Gundannavar et al. described two females with amelogenesis and localised aggressive periodontitis. There may be some overlap between these entities [96].

4.6.3 Clinical Manifestations

The disease is characterized by symmetric localized loss of attachment of primary teeth (Fig. 4.9), gingival inflammation, extensive plaque deposits and calculus. It may progress to localized aggressive periodontitis in the permanent dentition. *Actinobacillus actinomycetemcomitans* species are frequently isolated from gingival swabs.

4.6.4 Diagnosis

Inspection of the oral cavity with typical clinical signs, impaired chemotaxis to fMLP [238] and lack of systemic disease. Definitive diagnosis can be achieved by mutational analysis of the chemokine receptor *FPR1* (OMIM*136537).

4.6.5 Management

Therapy includes regular dental cleaning and antibiotic therapy to reduce plaque formation and extraction of affected teeth. Combination therapy with amoxicillin and metronidazole seems to be particularly effective [231, 240]. Nevertheless, periodontal surgery is often necessary. In a double-blind trial Palmer et al. found that tetracyclines significantly reduced the necessity of surgery in LJP [196].

Additional therapy with tetracyclines (in combination with normally recommended antibiotics) may further prevent infective endocarditis in LJP patients requiring surgery for other reasons [289].

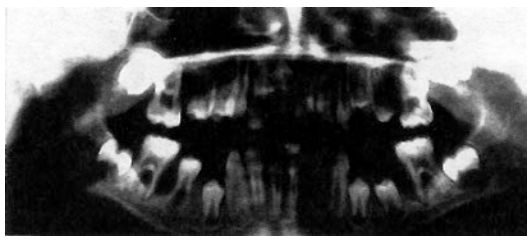

Fig. 4.9 Horizontal resorption of alveolar bone in a patient with localized juvenile periodontitis [Courtesy of B.H. Belohradsky; Munich, Germany]

4.7 Papillon-Lefèvre Syndrome

4.7.1 Definition

Papillon-Lefèvre syndrome (PLS; OMIM*245000) is characterized by premature loss of the primary and permanent teeth, hyperkeratosis of the palms, soles and less frequently knees and elbows [56].

4.7.2 Etiology

The gene responsible for this disease is the cathepsin C gene (*CTSC*) (OMIM*602365), located on chromosome 11q14 [191]. Mutations lead to defective function of the neutrophils [80], leading to gingival infection. Interestingly, reduced activity of the enzyme due to polymorphisms results in generalized aggressive periodontitis [186]. *Actinobacillus actinomycetemcomitans* species, *Fusobacterium nucleatum*, *Eikenella corrodens* are typical bacteria cultured from the gingival sulci [282]. On average 40–80 species were detected in PLS patients [4]. The loss of the teeth is a consequence of the gingival inflammation.

4.7.3 Clinical Manifestations

Typical symptoms are periodontal inflammation soon after eruption of the primary teeth with rapid and severe bone loss; in general primary teeth are lost by 5 years and permanent

teeth a few years after eruption [126]. In addition, brain abscesses, liver or renal abscesses may occur, as described in case reports [62, 117, 174].

4.7.4 Diagnosis

Inspection of the oral cavity with typical clinical signs, and hyperkeratosis of the palms, soles, knees, and elbows associated with impaired chemotaxis. Definitive diagnosis can be achieved by mutational analysis of the *CTSC* gene.

4.7.5 Management

Early antibiotic therapy specific for the above-mentioned pathogens normally slow the development of the disease. If antibiotics fail, extraction of all erupted teeth should be performed to preserve the non-erupted permanent teeth. Treatment with retinoids has been reported with variable success [130, 261].

A recent survey by Nickles et al. reported the outcome of eight patients with PLS [185]. In six patients, all teeth were extracted, almost entirely due to periodontal reasons. In four patients, teeth could be prosthodontically restored with implants. Currently, three patients already show peri-implantitis. Following oral hygiene instructions and aggressive treatment of the gingivitis may preserve normal implants [263]. Etöz et al. reported the implantation of so called "short implants" in a 34-year-old patient with already atrophic mandibles which may be a new treatment option in patients with reduced bone mass [76].

4.8 Specific Granule Deficiency

4.8.1 Definition

Specific granule deficiency (SGD) (OMIM*245480) is a very rare deficiency of neutrophil granules which leads to disturbed chemotaxis and receptor upregulation and increased susceptibility to bacterial infections (Fig. 4.10).

4.8.2 Etiology

The granulocytes lack expression of at least one primary granule component and all secondary and tertiary granule proteins. The failure of granule constituents to diffuse into the cytoplasm results in a decrease of oxygen independent bactericidal activity and a decrease in expression of adhesion molecules and chemotactic receptors on the cell surface.

The defect is caused by a mutation in a myelopoesis specific transcription factor (*C/EBPE*) or CCAAT/enhancer-binding protein, epsilon (OMIM*600749) [142], which regulates the synthesis of proteins in the specific granules. The specific granules contain 4 major proteins, namely, transcobalamin 1 (TC1), lactoferrin (LF), human neutrophil collagenase (HNC), and human neutrophil gelatinase (HNG), and their acquisition provides a unique marker of commitment to terminal neutrophil differentiation [18].

Khanna-Gupta et al. described a case with a heterozygous *C/EBPE* gene mutation with increased levels of CEBPε, but markedly reduced levels of the transcription factor GFI-1. As bone marrow cells from *Gfi-1* $^{+/-}$ mice are associated with reduced levels of secondary granule protein (SGP) gene expression the authors speculated that the patient's reduced expression of GFI-1 together with the mutant *C/EBPE* might have contributed to the lack of specific neutrophil granula [122].

Furthermore, the granules contain receptors for chemotactic factors like fLMF or adhesion proteins. Specific granule deficiency is an oxygen independent microbicidal defect. Targeted disruption of the gene in mice resulted in a phenotype very similar to that in humans. This includes bilobed nuclei, abnormal respiratory burst activity, and impaired chemotaxis and bactericidal activity [168]. The CEBPε-deficient mice are susceptible to gram negative bacterial sepsis, particularly with *Pseudomonas aeruginosa*, and succumb to systemic infection at 3–5 months of age [93].

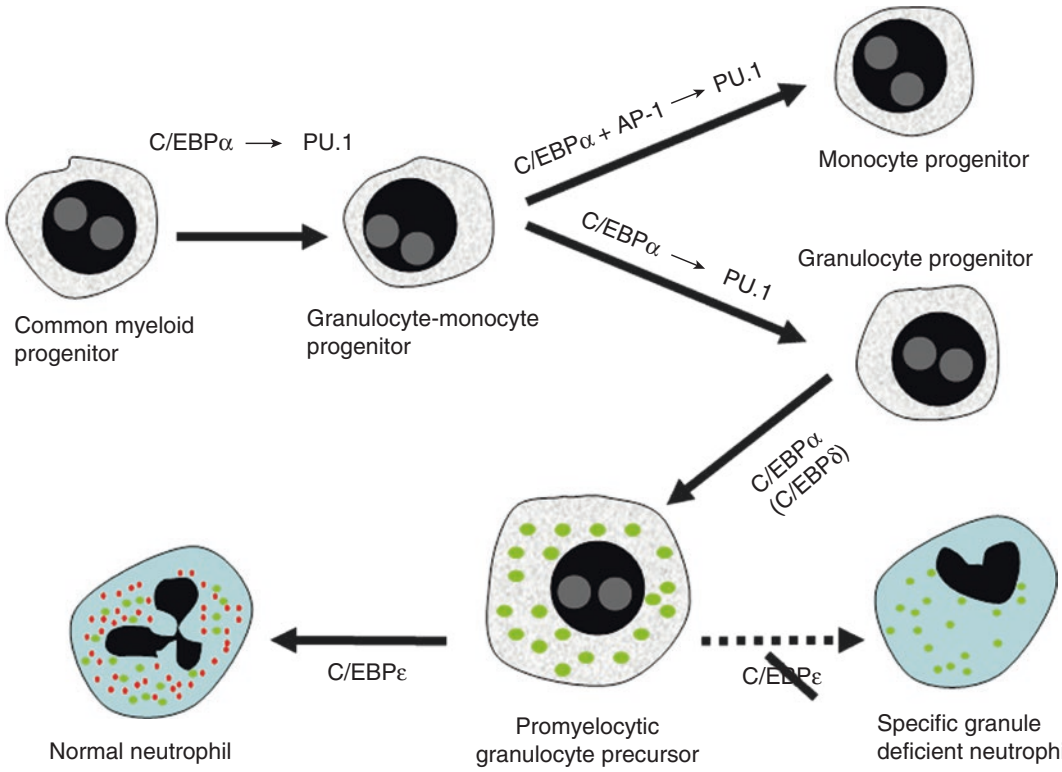

Fig. 4.10 Some of the members of the CCAAT/enhancer binding protein (C/EBP) family of DNA regulatory molecules play key roles in the development and differentiation of myeloid cells. This figure indicates the particularly essential role of C/EBPα and C/EBPε in granulopoiesis with emphasis on where in differentiation of neutrophils loss of function mutations of C/EBPε leads to specific granule deficiency phenotype. Growth factors and differentiation signals impinging on the common myeloid progenitor that enhance the production of C/EBPα lead to modest production of PU.1, another DNA regulatory factor that drives differentiation toward the granulocyte-monocyte progenitor. Growth signals conducive to monocyte differentiation mediate their effect by inducing production of AP-1 and other regulatory molecules which result in high levels of PU.1 that drive differentiation toward monocytogenesis. Interestingly, loss of C/EBPα blocks production of neutrophils and eosinophils, but does not fully block monocyte production. Growth signals conducive to granulocyte differentiation mediate their effect by maintaining C/EBPα, but with a low level of PU.1, driving differentiation toward the promyelocytic stage of differentiation. There is some evidence that C/EBPδ may play an important permissive role at this stage of granulopoiesis. At the late stage promyelocyte in the last phase of production of azurophil granules C/EBPε is absolutely required for activation and transcription of genes encoding some proteins that are packaged in the last group of azurophil granules, for all the proteins packaged in specific granules, for proteins needed to construct the actual specific granule structures, and for proteins required for producing the characteristic nuclear segmentation of mature neutrophils. Thus, in the absence of functional C/EBPε neutrophils are produced but lack some azurophil granule proteins, lack all specific granule proteins, and have incomplete neutrophil nuclear segmentation (*lower right side* of figure).

4.8.3 Clinical Manifestations

The patients suffer from ulcerative and necrotic lesions of the skin and mucus membranes as well as recurrent pneumonias frequently due to *Staphylococcus aureus* and/or *Pseudomonas aeruginosa*. Like in LAD, there is no pus formation.

4.8.4 Diagnosis

In the blood smear, abnormal segmentations of the granulocytes (bilobed nuclei) are common. Chemotaxis is significantly reduced as well as the number of specific granules in electromicroscopy of granulocytes. As SGD individuals express normal levels of lactoferrin and transco-

balamin I in their saliva but not in their plasma or neutrophils, determination of these two molecules in the two compartments may give a hint for the diagnosis. Definitive diagnosis is made by mutational analysis of the *CEBPE* gene.

4.8.5 Management

Long-term antibiotic prophylaxis is usually necessary. Antibiotics in acute infections should cover *Staphyloccus aureus*, *Pseudomonas aeruginosa* and *Klebsiella spp*. Wynn et al. described a case treated successfully with HSCT [287]. The patient had the typical histological, biochemical and eletronmicroscopic features of SGD, but no mutation in the *C/EBPE* was detected.

4.9 Shwachman-Diamond Syndrome

4.9.1 Definition

Shwachman-Diamond Syndrome (SDS) (OMIM*260400) is a syndrome comprising exocrine pancreatic insufficiency, bone marrow failure and metaphyseal chondrodysplasia. It was first described by Bodian et al. in 1964 [22] and subsequently by Shwachman, Diamond et al. in the same year [244]. It affects approximately 1 in 50,000 live births. In Italy, an incidence of 1:168,000 was observed [172]. Mutations in the *SBDS* gene (Shwachman-Bodian-Diamond syndrome) are found in appr. 90 % of patients with suggestive clinical disease [26, 179].

4.9.2 Etiology

SDS is a disease caused by mutations in a gene called Shwachman-Bodian-Diamond-Syndrome gene (*SBDS*) (OMIM*607444). Most *SBDS* mutations appear to arise from a gene conversion event between the *SBDS* gene and its adjacent pseudogene [26]. *SBDS* co-precipitates with molecules like 28S rRNA and nucleofosmin. The latter protein is implicated in the regulation of ribosome biogenesis [95], modulation of apoptosis [197] and chromatin transcription [259]. Homozygous expression of *SBDS* gene mutations leads to early fetal death, suggesting that the *SBDS* gene is essential for early mammalian development [295]. There is experimental support that SDS belongs to bone marrow failure syndromes affecting the ribosome [86] like dyskeratosis congenita [173] or Blackfan-Diamond anemia [46, 265]. Current studies indicate that SBDS functions in 60S large ribosomal subunit maturation and in mitotic spindle stabilization and it may also affect actin polymerization, vacuolar pH regulation, DNA metabolism and organisation of the stromal environment [107, 179].

Neutrophils show defective chemotaxis [3]. The amount of CD34 cells is reduced and the CD34 cells have a reduced capacity to form colonies. Apoptosis of CD34 cells is increased [68–71], which may partly explain the pancytopenia.

4.9.3 Clinical Manifestations

Patients with SDS suffer as infants initially from failure to thrive with foul smelling stools due to pancreatic insufficiency and persistent or intermittent neutropenia with recurrent infections like recurrent otitis media, sepsis, pneumonia etc. [91]. Later on pancreatic insufficiency improves significantly in more than 50 % of the patients older than 4 years, but anemia as well as thrombocytopenia develops in a high proportion of patients (up to 40 %). Neutropenia is intermittent in about two third and constant in the remaining third [57, 91]. Approximately 10 % of patients progress to myelodysplastic syndrome and acute myelogenous leukemia [179, 251]. Young age at first symptoms is associated with severe anemia/thrombocytopenia Hb <7.0 g/dL, platelets <20,000/μL), which occur at about 25 % of SBDS patients after 20 years. Severe cytopenia may, however, be transient [64]. Furthermore, patients suffer from skeletal abnormalities (irregularity of metaphyses, osteopenia, short stature) [152], neurode-

velopmental delay [119], dental caries [3], hepatic dysfunction [91] and cognitive and behavioural problems [27, 120].

4.9.4 Diagnosis

A presumptive diagnosis requires the demonstration of exocrine pancreatic insufficiency (increased fat in stool sample) and bone marrow failure, *i.e.* mainly neutropenia (<1500/μL, 3 times over 3 months), thrombocytopenia (<150,000/μL), or/and anemia (Table 4.4). There is some overlap with other bone marrow failure syndromes and common variable immunodeficiency, which should be considered in the differential diagnosis [101, 121, 265]. Abdominal ultrasound typically shows an echo-intense pancreas (Fig. 4.11) due to replacement of acini with adipose tissue which is also seen on magnetic resonance imaging (MRI) (Fig. 4.12) [262]. Chemotaxis of neutrophils is reduced and some patients show a metaphyseal dysplasia on long bone radiology. The diagnosis should be confirmed by mutational analysis of the *SBDS* gene, but a negative test does not exclude the diagnosis, as about 10 % of patients with a clinical diagnosis of SDS lack *SBDS* mutations. It seems, however, that patients with *SBDS* mutations have a more severe growth retardation than patients with a clinical diagnosis of SBDS without a mutation in the *SBDS* gene [180]. In patients younger than 3 years, serum trypsinogen is pathologically low.

Laboratory tests should include a complete blood and differential count, 72-h fecal fat collection, serum trypsinogen if available, bone marrow aspiration with cytogenetic studies particularly to look for MDS and cytogenetic changes such i7q, 20q(del) or monosomy 7. Tests could include imaging of the pancreas and long bone radiology. Cystic fibrosis should be excluded.

4.9.5 Management

First line therapy is directed to ameliorate the direct consequences of the disease. Exocrine pancreatic failure is treated with substitution of pancreatic enzymes similar to cystic fibrosis and fat soluble vitamins if needed. It has been suggested that CBC should be checked at least every 3–6 months, while bone marrow aspiration/biopsy should be done at diagnosis and at least every 1–3 years [179]. Gastroenterologic evaluation includes Fecal elastase, 72 h fat excretion, pancreatic isoamylase, trypsinogen at diagnosis and in the first years to detect amelioration of pancreatic function in young children. Fat soluble vitamins (A,D,E) and prothrombine time at diagnosis, 1 month after start of enzyme replacement therapy and then every 6–12

Table 4.4 Clinical and laboratory signs for the diagnosis of Shwachman-Diamond syndrome

1. Homozygous or compound heterozygous mutations in the *SBDS* gene *or*
2. Indications for pancreatic insufficiency[a] (<4 years old and exclusion of cystic fibrosis) *and* signs of bone marrow failure[b]

Supporting features: first or second degree relative with SDS, congentital, skeletal abnormailties like chondrodysplasia or congenital thoracic dystrophy, unclear dwarfism, deficiency in 2 or more fat soluble vitamins

[a]Fecal elastase < 100-(200) μg/g stool, elevated 72 h fecal fat excretion, pancreatic lipomatosis detected with ultrasound or magnetic resonsance imaging, low levels of trysinogen (age < 3 years)

[b]Hyporeductive cytopenias like neutropenia (<1500/μL), anemia (low reticulocytes, macrocytosis), thrombocytopenia (<150,000/μL), Myelodysplasia, hypocellularity, Leukemia, cytogenetic abnormalities (mainly chromosome 7 and 20; del(20)(q11), [i(7)(q10)], [add(7)(p?)], [del(7)(q22q23)]

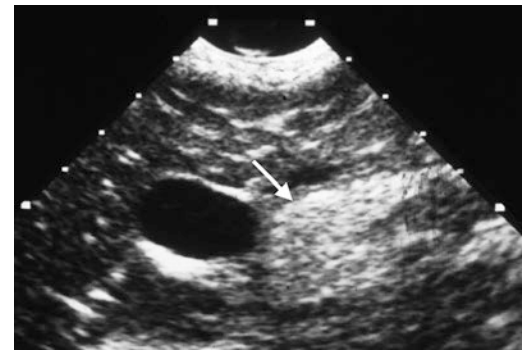

Fig. 4.11 Abdominal sonography of a 2 year old boy with SDS and typical "white" pancreas (*arrows*) due to lipomatosis [Courtesy of K. Schneider; Munich, Germany]

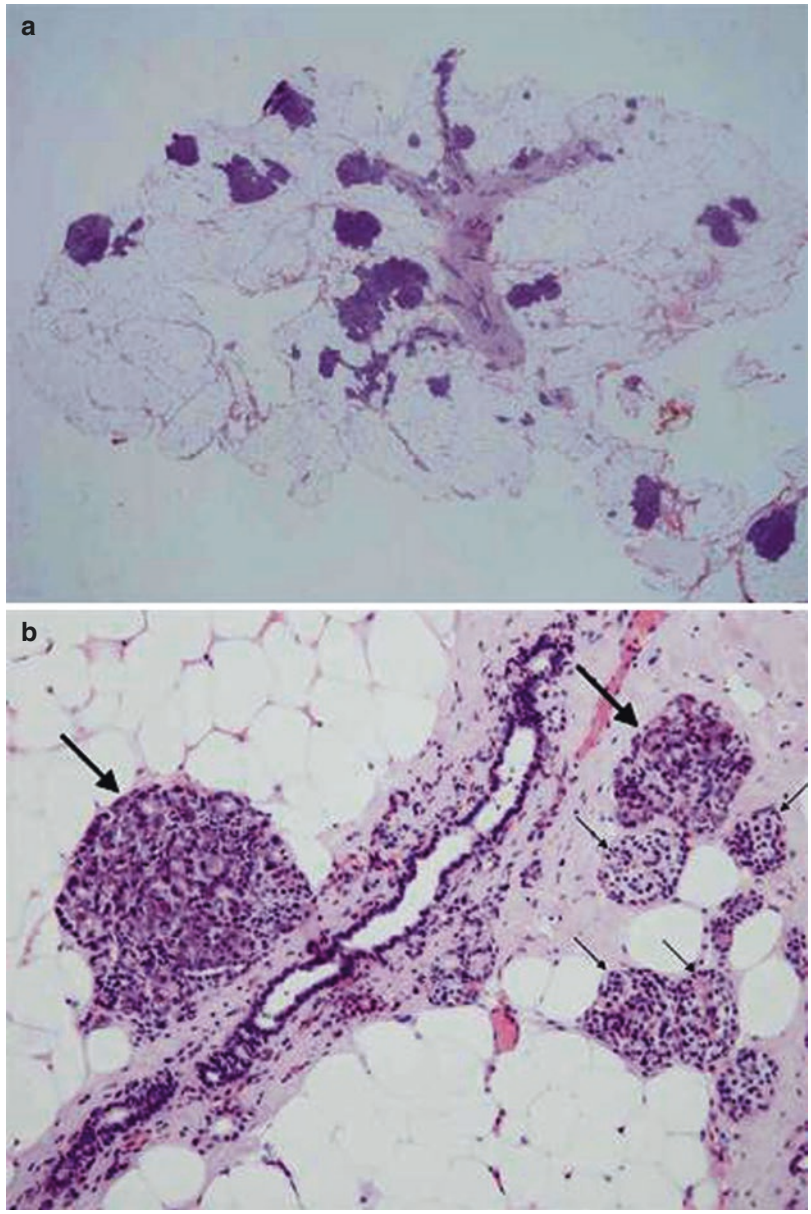

Fig. 4.12 Typical histology of the pancreas of a patient with SDS. Note the extensive replacement of the exocrine pancreas by adipose tissue surrounding acini (*large arrows*) with remaining small islands of parenchyma (*small arrows*). *(***a** and **b** *different magnifications)*

months should be checked. Liver function parameters (ALT, AST, etc.) could also be checked at diagnosis and when clinically indicated [179]. Neutropenia with recurrent bacterial infections or with a high risk of severe infections (e.g., ANC <500/μL) can be treated with granulocyte colony-stimulating factor (G-CSF). There is, however, a risk of stimulation of malignant pre-leukemic clones and therefore the risks and benefits should be considered. In the "Severe Chronic Neutropenia International Registry", the risk of acquiring AML was about 8 % over 10 years [52]. Leukocyte-depleted and irradiated erythrocyte

transfusions are recommended in patients with symptomatic anemia. In case of thrombocytopenia and bleeding platelet transfusions are indicated. HSCT should be offered to patients with pancytopenia, MDS or overt leukemia in remission [43, 241, 243]. HSCT may be complicated by the stromal defect and should be performed in centers with experience with this disease. Survival is only about 60–70 %. Today, reduced-intensity-conditioning protocols should be used [20, 229]. Finally, for bone and dental abnormalities anticipatory management is indicated.

4.10 Severe Congenital Neutropenias

(ELANE deficiency, GFI1 deficiency, HAX1 deficiency, G6PC3 deficiency, VPS45 deficiency, X-linked neutropenia, p14 deficiency, JAGN1 deficiency, G-CSF receptor deficiency)

4.10.1 Definition

Severe Congenital Neutropenia (SCN, OMIM*202700) is a rare primary immunodeficiency disease with an estimated frequency of 1–2 cases per 10^6 population [216, 249, 280]. SCN is characterized by early onset severe bacterial infections and persistent severe neutropenia [215, 216, 280, 292, 293]. Rolf Kostmann described this disorder for the first time in 1956, in a Swedish family with severe bacterial infections and severe neutropenia, which was characterized by a maturation arrest of myeloid differentiation at the promyelocyte-myelocyte stage [127, 128].

4.10.2 Etiology

Current knowledge indicates a multigene disorder with a common hematological and clinical phenotype [249]. Congenital neutropenia is genetically heterogeneous with different modes of inheritance, including autosomal recessive, autosomal dominant, X-linked and sporadic forms reported [9, 19, 24, 90, 187, 216, 280]. Considering the genetic heterogeneity of SCN, it seems that several pathologic mechanisms may lead to the same phenotype due to down-regulation of common myeloid transcription factors [249]. Absence of lymphoid enhancer-binding factor 1 (LEF1) could be an important pathologic mechanism, irrespective of mutation status [248, 249].

Heterozygous mutations in the gene encoding neutrophil elastase (*ELANE*, OMIM*130130) are the underlying genetic defect in more than half of the autosomal dominant and sporadic forms of SCN [55, 225, 280]. Biallelic mutations in the gene encoding HCLS1-associated protein X1 (*HAX1*, OMIM*605998) cause autosomal recessive SCN [123, 216], also known as Kostmann syndrome (OMIM*610738). Heterozygous mutations in the protooncogene growth factor-independent 1 (*GFI1*) gene (OMIM*600871), which targets *ELANE*, also cause an autosomal dominant form of SCN [202]. G6PC3 deficiency (OMIM*612541) is a syndromic neutropenia due to homozygous mutation in *G6PC3* (OMIM*611045) [28]. VPS45 deficiency (OMIM #615285) is another autosomal recessive neutropenia, characterized primarily by neutropenia and neutrophil dysfunction and lack of response to G-CSF, caused by mutation in *VPS45* (OMIM*610035) [256, 271]. X-linked congenital neutropenia (OMIM*300299) can be caused by a constitutively activating mutation in the *WASP* gene (OMIM*300392), which is also mutated in the Wiskott-Aldrich syndrome [61]. *(See* Sect. 9.16 *for more details)* p14 deficiency (OMIM*610798) is an autosomal recessive disease due to mutations in *P14* (OMIM*610389), an adapter molecule (*LAMTOR2*) [23]. *(See* Sect. 5.7 *for more details)*

JAGN1 deficiency (OMIM*616022) is another autosomal recessive neutropenia, which has been recently been described. It is caused by homozygous mutation in the *JAGN1* gene (OMIM*616012). An interesting finding in patients with *JAGN1* mutation is an abnormal and enlarged endoplasmic reticulum with almost complete absence of granules in neutrophils [29].

Inherited loss-of-function mutations in the *CSF3R* gene (OMIM*148971) encoding the granulocyte colony-stimulating factor (G-CSF)

receptor should also be considered as a neutropenia disorder [264].

Neutrophil elastase protein has a role in synthesizing the promyelocytes [11] and *HAX1* has a role in controlling apoptosis [47]. Mutant *HAX1* and also *ELANE* could accelerate apoptosis in myeloid progenitor cells of the patients [11, 39, 54].

Despite discovering the mutations mentioned above in SCN, there are still SCN patients without defined mutations [24, 232]. Future genetic studies should be performed to discover other responsible genes in controlling the survival of neutrophils in these patients.

4.10.3 Clinical Manifestations

Early onset recurrent bacterial infections are the hallmark of SCN. The patients usually experience such infections by the age of 1 year. The most common presenting features are superficial abscesses, oral ulcers, cutaneous infections, omphalitis, pneumonia, and otitis media [215, 216, 280]. During the course of disease, the patients usually develop abscesses in different sites, mucocutaneous manifestations, respiratory infections, and diarrhea [213, 215, 216]. Frequent aphthous stomatitis and gingival hyperplasia lead to loss of permanent teeth in childhood [280]. Recently, neurological disorders, including developmental delay and epilepsy, are reported in some SCN patients with *HAX1* mutations [39, 212].

Increased serum immunoglobulins are a common finding in SCN patients, which may be secondary to recurrent infections or due to a possible effect of the gene defect in both myelopoiesis and lymphopoiesis [216, 280].

It is estimated that splenomegaly can be detected in one-fifth of SCN patients before treatment with granulocyte colony-stimulating factor (G-CSF) and up to half of them through 10 years of treatment [280].

G6PC3 deficiency is a syndromic neutropenia, characterized by cardiac abnormalities, including atrial septal defect, cor triatriatum, mitral insufficiency, as well as a prominent superficial venous pattern in addition to neutropenia and increased susceptibility to bacterial infections [28, 30, 60].

VPS45 deficiency is characterized by bone marrow fibrosis, nephromegaly, prominent truncal venous pattern, renal extramedullary hematopoiesis, and neurological problems in addition to neutropenia and infections [169, 256, 271].

Patients with p14 deficiency exhibit beside oculocutaneous hypopigmentation and short stature in addition to neutropenia [23]. *(See* Sect. 5.7 *for more details)*

Similar to the phenotypes seen in neutropenia, patients with JAGN1 deficiency suffered from recurrent bacterial infections, especially in respiratory system and skin [29].

SCN is also considered as a preleukemic syndrome. While the course of a number of SCN patients is complicated by myelodysplastic syndrome and acute myeloid leukemia [224, 249, 280], the presence of these complications has a high correlation with occurrence of acquired mutation in the gene encoding the granulocyte colony-stimulating factor receptor (*CSF3R*) (OMIM*138971). Such mutations were detected in approximately 80 % of the SCN patients who developed acute myeloid leukemia [65, 249].

4.10.4 Diagnosis

Timely referral to a hematologist and/or clinical immunologist remains key to the successful diagnosis and management of patients with SCN, as delay in both reaching the diagnosis and starting the appropriate treatment increases the mortality in childhood [211, 216]. Presence of severe neutropenia in association with early onset severe and recurrent infections should raise suspicion of SCN, especially in those with superficial abscesses and oral ulcers. In fact, the presence of abscesses, ulcers and gingivitis implies clinically significant neutropenia [215].

SCN patients typically have persistent severe neutropenia with absolute neutrophil count of less than 500/mm^3, and increased susceptibility to recurrent severe bacterial infections from early infancy. In addition to performing serial complete blood cell count (CBC) in order to determine the

chronicity and severity, other causes of secondary neutropenia should be excluded. Review of the clinical history is important to rule out drug exposure and underlying illness such as autoimmune diseases [215]. CBC often indicates an increased number of platelets, monocytes, and eosinophils, while mild anemia is usually seen [249].

Immune neutropenia of infancy should be excluded by testing for the presence of anti-neutrophil antibodies [280]. When anti-neutrophil antibody mediated neutropenia is present in the newborn period, the antibodies generally are not a result of autoimmunity as it is in older children and adults, but are usually of maternal origin, arising from maternal-fetal incompatibility at neutrophil specific antigen loci. Many of these neutrophil specific antigens are expressed on the antibody Fc receptors of neutrophils. Maternal mediated immune neutropenia is a self-limited process that will improve over several months as maternal antibodies are cleared, and should be managed conservatively.

Indeed there are several primary immunodeficiency diseases, which could be associated with neutropenia; therefore an algorithmic approach is needed to make diagnosis (Fig. 4.13).

Bone marrow examinations of the patients with SCN usually show a maturation arrest of neutrophil precursors at an early stage (promyelocyte-myelocyte) [9, 215, 216, 280, 292, 293] (Fig. 4.14). Cellularity is usually normal or a little decreased, while increased number of eosinophils and monocytes is often detected in the bone marrow [280].

Molecular studies help confirm a definitive diagnosis in SCN patients and also help predict response to treatment and outcome; however the diagnosis of SCN rests primarily on the clinical features of the disease and peripheral blood studies [215].

4.10.5 Management

In the absence of appropriate treatment, affected children suffer from life-threatening infections [39, 215, 249, 280, 291]. Since GCSF therapy became available as a treatment option for SCN, it has become possible to manage patients even without a requirement for HSCT. GCSF therapy has made considerable impact towards prognosis and quality of life of these patients [25, 39, 216, 280, 291, 293]. Recombinant GCSF is the first choice of treatment for the SCN patients and more than 90 % of the patients respond to GCSF administration, which increase the number of neutrophils and consequently reduce the number of infections and days of hospitalization [249, 280]. However, in the patients with congenital mutations in *CSFR3* gene who do not respond to G-CSF treatment, HSCT is the only curative treatment option for SCN. In those patients with SCN which have acquired deletions in the cytoplasmic tail of the G-CSF receptor, the increased risk of AML/MDS should also undergo (pre-emptive) HSCT. Hence, both in those with continuing severe bacterial infections or complicated by myelodysplasia, HSCT is the recommended treatment [294]. The results of allogeneic HSCT on 136 patients during a 22-year period in European and Middle East centers show that the 3-year overall survival is about 82 % [82].

It is recommended that all SCN patients should be followed-up at least twice per year and complete blood cell counts should be performed at least every 3 months [280].

4.11 Cyclic Neutropenia

4.11.1 Definition

Cyclic Neutropenia (OMIM*162800) is a rare primary immunodeficiency disease with an estimated frequency of 1 case per 10^6 population, characterized by neutropenia occurring every 3 weeks and lasting for 3–6 days [50, 53, 77, 214, 215, 217]. Dr. Leale described this disorder for the first time in 1910, in an infant with recurrent episodes of fever, skin infections, stomatitis, and neutropenia [139]. Patients with cyclic neutropenia are usually asymptomatic; however, they can suffer from severe bacterial infections, oral lesions and cutaneous manifestations during the episodes of neutropenia [77, 214, 215, 217].

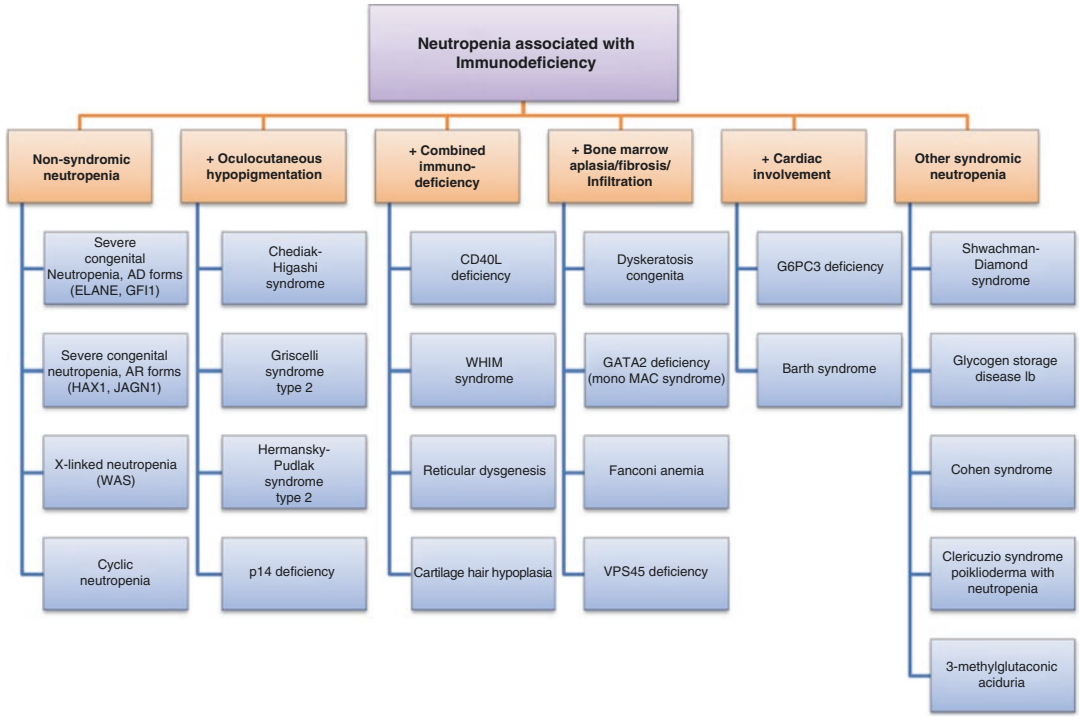

Fig. 4.13 Algorithmic approach to a patient with neutropenia

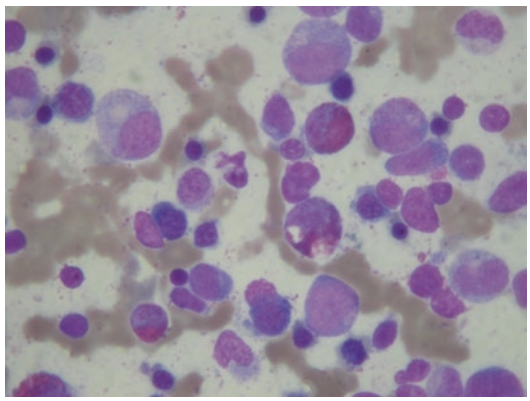

Fig. 4.14 The bone marrow morphology of a patient with severe congenital neutropenia

4.11.2 Etiology

Cyclic neutropenia is an autosomal dominant or sporadic disease, due to the periodic failure in production of granulocytes, presumably at the stem cell level [214]. The pathophysiology and the affected function in this disease has not been fully understood, but it seems that cyclic neutropenia is due to an abnormality in the regulation of early hematopoietic precursor cells [214, 215]. It could lead to oscillations in production of all types of blood cells. Neutropenia and leukopenia occur together in most situations, and cyclic (and for some non-neutrophil lineages counter-cyclic) fluctuations of monocytes, eosinophils, lymphocytes, platelets, and reticulocytes are also reported [50, 53, 214, 215, 217]. Mutations in the *ELANE* gene (OMIM*130130) are reported as the underlying genetic defect in several patients with cyclic neutropenia [11, 54, 55, 90, 187, 225]. It is also important to distinguish the congenital autosomal dominant form of cyclic neutropenia from acquired cyclic neutropenia that may complicate the clinical manifestations of benign and leukemic expansions of large granular lymphocytes [19]. Generally, congenital cyclic neutropenia is characterized by extremely regular cycles of almost exactly 21 days duration, while acquired cyclic neutropenias may have irregular cycles and/or cycles significantly different from 21 days duration. It is important to note, however, that administration of GCSF to patients

with congenital cyclic neutropenia may significantly alter the cycle duration in some patients.

4.11.3 Clinical Manifestations

Patients with congenital cyclic neutropenia are generally healthy between neutropenic periods, but during the episode of neutropenia that suffer aphthous stomatitis, oral ulcers, gingivitis, abscesses and occasionally overwhelming bacterial infections [54, 77, 214, 215, 217]. The symptomatic episodes of fever and infections usually recur approximately every 3–4 weeks. The neutropenic periods are associated with infections especially in oral cavity and mucous membranes, where oral ulcers and periodontitis are common. Cutaneous infections, upper respiratory infections and skin abscesses are also common. Perirectal and genital areas are susceptible to recurrent infections and abscesses [50, 53, 214, 215, 217]. Because many patients with congenital cyclic neutropenia tend to be clinically well between nadirs, it is easy to miss the early signs of the particularly life-threatening danger to these patients of the development of necrotizing enterocolitis (typhlitis), which may rapidly progress to acute perforation of the bowel with bacteremia and septic shock.

4.11.4 Diagnosis

Congenital cyclic neutropenia is diagnosed by documenting the very regular periodic oscillations in the circulating neutrophil count from normal to neutropenic levels through at least a 3 weeks period, lasting for 3–6 days [50, 53, 77, 214, 215, 217]. In the patients with neutropenia, the clinical history and examination of the peripheral blood smear the most important aspects of the diagnostic evaluation. Examination of the oral cavity, perianal region, and skin is necessary in order to assess the clinical impact of neutropenia [214, 215]. As previously noted, in patients not being treated with G-CSF, the period of cycling is generally very regular and most often is close to 3 weeks duration. However, the cycling periodicity can vary somewhat from one patient to another patient and can be altered by administration of G-CSF. It is recommended that for diagnosis a complete blood count with assessment of differential lineages be performed at least twice or even three times weekly over 6–9 weeks to document the typical cyclic pattern of neutropenia [214]. In sporadic cases where a family history is absent, evidence for cycling from early childhood is absent, and/or the cycling is erratic or very different from 21 days, acquired cyclic neutropenia must be considered in the differential diagnosis.

Bone marrow examination during neutropenic periods shows maturation arrest of neutrophil precursors at an early stage, but is not a necessary investigation in every patient [77, 214, 217].

4.11.5 Management

The quality of life and life expectancy of the patients with congenital cyclic neutropenia are good, if patients are diagnosed and followed regularly by attentive physicians and dentists [214, 215, 217]. Although the prognosis is good with a benign course, approximately 10 % of patients may experience life-threatening infections. Besides prophylactic antibiotics, in some patients treatment with recombinant human GCSF in anticipation of and into the time of ‘cycling nadir’ may be all that is needed over a period of several days to increase blood neutrophil counts sufficiently to achieve reduction in infection rate, and improvement in survival and quality of life [50, 51].

4.12 Glycogen Storage Disease Type 1b

4.12.1 Definition

Glycogen storage disease type 1B (GSD1B; OMIM*232220) is a metabolic disease, which was first described by Senior and Loridan in 1968, as functional deficiency of glucose-6-phosphate [239].

4.12.2 Etiology

GSD1B is caused by either homozygous or compound heterozygous mutations in the *G6PT1* gene, also named as *SLC37A4* (OMIM*602671), which

encodes glucose-6-phosphate translocase. Motility and respiratory burst of neutrophils are defective.

4.12.3 Clinical Manifestations

In addition to severe hypoglycemia, neutropenia leading to recurrent infections is one of the main features of GSD1B. Similar to other types of neutropenia, oral lesions and perianal abscesses can be seen in the patients with GSD1B [8]. The patients usually have a doll-like face, while they also have hepatomegaly and obesity.

4.12.4 Diagnosis

The diagnosis should be suspected based on the clinical phenotype of severe hypoglycemia and hepatomegaly in addition to neutropenia, while the definite diagnosis should be confirmed by liver biopsy with electron microscopy and assay of G6P activity in the tissue confirmed by genetic testing.

4.12.5 Management

GCSF therapy can increase the number of circulating neutrophils in the GSD1B. Dietary advice to minimize intake of carbohydrates can also be applied [272]. Liver transplantation may be necessary in some cases, in order to manage the glycemic condition [118].

4.13 3-Methylglutaconic Aciduria

(Type II, Type VII)

4.13.1 Definition

3-methylglutaconic aciduria type II (MGCA2), also known as Barth syndrome (OMIM*302060), is an X-linked disease, first described by Barth et al. in a large Dutch family. The syndrome is characterized by dilated cardiomyopathy, skeletal myopathy and abnormal mitochondria in addition to neutropenia [15].

3-methylglutaconic aciduria type VII (MGCA7), also known as 3-methylglutaconic aciduria with cataracts, neurologic involvement, and neutropenia (MEGCANN) (OMIM*616271), is an autosomal recessive inborn error of metabolism [230, 286].

4.13.2 Etiology

Barth syndrome is caused by mutation in tafazzin (*TAZ*) (OMIM*300394). Tafazzin has an important role in remodeling of cardiolipin, which is necessary to maintain mitochondrial structure [112, 228].

3-methylglutaconic aciduria type VII is caused by homozygous or compound heterozygous mutation in the *CLPB* gene (OMIM*616254) [230, 286].

4.13.3 Clinical Manifestations

Barth syndrome is characterized by dilated cardiomyopathy, proximal skeletal myopathy, growth retardation, while neutropenia and organic aciduria are also characteristic features of the syndrome [116, 257].

Patients with 3-methylglutaconic aciduria type VII usually have early onset progressive encephalopathy. Delayed psychomotor development and variable intellectual disability, neutropenia, microcephaly, movement disorder, and cataracts are other common features of disease [230, 286].

4.13.4 Diagnosis

Increase in organic acid excretion in addition to neutropenia, when associated with dilated cardiomyopathy should help in suspecting Barth syndrome [257]. Increase in 3-methylglutaconic acid in addition to neutropenia, associated with neurologic deterioration should suggest 3-methylglutaconic aciduria type VII.

4.13.5 Management

A flexible and multidisciplinary approach is needed in the management of Barth syndrome.

Cardiac medications to improve symptoms of heart failure may be recommended. GCSF therapy can increase absolute neutrophil counts, which may be combined with prophylactic antibiotics. Dietary interventions should also be recommended [210, 260].

4.14 Cohen Syndrome

4.14.1 Definition

Cohen syndrome (OMIM*216550) is an autosomal recessive disease, which was first described by Cohen et al. in a few patients with hypotonia, obesity, and some other features like characteristic facial dysmorphism, and mental retardation [48].

4.14.2 Etiology

Cohen syndrome is caused by homozygous or compound heterozygous mutations in *COH1* (*VPS13B*; OMIM*607817). Patients suffer from defective glycosylation, which is shown by accumulation of agalactosylated fucosylated structures and asialylated fucosylated structures [72].

4.14.3 Clinical Manifestations

Cohen syndrome is a multisystem disorder, characterized by facial dysmorphism, microcephaly, psychomotor retardation, truncal obesity, progressive retinopathy, associated with neutropenia [72]. Facial dysmorphism of patients includes a short philtrum, high nasal bridge, high-arched or wave-shaped eyelids, and thick hair.

4.14.4 Diagnosis

The diagnosis can be suspected based on clinical phenotype. Chandler et al. proposed the following criteria for diagnosis of Cohern syndrome: "presence of at least two of the following major criteria in a child with significant learning difficulties: (1) facial gestalt, characterised by thick hair, eyebrows and eyelashes, wave shaped, downward slanting palpebral fissures, prominent, beaked shaped nose, short, upturned philtrum with grimacing expression on smiling; (2) pigmentary retinopathy; (3) neutropenia" [44]. However, as is true for all inborn errors, genetic diagnosis is necessary for certainty.

4.14.5 Management

Treatment of patients with Cohen syndrome is limited to symptomatic and supportive therapy. Some surgical procedures could be recommended to correct facial dysmorphism, etc. GCSF therapy is also recommended in treatment of neutropenia. Psychological support and growth hormone therapy may also be needed.

4.15 Poikiloderma with Neutropenia

4.15.1 Definition

Poikiloderma with neutropenia (OMIM*604173), also named as Clericuzio syndrome, is an unique autosomal recessive genodermatosis.

4.15.2 Etiology

Poikiloderma with neutropenia, also named as Clericuzio syndrome, is caused by mutation in *C16ORF57* (OMIM*613276)

4.15.3 Clinical Manifestations

Patients with poikiloderma and neutropenia experience an early onset papular erythematous rash on the limbs, which gradually spreads centripetally. Skin hyper- or hypo-pigmentation as well as telangiectases and pachyonychia may also be seen.

Patients also suffer from persistent or cyclic neutropenia, leading to recurrent respiratory tract infections [74, 125].

4.15.4 Diagnosis

Genodermatosis in association with neutropenia should lead to suspicion of poikiloderma with neutropenia. Clericuzio syndrome has some similarities with Rothmund-Thomson syndrome (OMIM*268400); however, patients with Rothmund-Thomson syndrome usually have alopecia of the head and eyebrows, while their skin lesions are usually seen in sun-exposed areas. Skeletal manifestations, cataracts, and predisposition to malignancy in Rothmund-Thomson syndrome also distinguish it from poikiloderma with neutropenia [277]. *(See* Sect. 9.9 *for more details)*

4.15.5 Management

Treatment of patients with poikiloderma and neutropenia is limited to symptomatic and supportive therapy. GCSF therapy may be recommended in treatment of neutropenia.

4.16 Myeloperoxidase Deficiency

4.16.1 Definition

Myeloperoxidase (MPO) deficiency (OMIM*254600) is the most common phagocyte disorder (approximately 1 in 4000 population) and leads to a defective production of hypochloric acid in these cells [182, 198]. It was first described by Lehrer and Cline [140], who found no detectable activity of the lysosomal enzyme in neutrophils and monocytes from a patient with disseminated candidiasis. Other granule-associated enzymes were normal. Leukocytes from one of the proband's sisters also showed no MPO activity. Leukocytes from the proband's 4 sons showed about one-third normal levels. Salmon et al. [226] demonstrated immunologically the absence of MPO protein, or at least the absence of cross-reacting material in homozygotes. Eosinophil peroxidase, which is chemically distinct from MPO, was normal.

4.16.2 Etiology

Myeloperoxidase is abundant in azurophilic granules and catalyses the conversion of H_2O_2 into hypochlorous acid [183]. This molecule amplifies the toxicity of reactive oxygen radicals (ROS). The gene is encoded on chromosome 17q23. Congenital deficiency of MPO is inherited as an autosomal recessive disorder. A secondary form of MPO deficiency has been described in lead poisoning (due to inhibition of heme synthesis), in severe infections (due to consumption), neuronal lipofuscinosis, diabetes mellitus, in patients treated with cytotoxic drugs and malignant disorders like acute and chronic myeloid leukemia, myelodysplastic syndrome and Hodgkin lymphoma due to chromosomal rearrangements. MPO-deficient neutrophils are markedly less efficient in killing *Candida albicans* or *Aspergillus* hyphae when completely absent. However, it should be noted that most inherited mutations in *MPO* result in a partial peroxidase deficiency and a complete MPO deficiency is extremely rare. Because of its high frequency, mutation analysis of the *MPO* gene is often not performed. The remarkable effect on *in-vitro* findings [88] may have clinical consequences, but may be restricted to those with a complete MPO deficiency, which has not yet been well studied.

4.16.3 Clinical Manifestations

Interestingly, the vast majority (>95 %) of MPO deficient individuals are completely asymptomatic, despite the killing defect of the neutrophils. Symptomatic patients suffer from recurrent *Candida* infections in the setting of diabetes mellitus [42, 198]. Severe infections of the bones, meninges and septic episodes occasionally occur. In a recent study in MPO knock out mice showed more severe lung injury to administration of non-viable *Candida*

albicans than wild type mice indicating that MPO knock out mice have an altered immune response [106].

Anti-MPO antibodies are associated with certain forms of vasculitis (e.g. microscopic polyangiitis) and MPO derived oxidants seem to play a role in neurodegenerative disorders and atherosclerosis [183, 200, 266], but this is not uniformly accepted [171]. Interestingly, MPO knock out mice raised with a high cholesterol diet developed larger atheromata than wild type MPO mice [32].

4.16.4 Diagnosis

MPO deficiency can be suspected when a large proportion of "unstained" cells are reported from a differential blood count. The definite diagnosis requires the demonstration of the defective enzyme. MPO is easily detected using a hydrogen-peroxide/ethanol solution containing benzidine. Cells with intact enzyme show yellow-brown granules in the plasma, cells with MPO deficiency have clear plasma around the blue cell nucleus. The diagnosis can be confirmed by genetic analysis of the *MPO* gene [157, 184].

4.16.5 Management

There is no specific treatment for MPO deficiency. In symptomatic patients long-term antifungal prophylaxis with fluconazole or itraconazole may be beneficial.

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Genetic Disorders of Immune Regulation

5

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5.1 Introduction

The primary role of the immune system is defense against infection. Antimicrobial immune responses are highly dynamic processes that involve rapid expansion and contraction of immune cell populations, targeted exertion of highly potent effector functions and secretion of soluble mediators that have antimicrobial properties and influence cell functions and interactions. To maintain homeostasis, both innate and adaptive immune responses require tight regulation. Exaggerated inflammatory responses can be the consequence of uncontrolled activation of the immune system and failure to control immune responses against host antigens causes autoimmunity. There are many checkpoints that help to maintain homeostasis in the immune system involving a variety of cells and mediators. It is therefore not surprising that genetic deficiencies in many immunologically relevant molecules can lead to immune dysregulation in addition to but also in the absence of susceptibility to infection.

Failure to regulate immune responses may lead to various clinical manifestations including (benign) lymphoproliferation, febrile inflammatory responses and autoimmunity. In many cases infections trigger these aberrant responses. In some circumstances, failure to appropriately control pathogens contributes to their maintenance, but in others, no exogenous stimulus can be identified. The molecular and cellular mechanisms responsible for immune dysregulation vary in different forms of primary immunodeficiencies. In many diseases, several mechanisms are involved. Immunodeficiencies associated with

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immune dysregulation include humoral deficiencies, T cell deficiencies, phagocyte defects and complement deficiencies. These diseases are discussed in the respective sections of this book. This chapter describes several immunodeficiency syndromes that predominantly manifest with immune dysregulation. This includes the familial hemophagocytic syndromes, the closely related immunodeficiencies with hypopigmentation, X-linked lymphoproliferative disease, autoimmune lymphoproliferative syndrome, APECED and IPEX syndrome.

Hypopigmentation or even albinism combined with a variable degree of immunodeficiency is a characteristic hallmark of Chediak Higashi syndrome (CHS), Griscelli syndrome (GS) type II, and Hermansky-Pudlack syndrome (HPS) type II. In addition, mutations in the endosomal p14 adaptor protein cause a complex B-and T-cell immunodeficiency with neutropenia, short stature (usually not seen in any of the aforementioned syndromes) and partial albinism. Skin, hair and the iris may be affected to variable degrees, this predominant clinical appearance is usually seen at birth. Thus, oculocutaneous hypopigmentation may pave the way for early diagnosis of a profound immunodeficiency. The common pathophysiological cause for the astonishing variety of clinical symptoms is severe perturbation of lysosomal and endosomal pathways. On the molecular level, the various steps of biogenesis, transport, distribution and segregation of lysosomes are not yet understood in detail. However, given the complex spatiotemporal control of secretory lysosomes, particularly in melanocytes and immune cells, it becomes understandable why the clinical phenotype may differ widely.

Many but not all of the diseases summarized in this chapter are collectively named "inherited hemaophagocytic lymphohistiocytosis" (HLH), the fatal immune dysregulation resulting in uncontrolled lymphocyte and macrophage activation, hypercytokinemia, cell infiltration and severe organ damage [94].

Another subject of this chapter is primary immunodeficiencies that lead to a particular susceptibility to EBV-triggered HLH, pronounced lymphoproliferation, dysgammaglobulinemia and (aside from XIAP deficiency) lymphoma development of both categories, Hodgkin's lymphoma and Non-Hodgkin's lymphoma. Patients with EBV-induced lymphoproliferative syndromes may present with an X-linked (XLP1, XLP2, MAGT1) or autosomal-recessive mode of inheritance (ITK, CD27). *(See* Table 1.4 *and* Fig. 1.11 *for updated classification of genetic disorders of immune regulation)*

5.2 Familial Hemophagocytic Lymphohistiocytosis

(Perforin deficiency, UNC13D deficiency, Syntaxin 11 deficiency, STXBP2 deficiency)

5.2.1 Definition

Familial hemophagocytic lymphohistiocytosis (FHL) is a group of genetically determined, life-threatening diseases caused by the uncontrolled proliferation of activated lymphocytes and histiocytes secreting high amounts of inflammatory cytokines [46, 59, 60]. The symptoms were first described in 1952 and include prolonged fever, hepatosplenomegaly, pancytopenia and neurological symptoms [56]. Currently there are 5 known forms of FHL (FHL1-5), for four of which the causative genes have been identified: FHL-2 (OMIM*603553) is caused by mutations in the gene encoding perforin (*PRF1*; OMIM*170280) [192, 193], FHL-3 (OMIM*608898) is due to mutations in the gene encoding MUNC 13-4 (*UNC13D*; OMIM*608897) [57], FHL-4 (OMIM*603552) is caused by mutations in the gene encoding syntaxin 11 (*STX11*; OMIM*605014) [229], and FHL5 (OMIM*613101) as result of mutations in the gene encoding *STXBP2* (OMIM*601717) encoding the protein munc 18-2 [37, 228]. All of these proteins are involved in cellular cytotoxicity mediated by NK cells and T cells [64]. FHL-1 has been linked to chromosome 9q21.3-22; however, its genetic basis is still unknown [141]. In addition, there are further familial forms of the disease whose genetic basis remains to be elucidated.

5.2.2 Etiology

Contact-dependent cellular cytotoxicity by NK cells and CD8+ cytotoxic T cells (CTL) is one of the key effector mechanisms of the immune system against intracellular pathogens such as viruses and intracellular bacteria [100]. Cellular cytotoxicity is mediated by cytotoxic granules in the cytoplasm of NK cells and CTL containing perforin, granzymes and other components. After target cell recognition and formation of an appropriate contact area between effector and target cell (the immunological synapse), granules migrate to the site of cell contact, fuse with the plasma membrane and their contents are secreted into the intracellular space. Perforin and granzymes then cooperate to mediate rapid apoptosis of the target cell (Fig. 5.1) [194].

Perforin, MUNC13-4, Syntaxin 11 and munc 18-2 are all expressed in NK cells and CTL. Perforin is a pore-forming protein that can insert into the lipid bilayer of target cell membranes causing cell death by osmotic lysis and allowing entry of apoptosis-inducing granzymes [23]. MUNC 13-4 is involved in vesicle priming and MUNC 13-4 deficiency results in defective exocytosis despite polarization of lytic granules and docking with the plasma membrane [135]. Syntaxin 11 is also expressed in APC and an impaired interaction between CTL and APC may contribute to FHL-4 [229]. However, the association of syntaxin 11 with other lysosomal proteins and the recent description of impaired CTL and NK cell degranulation in patients with syntaxin 11 deficiency suggests that it is also important for granule exocytosis [31]. Munc 18-2 is important for controlling intracellular granule/membrane trafficking and exocytosis but not only in effector cell populations [228], but also in other cell types including neutrophils [225] and platelets [1].

In the context of its antimicrobial function, perforin-dependent cytotoxicity also plays an important role in the maintenance of T cell homeostasis [44]. During infections, pathogen-specific T cells undergo a massive expansion and activate their direct and indirect antimicrobial

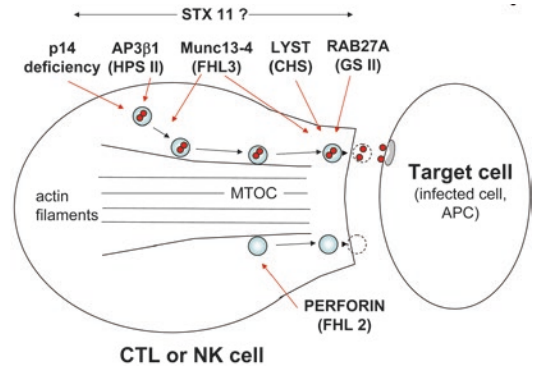

Fig. 5.1 Pathogenesis of cytotoxicity defects. *HPS* Hermansky-Pudlak syndrome, *FHL* Familial hemophagocytic lymphohistiocytosis, *CHS* Chediak-Higashi syndrome, *GS* Griscelli syndrome (Adapted with permission from [45])

effector pathways including cytotoxicity and release of inflammatory cytokines such as interferon-gamma. These pathways are also used by NK cells and lead to control of pathogen replication in infected tissues, but also to the elimination of antigen-presenting cells (APC). Both of these processes lead to a reduction in the level of antigenic stimulation of T cells. As a consequence, most of the effector T cells die leaving a pool of memory T cells that can mediate recall responses on further exposure to antigen. In the absence of perforin-dependent cytotoxicity, this "negative feed-back loop" is ineffective [45, 129]. Prolonged stimulation by APC and impaired pathogen control leads to uncontrolled expansion and persistence of the activated CTL.

Uncontrolled secretion of cytokines by activated CTL and NK cells leads to the hyperinflammatory state characteristic of hemophagocytic syndrome (HLH). Experiments with perforin-deficient mice have identified interferon-gamma (IFN-γ) as a key cytokine involved [99]. IFN-γ is toxic to hematopoietic cells, which contributes to the cytopenia of HLH [18]. It is also a crucial activator of macrophages and tissue infiltration by macrophages with increased phagocytic activity are key features of HLH. This includes phagocytosis of blood cells in bone marrow and other infiltrated organs such as the liver, spleen or the brain, the demonstration of which is relevant for the diagnosis of the disease [61].

5.2.3 Clinical Manifestations

In about 85 % of patients with FHL, the disease manifests within the first year, in 70 % before 6 months of life [95, 96]. A short period of absence of symptoms and normal development after birth is typical. Although the full picture of HLH is rather characteristic, the initial clinical presentation of the disease is highly variable. In most patients, high fever unresponsive to antibiotic therapy, often undulating, in combination with pallor, vomiting and weight loss, are the first signs of the disease. Hepatosplenomegaly is usually pronounced and progressive, lymphadenopathy can only be observed in about 30 % of patients. Jaundice and edema, purpura and bleeding and non-specific skin rashes may also be present. Neurological symptoms can manifest at the beginning of the disease, but more commonly develop later during disease progression. Typical symptoms and signs include irritability, bulging fontanelle, hyper- or hypotonia, seizures and apathy or coma [79]. These symptoms and signs of HLH may be progressive leading to a lethal outcome if untreated, or may be remittent occurring in several bouts that ultimately lead to a lethal episode. Although a milder course of the disease with recurrent exacerbations and remissions has been observed in some patients with syntaxin-11 deficiency [169], clinical criteria do usually not allow to differentiate between the different genetic variants of the disease. Late-onset forms of FHL have been described, in particular in patients with missense mutations in perforin. These patients manifested late into adulthood and frequently showed atypical presentations including predominantly neurological disease [58] or aplastic anemia [188].

5.2.4 Diagnosis

Due to the non-specific symptoms and signs, the diagnosis of FHL is difficult, in particular in patients with an incomplete, late-onset manifestation of the disease (Table 5.1). The two important challenges are to diagnose the hemophagocytic syndrome and to verify a genetically determined form of the disease. Typical laboratory findings of HLH include anemia, thrombocytopenia and, to a lesser extent, leukopenia. Clinical chemistry reveals signs of liver dysfunction including hypertriglyceridemia, hyperbilirubinemia, elevated transaminases, highly elevated ferritin (>500 ng/mL), hyponatremia and hypoproteinemia [95, 96]. In addition, coagulation abnormalities are common, in particular hypofibrinogenemia. Analysis of the cerebrospinal fluid frequently shows mononuclear pleocytosis and increased protein, but may also be normal despite the presence of significant MRI changes such as hyperdense areas, atrophy or brain edema [79].

Table 5.1 Diagnostic criteria for hemophgocytic lymphohistiocytosis (www.histio.org) [84]

Clinical criteria	Fever
	Splenomegaly
Laboratory criteria	Cytopenia ≥2 lineages
	Hypertriglyceridemia ± Hypofibrinogenemia
Histopathologic criteria	Hemophagocytosis in bone marrow, spleen or lymph node
New Criteria	Impaired NK cell function
	Ferritin >500 µg/L
	sIL2R >2400 u/mL

Immunological findings include markedly decreased cytotoxic activity by NK cells and increased levels of activated CD8+ T cells. High levels of several cytokines including TNF-α, IFN-γ, IL-1 and IL-6 can be demonstrated as well as high levels of soluble CD8 or soluble CD25, reflecting the massive T cell, NK cell and macrophage activation [83]. The major histopathological finding is the infiltration of various organs by activated CTL and macrophages. Hemophagocytosis of erythrocytes and leukocytes is frequently observed, but may be absent (Fig. 5.2). Most organs can be infiltrated, but most frequently the spleen, liver, lymph nodes, bone marrow and CNS.

Diagnostic guidelines for the diagnosis of HLH have been established and may help in the differential diagnosis [82, 84]. Five of the following 8 criteria must be fulfilled:

- Fever
- Splenomegaly
- Cytopenia ≥ 2 lineages (Hb < 9 mg/l, Platelets < 100,000/ul, Neutrophils < 1000/ul)

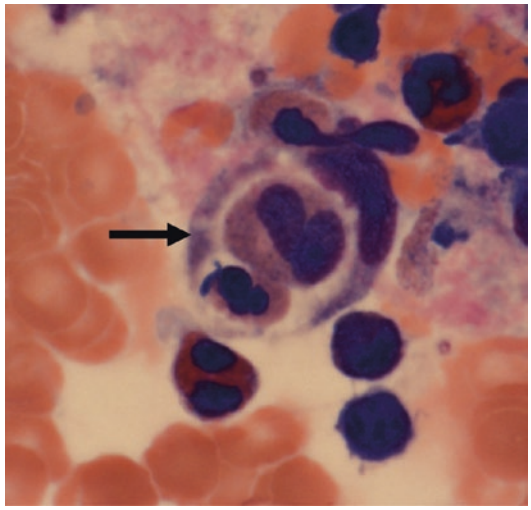

Fig. 5.2 Bone marrow aspirate smear from a HLH-patient showing a macrophage engulfing a granulocyte and a red cell precursor (hemophagocytosis)

- Hypertriglyceridemia and/or Hypofibrinogenemia
- Hemophagocytosis in bone marrow, spleen, lymph nodes or CSF
- Impaired NK cell function
- Ferritin > 500 ng/mL
- sCD25 > 2400 U/mL

In parallel to the diagnostic evaluation for HLH, the question must be addressed, whether this is a genetic or (more frequently) a secondary form of the disease. A positive family history and parental consanguinity and an early age at manifestation may suggest a familial form. However, secondary forms due to infections, hematopoietic malignancies or autoimmune disease may also manifest in the first year of life [95]. Since infections also contribute to the manifestation of HLH in genetic cases, a careful microbiological work-up is required [50]. This includes blood and CSF cultures, diagnostic evaluation for viral infections (EBV in particular, but also CMV, HIV, adenovirus, enterovirus, parvovirus or HHV-6), fungal infections (aspergillus), bacterial or parasitic infections (congenital lues, military tuberculosis, leishmaniosis, malaria, and brucellosis). Visceral leishmaniosis is particularly difficult to diagnose and may require repeated very careful analysis of bone marrow smears in addition to serological tests. It is not a rare cause of HLH and should be actively sought for [67].

Demonstration of an infectious trigger of HLH may allow directed therapy, but does not discriminate between primary and secondary forms of the disease. Although useful diagnostic algorithms have been proposed [7], the role of phenotypic functional immunological need further prospective evaluation in larger HLH cohorts. Absent intracellular staining of perforin in NK cells can support the diagnosis of FHL-2, but variants of the disease with remaining perforin expression have been reported [58]. Absent NK cytotoxicity and is a typical features of FHL, but can also be observed in secondary forms of the disease (Fig. 5.3a). Normalization of NK cell activity during remission is important evidence for a secondary form of the disease. Measurement of CTL mediated cytotoxicity can be more informative, since it is not compromised during active HLH. Recently, measurement of expression of the lysosomal marker protein CD107 on CTL or NK cells has been introduced as a parameter to quantify secretion of lytic granules (Fig. 5.3b) [16]. Reduced degranulation can be observed in patients with FHL-3, FHL-4, FHL-5 or yet undefined genetic disorders of degranulation [29, 30, 120]. The CD107 assay is also useful in the diagnosis of patients with more complex lysosomal trafficking disorders leading to albinism and immunodeficiency [53]. Hair microscopy and evaluation of granule morphology in granulocytes may be helpful in differentiating the FHL variants from these diseases (see below).

Genetic analysis can help to establish a definite diagnosis of perforin, Munc 13-4 or syntaxin 11 deficiencies. However, in a relevant proportion of cases, diagnosis of FHL still is a diagnosis of exclusion, depending on many anamnestic, clinical, laboratory, immunological and genetic criteria.

5.2.5 Management

Without treatment, FHL is usually lethal within the first year of life. Forms with very early onset of HLH tend to be more aggressive. There is no established prophylaxis to prevent HLH in

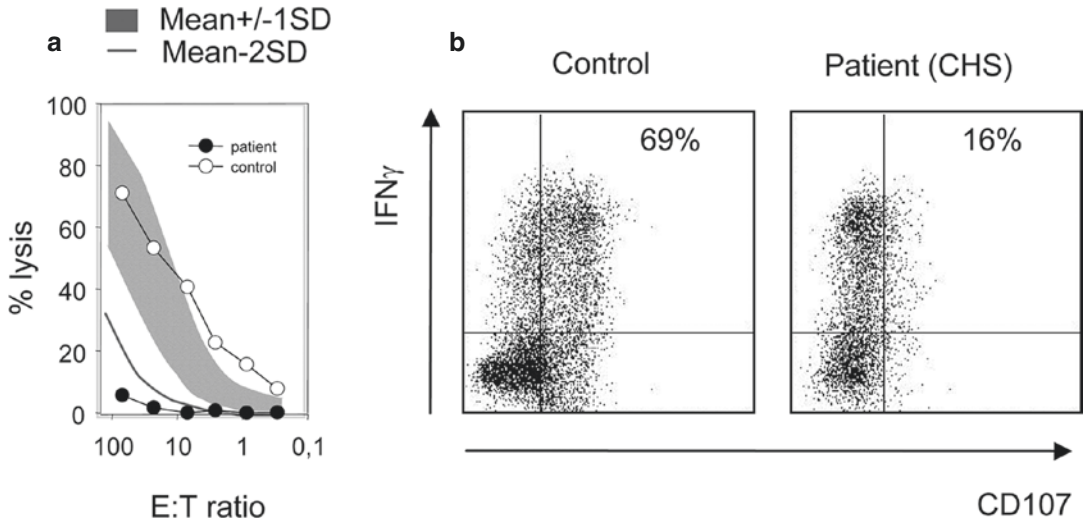

Fig. 5.3 (**a**) Results of an NK cell cytotoxicity assay showing severely impaired cytotoxic activity of patient cells in comparison to cells from a healthy control. (**b**) CD8+ T cell degranulation assay. Short-term PHA-blasts were stimulated with anti-CD3/anti-CD28 and stained for markers of T cell activation (IFNγ) and degranulation (using the lysosomal marker protein CD107). The T cells from a patient with Chediak-Higashi syndrome fail to degranulate despite normal activation

patients with a genetic diagnosis of FHL prior to the manifestation of HLH. Current protocols for the treatment of HLH (HLH-2004) include chemotherapeutic (etoposide) or immunotherapeutic (ATG) regimes in association with cyclosporine A and dexamethasone [84, 144]. Appropriate antimicrobial treatment may help to control the infectious trigger, although this will only sometimes modify the course of the disease. This includes the use of rituximab for control of EBV infection. Intrathecal MTX may help to treat the neurocerebral involvement and to limit further relapse. Unfortunately, these treatments are not always effective in controlling the primary disease and frequently fail to control relapses. Future strategies to control the acute phase of the illness may include attempts to neutralise the hypercytokinemia that is a major driver of the cellular activation. The use of a blocking anti-interferon gamma monoclonal antibody was able to induce recovery from LCMV (lymphocytic choriomeningitis virus) induced hemophagocytosis in two different murine models of HLH (perforin deficient and Rab27a) and is currently evaluated in a prospective human trial.

At present, hematopoietic stem cell transplantation (HSCT) is the only curative treatment [138, 180]. The success of HSCT depends on the extent of control of HLH prior to transplantation. Partial chimerism appears to be sufficient to prevent HLH reactivation in most cases. In a murine model of perforin deficient HLH, it has been shown that engraftment of wild type donor CD8 cells above a threshold of 10–20 % is sufficient to protect against immune dysregulation after viral challenge [202]. The estimated 3-year survival for patients with confirmed FHL in the HLH-94 study was about 50 % [85] and similar numbers have been reported in a recent single-center study of 48 patients [144]. However, the use of reduced intensity conditioning regimes (RIC) using agents such as Fludarabine, Melphalan in combination with Alemtuzumab sertherapy to effect T cell depletion may have significant benefits and can improve survival and disease free outcomes for all HLH forms [36, 124]. New targeted immunotherapeutic approaches are needed for the better control of the severe immune dysregulation prior to HSCT. Concerns

regarding the neurocognitive outcome following HSCT for HLH remain with a significant proportion of children showing long term cognitive and psychosocial difficulties despite the absence of significant motor defects [93]. The reasons for these problems need to be investigated in more details.

5.3 Autoimmune Lymphoproliferative Syndrome

(ALPS-FAS, ALPS-FASLG, ALPS-CASP10, CEDS, RALD, FADD deficiency, CTLA4 deficiency)

5.3.1 Definition

Autoimmune lymphoproliferative syndrome (ALPS) (OMIM*601859) is a disease of disturbed lymphocyte homeostasis [181]. Chronic non-malignant lymphoproliferation, various autoimmune manifestations (mainly autoimmune cytopenias) and an increased incidence of lymphoid malignancies are hallmarks of the disease. Most patients harbor mutations in genes, which regulate the extrinsic, Fas (CD95) mediated, apoptotic pathway (*FAS*, *FASLG* and *CASP10*). Nonetheless, the genetic basis remains unknown in a relevant number of patients, suggesting also alternative pathways of disease pathogenesis. As proof of principle, a few patients with lymphoproliferation and autoimmunity were found to carry mutations in *NRAS* and *KRAS,* affecting the intrinsic apoptotic pathway. This variant of ALPS has recently been summarized as RAS-associated autoimmune leukoproliferative disease (RALD; OMIM*614470). Moreover, chronic lymphoproliferation and cytopenias may also be the leading clinical manifestation in other defined primary immunodeficiencies (e.g. combined immunodeficiencies, XLP, ICOS, LRBA deficiency, CTLA4 deficiency or PKCdelta and PI3Kdelta associated immunodeficiency), but also in hematological (e.g. Evans syndrome) and rheumatological disorders (e.g. systemic lupus erythematosus, SLE) significant phenotypic overlap has been described [106, 176].

5.3.2 Etiology

The Fas death receptor pathway is crucial for lymphocyte apoptosis induction [8, 168] and defects in the molecular machinery of this and probably other extrinsic and intrinsic pathways of lymphocyte apoptosis are the pathophysiological basis of ALPS [65, 170]. Fas is a member of the death receptor family, a family of transmembrane proteins containing similar intracellular death domains (Fig. 5.4). Activation of Fas by binding of its ligand (FasL/CD95L) requires formation of homotrimers of both molecules [153]. Their interaction mediates formation of the death inducing signaling complex (DISC), which is formed by interaction of the death domains of Fas trimers with the adaptor protein FADD and subsequent recruitment and activation of the proteases caspase 10 and 8 [168]. These molecules cleave multiple downstream targets including

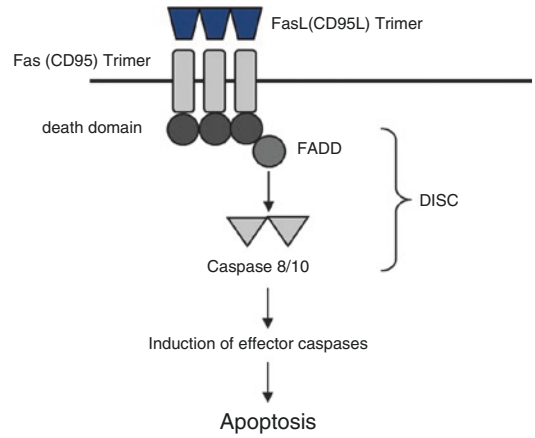

Fig. 5.4 Simplified overview of the CD95 mediated apoptosis pathway. Both FasL and its receptor Fas need to be trimerized to be activated. Upon interaction a so called „death-inducing signaling complex" – DISC is initiated. This complex consists of the trimerized death domain, the adaptor molecule FADD (Fas-associated death domain) and activated Caspase 8 (also called FLICE-1) and Caspase 10 (FLICE-2). This complex activates effector caspases which then further mediate the induction of apoptosis

effector caspases that induce the death of the cell. Apart from this receptor-mediated "extrinsic" pathway of lymphocyte apoptosis, an "intrinsic" pathway triggered by cytokine deprivation, DNA damage or treatment with cytotoxic drugs has been described [137, 142]. This "intrinsic" pathway is dependent on the induction of mitochondrial enzymes. Members of the bcl-2 family of proteins such as BIM are the key molecules involved. Disturbed intrinsic apoptosis can also cause an ALPS phenotype [137, 142].

Fas is highly expressed on activated B and T cells, which appear to take a different differentiation pathway in the absence of Fas signaling. Accumulation of such abnormally differentiated cells due to impaired death leads to chronic enlargement of lymphoid tissues, in particular lymph nodes, liver and spleen [109]. Both B and T cells accumulate, but the most characteristic lymphocyte population in patients with ALPS are CD4-CD8- "double negative T cells" that express an α/β T cell receptor (DNT cells) [19]. Neither the origin of these cells nor their differentiation pathway in vivo is fully understood. Since DNT cells are polyclonal and express markers of terminally differentiated T cells, linear differentiation from formerly single positive T cells failing to undergo apoptosis has been suggested [20, 27]. However, a more recent study suggests that DNT resemble a unique T cell subset, which originates from both CD4+ and CD8+ cells and have features of terminally differentiated effector memory T cells (TEMRA), but are CD27+CD28+KLRG1+ and do not express the transcription factor T-bet [163]. DNT cells may contribute to the pathogenesis of ALPS by producing high amounts of IL-10 and other Th2 cytokines favoring the production of autoantibodies [66, 114]. However, increased DNT cells are not exclusively observed in patients with defects of the Fas apoptotic pathway and elevated numbers may also be observed in patients with lymphoproliferation and autoimmune cytopenias of undetermined genetic cause [162]. Only markedly elevated DNT (>8 %) are clearly associated with the presence of *FAS* mutations [162]. B cell differentiation is also altered in the absence of Fas and data from mouse models have shown an impaired germinal center reaction leading to inappropriate survival of autoreactive B cells [80, 164].

Due to advances in the immunological and genetic understanding of the disease, the classification of ALPS has recently been revised [143]:

ALPS-FAS represents the largest subgroup and summarizes all patients who harbor germline mutations in the *FAS* (OMIM*134637) gene. Most patients carry heterozygous mutations (formerly referred to as ALPS type Ia), leading either to decreased Fas expression and thus haploinsufficiency or to expression of dominant negative Fas receptors [105]. In 75 % of cases the mutation is located within the intracellular death domain [186]. The penetrance of the disease is highly variable even within families, pointing towards a role of additional intrinsic or extrinsic factors, which may alter the phenotype. As proof of principle it has been observed that occurrence of a second somatic *FAS* mutation or somatic loss of heterozygosity (LOH) can aggravate the clinical manifestation in some patients [81, 117]. The most severe phenotype of ALPS has been observed in patients with homozygous germline mutations in *FAS* (formerly described as ALPS Type 0) [170, 207].

ALPS-sFAS refers to patients with somatic mutation in *FAS* (about 15 % of patients with *FAS* mutations) [51, 86]. In these patients the mutation can only be detected in sorted DNT, which harbor the mutation to nearly 100 % due to their Fas dependent accumulation [86]. Clinically the phenotype is not distinguishable from patients with germline mutations (ALPS-FAS). However, *in vitro* analysis of FasL induced apoptosis of T cell blasts is normal in most ALPS-sFAS patients [86].

ALPS-FASLG summarizes a small subgroup of patients with mutations in the gene encoding the FAS ligand (formerly ALPS type Ib and c). So far, only germline mutations have been reported [47, 119, 220]. The first described patient had a heterozygous dominant negative mutation, lacked DNT cells,

had no splenomegaly and presented rather with features of SLE [220]. Later, two patients with homozygous mutation in *FASLG* (OMIM*134638) were reported [47, 119]. The clinical phenotype of autoimmune cytopenias and lymphoproliferation was similar to ALPS-FAS. In addition, one patient suffered from recurrent bacterial and viral infections [47]. In vitro apoptosis studies are normal in ALPS-FASLG and sFasL (typically elevated in ALPS-FAS) is not detectable in null mutants [119].

ALPS-CASP10 refers to a small group of patients with mutations in the gene coding for caspase 10 (formerly ALPS IIb) (*CASP10*; OMIM*601762). The contribution of identified mutations to the clinical phenotype of ALPS is not fully understood. While the L285F and I406L mutations seem to result in impaired apoptosis, other initially reported variants were later identified as common polymorphisms [211, 226].

Other apoptotic pathway defects Mutations in *CASP8* (OMIM*601763) were formerly referred to as ALPS IIb. However, since the clinical phenotype of these patients is more severe and includes a profound immunodeficiency due to activation defects of T and B cells, caspase-8 deficiency has been removed from the current ALPS classification and has been termed **Caspase-Eight Deficiency State (CEDS)** [143].

ALPS related features combined with severe bacterial and viral infections were also identified in a consanguineous kindred with homozygous missense mutations in *FADD* (OMIM*602457), which encodes the Fas-associated death domain protein (FADD) [24]. Although impaired Fas mediated apoptosis has been observed in vitro, **FADD deficiency** is not included in the current ALPS classification.

In addition, there is a significant number of patients with autoimmunity, lymphoproliferation and elevated DNT cells in whom no mutation can be found in known molecules of the Fas apoptotic pathway [162, 169]. These patients were formerly referred to as ALPS III and more recently as **ALPS-U** (undetermined), if Fas mediated apoptosis induction is defective or as ALPS phenotype if apoptosis is normal [143]. In most of these patients, there is no defect in Fas mediated apoptosis, indicating that defects in other intrinsic and extrinsic pathways of apoptosis might contribute to the clinical onset of ALPS.

As proof of concept, patients with activating *NRAS* (OMIM*164790) or *KRAS* (OMIM*190070) mutations leading to a defect in "intrinsic" apoptosis induction have been described with features of ALPS and significant propensity to hematopoietic tumors [137, 142]. This condition is now termed **RAS-associated autoimmune leukoproliferative disease (RALD)** [143].

5.3.3 Clinical Manifestations

The phenotype of ALPS is highly variable. Onset of disease ranges from birth to adulthood, but usually occurs within the first 2–5 years of life [169, 186, 187]. The typical presentation in patients with mutation in *FAS* includes features of lymphoproliferation, in many cases accompanied by autoimmune cytopenia of one or more cell lineages. Patients from the originally published National Institutes of Health (NIH) cohort presented with lymphadenopathy in >90 %, splenomegaly in 88 % and hepatomegaly in 72 %. Coombs positive anemia occurred in 51 %, autoimmune thrombocytopenia in 47 % and neutropenia in 23 % of the patients [186]. Autoimmune cytopenia may also be the first manifestation of the disease in the absence of lymphoproliferation. Therefore, any patient with unexplained autoimmune bi- or tricytopenia ("Evans syndrome") should be investigated for ALPS [179, 200]. Aside from hematological symptoms, many other signs of autoimmunity like urticarial rashes, hepatitis, uveitis, thyroiditis or glomerulonephritis have been described. ALPS might therefore clinically mimic symptoms of SLE. The risk to develop malignancy is estimated to be around 10–15 % for ALPS-FAS patients and is mainly

due to B-cell lymphomas [136, 195]. The majority of ALPS patients do not suffer from an increased susceptibility to infections, but those who underwent splenectomy have a high risk for overwhelming sepsis despite appropriate antibiotic prophylaxis [136].

Lymphoproliferation leading to local anatomic obstructions and autoimmune neutropenia may also predispose to bacterial infections in some patients. Although many ALPS patients have elevated IgG levels, about 10 % develop symptomatic hypogammaglobulinemia over time [164].

5.3.4 Diagnosis

The NIH defined the first diagnostic criteria for ALPS in 1999. These criteria required the presence of chronic, non-malignant/non-infectious lymphadenopathy and/or splenomegaly, elevated DNT cells and a reduced apoptosis response of T cell blasts to Fas stimulation in vitro [196].

Over the years, several clinical observations and new insights into the pathophysiology and genetics of ALPS increasingly challenged these original criteria: (1) The clinical penetrance of ALPS is highly variable and clinical presentation without lymphoproliferation (e.g. Evans Syndrome) can occur [136, 179, 187]. (2) A relevant number of patients that are positive for the original NIH diagnostic criteria (including DNT cells) do not have mutations in the Fas apoptotic pathway [162]. Thus, a number of conditions including RALD and other genetically undefined diseases (e.g. SLE) can mimic the clinical phenotype [137, 142, 220]. (3) ALPS patients with somatic mutations in *FAS* or mutations in *FASLG* have normal in vitro apoptosis [51, 86, 119]. In addition, apoptosis testing is labor intensive, costly and only available at few specialized centers.

The recently revised ALPS diagnostic guidelines address these problems [143]. A pathological apoptosis test is no longer required, if other criteria (e.g. a proven mutation in *FAS*) are fulfilled. The guidelines now also include the evaluation for characteristic histological changes of lymph nodes (i.e. paracortical expansion with proof of DNT cells) and positive family history. Moreover, they include vitamin B12, IL10 and soluble FasL as new diagnostic biomarkers for the disease. While these biomarkers were originally identified in retrospective analyses of two large ALPS cohorts [31, 118], a more recent prospective study confirmed their a priori positive and negative predictive value also in an unselected cohort of patients with lymphoproliferation and autoimmune cytopenias [162]. In fact, in this study the combination of vitamin B12 (cut-off 1255 pg/mL) and sFasL (cut-off 559 pg/mL) was even more useful to predict or exclude *FAS* mutations than the determination of DNT, apoptosis studies or germline sequencing of the *FAS* gene [162]. Nevertheless, the determination of DNT in combination with analysis of their Fas expression remains useful for identification of patients with a second somatic genetic event such as LOH, leading to loss of Fas expression on DNT (Fig. 5.5) [81, 117].

5.3.5 Management

The clinical management of patients with ALPS is mainly focused on the problems of lymphoproliferation and autoimmunity. Patients with a probable diagnosis of ALPS should be clinically managed in the same way as patients with a definitive diagnosis [143].

While aggravations of autoimmune cytopenias frequently respond to short-term steroid treatment, chronic or refractory courses require the use of additional and steroid sparing agents [160, 201]. Although rituximab has been used successfully to treat refractory autoimmune cytopenias [161, 214], the generally increased susceptibility of ALPS patients to develop hypogammaglobulinemia (and the observed disturbed B cell development) should generally warrant caution with B-cell depleting therapies [164]. Mycophenolate mofetil (MMF) is another drug that has shown good response in the control of chronic autoimmune cytopenias and is generally well tolerated by patients [104, 159, 160]. But like other widely used immunosuppressants (e.g. azathioprine or cyclosporine) also MMF

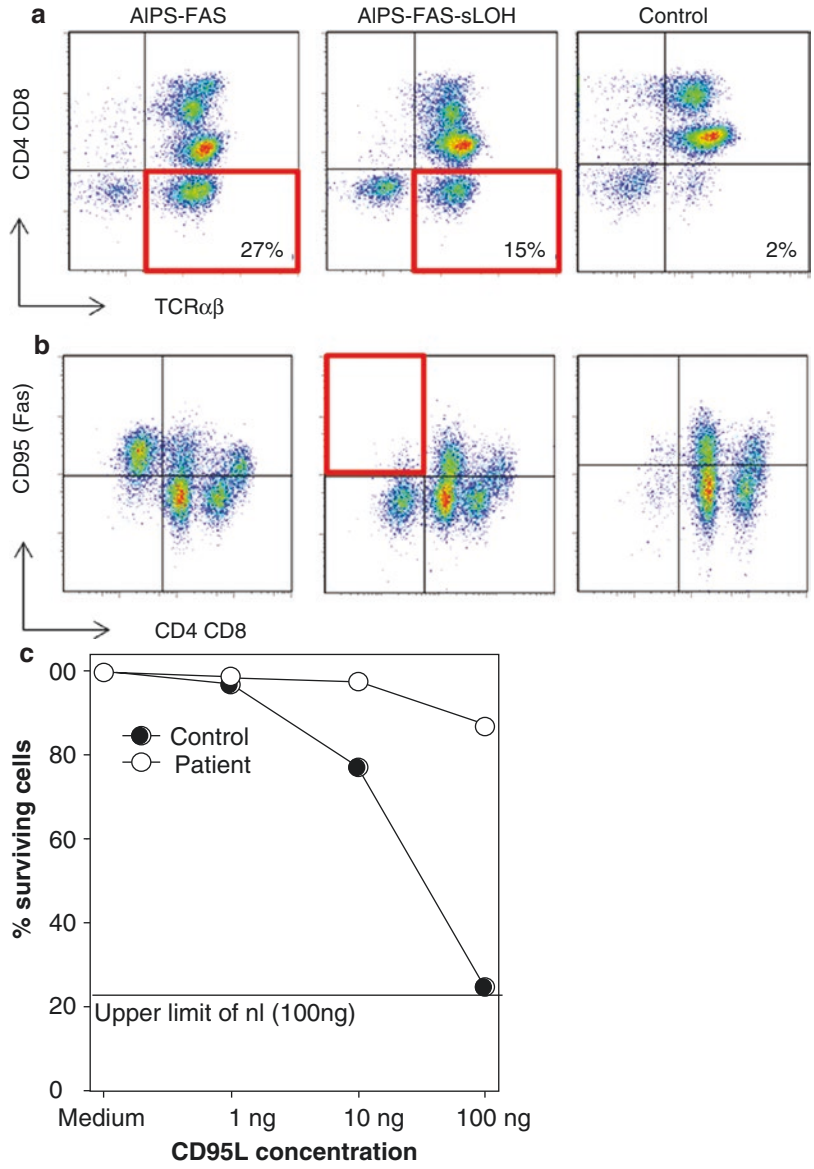

Fig. 5.5 (**a**) Flow cytometric evaluation of peripheral blood lymphocytes. In ALPS patients with germline mutation in *FAS* (ALPS-FAS) and germline plus additional somatic *FAS* mutation, resulting in loss of heterozygosity (ALPS-FAS-sLOH). The number of TCR a/b+CD4-/CD8- T-cells (DNTs) are elevated in both patients. (**b**) LOH results in decreased FAS expression. Pathological findings are highlighted in red. (**c**) Induction of apoptosis in lymphocytes via stimulation with FasL (CD95L). After ligation of Fas, T cell blasts of an ALPS-FAS patient show a reduced number of apoptotic cells in comparison to a healthy control. However, in patients with somatic *FAS* mutations (ALPS-sFAS) apoptosis analysis is frequently normal

does not reliably reduce the size of spleen or lymph nodes [159, 201].

In contrast, the mTOR inhibitor sirolimus was found to control not only cytopenias but also lymphoproliferation (including splenomegaly) in a small case series of steroid refractory patients with ALPS [199]. Since this report the use of sirolimus has been increasingly recommended (i.e. in patients with pronounced lymphoproliferation and FAS mutations) [198, 201].

Half of the patients from the originally reported NIH cohort have been splenectomized [186]. Indications for splenectomy included refractory cytopenias, rupture or simply tremendous size, which limits quality of life or planned pregnancy. However, more recent long-term data from a European cohort suggests that splenectomy should be avoided whenever possible, as splenectomized ALPS patients are at particular risk to develop overwhelming bacterial sepsis despite appropriate antibiotic prophylaxis [136]. The successful use of sirolimus might be beneficial to avoid splenectomy in ALPS-FAS patients.

Long-term monitoring of ALPS patients for lymphoma development remains a challenge. In many cases, repeated lymph node biopsy is warranted since imaging studies, including MRI or PET-CT, are not helpful in differentiating between benign and malignant lymphoproliferation [158]. HSCT can cure the disease and has been performed in some patients with very severe refractory cytopenias [184], but is usually only indicated in a small subgroup of patients with homozygous mutations in *FAS*. Overall, the life expectancy of patients with ALPS is not significantly reduced. Reported deaths were mainly due to sepsis after splenectomy, bleedings and lymphoma [136].

5.4 Chediak-Higashi Syndrome

5.4.1 Definition

Chediak-Higashi syndrome (CHS) is an autosomal recessive disorder (OMIM*214500), caused by homozygous or compound heterozygous mutations in the large lysosomal trafficking protein *LYST* (OMIM*606897) [134]. The human gene is located on chromosome 1q. Curiously, CHS-similar syndromes have been described in many mammalian species including cats, foxes and even killer whales, one of them become famous and was held in captivity as tourist attraction (“Chimo”) in British Columbia, Canada, but likely died early due to infectious complications [167].

5.4.2 Etiology

LYST stands for lysosomal trafficking regulator which plays an important role in steps like vesicle docking and vesicle fusion. Perturbations in specific steps during the formation, maturation and trafficking of melanosomes produce the recognizable albinism. In CHS, lysosomal proteins like MHC II and CTLA-4 and perforin are abnormally distributed leading to the formation of giant organelles and inclusion bodies [54, 212]. Analysis of cytotoxic T-cells suggest that the early steps of granule formation are normal. The defect is seen as the secretory granules mature [98]. In addition, LYST is likely to play a role in mediating intracellular membrane fusion (Fig. 5.1).

5.4.3 Clinical Manifestations

The phenotype may range from mild pigmentary dilution to complete albinism. Strikingly, hyperpigmentation in sun-exposed areas are misleading in some cases. It is also characterized by a bleeding tendency, progressive primary neurological impairment and severe immunodeficiency due to lack of natural killer cell function, resulting in recurrent pyogenic infection. According to reduced iris pigmentation photophobia, strabismus and decreased visual acuity may occur.

Neurological symptoms may include seizures, cranial nerve palsy and peripheral neuropathy. Children may die early due to severe bacterial infections. The majority of children progress to the so-called “accelerated phase” with fever, jaundice, lymphoproliferation, and pancytopenia [101]. In summary, children develop the full-blown picture of severe HLH.

A small but significant number of children have a relatively mild phenotype sometimes associated with residual function of LYST (hypomorphic mutations) [215].

5.4.4 Diagnosis

Diagnosis is suspected by the clinical phenotype with albinism. The ultrastructural characteris-

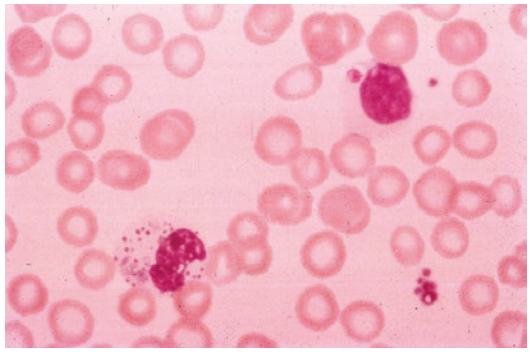

Fig. 5.6 Blood smear from a patient with Chediak-Higashi syndrome showing giant granules in the cytoplasm of leukocytes

tics – giant organelles with inclusion bodies – occur in virtually all granulated cells and can easily be recognized by light microscopy (Fig. 5.6). Neutrophils, eosinophils and basophils and even platelets may contain abnormal granules. Loss of T-cell and NK cytotoxicity results from inability to secret appropriate amounts of cytolytic proteins. Light microscopy of hair shafts may even help to differentiate between other immunodeficiencies with albinism, e.g. Griscelli syndrome type 2 (Fig. 5.7). MRI scanning may document brain and spinal cord atrophy. The human LYST gene is considerably large with 55 exons and mutations are scattered over the entire gene. In future, it is likely that whole exome sequencing will facilitate molecular diagnostics also in CHS as well as many other Mendelian disorders [10].

5.4.5 Management

HSCT is the only curative approach for those children [206]. Although numbers are limited, transplantation appears to be an effective therapy for correcting and preventing hematologic and immunologic complications of CHS. An unrelated donor may be a suitable alternative for patients without an HLA-matched sibling. Long-term follow-up suggests that HSCT does not prevent progressive neurological complications.

Eapen et al. reviewed the outcome in 35 children with CHS after transplantation [52]. The group was heterogeneously treated and matched sibling donors as well as unrelated donors were used. The overall survival after 5 years was about 60 % with clearly worse outcome when patients were transplanted in accelerated phase. This argues for early HSCT once the diagnosis has been established. The 10–15 % of patients with milder phenotypes may survive up to an age of 30–40 years.

5.5 Griscelli Syndrome Type 2

5.5.1 Definition

In 1978, Griscelli et al. described two unrelated patients, a girl and boy who had been presented with many clinical features of CHS, but without the giant organelles typically for CHS [78]. Despite normal numbers of B- and T-lymphocytes the patients showed hypogammaglobinemia.

Klein et al. reviewed the immunological findings and the clinical course of seven patients showing additional differences to CHS also in terms of the pigmentation defect [175]. The hair shafts show large clumps of pigment (Fig. 5.7).

Subsequently, linkage analysis and candidate gene sequencing revealed that homozygous mutations in the ras-associated protein 27 A (*RAB27A*) (OMIM*603868) located on chromosome 15 cause Griscelli syndrome type 2 (GS2) (OMIM*607624) [130].

5.5.2 Etiology

RAB27 is instrumental for proper exocytosis of cytotoxic granules and thus activity of CD8+ T-cells and NK cells are severely impaired in GS2 (Fig. 5.1). In the absence of functional RAB27, granules are correctly generated, but fail to detach from the microtubules [205].

Thus, a relatively late step in the endosomal pathway is impaired. Other forms of Griscelli syndrome (GS1 and GS3) comprise albinism,

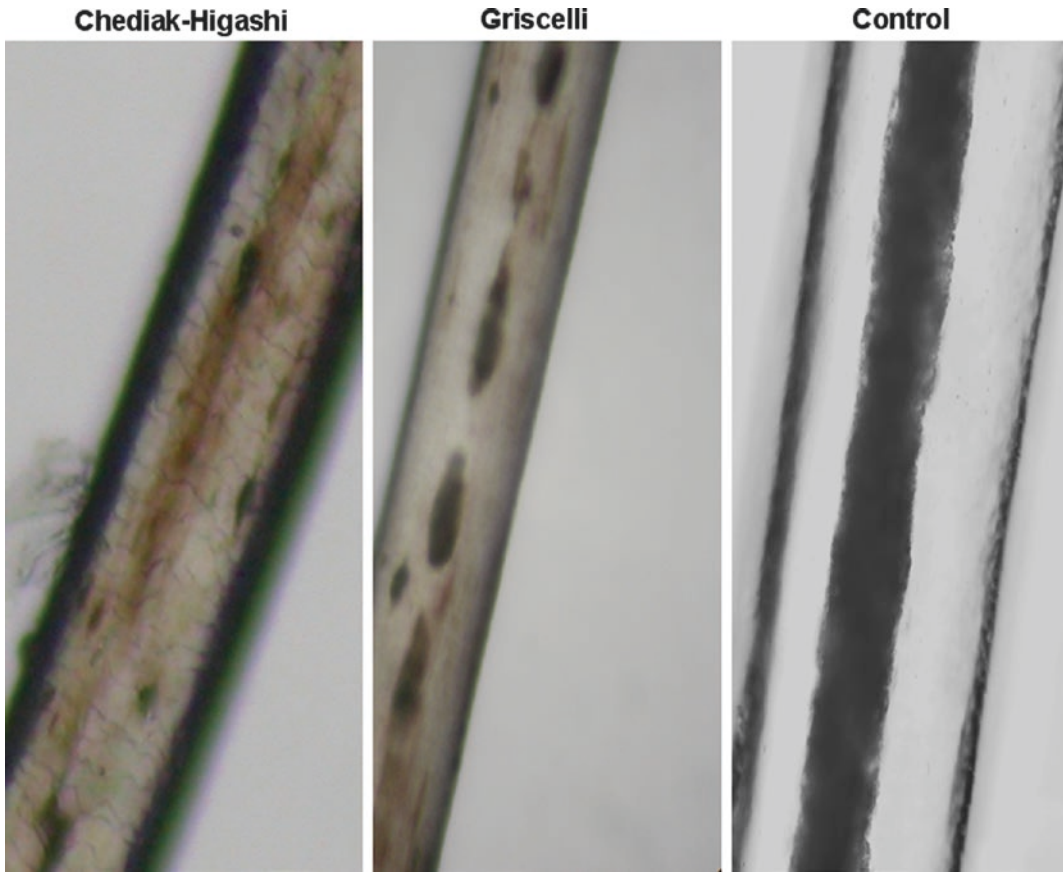

Fig. 5.7 Light-microscopic hair shaft analysis of Chediak-Higashi and Griscelli syndrome type 2, compared with hair shaft of a healthy control

but not the immunological anomalies leading to the extremely high risk for development of HLH.

5.5.3 Clinical Manifestation

The pigment dilution is usually more severe than in patients with CHS. Patients were described as having silvery gray hair and very light skin (Fig. 5.8). Some patients have serious neurologic problems, with spasticity, rigidity and convulsions, but this is inconsistently found. When progressing to HLH, CNS involvement as a result of brain infiltration is often described. The risk of HLH is particularly high in GS2 and may exceed that of CHS. Thus, prognosis is relatively poor and most patients die to HLH if not transplanted before.

Fig. 5.8 Patient with Griscelli syndrome type 2 presenting with silver-grey hair at eyelashes and eyebrows

5.5.4 Diagnosis

GS2 should be suspected in any child with oculocuteneous hypopigmentation. Hair shafts contain a typical pattern of uneven accumulation of large pigments. Microscopy of hair shafts is a simple diagnostic test and may substantiate clinical observations. Patients usually have normal numbers of B- and T-lymphocytes and no platelet defect. The characteristic hallmark is the inability of $CD8^+$ T-lymphocytes and NK cells to lyse target cells. Lymphocyte proliferation in response to non-specific stimuli e.g. (PHA) is not impaired.

5.5.5 Management

HSCT is the only curative treatment for GS2. Due the limited number of patients no standardized procedure in terms of conditioning or donor selection has been established. Pachlopnik-Schmid reviewed a single center experience from 10 patients [146]. Four out of the seven surviving patients were cured without neurological sequelae whereas three patients succumbed due to HLH relapse or the HSCT procedure, respectively. Beside that report many small case series or single case reports document effectiveness of HSCT. It is reasonable to assume that outcome of GS2 patients may be in the same range as in other inherited HLH syndromes.

5.6 Hermansky-Pudlak Syndrome

(Type 2, Type 9, Type 10)

5.6.1 Definition

Hermansky-Pudlak syndrome (HPS) defines a group of nine different genetic disorders associating hypopigmentation with bleeding disorders. One of those nine syndromes, HPS2 (OMIM*608233), shows severe immunodeficiency with congenital neutropenia and, like the other syndromes discussed in this chapter, defective cytotoxicity of $CD8^+$ T-lymphocytes and NK cells. Hence, also HPS2 can be regarded as an inherited HLH syndrome. Recently, an HPS-like primary immunodeficiency disease was described in a case (HPS9; OMIM*614171), caused by homozygous mutation in the gene encoding palladin (BLOC1S6; OMIM*604310) [9]. Very recently, a new type of HPS has been explained, in which mutation in the *AP3D1* gene, leads severe neurologic disorder and immunodeficiency in addition to oculocutaneous hypopigmentation, which could be named as HPS10 [5].

5.6.2 Etiology

HPS2 is caused by mutations in *AP3B1* (OMIM*603401), encoding the ß-subunit of AP-3 which is an endosomal adapter protein [89]. Granules fail to travel towards the immunological synapse. Loss of microtubule-mediated movement of perforin- and granzyme-containing lytic granules results in profound loss of CTL-mediated killing. Interestingly, AP3 also regulates the neutrophil elastase which may explain the neutropenia in those patients. The cell type specific AP3 expression in pulmonary epithelial cells and osteoclasts may explain the bone abnormalities and progressive pulmonary fibrosis in a significant number of patients. Impaired pulmonary repair mechanisms are thought to be the main contributing factor.

5.6.3 Clinical Manifestation

The combination of bleeding abnormalities, neutropenia and oculocutaneous hypopigmentation may guide diagnostic procedures; however, some patients were misclassified as GS2 before genetic identification revealed occurrence of HPS2. Facial dysmorphia, hepatosplenomegaly and susceptibility to bacterial infections are typical clinical symptoms described in the limited number of patients so far. The neutropenia usually responds to G-CSF treatment, the bleeding tendency shows great variability among the patients. In addition, some patients have a history of only few, mild

infections whereas other succumbed due to this complication. Pulmonary fibrosis may develop early in childhood and can lead to serious sequelae. In fact, the fatal combination between fibrosis and pneumonia jeopardize patients with HPS2 substantially [72, 216].

The risk for development of HLH is not fully clear yet but a recent comprehensive survey of 22 HPS2 patients only 1 full blown HLH and 2 incomplete HLHs were found. Thus, the authors conclude that the risk for HLH is obviously lower than in GS2 or Chediak-Higashi syndrome [97].

5.6.4 Diagnosis

AP-3 deficiency resulted in increased surface expression of the lysosomal membrane protein CD63. CD63 belongs to the so-called family of tetraspannins, cell surface proteins characterized by four hydrophobic domains. Thus, flow cytometry showing bright CD63 expression together with the clinical triad of albinism, neutropenia and bleedings may lead to the diagnosis which, however, should by genetically verified [49]. Major lymphocyte subset values are within normal limits. Immunoglobulin levels as well as antibody response to vaccines are unremarkable.

5.6.5 Management

Given the apparently lower risk of HLH the preemptive HSCT cannot be recommended to date. Neutropenia can be well controlled by G-CSF but if this may trigger development of HLH is not clear yet. Control of bleedings and infections should be done according to common procedures. Patients should be monitored closely in order to detect impairment of the lung function.

5.7 Other Immunodeficiencies with Hypopigmentation

(p14 deficiency, VICI syndrome)

5.7.1 Definition

Recently, an even more complex multisystem disorder, the VICI syndrome (OMIM*242840), was added to the list of diseases with immunodeficiency and hypopigmentation [48]. In addition to immunodeficiency, it comprises defects of the corpus callosum, pontine and cerebellar hypoplasia, psychomotoric retardation, seizures, cardiomyopathy, hypopigmentation and cataracts [63]. In contrast, the few patients described with p14 deficiency (OMIM*610798) show, beside oculocutaneous hypopigmentation, short stature, severe neutropenia, defective cytotoxic T-cell function and humoral immunodeficiency [21].

5.7.2 Etiology

VICI is caused by recessive mutations in *EPG5* (OMIM*615068), a key regulator gene of autophagy and implicated in the formation of autolysosomes [39]. It results in a severe block of autophagosomal clearance in the tissues where EPG5 is expressed, e.g. brain, heart and bone marrow. Thus, VICI syndrome can be regarded as a multisystem disorder of defective autophagy. In the immune system, autophagy is highly relevant for delivery of microorganisms to the lysosomes, as well as T- and B-cell survival and proliferation. P14 (OMIM*610389) is an adapter molecule (*LAMTOR2*) involved in the configuration of the endosomal compartment. Biallelic mutations within its 3' untranslated region (UTR) suppresses proper processing of p14 mRNA. It serves as an instructive example that even mutations outside the coding region cause a monogenic disease [21, 108]. Strikingly, in contrast to the Chediak-Higashi or Griscelli syndrome patients, there is no defect in granule release in cytotoxic T-cells. The underlying mechanism of their defective function remains unexplained so far.

5.7.3 Clinical Manifestation

Agenesis of corpus callosum, cerebellar and pontine hypoplasia, hypopigmentation, cardiomyop-

athy – either dilated or hypertrophic – and a variable degree of immunodeficiency with recurrent infections may lead to early diagnosis of VICI syndrome. The prognosis is rather poor with early deaths due to cardiac failure or severe infections.

5.7.4 Diagnosis

There are several differences on clinical and laboratory findings of p14 deficiency and other immunodeficiencies associated with oculocutaneous hypopigmentation (Table 5.2). The four patients with p14 deficiency came from a large white Mennonite index family. They were presented with short stature, coarse facial features and recurrent bronchopulmonary infections. Their absolute neutrophils counts were <500/µl. Memory B-cells were reduced with consistently reduced serum IgM levels. Two of the four patients reported developed low IgG levels during adolescence requiring substitution therapy. Overall, assessment of the full phenotypical spectrum is somewhat limited due to the low numbers of patients identified yet. Immunodeficiency seems to be milder than in other syndromes described in this chapter.

5.7.5 Management

The multi-systemic nature of the disease prevents aggressive therapeutic approaches like HSCT. Patients with p14 deficiency were noted to have reduced memory B-cells and specific antibodies upon vaccination were partially missing. IgG substitution might therefore be indicated in selected individuals [21].

5.8 X-linked Lymphoproliferative Syndromes

(SAP deficiency, XIAP deficiency, MAGT1 deficiency)

5.8.1 Definition

The first EBV-lymphoproliferative disease was originally described as "Duncan Syndrome" more than 35 years ago [156]. In the initial kindred described by Purtillo ("Purtillo-Syndrome") only males were affected with fulminant infectious mononucleosis and lymphoproliferation leading to subsequent HLH and death.

Up to now, there are three different X-chromosome encoded genes [*SAP* or *SH2D1A* (OMIM*300490); *XIAP* (OMIM*300079) and the magnesium transporter *MAGT1* (OMIM*300715)], whose loss-of function mutations were associated with EBV-triggered lymphoproliferation as a characteristic clinical hallmark. Mutations in the above-mentioned genes lead to X-linked Lymphoproliferative Syndrome 1 (XLP1) (OMIM*308240), XLP2 (OMIM*300635), X-Linked Immunodeficiency associated with Magnesium defect, EBV infection, and Neoplasia (XMEN) (OMIM*300853), respectively. More recent observations, however, suggest that the

Table 5.2 Differential diagnosis of oculocutaneous hypopigmentation and immunodeficiency

	Griscelli syndrome, type 2	Chédiak-Higashi syndrome	Hermansky-Pudlak syndrome, type 2	p14 deficiency	VICI syndrome
Oculocutaneous hypopigmentation	+	+	+	+	+
Immunodeficiency	+	+	+	+	+
Developmental delay	–	+	–/+	–	+
Neutropenia	–	–	+	+	–/+
Bleeding disorder	–	+	+	–	–

clinical phenotype is much broader, e.g. XIAP deficiency is not limited to lymphoproliferation, but also includes an increasing spectrum of autoinflammatory conditions, i.e. variants of inflammatory bowel disease [145, 165, 166, 189, 219].

5.8.2 Etiology

SAP directly associates with members of the signaling lymphocytic activation molecule (SLAM) family and the protein tyrosine kinase FynT. Absence of functional SAP also perturbs SLAM-SAP signaling outcome in a manner that leads selectively to augmented Th1 cytokine production [87, 127]. There is a remarkable parallelism to the function of the IL2-inducible kinase (ITK, see below) whose inactivation also affects Th2 response [88, 110]. The uncontrolled Th1 response in combination with hyperproliferation of CD8+ cells and interferon- gamma production may contribute significantly to the parenchymal damage seen in XLP1 patients. Despite hyperproliferation, CD8+ and NK cytotoxicity is reduced when SAP is affected by loss-of function mutation. In addition to its physiological role in acquisition of T-cell effector functions, the SAP-SLAM interaction plays a critical role for the generation of T-cell dependent humoral immune responses [111] and thus may explain the low amounts of immunoglobulins secreted from B-cells of XLP1 patients. NKT cells cannot be developed when SAP expression is absent and the generation of long-lived plasma cells is also severely impaired.

The pathogenesis of XIAP deficiency has initially been linked with the ability of XIAP to inhibit apoptotic caspases, presumably leading to an increased apoptosis of patient derived lymphocytes, i.e. invariant natural killer T-cells (iNKT-cells) [171]. However, other reports have also shown that activation induced cell death and iNKT cells can be within normal limits in XIAP deficient patients [125, 189]. More recently, a second function of XIAP was published demonstrating that XIAP is crucial to facilitate innate immune signaling downstream of the bacterial sensors NOD1 and 2 [41–43]. NOD2 induces NF-kB activation leading to the production of various cytokines (e.g. TNFα, IL-1β, IL6 and IL-8) [42]. Disease-causing mutations in various areas of *BIRC4* including the RING and BIR2 domains result in an impaired NF-kB response after NOD2 activation [41]. Interestingly, certain mutations in *NOD2* itself are associated with the development of Crohn's disease or an autoinflammatory condition called Blau syndrome (associated with arthritis, uveitis and granulomatous skin lesions). An increasing numbers of XIAP deficient patients are reported to suffer from overlapping autoinflammatory symptoms [145, 189, 219, 223]. MAGT1 encodes for a membrane-associated transporter which is highly selective for Mg2+ and is important for delivering Mg^{2+}as a second messenger for PLCγ1-dependent T cell receptor signaling. Loss of function of MAGT1 abrogates Mg2+ flux in response for stimulation of the T-cell receptor. MAGT1 acts downstream of PLCgamma1 as early events in TCR signaling like phosphorylation of LAT and ZAP70 are preserved [110].

5.8.3 Clinical Manifestations

When not encountered to EBV, boys with SAP deficiency seem to be apparently healthy. Once infected by EBV, clinical consequences comprise fever, cytopenia, and hepatosplenomegaly. Aplastic anemia, vasculitis, development of bronchiectasis and lymphoid granulomatosis are more infrequently seen. Some patients develop severe signs of autoimmunity with colitis and psoriasis [62]. HLH occurs in more than 50 % of the cases, and in a recent collection of 33 SAP-deficient boys, 18 of them developed severe HLH from which 11 subsequently died [145]. Some other rare clinical manifestations have also been described: aplastic anemia, pulmonary lymphoid granulomatosis (Table 5.3). Clinically spoken, XLP1 (and XLP2, see below) should be suspected in any male patient in whom severe infectious mononucleosis progresses to HLH.

Patients with XIAP deficiency were initially identified among patients with XLP but normal

Table 5.3 Clinical and laboratory findings of SAP, XIAP and MAGT1 deficiencies

Feature	SAP deficiency	XIAP deficiency	MAGT1 deficiency
Clinical presentation			
HLH	Frequent	Very frequent	Not reported
Fever, hepatospenomegaly	Yes	Yes	Yes
Hypogammaglubinemia	Yes	Yes	Yes
Malignant lymphoma	Yes, mostly Burkitt	No	Yes
Aplastic anemia	Yes	No	No
Vasculitis	Yes	No	No
Genetics and function			
Locus	Xq25	Xq25	Xq21
Gene	SH2D1A	BIRC4	MAGT1
Protein	SAP	XIAP	MAGT1
Expression pattern of wt	T, NK, NKT cells, platelets, some neuronal cells	widely expressed in many human cell types	widely expressed in many human cell types
Signaling pathway affected	TCR, SLAM family receptors, FynT,	Apoptosis and survival, TGFbeta, TNF, NFkappaB, Fas	TCR
Cellular immune defects			
CD4+	Th2 lineage differentiation and function reduced	AICD increased	Low inverted
CD8+	Cytotoxicity reduced	AICD increased	CD4/CD8 ratio
NK cells	Cytotoxicity reduced,	Normal	Low inverted CD4/CD8 ratio
NK cells	Strongly reduced or absent	Conflicting data in literature	Normal
B cells	Antibody production, isotype switching and affinity maturation reduced, strong reduction of memory cells	AICD increased	Normal

sequence in *SH2D1A* [171]. Following this report, it has been debated whether XIAP deficiency is correctly classified [122, 145]. While SAP and XIAP-deficiency both predispose to EBV-induced HLH, XIAP deficient patients apparently do not share the same risk as SAP-deficient patients of developing lymphoma [122, 145, 189, 223]. EBV-driven HLH is often an unrelenting disease with significant mortality. The term "HLH" refers to the characteristic morphological accumulation of lymphocytes and macrophages in the bone marrow, which phagocyte own erythrocytes or thrombocytes. Further, laboratory signs may include high ferritin, elevated sCD25 levels, hypertriglycinemia, and absent NK cell activity. Patients may deteriorate rapidly. Notably, typical phagocytosis may be missed in initial bone marrow smears although all other clinical and laboratory signs favor diagnosis of HLH. At least one third of the patients with XLP1 and XLP2 develop dys-and hypogammaglobulinemia. When boys survived initial encounter with EBV and fulminant mononucleosis, they often develop humoral immunodeficiency sometimes misinterpreted as CVID. The risk of developing lymphomas in XLP1 patients has been estimated to be nearly 200 times greater than that in the general population, also exceeding the risk in other primary immunodeficiencies, for example, Wiskott-Aldrich syndrome [76]. About 30 % of all SAP-deficient patients develop malignant lymphomas, with extranodal Burkitt's lymphoma as being the most common subtype. The ileocecal localization is typical for those

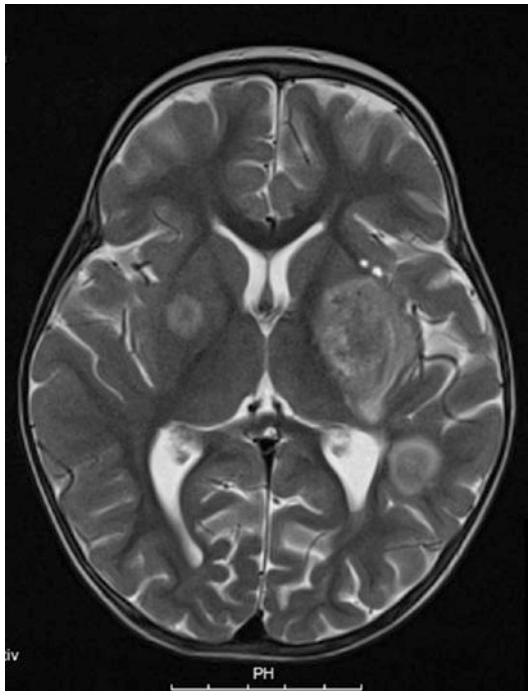

Fig. 5.9 CNS involvement of EBV-driven lymphoproliferation in a SAP-deficient patient

cases, but other localizations including the CNS may occur as well (Fig. 5.9) [145].

Accordingly, abdominal complains nausea, vomiting, diarrhea are typical clinical symptoms. Clinical suspicion of appendicitis and surgical intervention may lead to the diagnosis of Burkitt lymphoma on the basis of XLP1.

Interestingly, some patients demonstrate no evidence of EBV infection, indicating that loss of SAP itself may prone to lymphoma development [26, 197]. It is conceivable that impaired immune-surveillance by T- and NK-cells may be linked to this inherent lymphoma risk.

When compared to XLP1, XIAP-deficient boys display several important clinical differences: HLH seems to be even more prevalent (up to 80%) than in XLP1 patients, HLH occurs recurrently, which is rarely seen in XLP1 patients in whom single and often fatal HLH episodes are described more often. In addition, XLP2 patients do not have lymphoma-proneness associated with XLP1, but instead show chronic colitis with hemorrhagic diarrheas or rectal bleeding in approximately 20% of the patients [145]. They also show remarkable cytopenia and splenomegaly even in the absence of full-blown HLH. Because of the high prevalence of HLH, some authors prefer the term "X-linked familiar HLH" to underline the predominant clinical feature of the disease [122].

However, very recent reports have also highlighted the occurrence of additional inflammatory manifestations in XIAP deficiency, including early and late-onset inflammatory bowel disease, liver disease, periodic fevers, arthritis and uveitis [145, 189, 219, 223]. In a European cohort reported by Speckmann et al., 17 out of 25 symptomatic patients (68%) had presenting manifestation other than HLH [189].

Due to the limited number of patients described, the full clinical phenotype of MAGT1 deficiency is only beginning to emerge. The patients identified so far showed respiratory tract infections, viral pneumonia, chronic diarrhea and – importantly – chronic EBV infection and EBV associated lymphoma. HLH has not been reported yet.

5.8.4 Diagnosis

In XLP, EBV virus load in plasma is elevated but usually not up to the level to several millions/mL as it can be seen in ITK-deficiency (see below). EBV antibodies against EBV nuclear antigen (EBNA) are frequently absent. XLP1 patients often have a marked reduction of CD27 memory B-cells, but -generally spoken- immunophenotypic analysis of lymphocyte subpopulations are rather unspecific. Lack of iNKT cells, impaired NK cytotoxicity and highly activated CD8+ T-cells are usually seen.

Analysis of XIAP expression and activation induced cell death of patient derived lymphocytes are frequently used as screening assays for XIAP deficiency [121, 171, 189, 223]. However, apoptosis tests are highly variable and protein expression can be normal in some patients with missense mutations [189]. Yet, flow cytometry with membrane permeable antibodies against SAP or XIAP are a rapid and inexpensive diagnostic tool (Fig. 5.10). Investigations of the

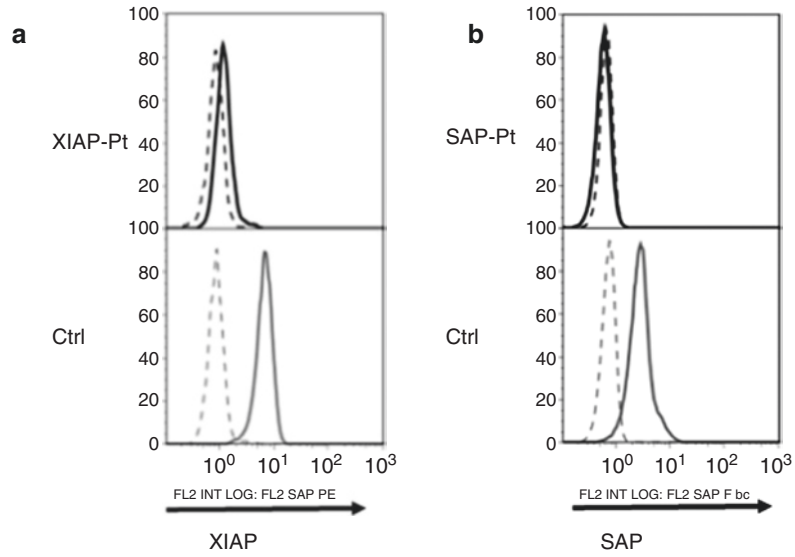

Fig. 5.10 Flow cytometry screening for intracellular XIAP (**a**) and SAP (**b**) expression allows for a fast an efficient screening in patients with suspected XLP1/2. *Bottom panel* represent normal XIAP/SAP expression in a healthy control (Ctrl). The *dashed line* represents the isotype control. Caution is warranted as patients with missense mutations or mutations not affecting the binding region of the diagnostic antibody (i.e. the BIR3 or UBA domain of XIAP) might not be detected. In doubt, genetic analysis is mandatory to exclude the diagnosis

NOD2 axis in monocytes by flow-cytometry has also been described as a reliable functional screening test, including those patients with partial XIAP protein expression [4].

Alternatively, targeted PID gene or whole exome sequencing will be become the method of choice for diagnosis of many PIDs.

The iNKT cell numbers, typically reduced or absent in SAP and XIAP deficiency, seem to be normal in MAGT1-deficient patients.

5.8.5 Management

HLH should be treated according to established guideline with etoposide, dexamethason and cyclosporine A. Immunoglobulin replacement therapy may ameliorate the susceptibility to bacterial infections, but will not be effective against lymphoma development or other XLP manifestations. B-cell lymphomas are sometimes overwhelmingly rapid-growing and may resistant to current conventional approaches for treatment of B-cell lymphoma, including rituximab [128]. In XLP1, allogenic HSCT is the method of choice. In a large, international effort, Booth et al., collected outcome data from 32 centers worldwide that oversee children with primary immunodeficiencies and performed HSCT [25]. They identified 43 XLP1 patients who had received HSCT. Thirty-five survived the procedure with a median follow- up of 52 months. Most importantly, all patients without HLH (n = 27) survived HSCT, whereas this rate dropped down to under 50 % when HLH was present at some point before and during transplant. For details of the donor selection (four haplo donors with good outcome) and conditioning regimens, which consisted of either myeloablative and reduced-intensity approaches (one half each) [25]. The course of the non-transplanted patients was highly variable without apparent correlation to the specific side of mutation in the *SH2D1A* gene. Seventy percent of those patients received immunoglobulin replacement therapy. As in transplanted patients, HLH was associated with rapid decline and death, especially in younger boys. The mortality rate of HLH in the non- transplanted group was higher than 80 %. This report doubtlessly demonstrated that XLP1 has a very poor prognosis when

left untransplanted. Thus, the current data suggest early transplantation from any available donor soon after definitive genetic diagnosis has been established.

In contrast, the value of HSCT in XIAP deficiency is uncertain. Marsh et al. summarized their experience from 19 patients of which 16 presented with a XLP phenotype [123]. The mortality was high, i.e. in patients who received myeloablative conditioning prior to the procedure. It remained unclear whether the high incidence of reported complications was due to specific factors in the pathogenesis of XIAP deficiency or the low remission rate from HLH prior to HSCT. Nonetheless, HSCT is the only currently available curative treatment option and has been successfully performed not only in XIAP deficient patient with XLP but also Crohn's disease phenotype [123, 189, 219]. However, the reported good long-term outcome in several untransplanted XIAP deficient patients and a confirmed low risk for lymphoma development also warrants general caution with this procedure. At presence, more prospective natural history data on the variable clinical phenotypes of XIAP deficiency needs to be obtained to improve therapeutic recommendations for this disease. The same holds true for MAGT1 deficiency which has only been described in three (two of which were siblings) patients yet.

5.9 Autosomal-Recessive Lymphoproliferative Syndromes

(ITK deficiency, CD27 deficiency)

5.9.1 Definition

Defects of the IL2-inducible T-cell kinase (*ITK*) (OMIM*186973) can mimic the clinical phenotype of XLP, but are inherited in an autosomal recessive fashion and are associated with early onset Hodgkin's disease [88, 191].

EBV–driven lymphoproliferation may also become the key clinical feature, when mutations within the *CD27* (OMIM*186711) molecule leads to loss of its expression on the cell surface of memory B-cells, CD4+ and CD8+ T-cells. CD27 belongs to the tumor necrosis factor receptor (TNFR) superfamily of co-stimulatory molecules suggesting that this axis is crucially important for proper immune control of EBV-infected B-cells.

5.9.2 Etiology

The T cell kinase ITK can be regarded as "brother or sister kinase" of Bruton's tyrosine kinase, *BTK*, the gene which is mutated in X-linked Agammaglobulinemia. Whereas BTK is expressed in B-cells and instrumental for normal B-lineage development, ITK is selectively expressed in T-cells and mast cells only. ITK is an integral part of T-cell receptor (TCR) multiprotein signaling complex and phosphorylates its downstream target phospholipase gamma 1. Besides its role in T-cell signaling, ITK represents a master regulator whose deficiency alters severely the whole spatiotemporal organization of the T-cell-APC- interface [183]. CD27 regulated cellular activity of subsets of B-cells, T-cells and NK cells. It binds to its ligand CD70 and the signaling axis is crucial for generation of virus specific memory T-cells [221, 222].

5.9.3 Clinical Manifestations

The clinical symptoms are partially overlapping with that mentioned in X-chromosomal lymphoproliferation with some important exceptions. Obviously, both sexes affected by ITK or CD27 deficiency whereas only boys may suffer from SAP; XIAP and MAGT1 deficiency. In six from the eight ITK-deficient patients identified so far pulmonary involvement with large interstitial nodules was observed in the majority of patients (Fig. 5.11). In contrast to most SAP-deficient lymphomas which are mostly Burkitt-lymphoma, ITK-deficiency rather seems to cause proneness for the development of Hodgkin's lymphoma. EBV-related symptoms like hepatosplenomegaly, cytopenias or autoimmune phenomena

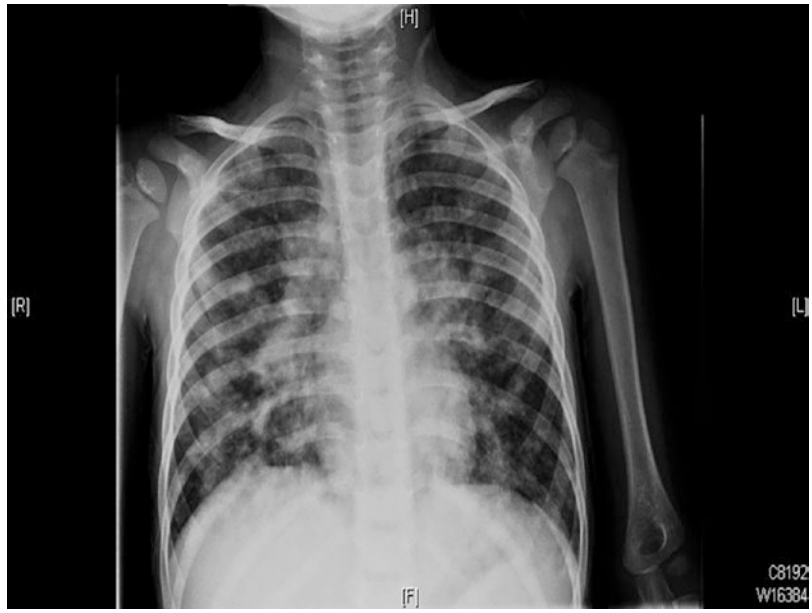

Fig. 5.11 Diffuse EBV lymphoproliferation in the lung of an ITK-deficient patient

were similar to those seen in SAP/XIAP-deficiency. Patients develop progressive hypogammaglobulinemia. As no asymptomatic EBV-seronegative patient with ITK-deficiency has been identified yet, it remains unknown whether those patients are prone to develop lymphoma in the absence of EBV. The clinical picture in CD27 is quite broad: it varies from asymptomatic memory B cell deficiency to persistent symptomatic EBV viremia, and EBV-driven lymphoma [2, 174, 208].

Hypogammaglobulinemia developed in three of the affected individuals. Vaccination with pneumococcal polysaccharide and meningococcus C-conjugated vaccines resulted in normal levels of specific antibody production. On the other hand, tetanus booster vaccination and rabies vaccination failed in terms of sufficient antibody production. As with ITK-deficiency, more patients with CD27-deficiency are required to characterize the clinical picture in full details (Table 5.4).

5.9.4 Diagnosis

EBV viral load is usually extremely high in ITK-deficiency and often exceeds that in SAP/XIAP deficiency. Lack of ITK results in progressive loss of CD4+ T-cell cells and iNKT cells are generally absent. In the CD8+ compartment, patients show low numbers of naïve CD45+ RA cells.

CD27 expression is widely recognized in clinical practice as a marker for memory B-cells. All CD27-deficient patients reported to date showed loss of its surface expression which makes diagnosis by flow cytometry straightforward and cost-effective.

5.9.5 Management

Based on the patients known, ITK deficient patients have a poor prognosis when left untransplanted. However, one patient died shortly after HSCT due to severe GvHD. Treatment of Hodgkin's lymphoma in ITK-deficiency should be discussed on an individual basis with pediatric oncologists as no general recommendations can be given yet. HLH and EBV-related symptoms should be managed as in X-linked lymphoproliferative syndromes. From the ten patients with CD27 deficiency three patients died, two others underwent successful allogeneic HSCTs and two received anti-CD20 therapy repeatedly [148].

Table 5.4 Clinical and laboratory features of ITK and CD27 deficiencies

Feature	ITK deficiency	CD27 deficiency
Clinical presentation		
HLH	Rare	Possible
Fever, hepatospenomegaly	Yes	Yes
Hypogammaglubinemia	Yes	Yes
Malignant lymphoma	Yes, mostly Hodgkin's disease	Yes, T-cell NHL
Aplastic anemia	No	Yes
Vasculitis	No	No
Genetics and function		
Locus	5q31	12p13
Gene	ITK	CD27
Protein	ITK	CD27
Expression pattern of wt	T- and mast cells	B-, T- and NK-cells
Signaling pathway affected	TCR, master regulator of spatiotemporal organization in T-cells	Apoptosis and survival, TNF family pathway
Cellular immune defects		
CD4+	Th2 lineage differentiation and function reduced	Normal
CD8+	Innate phenotype with high expression of transcription factor eomes	Subtle abnormality, reduced number of IL-2 producing EBV-specific cells
NK cells	Normal	Normal
NK cells	Strongly reduced or absent	Normal or reduced
B cells	Unknown	Subtle abnormality, reduced T-cell dependent immune response upon rabies vaccine

5.10 Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked

5.10.1 Definition

IPEX (Immune-dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome (OMIM*304790) is a rare autoimmune genetic disorder caused by mutation of *FOXP3* gene (OMIM*300292), which is located on X-chromosome and encodes a putative DNA-binding protein, key regulator of immune tolerance. IPEX is one of the few existing examples of a genetically determined autoimmune disease. Unlike most primary immunodeficiencies, in which increased susceptibility to infectious agents is the most prominent feature, patients with IPEX present most commonly with multi-organ autoimmunity. Symptoms typically become evident during infancy and include moderate to severe enteropathy, dermatitis (eczema and/or other skin manifestations), early-onset endocrinopathy, elevated IgE and variable autoimmune phenomena [12, 140]. Patients generally develop symptoms early in infancy and most die prematurely either due to severe diarrhea, unresponsive to immunosuppression, or severe infections. Nevertheless, similarly to other genetic disorders of the immune system (i.e. Omenn Syndrome), the disease course is variable and somehow unpredictable, despite the type of *FOXP3* mutations [69]. A clear correlation between autoimmunity, mutation of the foxp3 gene and Treg cells, has been demonstrated in the natural foxp3 mouse mutant called scurfy mouse, which is the murine counterpart of IPEX and was described initially more than 40 years ago [173]. Scurfy mice completely lack functional CD4+CD25+ Treg cells, and adoptive transfer of

this missing population can correct the autoimmune phenotype and rescue affected mice from lethality. Affected male mice have a characteristic appearance of scaly skin rash, small-thickened ears, conjunctivitis, and marked runting secondary to diarrhea and malabsorption. On closer evaluation, the mice also have organs infiltrated with activated lymphocytes with modification of cellular architecture (i.e. lymphadenopathy, hepatosplenomegaly, hypogonadism etc.) [74, 116]. Mice typically die by 3–4 weeks of age. Adoptive transfer, bone marrow transplant, and T cell subset depletion studies have provided the most direct evidence that Scurfy and IPEX are the results of immune dysregulation suggesting that mutations in Foxp3 lead to an escape from tolerance that can be rescued and maintained by a population of regulatory T cells present in wild-type mice [73, 150].

5.10.2 Etiology

The *FOXP3* gene was mapped to Xp11.23–Xq13.3 by linkage analysis and identified by positional cloning [28]. The gene consists of 11 translated exons that encode a protein of 431 amino acids in humans and 429 amino acids in mice. The two proteins are 86% similar. The gene is expressed primarily in lymphoid tissues (thymus, spleen, and lymph nodes) with the highest expression levels in CD4+ T cells [28]. The FOXP3 protein has several interesting structural features including a proline-rich domain at the N-terminus, a zinc finger and leucine zipper (both conserved structural motifs involved in protein-protein interactions) in the central portion, and a forkhead DNA-binding domain at the C-terminus [28, 33]. There is a putative nuclear localization signal at the C-terminal portion of the forkhead domain. Proteins bearing forkhead DNA-binding motifs comprise a large family of related molecules that play diverse roles in enhancing or suppressing transcription from specific binding sites and several members of this protein family are involved in patterning and development [68]. FOXP3 was shown to localize to the nucleus through the forkhead domain and functions as a transcriptional repressor in T cells and inhibits activation-induced IL-2 gene transcription [177]. It is clearly described the existence of two *FOXP3* isoforms, one corresponding to the canonical full-length sequence and the other lacking the sequence encoded by exon 2, which work cooperatively in exerting immune suppression [3, 185]. The dramatic suppressive effect of FOXP3 was also demonstrated *in vivo* by generation of transgenic mice expressing multiple copies of the *Foxp3* gene. These mice showed markedly decreased numbers of $CD4^+$ T cells in the periphery and no lymphocytic infiltrates. In contrast to the Scurfy T cells, the T cells derived from the transgenic mice were hypo-responsive to stimulation both *in vivo* and *in vitro*. The suppressive effect was shown to be dependent entirely on peripheral T cells, as overexpression of wild-type Foxp3 in thymus did not affect peripheral blood T cell numbers or function [102]. These data suggest a model in which Foxp3 functions as a rheostat for the immune system with activation responses being inversely proportional to the amount of Foxp3 protein expressed by $CD4^+$ T cells [17].

Peripheral immunological tolerance is primarily mediated by Treg cells. Among CD4+ T cells, the CD4+CD25+ Treg expressing constitutive high levels of FOXP3 and CD25 are defined, in both mouse and human, as naturally occurring since they emerge from the thymus. They represent less than 10% of the CD4+ T cells in the periphery and their proportion remains stable throughout life.

The precise mode of action of Treg cells is not known. However, stable FOXP3 expression is necessary for their function, rather than for their development. High expression of FOXP3 upregulates CD25, the high affinity subunit of the trimeric receptor for IL-2 that is important for Treg maintenance and survival. IL-2 signaling targets the *FOXP3* gene due to the presence of STAT-binding motif in the promoter region. Thus, Stat-5 is also an essential intermediate molecule for FOXP3-dependent Treg cell function [149].

However, human FOXP3 is not uniquely expressed by Treg cells, but it is also expressed by T effector (Teff) cells, although transiently, upon activation, similarly to CD25 and CTLA-4. This overlap of expression between Treg and Teff

cells represents a hurdle for an accurate identification of these two subsets by immunofluorimetric analysis, especially in patients' peripheral blood or tissues during autoimmune/inflammatory pathologies. Recently, a highly conserved CpG enriched element, located in the 5' untranslated region (5'UTR) of *FOXP3* has been identified as the Treg-cell-specific-demethylated-region (TSDR), since it is constantly demethylated exclusively in Treg cells. Demethylation of the TSDR leads to high and stable expression of FOXP3 and the quantification of the cells carrying demethylated TSDR allows to measure the peripheral proportion of *bona fide* Treg cells vs activated Teff cells, that maintain a fully methylated TSDR [11, 155].

5.10.3 Clinical Manifestations

Most IPEX patients are born at term after an uneventful pregnancy from unrelated parents. A careful family history may reveal the presence of male subjects in the maternal lineage with similar clinical phenotype, early death, or multiple spontaneous abortions. Notably, these patients may have other affected brothers, but females belonging to the same lineage are usually healthy. The onset of IPEX syndrome usually occurs in males within their first months of life and can be rapidly fatal if not diagnosed and treated. The classical IPEX picture is characterized by the early onset of a triad of clinical manifestations: intractable diarrhea, type-1 diabetes mellitus (IDDM), and eczema. The enteropathy is the hallmark of IPEX and is typically characterized by profuse watery and sometimes mucoid or bloody acute diarrhea. It often begins in the first days of life or during breast-feeding, thus showing to be independent from cow milk or gluten introduction in the diet. IPEX patients displayed a spectrum of histological patterns characterized by total or subtotal villous atrophy on duodenal biopsies and inflammation with glandular destruction in all parts of the digestive tract; however, mainly Graft-vs-host Disease-like and Coeliac Disease-like Pattern patterns were identified [151]. In addition to diarrhea, other gastrointestinal manifestations can be present, such as vomiting, gastritis, ileus and colitis. Almost all patients with IPEX present with enteropathy within the first 6 months of life.

The majority of patients have dermatitis that typically begins in the first months of life. Dermatitis can be eczematiform (mainly atopic dermatitis), ichthyosiform or psoriasiform. Skin involvement is severe and diffuse. Pruritus can be a major complain in these patients and sometimes difficult to control by conventional therapies. Cutaneous lesions can be complicated by bacterial infections (most commonly *Staphylococcus aureus and epidermidis*). Other cutaneous manifestations described in these patients are cheilitis, onycodystrophy and alopecia [12].

About 70 % of patients also develop an early onset endocrinopathy that is almost exclusively either thyroiditis or IDDM. IDDM is present in the majority of patients including newborns, and is usually difficult to control. Imaging studies or autopsy and histological examination often reveal destruction of the pancreas and intense lymphocytic infiltrate, suggesting that an immune mediated damage of this organ may have a role in the pathogenesis. Thyroiditis usually manifest with hypothyroidism more commonly than hyperthyroidism. In addition to these characteristic clinical features, patients also have a high incidence of other severe autoimmune disorders including: hemolytic anemia, thrombocytopenia, neutropenia, hepatitis, renal disease, and others. Recently hypotonia at birth with dysmorphic facial appearance was also observed in some cases [70].

The most consistent laboratory abnormality among patients is a significantly elevated serum IgE level and eosinophil counts, early hallmark of the disease. Serum immunoglobulin levels are generally normal or low due to the protein-losing enteropathy. Different lymphocyte subpopulations (CD3, CD4, CD8, CD16, CD19) are conserved despite immune dysregulation. The CD4 + CD25 + FOXP3+ Treg cells are present but FOXP3 expression can be reduced if *FOXP3* mutation prevents the expression of the protein or if the patient is undergoing immunesuppression treatment. Moreover, *in*

vitro lymphocyte proliferative responses to mitogens are not impaired unless the patient is immunesuppressed.

A variety of autoantibodies are detected in most patients and their presence usually correlates with organ involvement, but their production may also be a sign of immune dysregulation without an obvious clinical manifestation. The autoimmune enteropathy-related 75 kDa antigen (AIE-75), predominantly expressed in brush border of the small intestine and proximal tubules of the kidney, has been identified as a characteristic autoantibody present in IPEX. Other peculiar autoantibodies found in IPEX syndrome are anti-villin (a brush border antigen also expressed in microvilli of the small intestine and in the proximal renal tubules) and anti-harmonin (scaffold protein reported to be part of supra-molecular protein networks linking transmembrane proteins to the cytoskeleton in photoreceptor cells and hair cells of the inner ear [107]). Early presence of detectable autoantibodies against insulin, pancreatic islet cells, or anti-glutamate decarboxylase correlates with occurrence of IDDM. Moreover, anti-thyroglobulin and anti-microsome peroxidase antibodies are detected in autoimmune thyroiditis even in the absence of functional impairment. Coombs antibodies, anti-platelets, anti-neutrophils antibodies are often present in autoimmune cytopenias as well as anti-smooth muscle (anti-SMA) and anti-liver-kidney-muscle (anti-LKM) antibodies in autoimmune hepatitis [12, 70, 204, 217].

5.10.4 Diagnosis

Recognition of the clinical features of IPEX is the first step in diagnosing this disorder. Sequencing of the *FOXP3* gene remains the gold standard for making a diagnosis of IPEX although the molecular analysis needs to encompass non-coding areas of the gene including the upstream non-coding exon and the polyadenylation signal sequence in order to cover all regions in which pathogenic mutations have been identified [12, 13, 40, 70, 203]. To date, nor duplications neither deletions within the *FOXP3* gene were found in patients with IPEX. Flow cytometry to evaluate FOXP3 protein expression and FOXP3+ regulatory T cells (Treg) is a helpful addition to gene sequencing, although only ~25 % of patients have mutations that are predicted to completely abrogate FOXP3 protein expression. The remainder of patients has variable degrees of FOXP3+ Treg deficiency due to the fact that mutant FOXP3 may not support normal Treg development. As a result, flow cytometry by itself is not considered to be a sufficiently reliable screening test for IPEX.

5.10.5 Management

The current treatments available for IPEX syndrome include supportive therapy, immunesuppression therapy, and HSCT.

Initial therapy for IPEX typically consists of aggressive supportive care (parenteral nutrition, insulin, thyroid hormone, etc.) combined with immunesuppression. Prophylactic antibiotics should be also used considering the multiple potential sources of infection such as skin lesion, damaged gastrointestinal lining, and central venous catheter. Immunosuppressive therapy mainly consists of glucocorticoids (prednisone and methylprednisolone), used as the first line therapy to limit progression of organ damage. Then T cell-directed immune suppression using agents such as calcineurin inhibitors (Tacrolimus, Cyclosporine) have been most commonly used in conjunction with steroids. Other immunosuppressive drugs used to control the symptoms in IPEX and reported in literature are azathioprine and methotrexate, with incomplete response. Recently it has been shown that Rapamycin (mTOR inhibitor) selectively targets Teff cells and does not interfere with the function of Treg cells. The use of rapamycin (alone or in combination with azathioprine or steroids) has given promising clinical results.

HSCT is currently the only curative therapy for IPEX [12, 70]. Early allogeneic HSCT using a non-myeloablative conditioning regimen prior to the onset of autoimmune-mediated organ damage, usually leads to the best outcome and limits

the adverse effects of therapy [115, 157]. Since Tregs constitutively express the high-affinity IL-2 receptor, they have a selective growth advantage *in vivo*. As a result, complete donor engraftment in all hematopoietic lineages may not be necessary because preferential engraftment of donor Treg cells can be sufficient to control the disease [178].

5.11 CD25 Deficiency

5.11.1 Definition

CD25 deficiency or interleukin 2 receptor alpha (IL2RA) deficiency (OMIM*606367) is an immunodeficiency disorder associated with mutations in the *IL2RA* or *CD25* gene (OMIM*147730). The mutations cause defective or absent expression of the α chain, an essential part of high-affinity interleukin-2 (IL-2) receptors. The immunological consequence resulting from the loss of CD25 results in a SCID/immunedyregulation phenotype in man. Roifman's group was the first to describe a CD25 deficient patient who suffered from chronic infections and severe autoimmunity. Then two other unrelated patients have been reported in literature. CD25 deficiency is a distinct immunological disease that leads to both an autoimmune and immunodeficiency syndrome that clinically resembles IPEX syndrome [32, 75, 172, 182]. Moreover CD25 is required to maintain immune homeostasis therefore in view of the molecular pathway involved, CD25 deficiency is considered an IPEX-like disease.

5.11.2 Etiology

The high-affinity receptor for IL-2 is composed of three subunits: α (CD25), β (CD122), and γ (γ common, CD132) and plays a vital role in maintaining the immune system. Whereas the β and γ chains are constitutively expressed upon T lymphocytes, α expression is restricted to the early stages of thymocyte development and to activated mature T lymphocytes. Although the β and γ chains together can form an IL-2 receptor (IL-2R) of low affinity, the α chain cannot form a functional receptor in the absence of the others. The presence of the high-affinity receptor upon activated peripheral T cells is necessary for optimal proliferative responses to IL-2 after stimulation of the T-cell antigen receptor. Among the IL-2 receptors, CD25 exclusively binds IL-2, while CD132 binds the γ common family cytokines (IL-4, IL-7, IL-9, IL-15 and IL-21), and the CD122 subunit binds IL-15. CD25 is constitutively expressed at high levels by $CD4^+CD25^+FOXP3^+$ regulatory T cells (Tregs), and enables them to be the first responders to IL-2 during an immune response and promotes the transcription of FOXP3 by amplifying IL-2 signaling in a STAT5-dependent fashion [131, 139, 227]. This ability to respond to low concentrations of IL-2 is critical for maintenance of FOXP3 expression in Tregs. In fact, in mice lacking either IL-2 or CD25, Tregs are generated normally in the thymus but there is a marked defect in the survival, maintenance, and competitive fitness of mature Tregs, which appears to underlie the immune dysregulation observed in these models. The absence of CD25 in mice appears to cause a progressive impairment of phenotypically normal T- and B-cell populations, ultimately showing in elderly mice enlarged lymphoid glands due to increased B- and T-cell populations (as the result of inefficient activation-induced cell death) and a propensity to develop autoimmune disorders [218].

CD25 mutations described in humans so far are point or frame shift aberrations leading to a truncated and/or dysfunctional receptor. The phenotype is similar to the mouse model with early onset of symptoms, recurrent infections and overwhelming autoimmunity. In one CD25 deficient patient it was demonstrated that despite the lack of surface CD25, both Tregs and T effector cells remained able to respond to cytokines. Among the peripheral T effector cells, patient's CD8+ T cells highly expressed CD132, and this increased expression made them more responsive to IL-2 than CD4+ T effector cells. However, Ag-specific T cell responses were deeply impaired in vitro and in vivo. Importantly, in dif-

ferent patients it was seen that the proliferative defect of CD4 cells can be rescued with IL-15 or high concentrations of IL-2, but under these conditions, CD25 is not expressed [32, 70, 182].

5.11.3 Clinical Manifestations

Combination of immunodeficiency and autoimmunity is the pivotal feature of CD25 deficiency syndrome. Similar to IPEX, the three patients reported suffered from severe, chronic diarrhea and villous atrophy in infancy within the first year of life. Two also developed early onset insulin-dependent diabetes and eczema. Subsequently, patients developed autoantibodies, hepatosplenomegaly, lymphadenopathy, and lymphocytic infiltrates in various organs (gut, liver, etc.) indicative of ongoing immune dysregulation. Unlike patients with FOXP3 mutations, serum IgE levels were either normal or only mildly elevated [32, 70, 75, 182].

In addition to autoimmune features, both CD25-deficient patients had infectious complications suggestive of a more extensive defect in cellular immunity. The most prominent of these was early onset, recurrent CMV pneumonitis in both patients although persistent thrush, candida esophagitis, chronic gastroenteritis, and EBV infection were also observed [32, 70, 75, 182].

5.11.4 Diagnosis

In all described cases, inheritance was autosomal recessive. Two unrelated patients, born from consanguineous parents, were homozygous one for a four base pair deletion in the coding region of CD25 causing a frameshift and early termination codon and the other for a single nucleotide mutation resulting in an amino acid change. Another patient had compound heterozygous mutations in the CD25 gene that led to a frameshift on one allele and a premature stop codon on the other [32, 70, 182]. In all cases, the mutations caused the absence of CD25 expression on T cells. Flow cytometry is therefore a reasonable initial screening tool to evaluate patients suspected of having CD25 deficiency. Moreover impaired lymphocyte proliferation to IL2 can help to strengthen the diagnostic suspect. Sequencing of the IL2RA (CD25) gene is however recommended to confirm the diagnosis in all cases [70].

5.11.5 Management

Both patients required significant supportive care to control disease symptoms. Immunesuppression therapy was also required to control autoimmune manifestations. Because of the "SCID-like" features of this syndrome, one patient underwent a successful bone marrow transplant from a matched sibling donor and has done well. It is theoretically possible; however, that patients may respond to IL-2 therapy since the in vitro T cell proliferative defect could be overcome by treatment with exogenous high dose IL-2 or IL-15. Exogenous IL-2 may provide enough stimulation through the remaining "low-affinity" IL-2 receptor β-chain to allow Treg cells to survive and control autoreactive effector T cells [6, 70, 172].

5.12 STAT5b Deficiency

5.12.1 Definition

Deficiency of the STAT5b transcription factor was first described in 2003 in patients with significant growth failure and autoimmunity [103]. Like other STAT transcription factors, STAT5b plays essential roles in cytokine and growth factor signaling, particularly in response to IL-2, IL-15, and growth hormone. As a result, deficiency of STAT5b (OMIM*245590) results in a combination of marked growth failure due to growth hormone insensitivity and immune deficiency/immune dysregulation [14, 91, 133].

5.12.2 Etiology

Cytokines as interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, IL-21, and growth hormone (GH) mediate

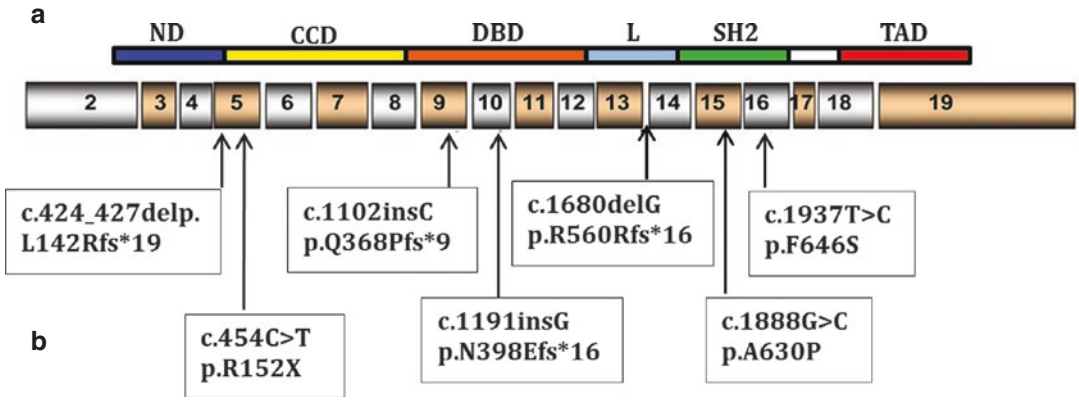

Fig. 5.12 *STAT5b* mutations reported in literature. (**a**) Schematic representation of protein domains: *ND* N-terminal, *CCD* coiled-coil, *DBD* DNA binding, *L* linker, *SH2* Src-homology2, *TAD* transactivation. (**b**) Schematic representation of the gene with site of mutations

their responses through activation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway [38]. The GH receptor (GHR) and the IL-2 receptor (IL-2R), in the presence of their specific ligands, besides recruiting and activating different cytosolic JAK proteins, at last they share STAT5 proteins (DNA binding factors) for their signaling pathways. STAT5a and STAT5b have been implicated in cellular functions of proliferation, differentiation, and apoptosis, with relevance to processes of hematopoiesis, immunoregulation, reproduction, prolactin production, and lipid metabolism. The STAT5 proteins a and b show 96 % homology2 and are encoded by 2 distinct but closely related genes, STAT5a and STAT5b. They have been described as having both redundant and non-redundant roles in cellular responses to a variety of cytokines and growth factors [77]. In transducing signals from IL-2, STAT5b plays a key role in sustaining FOXP3 protein expression in regulatory T cells (Treg). Under normal circumstances, STAT5b is present in the cytoplasm as an inactive dimer that, once phosphorylated after activation of cytokine receptors by receptor-associated tyrosine kinases, forms the active STAT5b dimer that localizes to the nucleus and binds DNA to regulate gene transcription of a variety of target genes including *FOXP3*. All *STAT5b* (OMIM*604260) mutations identified to date are autosomal recessive and destroy the function of both *STAT5b* alleles in the cell [133]. A total of 7 different *STAT5b* mutations have been reported in ten patients. Four of them are frameshift mutations, due to insertion or deletion of one or more nucleotide, affecting different domains of the protein; one is a nonsense mutation due to a single nucleotide substitution that lead to the introduction of a stop codon in the coiled-coiled domain; two are missense mutations that produce a single amino acid change, both affecting the SH2 domain of the protein (Fig. 5.12).

5.12.3 Clinical Manifestations

The cardinal feature of STAT5b deficiency is severe growth failure associated with elevated serum concentrations of GH, resulting in a phenotype that is undistinguishable from GH insensitivity (GHI), caused by mutations in GH receptor and insulin growth factor-I genes. However, what makes STAT5b deficiency different from GHI is the combination of severe GH-resistant growth failure, chronic infections and autoimmune diathesis [70, 90, 133].

In general, gestational growth and birth size in subjects with STAT5b deficiency are within normal limits. Then they typically show a severe growth failure after birth (heights −3.0 to −10 standard deviations below the mean for age). A modest delayed puberty was noted in some cases as well.

Most of the cases of STAT5b deficiency had medical conditions involving severe pulmonary disease, often presenting in childhood and reported to be fatal in some affected individuals. In most cases, severe eczema, thrombocytopenic purpura, and/or autoimmune disease (for example, juvenile idiopathic arthritis) were present, in addition to severe lung disease. The pneumonitis causes respiratory failure and death. However, in one case it was observed a less severe immune dysfunction. The patient suffered from congenital ichthyosis at birth and had hemorrhagic varicella at 16 years of age but had no history of pulmonary or immunological disorders [14, 91, 92, 133, 210].

Because STAT5b is essential for normal signaling from Interleukins-2 (IL-2) and -15 (IL-15), key growth factors for T cells and NK cells respectively, patients typically have moderate T cell (CD4+ and CD8+) an NK cell lymphopenia and frequently suffer from recurrent viral infections with pathogens such as Cytomegalovirus (CMV). Since signaling from IL-2 is essential for sustaining FOXP3 expression in natural Tregs, patients with STAT5b deficiency were found to have markedly decreased FOXP3 expression in CD4+ T cells and defective Treg function. On the contrary, B cell counts and immunoglobulin levels were found increased and autoantibodies were also prevalent, which is consistent with autoimmune diseases [34, 133].

5.12.4 Diagnosis

Because of the pivotal features of marked growth failure and growth hormone insensitivity, immune deficiency, and immune dysregulation, the physical exam and routine laboratory testing (lymphopenia, low T and NK cells, etc.) can strongly suggest a diagnosis of STAT5b deficiency. The presence of normal plasma growth hormone levels and very low plasma IGF-1 and IGFBP-3, and elevated prolactin suggests a possible defect at the level of GH receptor. Nevertheless, together with the other clinical and immunological indices, STAT5b deficiency should be highly suspected. Definitive diagnosis is however made by sequencing of the *STAT5b* gene [70, 133].

5.12.5 Management

So far symptomatic therapy and prophylaxis against infections have been the cardinal treatments for STAT5b deficiency. GH replacement is ineffective, however IGF-I therapy should improve the growth response unless the presence of severe chronic infections that might impact the growth themselves. Immune suppression resulted in controversial success and no therapies have been reported to be significantly beneficial for the severe lung disease that affects most patients. Conversely, pulmonary function tests are important to monitor the lung disease and delay the disease progression with timely treatment. HSCT was never undertaken in STAT5b deficient patients although it could be speculated that it would correct the significant immunodeficiency and immune dysregulation typically associated with the disorder. However, HSCT is not expected to cure the severe growth failure and this should be seriously considered before attempting HSCT. Correction of the immune defect can although decrease morbidity and mortality and therefore improve the disease course [70, 92, 133].

5.13 ITCH Deficiency

5.13.1 Definition

ITCH deficiency (OMIM*613385) or autoimmune disease with facial dysmorphism (ADMFD) is an early-onset syndromic autoimmune disorder, that so far has only been reported in one extended Amish kindred [113]. Key symptoms in those patients were failure to thrive, developmental delay, relative macrocephaly, hepato-/splenomegaly and chronic lung disease. *ITCH* (OMIM*606409) encodes for an E3 ubiquitin ligase, which belongs to the HECT family. The exact molecular function contributing to disease manifestation remains to be elucidated; yet *in vitro* studies indicate that Itch is a multifunctional protein, which interacts with various molecular targets involved in balancing T-cell responses that are crucial for the induction and maintenance

of self-tolerance [112, 132]. The previously reported "itchy" mice shares some of the autoimmune manifestations observed in Itch deficient patients [152].

5.13.2 Etiology

The molecular processes driving the pathology of human Itch deficiency are yet incompletely understood. Autozygosity mapping identified Itch deficiency as the genetic cause of syndromic autoimmune disease in 10 affected patients from a recently reported consanguineous Amish family [113]. The pedigree of the index family suggests an autosomal recessive mode of inheritance. The fact that "itchy" mice (which carry an insertion disrupting the agouti and the Itch genes) are also prone to profound autoimmunity (i.e. of lung, intestine and skin) supports the hypothesis, that *ITCH* is indeed the causative gene linked with the reported human phenotype. *ITCH* encodes for an E3 ubiquitin ligase, which belongs to the so called HECT family [15]. Ubiquination is a post-translational process, important to modulate the function of proteins and crucial to steer various molecular processes, e.g. protosomal degradation or transcriptional regulation [35, 154]. Deficiencies of LUBAC and XIAP, two further recently described ubiquitin ligases, evidently emphasize the essential role of ubiquination processes in the regulation of immune responses [22, 43]. As for most ubiquitin ligases, a plethora of binding motifs have been described for Itch [112]. Several of these potentially interacting partners are important for regulating T-cell functions including proliferative responses and the maintenance of peripheral tolerance (e.g. JunB or FOXP3) [55, 71, 209]. In mice, both antigen processing and T-cell anergy are abnormal and T-cells demonstrate an activated phenotype [126, 224]. Levels of the Th2 cytokines IL-4 and IL-5 are increased and ubiquination of JunB through Itch seems to be the driving mechanism of this upregulation [55, 71]. In line with this Th2 phenotype IgE levels are increased in mice [147]. Hitherto, detailed humoral or cellular immunological data is unavailable from Itch deficient patients. While significant phenotypic overlap between Itch deficient human and mice suggests similar underlying mechanisms, the observation of multiple dysmorphic features in all reported patients also points towards additional roles of Itch in humans.

5.13.3 Clinical Manifestations

Human ITCH deficiency was recently identified in 10 patients from a single Amish kindred with an early-onset syndromic autoimmune disorder [113]. All patients presented with failure to thrive, developmental delay and had numerous dysmorphic features. These included relative macrocephaly, frontal bossing, dolichocephaly, orbital proptosis, flattened mid-face, small chin and posteriorly rotated ears. 90 % of patients had hepato- or splenomegaly. 60 % of patients presented with autoimmune disease (hypothyroidism in 40 %, hepatitis in 30 %, enteropathy in 20 % and diabetes mellitus in 10 %). Eczematous, itchy skin (a key feature in the corresponding mouse model) was not reported so far. Chronic lung disease was present in 90 % of patients and three patients succumbed from respiratory failure <3 years of age. In several patients lung disease was clinically reminiscent of chronic asthma. Biopsy in one patient revealed unspecific interstitial pneumonitis. While individual patients received treatment for recurrent infections, Lohr et al. did not report a specific susceptibility for infectious diseases in the entire cohort.

5.13.4 Diagnosis

A diagnosis of Itch deficiency should be suspected in patients with failure to thrive, relative macrocephaly, chronic lung disease, hepato-/splenomegaly and autoimmune disease. However, with clinical observations available from only one family, the actual phenotype of the disease may vary. Detectable autoantibodies in some reported patients included antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (pANCA), anti-liver/kidney microsomal (LKM) antibodies, anti-enterocyte and anti-thyroid per-

oxidase (TPO) antibodies. The blood count was not altered in reported patients. Unfortunately, detailed information on the humoral or cellular immunological phenotype of human Itch deficiency is unavailable. A definite diagnosis of Itch deficiency therefore relies on the genetic analysis of the *ITCH* gene.

5.13.5 Management

The reported experience in managing Itch deficiency is limited [113]. All patients with autoimmune disease required systemic immunosuppressive treatment. Steroids, rapamycin, tacrolimus and azathioprine were used to control symptoms in patients with severe autoimmune enteropathy and hepatitis. Chronic lung disease has been life limiting for three reported patients and optimal treatment for this complication is uncertain. While HSCT can correct the immunological phenotype of "itchy" mice [147], HSCT reports from humans are not available. The observation of multiple dysmorphic features in all reported patients certainly also points towards roles of Itch beyond the immune system. At present, more prospective natural history data on the variable clinical phenotype and understanding of the molecular basis in humans needs to be obtained to improve therapeutic recommendations for this disease.

5.14 TPP2 Deficiency

5.14.1 Definition

Tripeptidyl-peptidase II deficiency or TPP2 deficiency is a recently described disease in two siblings with Evans syndrome, viral infections, and progressive leukopenia [190].

5.14.2 Etiology

Homozygous mutation in *TPP2* gene (OMIM*190470), encoding tripeptidyl-peptidase II, a serine exopeptidase involved in extralysosomal peptide degradation, abolishes protein expression. TPP2 deficiency could be considered as the first immunodeficiency disease, linking premature immunosenescence to severe autoimmunity [190].

5.14.3 Clinical Manifestations

Two siblings of consanguineous Palestinian parents have already been reported with TTP2 deficiency. Both presented autoimmune hemolytic anemia and immune thrombocytopenia. The younger sibling also suffered from cervical and axillary lymphadenopathy, and splenomegaly [190].

5.14.4 Diagnosis

Immunological studies are available on only one patient with TTP2 deficiency; therefore there are not enough evidences to make diagnosis based on that report. Meanwhile that case had mild leukopenia and lymphopenia with reduced number of naïve CD4+ T-cells and B-cells; albeit after rituximab therapy. Normal levels of serum vitamin B12 and soluble Fas Ligand, and normal proportion of CD4+CD25+FOXP3+ regulatory T-cells were detected [190].

5.14.5 Management

Immunoglobulin replacement therapy and steroids could be recommended for autoimmune cytopenia. In a case of refractory course of Evans syndrome, HSCT could be proposed. The case with TTP2 who underwent HSCT was well at the time of report without any immunosuppressive medication [190].

5.15 COPA Deficiency

5.15.1 Definition

COPA deficiency (OMIM*616414) or autoimmune interstitial lung, joint, and kidney disease (AILJK) is a very recently described autoimmune disease on five families with inflammatory arthritis and interstitial lung disease [213].

5.15.2 Etiology

COPA deficiency is caused by heterozygous mutation in the *COPA* (Coatamer Protein Complex, Subunit Alpha) gene (OMIM*601924). T717 dysregulation and high titer of autoantibody production lead to inflammatory arthritis and immune complex-mediated renal disease in addition to interstitial lung disease [213].

5.15.3 Clinical Manifestations

Our the reported findings uncover an unexpected molecular link between a vesicular transport protein and a syndrome of autoimmunity manifested by lung and joint disease. A variety of autoimmune manifestation is expected to be seen in COPA deficiency in first two decades of life. Systemic autoimmune conditions, including interstitial lung disease, inflammatory arthritis, and immune complex-mediated renal disease are the main characteristics of disease [213].

5.15.4 Etiology

In addition to high titer of autoantibodies, upregulation of cytokines priming for a T helper 17 response could be expected in those with *COPA* mutation [213].

5.15.5 Management

Although the disease is considered as an immunodeficient condition, long-term immunosuppressive therapy is needed. Further necessary treatment like renal transplantation might be needed in a case of further complications.

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6 Defects in Intrinsic and Innate Immunity: Receptors and Signaling Components

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6.1 Introduction

Immune responses comprise innate and, where needed, adaptive steps. The responses of the innate immune system are mostly phylogenetically old, fast (e.g., phagocytosis of a bacterium) and encoded within the germ-line DNA, while responses of the adaptive immune system are first described in jawed vertebrates, and are slow, long-lived and antigen-specific as a result of somatic DNA recombination (e.g., T cell cytotoxicity to a virus infected cell).

Examples of the innate immune components are epithelial barriers, antimicrobial peptides, soluble factors (e.g., complement, chemokines) and cellular elements (e.g., neutrophils, monocytes and natural killer cells). Humoral and cellular components of the innate immune system are diverse, and their responses are often initiated by pattern recognition receptors (PRR) such as Toll-like receptors (TLRs) and NOD-like receptors (NLR; NOD, nucleotide-binding and oligomerization domain) that recognize pathogen-associated molecular patterns (PAMPs).

The important role of innate immunity in host defense is verified by potentially serious infections that result from naturally occurring defects of the innate immune system.

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This chapter reviews PIDs that have been defined as defects of the innate immune system. The defects of neutrophil phagocytes and the complement system are covered in Chaps. 4 and 8, respectively. The development of human genetic theory of infectious diseases boosted up the field in the past two decades [47]. The study of otherwise healthy children, who develop a severe infectious disease, resulted in identification of monogenic inborn errors of immunity, mainly the innate system [47, 48]. The field is rapidly growing and description of more PIDs in this group can be expected in the near future. (*See Table 1.5 and Fig. 1.12 for updated classification of defects in intrinsic and innate immunity: receptors and signaling components*)

6.2 Anhidrotic Ectodermal Dysplasia with Immunodeficiency

(***NEMO deficiency, IKBA gain-of-function mutations***)

6.2.1 Definition

As NF-kB is a central transcription factor through which classical TLR activation triggers inflammatory responses, inadequate NF-kB activation will uniformly result in impaired TLR function. NF-kB is composed of homo- or heterodimers of five proteins belonging to the Rel family (p50, p52, RelA, c-rel and RelB) [118]. In resting cells, NF-kB is kept inactive in the cytoplasm through interaction with the inhibitors of NF-kB (IkBα, IkBβ and IkBε). In response to cell stimulation, IkBs are phosphorylated by the IkB kinase (IKK) complex, leading to subsequent degradation by the proteosome apparatus (Fig. 6.1) [170]. IKK consists of two catalytic subunits, IKKα and IKKβ, and a regulatory subunit, IKKγ, also known as the NF-kB essential modulator (NEMO) [155]. The release of NF-kB from IkB allows it to translocate to the nucleus and activate transcription of various genes involved in immunity [170]. Transcriptionally active NF-kB dimers are induced upon stimulation of a wide range of receptors of the immune system (TLRs, TNF receptor superfamilies, IL1 receptor family, and T and B cell antigen receptors and of receptors of ectodermal and bone cells). Impaired NF-kB activation by ectodysplasin in skin and altered receptor activator of NF-kB (RANK)-Ligand signaling in bone cells have been observed in ectodermal dysplasia (EDA) [88]. This explains the broad phenotype of patients with defects in NEMO-regulated NF-kB activation involving the immune system, ectoderm and bones. EDA is a unique feature of defects of NF-kB activation due to altered NEMO that is not observed in other disorders of TLR signaling.

6.2.2 Etiology

The *NEMO* (*IKBKG*, OMIM*300248) gene is located on the X-chromosome, consists of ten exons and encodes a protein of 419 amino acids. This protein is an essential part of the IKK complex and consists of two N-terminal coiled coil domains followed by a leucine zipper and C-terminal zinc finger, all separated by α-helical regions [272]. X-linked anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID, OMIM*300291, 300584, 300301, 300636 and 300640) is a rare inherited disease caused by hypomorphic mutations in *IKBKG*, the gene encoding NEMO [12, 46, 52, 57, 72, 80, 88, 95, 100, 111, 114, 136, 138, 150, 159, 187, 188, 196, 207, 210, 222, 231, 240, 242–244, 251, 260, 277, 285, 298, 352]. More than 100 male patients with hemizygous hypomorphic mutations of NEMO have been reported to date and about 50 different mutations have been identified [12, 46, 52, 57, 72, 80, 88, 95, 100, 111, 114, 136, 138, 150, 159, 187, 188, 196, 207, 210, 222, 231, 240–244, 251, 260, 277, 285, 298, 352]. The disease is normally confined to males, although it has rarely been reported in females with skewed X-inactivation [182, 210]. More recently, mutations in the leucine zipper domain of the *NEMO* gene have been diagnosed as the X-linked form of Mendelian

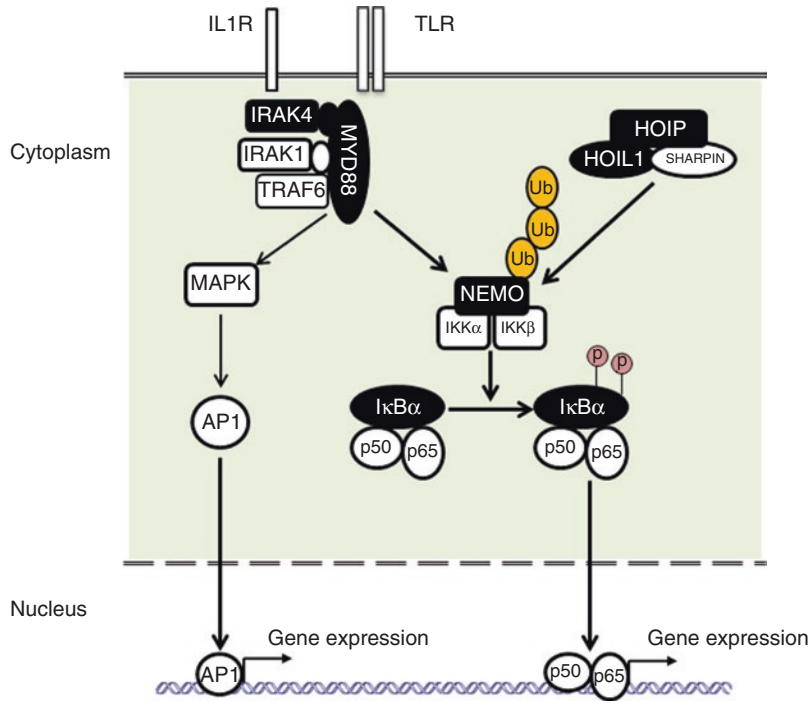

Fig. 6.1 Toll–IL-1R domain (TIR) and NF-kB signaling pathways. Six proteins responsible for PIDs are shown in *black*

Susceptibility to Mycobacterial Diseases (XL-MSMD) [111, 150]. This finding illustrates the importance of NEMO for the IL12/IFNγ pathway. In contrast to hypomorphic mutations, amorphic mutations of *NEMO* cause incontinentia pigmenti which is a genodermatosis seen in females, as affected males die *in utero* [298].

Furthermore, an autosomal dominant form of EDA-ID (AD-EDA-ID, OMIN#612132) was identified in seven patients from six kindreds [66, 161, 201, 215, 237, 292]. In these patients, a heterozygous missense mutation has been identified in *IKBA* (*NFKBIA*, OMIM*164008) gene, which encodes an inhibitor of NF-kB, IkBα, have been identified [66, 161, 201, 215, 237, 292]. One of these patients displays complex partial mosaicism [161]. AD mutation in *IKBA* leads to a severe impairment of TCR signaling [66, 161, 201, 215, 237, 292]. The same heterozygous 94G>T mutation was identified in two unrelated kindreds. This mutation is responsible for the replacement of a serine residue important for the phosphorylation of IkBα with an isoleucine residue (S32I). The S32I, Q9X, Q14X and M37K mutations are gain-of-function mutations, as they increase the inhibitory capacity of IkBα by preventing its phosphorylation and degradation, resulting in the impairment of NF-kB activation [66, 161, 201, 237, 292]. The W11X nonsense mutation is responsible for haplo-insufficiency and less severe clinical, immunological and functional phenotypes in the patient bearing this mutation [215]. IkB molecules are involved in several pathways, including those triggered by the many members of the TNF-R, IL1R, TCR, BCR and TLR families. The T cell phenotype seen in AD-EDA-ID may reflect NEMO-independent NF-kB signaling in response to TCR/CD3-ligation [136, 260, 320].

6.2.3 Clinical Manifestations

The range of clinical manifestations of XL-EDA-ID is broad [136, 260]. About 80 % of the reported NEMO-deficient patients to date have had abnormal development of ectodermal derived structures, which is characterized by hypohidrosis, widely spaced cone- or peg-shaped

teeth and hypotrichosis [136, 260]. These features result from defective signaling via the ectodysplasin receptor (EDAR) signaling pathway. A severe form of XL-EDA-ID exhibiting osteopetrosis and lymphedema (XL-OL-EDA-ID) has been reported in few patients carrying mutation in *NEMO* at the C-terminus of the molecule [95, 207, 277]. In contrast, some NEMO-deficient children had ID without EDA [100, 222, 231, 242]. Poor clinical and biological inflammatory responses during infectious episodes are remarkable in NEMO-deficient patients [260, 272]. The severity of the course of infections is in contrast to the paucity of abnormalities in routine immunological tests.

NEMO-deficient patients are susceptible to severe bacterial infections of the respiratory and gastrointestinal tracts, skin, soft tissues and bones, and suffer from meningitis and septicemia during infancy [136, 260]. The infectious phenotype is characterized mostly by infections due to encapsulated pyogenic bacteria, such as Gram-positive (*Streptococcus pneumoniae*, *Staphylococcus aureus*) and Gram-negative (*Haemophilus influenza*, *Pseudomonas aeruginosa*) organisms [136, 260]. Infections caused by weakly pathogenic mycobacteria, such as *Mycobacterium kansasii*, *Mycobacterium avium*, and *Mycobacterium bovis*, have also been diagnosed in some NEMO-deficient patients [136, 260]. Viral infections reported include cytomegalovirus, herpes simplex virus, adenovirus, *Molluscum contagiosum* and human papilloma virus [136, 260]. *Pneumocystis jiroveci* has also been found as an opportunistic infection [136, 260]. One third of the NEMO-deficient patients died from invasive infections, demonstrating the severity of this disorder [136, 260]. Finally, the phenotype caused by *NEMO* mutations includes autoimmune phenomena such as hemolytic anemia, arthritis and inflammatory bowel disease-like colitis [136, 231, 244, 260].

Seven patients with AD mutation in *IKBA* have EDA, failure to thrive, recurrent opportunistic infections and chronic diarrhea early in infancy [66, 161, 201, 215, 237, 292]. One patient, whom displayed complex partial mosaicism, had a milder EDA phenotype [161]. The broad and profound immunological impairments of patients with AD mutation in *IKBA* are responsible for broad susceptibility to severe pyogenic bacterial infections (meningitis, sepsis, arthritis, enteritis, abscesses and pneumonia), fungi and severe viral infections [66, 161, 201, 215, 237, 292]. All patients have developed recurrent pyogenic bacterial infections, due to β hemolytic type A streptococci, *S. aureus*, *P. aeruginosa*, *Klebsiella pneumoniae*, *Serratia marcesens* and *Salmonella typhimurium* [66, 161, 201, 215, 237, 292]. Finally, six of these patients presented recurrent diarrhea and/or colitis [66, 161, 201, 215, 237, 292]. Thus, a diagnosis of gain of function mutation in *IKBA* should be considered in children with EDA and combined immunodeficiency.

6.2.4 Diagnosis

Severe infections in combination with the symptoms of EDA are indicating clinical signs. Scanty hair, thin skin, defective tooth formation, abnormal nails, and/or heat intolerance can be striking, but are variable, can also be discrete, and are sometimes absent. Poor inflammatory responses during severe infections raise suspicion [136, 260]. In XL-EDA-ID, immunodeficiency results from defective NF-kB activation through Toll-interleukin-1 receptor (TIR), CD40 and TNF signaling pathways [136, 260]. Immunologic evaluation shows an abnormal antibody response to glycans due to the altered TLR signaling [136, 260]. Most patients exhibit hypogammaglobulinemia with low serum IgG levels [136, 260]. A subset of patients may present with hyper-IgM phenotype due to altered CD40 signaling and isotype-class switching [136, 160, 260]. NK cell abnormalities have been demonstrated as well [240]. Most NEMO-deficient patients fail to produce IL10 in response to activation with TNF-α in whole-blood assays [136, 260]. AD-EDA-ID shares many similarities with XL-EDA-ID, but is also associated with severely impaired T cell function. Five of these patients had low proportions of memory $CD4^+$ and $CD8^+$ T cells and no TCR gamma/delta T cells. They displayed severe impairment of T-cell proliferation in response to

anti-CD3 [66, 161, 201, 237, 292], had hypogammaglobulinemia and no production of specific antibodies [66, 161, 292]. The child with the W11X mutation presented only a defect of glycan antibody production [215]. To confirm the diagnosis and to differentiate it from specific defects of adaptive immunity *NEMO* and *IKBA* genes should be sequenced.

6.2.5 Management

All NEMO-deficient patients should receive prophylactic trimethoprim-sulfamethoxazole and/or penicillin V treatment. IgG substitution should be carried out in patients with NEMO deficiency presenting with a humoral defect. NEMO-deficient patients with functional B-cell defect should receive vaccines against *S. pneumonia*, *H. influenza and N. meningitidis*. Vaccination with live BCG is contraindicated for NEMO-deficient patients. The families and physicians of NEMO-deficient patients should note that it is important to initiate empiric parenteral antibiotic treatment against *S. pneumoniae*, *S. aureus*, *P. aeruginosa* and *H. influenzae* as soon as infection is suspected or the patient develops a moderate fever, without considering inflammatory parameters, as patients may die from rapid invasive bacterial infections despite appropriate prophylaxis. Intensive four-drug regimens for at least 12 months are necessary to treat atypical mycobacteria. Patients with a severe infectious phenotype should be considered for HSCT, but experience is very limited [95, 112, 218, 252, 259, 313]. For patients with AD *IKBA* mutation, a preventive treatment, including antibiotic prophylaxis with cotrimoxazole and/or penicillin V, should be proposed and IgG replacement are recommended. The recommendations for NEMO-deficient patients with fever should also be applied to *IKBA* mutated patients. HSCT has been reported in two patients with *IKBA* mutation having combined immunodeficiency [94, 112]. One of these patients is alive and well, 8 years after haploidentical HSCT, whereas the other patient died of bacterial sepsis during the period of aplasia [94, 112].

6.3 HOIL1 and HOIP Deficiencies

6.3.1 Definition

The linear ubiquitination chain assembly complex (LUBAC) has important functions in immunity and inflammation [32]. LUBAC assembled by a complex containing HOIL1 (also known as RBCK1), SHARPIN, and HOIP (also known as RNF31) were implicated in IL1R and TNFR signaling pathways [117]. This E3 ligase complex, which adds head-to-tail linear polyubiquitin chains to substrate protein, has been implicated in NF-kB signaling. SHARPIN and HOIP protein levels are low in the absence of HOIL1 and their restoration following HOIL1 re-expression suggests that LUBAC is a ternary complex [32]. LUBAC is involved in the NF-kB pathway and conjugates linear polyubiquitin chains onto specific lysine residues of NEMO [312]. It has been suggested that LUBAC facilitates the recruitment of the NEMO-/IKK complex to cytokine receptors, in at least some cell types [312]. The recognition of these linear ubiquitin chains by NEMO itself and, probably, by other components of the NF-kB cascade may then lead to a local accumulation of IKK kinases, favoring their trans-phosphorylation and activation. LUBAC in human is required for optimal responses to other members of the TIR family, such as TLR3, and of the TNF-R family, such as CD40 [32].

6.3.2 Etiology

The *HOIL1* (*HOIL1/RBCK1*, OMIM*610924) gene encodes hemoxidized iron-regulatory protein ubiquitin ligase-1 (HOIL1). HOIL1 deficiency or Polyglucosan Body Myopathy 1 with Immunodeficiency (PGBM1) is an autosomal recessive (AR) immunodeficiency caused by homozygous or compound heterozygous mutation in *HOIL1* gene. Two siblings with a compound heterozygous mutations have been reported [32]. They have a large deletion in *HOIL1* (genomic rearrangement due to recombination between intron 1 of *TRIB3* and intron 4

of *HOIL1*) which was predicted to result in the deletion of the HOIL1's ubiquitin-like (Ubl) domain [32]. Their second mutation is a nonsense mutation (p.Q185X) and was predicted to result in premature truncation within the novel zinc finger domain of HOIL1 [32]. A homozygous small nucleotide deletion in the gene was identified in a third patient, which was predicted to result in the deletion (c.121_122delCT) of all functional domains of HOIL1 [32]. The Ubl domain is required for LUBAC formation and linear ubiquitination. Collectively, these genetic data suggest that the three patients have rare deleterious alleles of *HOIL1* [32]. More recently, 14 patients from 10 unrelated kindreds with HOIL1 deficiency caused by homozygous or compound heterozygous mutations have been reported [232, 335]. All mutations except one are localized after Ubl domain. Only one missense mutation is localized before Ubl domain [232].

The *HOIP* (*RNF31*, OMIM*612487) gene consists of 21 exons and encodes a protein of 1072 amino acids. The encoded protein (HOIL-1-interacting protein, HOIP) contains RING finger motifs, ubiquitin-associated domains and ubiquitin-associated domain and is a component of E3 ubiquitin-protein ligase, LUBAC. Recently, HOIP deficiency is recognized as a hypomorphic autosomal recessive trait in a single patient [31]. Homozygous L72P missense mutation in the Pub domain resulted in diminished mRNA and protein expression. This domain is highly conserved and is important for the interaction of HOIP with OTULIN and CYLD, two deubiquitinases [101, 113, 291]. The L72P mutation destabilizes HOIP and, consequently, SHARPIN and HOIL1 [31].

6.3.3 Clinical Manifestations

The first three patients reported with HOIL1 deficiency were from two unrelated families displaying a paradoxical clinical phenotype combining auto-inflammatory syndrome and pyogenic bacterial diseases [32]. All three patients had recurrent systemic inflammatory symptoms from the first months of life [32]. These episodes generally occurred after simple viral infections of the upper respiratory tract and associated with cervical lymphadenitis and hepatosplenomegaly (HSMG). These episodes are recurrent and no infectious agent could be identified. Some of these episodes are associated with inflammatory bowel disease with abdominal pain, blood and mucus in the stools [32]. Gastrointestinal endoscopy revealed minimal colonic inflammatory lesions with moderate eosinophilic infiltration in the gut epithelium in two patients [32]. One patient also developed diffuse desquamative dermatitis and cheilitis. All three patients have developed recurrent pyogenic bacterial infections, due to *S. pneumoniae*, *H. influenzae*, *Escherichia coli*, *Staphylococcus spp* and *Enterococci*. Two of them died from invasive pyogenic bacterial infection in childhood [32]. The third patient had also chronic cytomegalovirus infection. *Giardia intestinalis* caused a gut infection in one other patient [32]. Amyotrophia, muscle weakness and failure to thrive have been observed in the three patients since infancy [32]. These patients developed muscular amylopectinosis, consisting of intracellular glycogen inclusions, complicated by myopathy and cardiomyopathy [32]. More recently, 14 patients from 10 unrelated kindreds with HOIL1 deficiency presented after neuromuscular and cardiac involvement secondary to amylopectinosis. Their clinical descriptions are succinct, but one of these patients, who had compound heterozygous mutations, including the same large deletion of HOIL1 of the first kindred reported and frameshift mutation, displayed a similar inflammatory clinical phenotype as the three patients firstly identified [232].

The phenotype of reported HOIP-deficient patient is reminiscent of HOIL1 deficiency with some distinctions [31]. The patient was susceptible to encapsulated bacteria since early infancy. She displayed auto-inflammation, like the first described HOIL1-deficienct patient series, but amylopectinosis was mild and limited to the skeletal muscles, sparing the cardiac muscle. A distinctive feature of the disease was development of lymphangiectasia during the second decade of life.

6.3.4 Diagnosis

Chronic clinical and biological (high rate of CRP and leukocyte count) inflammation with acute episodes of fever with cervical lymphadenitis and HSMG, diarrhea, are remarkable [32]. Between these episodes, biological indicators of inflammation can decrease, but never reach normal levels. Immunologic evaluation shows a B-cell deficiency and a partial defect in antibody production against *H. influenza* type b and pneumococcus in two patients [32]. All patients with HOIL1 deficiency developed accumulation of polyglucosan (amylopectinosis), consisting of intracellular glycogen inclusions, that is associated with muscle weakness and cardiomyopathy [32, 232, 335].

Despite clinical similarity, mild amylopectinosis of skeletal muscles and presence of lymphangiectasia are specific features of HOIP deficiency that have not been observed in HOIL1 deficiency [31].

Characteristic immunological features of HOIP deficiency include, broad impairment of antibody production, defects of CD40-ligand induced B cell activation and plasmablast differentiation. In contrast to HOIL1 deficiency, the HOIP-deficient patient had severe naïve T lymphocytopenia and increased effector memory $CD4^+$ and T_{EMRA} $CD8^+$ T cells [31].

6.3.5 Management

HOIL1-/HOIP-deficient patients should be immunized with *S. pneumoniae* conjugated and nonconjugated vaccines, *H. influenzae* conjugated vaccine and *N. meningitidis* conjugated and nonconjugated vaccines. They should receive prophylactic penicillin V treatment. IgG substitution should be considered in patients presenting with an impairment of B-cell immunity [31, 32]. Pyogenic bacterial infections should be treated aggressively. Patients with heart failure should be considered for heart transplantation, but experience is limited [232, 335]. Only one HOIL1-deficient patient with a severe infectious phenotype received HSCT [32]. After HSCT, the biological indicators of inflammation reached normal levels. The patient presents no further invasive bacterial infections after HSCT [32]. Due to underlying T cell deficiency, HOIP-deficient patients should be closely monitored for development of pertinent infections.

6.4 IRAK4 and MyD88 Deficiencies

6.4.1 Definition

TLRs play a crucial role in the evolutionary conserved innate immunity. TLRs are type I transmembrane proteins that function as homodimers or heterodimers. They are activated upon binding to bacterial, viral and fungal components [172]. To date, ten human TLRs have been identified [172]. It has been shown that TLRs are activated by specific agonist. For example, lipopolysaccharide (LPS) of Gram-negative bacteria is recognized by TLR4 in connection with LPS-binding protein and CD14 [223]. TLR2, in concert with TLR1 or TLR6, recognizes various bacterial components, including peptidoglycan, lipopeptide and lipoprotein of Gram-positive bacteria [223]. TLR3 recognizes double-stranded RNA (dsRNA) that is produced from many viruses during replication [223]. Agonists for other TLRs include flagellin for TLR5, synthetic imidazoquinoline-like molecules and single-stranded RNA (ssRNA) for TLR7 and TLR8, and bacterial and viral CpG DNA motifs for TLR9 [223]. After recognition of microbial pathogens, TLRs trigger intracellular signaling pathways that result in the induction of inflammatory cytokines and type I interferons (IFN) (Fig. 6.1). TLRs share with members of the IL1 receptor family an intracellular domain called the Toll-interleukin-1 receptor (TIR) domain [86]. The classical TLR-mediated intracellular signaling involves TIR-containing cytosolic adaptor molecules myeloid differentiation factor-88 (MyD88) and Toll-interleukin-1 receptor domain containing adaptor protein (TIRAP). Activation through this pathway results in the activation of NF-kB and mitogen-activated protein kinases (MAPKs), via the interleukin-1 receptor-associated kinase

(IRAK) complex. The classical pathway culminates in the induction of inflammatory cytokines such as TNFα, IL6, IL1β and IL12. IRAK4 and MyD88 are molecules acting downstream from all TLRs except TLR3.

6.4.2 Etiology

Two Mendelian PIDs associated with impaired signaling of the TIR canonical pathway have been reported; mutations in *IRAK4* (OMIM*607676) and *MYD88* (OMIM*612260) [262, 333]. IRAK4 is a protein kinase that plays an essential role in TLR signaling of all known TLRs (except for TLR3) (Fig. 6.1) [2]. It interacts with MyD88 and activates IRAK1. Once hyperphosphorylated, IRAK1 associates with TNF receptor-associated factor 6 (TRAF6), triggering activation of NF-kB and MAPKs pathways [236]. IRAK4 deficiency is an autosomal recessive immunodeficiency caused by homozygous or compound heterozygous *IRAK4* gene mutations [11, 36, 46, 54, 64, 74, 75, 137, 142, 184, 189, 216, 260, 262, 265, 282, 306, 307, 322, 344, 345]. All the reported mutations truncated the kinase domain. The Q293X mutation is seen in half of identified patients, reflecting a mutational hot spot [265]. MyD88 deficiency is an autosomal recessive immunodeficiency caused by homozygous or compound heterozygous *MYD88* gene mutations [65, 260, 265, 333].

6.4.3 Clinical Manifestations

Patients with IRAK4 and MyD88 deficiencies present narrow susceptibility to invasive pyogenic bacterial infections and have normal resistance to common fungi, parasites, viruses, and many other bacteria. In both IRAK4 and MyD88 deficiencies, most of the invasive bacterial infections observed are caused by *S. pneumoniae*, *S. aureus* and *P. aeruginosa*, in particular [260, 265]. These infections can be recurrent. Gram-negative bacteria have been found in two such patients (*Neisseria meningitides*, *Shigella sonnei* and *Salmonella spp*) [54, 216, 265]. Infections mostly strike in infancy and early childhood, frequently presenting as meningitis, arthritis, and/or septicemia. Fever and other systemic inflammatory responses are low or absent [265]. About 40 % of IRAK4- and MyD88-deficient patients died of invasive bacterial infections (mostly of invasive pneumococcal disease), all before the age of 8 years, and most before the age of 2 years [265]. However, both PIDs improved with age, and patients with IRAK4 and MyD88 deficiencies present no further invasive bacterial infections after their teens. Patients with IRAK4 and MyD88 deficiencies also develop non-invasive pyogenic bacterial infections, mostly affecting the skin and upper respiratory tract sites, at which necrotizing infections are particularly common. All these patients are continuing to suffer from skin infections, sinusitis or pneumonia, including those that have reached adulthood [265]. Transient neutropenia can be associated with the infections. Delayed separation of the umbilical cord may also occur in IRAK4 deficiency [307].

6.4.4 Diagnosis

In whole-blood assays, leukocytes from IRAK4- and MyD88-deficient patients do not produce IL6 and no CD62L shedding from granulocytes is observed in response to activation with most of the TLR and IL1R agonists tested [265, 332]. The defects observed abolished all TLR responses (with the exception of those to TLR3 and a few TLR4 responses), and all IL1R responses (at least IL-1β, and IL18) tested, in all hematopoietic and non-hematopoietic cells from all patients tested. However, there seems to be no overt defect of leukocyte development in IRAK4- and MyD88-deficient patients and these patients have normal antigen-specific T- and B-cell responses, as shown by normal findings for immunological analyses, with three notable exceptions [265]. First, impairment of neutrophil migration [36]. Second, marginal zone B ($IgM^+IgD^+CD27^+$) cells are markedly reduced in IRAK4- and MyD88-deficient patients [338]. Third, specific IgG and IgM antibody responses

to pneumococcal and isohemagglutinuns have been shown to be impaired in up to 50 % of the patients explored [265]. MyD88 has recently been shown to control signaling downstream from TACI [154]. Some of the modest, subclinical abnormalities of B-cell responses, such as the production of low levels of antibodies against carbohydrates in some patients, may thus reflect impaired TACI responses, rather than impaired TLR and IL1R responses [265]. Low fever and low systemic inflammatory parameters in a patient's serum such as CRP that contrast with a severe clinical course of infectious diseases should alert the physician to consider IRAK4 or MyD88 deficiency or other defects in TLR signaling. However, pus formation has been observed at various sites of infection.

6.4.5 Management

MyD88 and IRAK4 deficiencies are phenocopies in terms of their immunological and clinical phenotypes [333]. IRAK-4 and MyD88 deficiencies are life-threatening, resulting in the deaths of half of identified patients [117]. Patients with IRAK4 and MyD88 deficiencies should be immunized with conjugated and non conjugated *S. pneumoniae* vaccines, conjugated *H. influenzae* vaccine and conjugated and non conjugated *N. meningitidis* vaccines. A preventive regimen, including antibiotic prophylaxis with cotrimoxazol plus penicillin V (or equivalent), is required throughout the patient's life, with empirical intravenous or subcutaneous IgG injections until at least the age of 10 years [87]. This prophylaxis seems to have an impact on the incidence of invasive bacterial infections [265]. Both clinical status and outcome improve with age and prophylactic treatment appears to be beneficial in these patients. This dramatic improvement with age may be related to the development of adaptive antigen-specific T- and B-lymphocyte responses. The caregivers must be aware that the clinical and laboratory signs of infection are subtle. Early detection of pyogenic infections and rapid institution of appropriate antibiotics are lifesaving.

6.5 Herpes Simplex Encephalitis

(***TLR3*, *UNC93B*, *TRAF3*, *TRIF*, *TBK1*, *IRF3* deficiencies**)

6.5.1 Definition

This group of inherited disorders leads to impaired TLR3 signaling and susceptibility to Herpes simplex encephalitis (HSE) in childhood. The affected patients bear mutations in *TLR3*, *UNC93B1*, *TRAF3*, *TRIF*, *TBK1* or *IRF3* genes. The signaling pathway controlled by TRIF, which is mediated by TLR3 and TLR4, leads to activation of the transcription factors IRF3 and NF-kB (Fig. 6.2) [172]. TRIF recruits TRAF6 and activates TAK1 for NF-kB activation. TRIF also recruits a signaling complex involving TBK1 and IKKε via TRAF3 for IRF3 activation [172]. This

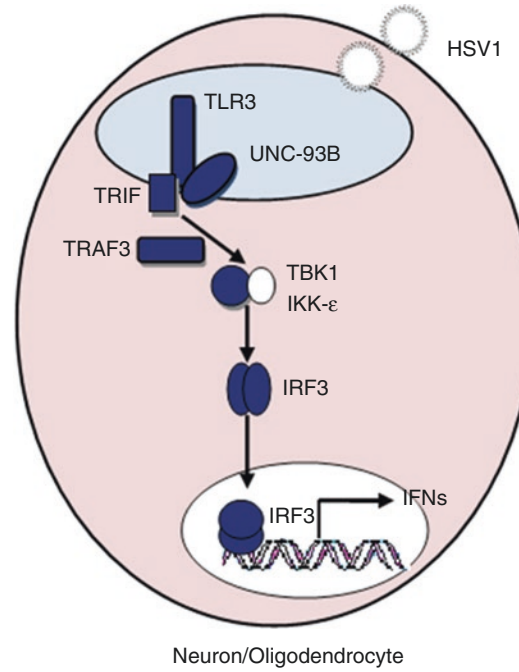

Fig. 6.2 TLR3 signaling pathway. TLR3 signaling is initiated by the recognition of dsRNA, inducing activation of the IRF3 and NF-kB pathways via TRIF, leading to the production of IFNα/β and/or IFN-λ. Deficiencies of the components of this pathway lead to herpes simplex encephalitis (HSE)

signaling pathway induces the production of type I and type III IFNs and inflammatory cytokines, and is important in anti-viral immunity [177]. UNC93B is a 12-transmembrane domain protein present in the ER and delivers the nucleotide-sensing receptors TLR3, 7, 8 and 9 from the ER to endolysosomes [177]. TRAF3 has functions downstream from multiple TNF receptors and the receptors inducing IFNα, β, and λ production, including TLR3. UNC93B and TRAF3 defects also impair the TLR7-9 pathway, but with no known clinical consequences.

6.5.2 Etiology

Heterozygous mutations of *TLR3* have been documented as cause of HSE in otherwise healthy children [350]. Autosomal Dominant (AD) form of TLR3 deficiency due to a heterozygous mutation of TLR3 with dominant-negative effect was identified in 2007 [350]. The recent report of an AR form of complete TLR3 deficiency (OMIM*613002) in a young adult who had developed HSE during childhood further illustrates the crucial importance of TLR3 signaling in fibroblasts for protective immunity to HSV1 in the Central Nervous System (CNS) [129]. AR UNC93B deficiency was identified in 2006 as the first genetic etiology of isolated HSE (OMIM*610551) [50]. Three individuals from two consanguineous kindreds were found to carry homozygous mutations in *UNC93B1*. As UNC93B is implicated in TLR3 signaling, it seems that impaired TLR3-dependent induction of IFNα/β and γ is involved in HSE [349]. A French patient with AD TRAF3 deficiency (OMIM*614849) and HSE has been identified in 2010 [257]. The *de novo* germline *TRAF3* heterozygous missense mutation in this patient is loss-of-expression, loss-of-function and dominant-negative. Two kindreds with childhood HSE associated with TRIF deficiency (OMIM*614850) were recently identified in 2011 [289]. The first patient, from consanguineous kindred, was found to have a homozygous nonsense mutation (R141X) in the N-terminal region of the *TRIF* gene resulting in complete absence of protein [289]. The second patient, from a non-consanguineous kindred, has a heterozygous missense mutation (S186L) in the N-terminal part of the *TRIF* gene, suggesting that this hypomorphic S186L allele of TRIF is dominant negative and responsible for autosomal dominant AD TRIF deficiency [289]. Two kindreds with childhood HSE associated with TBK1 deficiency were recently identified carrying different heterozygous mutations (D50A and G159A) in *TBK1*, the gene encoding TANK-binding kinase 1, a kinase at the crossroads of multiple IFN-inducing signaling pathways [140]. Both mutations are associated with an AD trait but by different mechanisms, haplotype insufficiency (D50A) or negative dominance (G159A) [140]. Finally, heterozygous mutation of *IRF3* has been documented as cause of HSE (OMIM*616532) in 2015 [9]. AD R285Q mutation impaired signaling trough TLR3-TRIF pathway.

6.5.3 Clinical Manifestations

Two of seven patients with AD TLR3-deficiency had developed HSE during childhood [350]. Five individuals, who carry the same heterozygous mutation in TLR3, are now adults and have not developed HSE, despite serologically documented HSV1 infection. The patient with AR complete TLR3 deficiency developed one HSE episode during childhood [129]. Two of the three UNC93B-deficient individuals developed HSE [50]. The first patient had recurrent episodes of HSE at the age of 11 months, 14 months and 3 years and half. The second UNC93B-deficient patient presented recurrent episodes of HSE at the ages of 5 and 17 years. Both UNC93B-deficient patients are now adults and have experienced no subsequent acute events [50]. One sibling of the second patient, who carries the same homozygous mutation in *UNC93B1*, is now adult and has not developed HSE, despite serologically documented HSV1 infection [50]. The first clinical signs of HSE in the TRAF3-deficient patient appeared at the age of 4 years [257]. The patient with TRAF3 deficiency and HSE described here is now adult and has otherwise remained healthy with no prophylaxis. She shows normal resistance to other

infectious diseases, including viral diseases in particular. The patient with the AR TRIF deficiency had no infectious problems until age 2, when he developed HSE complicated by seizures, EEG abnormalities, atrophy of the left temporal lobe, and delayed speech [289]. Patient with AD TRIF deficiency has HSE, although with incomplete penetrance as only one of the three S186L *TRIF* heterozygote individuals developed HSE following HSV1 infection at age 21 months [289]. She responded to treatment with acyclovir and never relapsed, but has neurologic sequelae, consisting of blindness and epilepsy. Two of three patients with TBK1 deficiency suffered from HSE at the ages of 11 months and 7 years [140]. They are now 17 and 26 years old, respectively, and have suffered no other unusual infectious diseases, viral in particular, in the absence of prophylaxis. One adult individual who carry the same heterozygous mutation in *TBK1*, has not developed HSE [140].

A Danish girl was found to carry homozygous mutations (R285Q) in *IRF3* [9]. She received acyclovir as inpatient treatment; however, the neurologic deficits persisted after discharge. The mutation was also present in the healthy father, consistent with incomplete clinical penetrance.

6.5.4 Diagnosis

HSE certainly raises suspicion of TLR3, UNC93B, TRAF3, TRIF, TBK1 or IRF3 deficiency. However, it is reasonable to presume that any severe HSE infection, even a single one, is due to an immunodeficiency of a known or unknown type. All standard immunological parameters, such as the numbers of blood phagocytes, B and T lymphocytes, lymphocyte subset distribution, NK cells, antibody production, and T-cell proliferation in response to the mitogens and antigens tested, were all normal in all patients tested. Blood leukocytes (monocyte-derived dendritic, NK, and CD8 T cells) from TLR3-deficient patients have an impaired response to stimulation with TLR3 agonist (polyinosinic-polycytidylic acid (polyI/C)). The fibroblast cells of the TLR3-deficient patients produce low levels of the antiviral molecules IFNβ and IFNλ in response to TLR3 agonist, HSV1, and vesicular stomatitis virus (VSV), leading to higher levels of viral replication and virus-induced cell death than for healthy control cells [350]. These observations suggest that the TLR3-dependent generation of IFNα, IFNβ, and IFNλ is critical for primary immunity to HSV1 in the CNS but redundant for immunity to most other viral infections [350]. UNC93B deficient fibroblasts and leukocytes did not respond to TLR3, or to TLR7-9 agonists respectively, in terms of IFNα, β and λ production [50]. The fibroblasts from UNC93B-deficient patients displayed abnormally high levels of viral replication and cell death after infection with HSV1. Fibroblasts from the patients displayed impaired responses to TLR3 agonist stimulation, in terms of IFNβ and λ production. Various TRAF3-dependent pathways were impaired in the patient's cells, including the IFNα/β-, and λ-inducing and TNFR-responsive pathways [257]. However, there was sufficient residual TRAF3-dependent signaling for most defects to remain clinically silent. By contrast, the impaired TLR3 response was symptomatic and caused HSE, implying that the TLR3 pathway is critically dependent on TRAF3 and essential for immunity to HSV1 in the CNS [257]. The loss-of -expression/function of TRIF resulted in the abolition of TLR3-mediated signaling and TRIF-dependent TLR4 responses as measured by IFNβ and IFNλ production [289]. A defect in polyI/C–induced TLR3 responses can be detected in fibroblasts heterozygous for G159A but not for D50A *TBK1* variant [140]. Nevertheless, viral replication and cell death rates caused by two TLR3-dependent viruses (HSV1 and VSV) were high in fibroblasts from both patients, and particularly so in G159A TBK1 fibroblasts. The IFN responses to the TLR3-independent agonists and viruses tested were maintained in both patients' peripheral blood mononuclear cells and fibroblasts [140].

The R285Q IRF3 variant cannot undergo serine phosphorylation or dimerization and thus fails to activate transcription [9, 348]. This IRF3

mutation impairs the induction of antiviral IFNα/β in response to various stimuli. Moreover, IFNβ induction in heterozygous fibroblasts stimulated by poly(I:C), and HSV1 is also impaired.

6.5.5 Management

A secondary preventive treatment regimen with acyclovir should be proposed in patients presenting an impairment of TLR3 signaling pathway. Treatment with recombinant IFNα, in parallel with acyclovir, may be considered in patients with TLR3, UNC93B, TRAF3, TRIF, TBK1 and IRF3 deficiencies during acute HSE episode. The management of these patients is not still well established and will require supplementary clinical studies, notably regarding the duration of the preventive treatment.

6.6 Mendelian Susceptibility to Mycobacterial Diseases

(***IFNγ receptor 1/2 deficiencies, IL12/23 receptor β1 chain deficiency, IL12p40 deficiency, DP-STAT1 deficiency, LZ-NEMO deficiency, Macrophage-specific CYBB deficiency, AD-IRF8 deficiency, ISG15 deficiency***)

6.6.1 Definition

The IL12/Interferon-γ dependent signaling pathway is central to controlling mycobacterial infections (Fig. 6.3). Upon phagocytosis of such bacteria, macrophages secrete IL12p70, a heterodimer of IL12p40 and IL12p35 that stimulates Th1 T cells and NK cells through activation of IL12R. This receptor is composed of two chains, IL12Rβ1 and IL12Rβ2 [110] that associate with TYK2 and JAK2 kinases. Activation of this complex by IL12 ligand promotes signal transducer and activator of transcription-4 (STAT4) phosphorylation and nuclear translocation, and thereby induces IFNγ production and secretion [337]. IFNγ acts through its receptor, IFNγR, a heterodimer of IFNγR1 and IFNγR2, on macrophages and other cells.

Analogous to IL12 signaling, IFNγR associates with JAK1 and JAK2. A series of phosphorylation steps leads to homodimerization of signal transducer and activator of transcription-1 (STAT1). This phosphorylated STAT1 translocates to the nucleus to initiate the transcription of IFNγ-inducible genes [16]. The respective gene products endow the macrophages with tools to confine (e.g., via granuloma formation) and finally kill mycobacteria.

Molecular defects in IL12/IFNγ dependent signaling cause rare genetic disorders. Theses defects belonging to the group of Mendelian susceptibility to mycobacterial diseases (MSMD) are characterized by disseminated or localized infections caused by either environmental mycobacteria (EM), BCG vaccine strains, or even *Mycobacterium tuberculosis* in otherwise healthy individuals [3, 49, 110]. Severe disease caused by non-typhoidal and typhoidal *Salmonella* serotypes is also common. Defects in *IFNGR1* (OMIM*107470), *IFNGR2* (OMIM*147569), *IL12RB1* (OMIM*601604), *IL12B* (OMIM*161561), *STAT1* (OMIM*600555), *IRF8* (OMIM*601565), *ISG15* (OMIM*147571), *CYBB* (OMIM*300481) and *NEMO* (OMIM*300248) have been identified in MSMD patients (Table 6.1) [3, 28, 42, 133].

6.6.2 Etiology

IFNγR1 deficiency was the first identified genetic disorder recognized as MSMD [163, 229]. Such mutations can be recessive or dominant and are reported in about 39 % of patients with MSMD [3, 110]. In recessive complete (RC) forms, mutations involve the extracellular domain of IFNγR1 and most of them result in complete lack of cell surface receptor (nonsense mutations, frameshift) [8, 91, 144, 163], whereas some allow for receptor expression, but lead to impaired IFNγ binding (in-frame deletions) [164].

A recessive partial (RP) IFNγR1 deficiency with reduced, but not absent, IFNγR1 responsiveness caused by an I87T mutation has also been reported [166, 274].

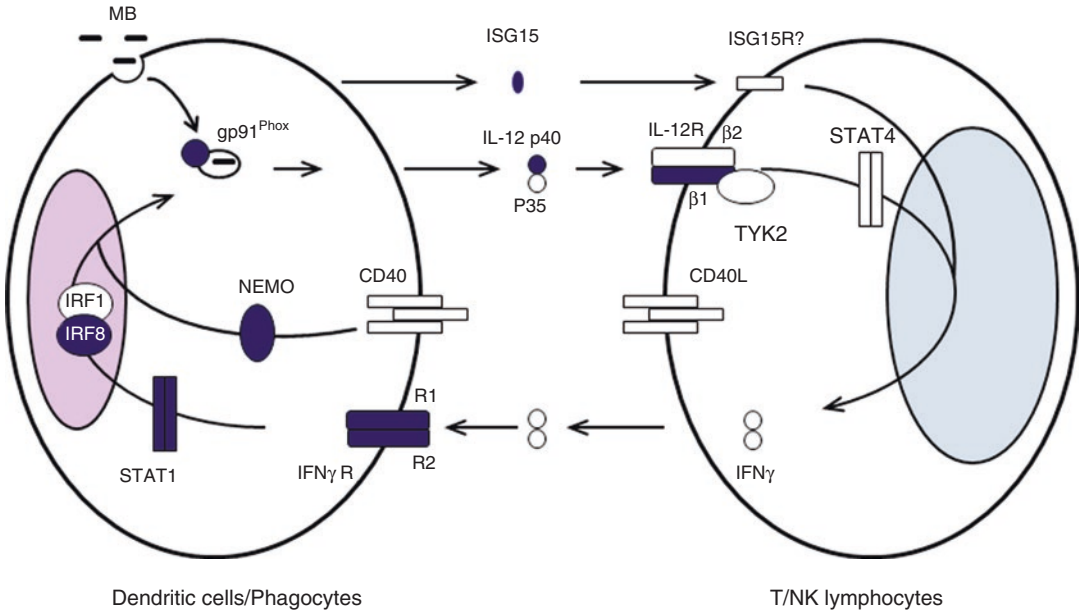

Fig. 6.3 IFNγ and IL12 signaling pathways in immunity against mycobacteria and some other intracellular organisms. Structures affected in MSMD are marked in *blue*. *MB* mycobacteria

Table 6.1 Genetic defects that cause Mendelian susceptibility to mycobacterial disease

		Infections			
Gene	Inheritance	Mycobacteria	Salmonella	Viruses	Other
IFNGR1	AR	++	+	+, HHV8	*Listeria monocytogenes*, *Shigella sonei*, *Haemophilus influenza*, *Leginella spp.*, *Mycoplasma pneumonia*, *Klebsiela spp.*
	AD	++	+	–	*Histoplasma capsulatum*, *coccidioidomycosis*
IFNGR2	AR	++	–	+, CMV	–
	AD	++	–	–	–
IL12B	AR	++	++	–	*Nocardia astroides*
IL12RB1	AR	++	++	–	*Paracoccidoides brasiliensis*, chronic mucocutaneous candidiasis, leishmaniasis
STAT1	AD	++	–	–	–
ISG15	AR	++	–	–	–
IRF8	AD	++	–	–	–
NEMO	XR	++	+	+	+
CYBB	XR	++	–	–	–

Dominant partial (DP) IFNγR1 deficiency is due to heterozygous truncations of the cytoplasmic domain of IFNγR1 resulting in accumulation of non-functional receptor molecules at the cell surface [14, 167, 327, 334]. 818del4 is a hotspot for DP-IFNγR1 deficiency. Mutations in *IFNGR2* have been identified less often than in *IFNGR1*.

Recessive complete forms (RC) of IFNγR2 deficiency result mostly in an entire loss of receptor. Sometimes the expression of non-functional

receptor molecules has been documented [90, 281, 331]. Several of *IFNGR2* mutations cause abnormal N-glycosylation and misfolding of the IFNγR2 protein [221, 331]. The additional polysaccharide is responsible for defective IFNγ signaling. Recessive partial (RP) IFNγR2 deficiency has been reported in a patient with the missense mutation located in the extracellular domain [87]. Furthermore, a 791delG mutation that causes complete IFNγR2 deficiency in the homozygous cells exerts a dominant-negative effect in heterozygous state [281]. Recently the heterozygous loss-of-function 186delC mutation in *IFNGR2* is reported as the underlying defect of MSMD in a single patient [181].

IL12RB1 is the most frequent known genetic cause of MSMD seen in about 40% of cases [3, 110]. The mutations are diverse and all cause recessive complete (RC) IL12 receptor β1 chain deficiency [6, 107, 108, 325]. IL12 comprises two subunits, p35 and p40, encoded by the *IL12A* and *IL12B* genes, respectively [317]. P40 subunit is also included in the structure of IL23.

STAT1 is required for cellular responses to both type I (IFNα/β) and type II (IFNγ) interferons. Activation through IFNα/β results in the formation of the transcription factor IFN-stimulated-γ-factor-3 (ISGF3) in addition to the transcription factor gamma activating factor (GAF). The latter is also the main transcription factor mediating cellular activation by IFNγ. Heterozygous missense mutations in *STAT1* cause dominant partial (DP) STAT1 deficiency [55, 96]. In these mutations, the formation of sufficient ISGF3 is still possible and, consequently, type I interferon-mediated viral defense is not or only marginally impaired.

Mutations in the leucine zipper (LZ) domain of the NEMO have been discovered as the X-linked form of MSMD [111]. Impaired production of IL12 and IFNγ in response to CD40L largely accounts for the pathogenic effect of LZ-NEMO mutations in these patients [3, 111].

Another X-linked form of MSMD is caused by defect in CYBB-dependent NADPH oxidase assembly and respiratory burst in macrophages [42, 43]. Interestingly, the granulocytic respiratory burst is intact. The connection of the CYBB mutation with the IL12–IFNγ circuit is elusive.

Mutations in interferon regulatory factor 8 (IRF8), inducible by IFNγ, impair IL12 secretion by monocytes and dendritic cells [133]. Heterozygous IRF8 mutations underlie the partial IRF8 deficiency in a dominant-negative manner. Moreover, the circulating dendritic cells that produce large amounts of IL12 are lacking. Complete recessive IRF8 deficiency has a broader immunologic and clinical phenotype and discussed in Sect. 6.14.

Interferon-stimulated gene 15 (ISG15) is an intracellular ubiquitin-like molecule involved in ISGylation. However, it can be secreted from different leukocytes and induces the production of IFNγ from T cells and NK cells [27]. This function complements the role of the IL12– IFNγ circuit in the control of mycobacterial infection. Homozygous *ISG15* mutations are reported in patients with MSMD only phenotype [28].

6.6.3 Clinical Manifestations

Susceptibility to weakly virulent mycobacteria, such as BCG vaccines is the rule. The patients are also vulnerable to more virulent species such as *M. tuberculosis* [3, 110]. Besides the exceptional diseases caused by some intracellular organisms, MSMD patients are resistant to most other microbial infections.

RC-IFNγR-deficient patients are most susceptible to severe, early onset mycobacterial infections with profoundly impaired granuloma formation [102]. In contrast, patients with partial IFNγR deficiencies acquire mycobacterial infections later in life, still sprout granulomas, and are likely to respond well to antimycobacterial antibiotics [44, 334]. A few of these patients present with nontyphoidal salmonellosis not restricted to the gut, histoplasmosis, or listeriosis [91, 279]. Viral infections with cytomegalovirus (CMV) and human herpes virus 8 (HHV-8) are reported in a few patients with RC-IFNγR1 deficiency [44, 92]. Interestingly, in DP-IFNγR1 deficiency osteomyelitis caused by environmental mycobacteria or BCG is common and more frequently observed than in RC-IFNγR deficiency (Fig. 6.4) [91, 279]. A clinical disease similar to Langerhans' cell histiocytosis is reported in two patients with DP-IFNγR1 deficiency [98].

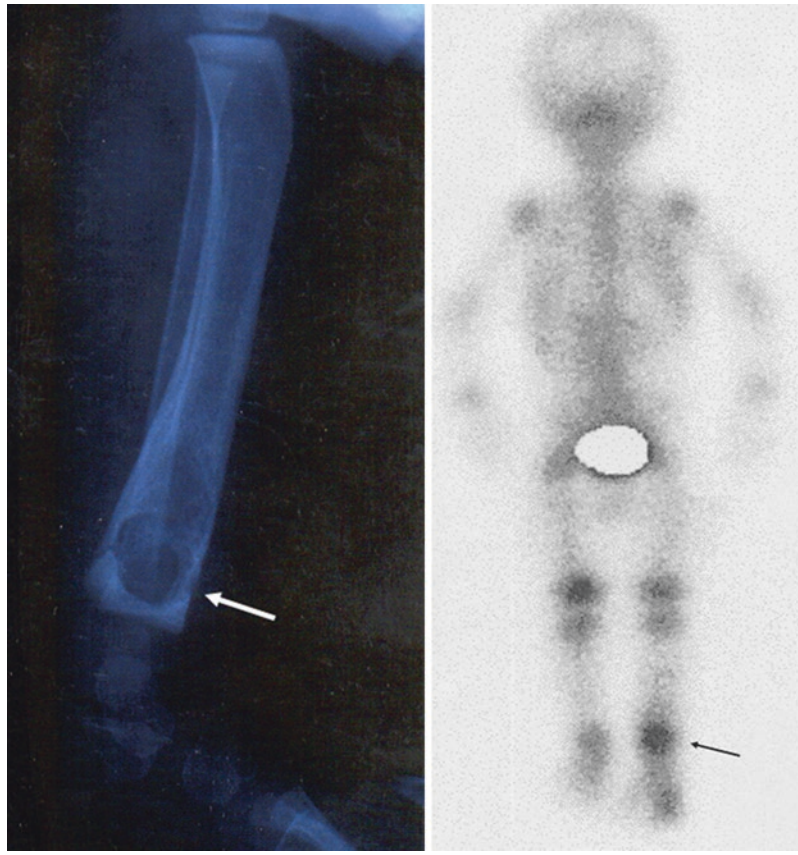

Fig. 6.4 Osteomyelitis in a patient with dominant partial IFNγR1 deficiency. Radiograph of the left shin showing osteolytic lesion in the left tibia (*white arrow*). Skeletal scintigram, showing an area of increased uptake of technetium in the distal end of the left tibia (*black arrow*)

The clinical phenotype of IL-12Rβ1 deficiency resembles that of DP-IFNγR deficiency, but nontyphoidal salmonellosis is more frequent as half the patients acquire this infection [76, 204]. Interestingly, these patients are also susceptible to clinical diseases caused by *M. tuberculosis* [7, 29, 45, 250]. Granulomas can still be formed but are often multibacillary [261].

A substantial portion of IL12Rβ1 deficient patients develop mucocutaneous candidiasis that is recurrent or persistent [76, 249]. Recurrent leishmaniasis has been reported in a patient with IL12Rβ1 deficiency [287]. The picture of IL12p40 deficiency is similar to IL12Rβ1 deficiency, although the clinical course is mostly more severe [266].

DP-STAT1 deficiency is associated with a relatively mild clinical course, resembling that of partial IFNγR deficiencies [55, 96]. Reported CYBB-MSMD and AD-IRF8 deficient patients were presented solely with mycobacterial diseases [229, 317].

Reported patients with LZ-*NEMO* mutations were vulnerable to mycobacteria primarily, or in association with other bacteria (e.g. *H. influenza*) [111].

The clinical and immunologic phenotypes of ISG15 deficiency resembled those of IL12Rβ1 deficiency, with impaired IFNγ immunity and relatively mild MSMD [28].

6.6.4 Diagnosis

In regions of the world that BCG vaccination is routine, clinical BCG disease could be the first and only presenting feature. Infections with environmental mycobacteria that clinically differ

from the common and frequent infections of cervical lymph nodes in any respect such as unusual spreading, unusual types of mycobacteria, affection of internal organs and especially of bones are indicating clinical signs. It is important to note, however, that contaminations of patients' samples with *M. avium* are common. These bacteria can also sometimes be found at sites of infections without doing much harm, e.g., at teeth. A careful histopathological and microbiological evaluation is therefore necessary.

It is revealing to look at the diagnoses that had been considered over long time periods by physicians before the right diagnosis of an MSMD was made. Environmental mycobacterial osteomyelitis was confused with eosinophilic granuloma, with chronic recurrent multifocal osteomyelitis or with tuberculosis several times, and infection of the gut with Crohn's disease. Persistent pneumonia and hepatitis can also be due to mycobacteria in MSDM.

Diagnostic tests require in depth experience with cellular immunology laboratory testing and are only available in specialized laboratories.

IFNγR and STAT1 deficiencies are diagnosed by impaired cellular responses to IFNγ. In the PBMC (peripheral blood mononuclear cell) cultures, expression of MHC and TNFα production are impaired in response to LPS and IFNγ [90, 164]. In a whole blood assay, production of IL12 is impaired in response to BCG and IFNγ [105]. In the RC-IFNγR deficiency, high circulating levels of IFNγ are seen, presumably due to impaired receptor-mediated clearance [109]. Flow cytometric evaluation of IFNγR1 shows over accumulation of receptor subunit in patients with AD-IFNγR1 deficiency but the IFNγR2 expression is diminished in the case of AD-IFNγR2 deficiency [167, 181].

In most cases of IL12Rβ1 deficiency, no IL12Rβ1 is expressed on the cell surface and no response is seen to in vitro IL12 or IL23 [76, 108]. All known mutations of *IL12B* are recessive complete (RC) with a lack of detectable IL12p40 secretion by patients' blood cells [261, 266].

Unlike the cells of CGD patients, neutrophils and monocytes from macrophage-specific CYBB deficiency display a functional respiratory burst and kill *Staphylococcus aureus* efficiently. However, monocyte-derived macrophages and EBV-transformed B cells show completely abolished respiratory burst function [42]. The IL12/IFNγ whole blood assay is normal in AD-IRF8 deficiency. However, the patients lacked $CD1c^+$ $CD11c^+$ circulating dendritic cells [133]. The immunological phenotype of ISG15 deficiency resembles those of patients with IL12p40 or IL12Rβ1 deficiency, with impaired IFNγ production in the whole blood assay [28]. Determination of ISG15 secretion from leukocytes could be used as screening. Finally, the diagnosis can be confirmed by sequencing the affected genes.

6.6.5 Management

In general, mycobacteria should be typified and infections treated according to growth pattern (slow or fast) and sensitivity. RC-IFNγR deficiency is a very severe disease with a poor prognosis. Most of the patients die during early infancy or childhood. The mycobacterial infections hardly respond completely to available therapy and subcutaneous application of pharmacological doses of IFNγ is useless [91]. Instead, IFNα could perhaps be helpful [336]. HSCT has been performed in some patients with variable results. A high rate of graft rejection was observed, at least when reduced conditioning was applied [53, 110, 147, 278].

Such infections in partial IFNγR deficiencies mostly respond favorably to appropriate antibiotics or even resolve spontaneously. Subcutaneous application of pharmacological doses of IFNγ in addition to antibiotics can be very helpful. Antimycobacterial treatment can eventually be stopped, but not within the first year after control of the infection is achieved [264]. However, a lifelong antimycobacterial prophylaxis may be required in some patients [139].

It is important to note that bone lesions caused by environmental mycobacteria are not always painful and bone stability may not always be secured. DP-STAT1 deficiency has a clinical course similar to those of patients with partial IFNγR deficiency and should be treated similarly.

Patients with IL12Rβ1/IL12p40 deficiency respond well to antibiotics and IFNγ; the overall prognosis is quite good [76, 266]. Salmonellosis is recurrent and may become resistant to eradication. Recurrent candidiasis should be treated with azole regimens, secondary prophylaxis is recommended for severe cases [249]. Mycobacterial infections in IRF8, ISG15 and macrophage-specific CYBB deficiencies are amenable to antibiotic combinations and possibly recombinant IFNγ.

6.7 Genetic Defects of Interferon Type I and III Responses Other than TLR3 Pathway

(***AR STAT1 and STAT2 deficiency, TYK2 deficiency, IRF7 deficiency***)

6.7.1 Definition

The significance of STAT1 has already been pointed out in Sect. 6.6. The different compositions of the transcription factors GAF (STAT1/STAT1) in the IFNγ pathway and ISGF (STAT1/STAT2/p48) in the IFN-α/β pathway provide an explanation for the different effects of variant forms of STAT1 and STAT2 deficiencies. In contrast to the dominant partial form (DP STAT1 deficiency), autosomal recessive STAT1 deficiency (AR STAT1 deficiency) does not only affect cellular responses to IFN-γ, but also those to IFN-α/β [97]. DP STAT1 deficiency is only dominant in the IFN-γ pathway, but recessive in the IFN-α/β pathway. However, if a mutated *STAT1* allele has no dominant negative effect, it is recessive in both pathways because haploinsufficiency could never be found [30].

AR STAT1 and STAT2 deficiencies can cause diminished defenses against viral infections due to a lack of ISGF [30, 132]. The resulting disorders can be life threatening or moderate or even lack complete heritable penetrance. Furthermore, the STAT1 and two deficiencies reveal redundant defenses against many viruses [57, 132].

TYK2 (OMIM*176941) is a member of the JAK kinase family, with unclear role in different signaling pathways in the mouse model [302, 326]. However, it seems to be non-redundant in mice for cellular responses to IL12 and IFNα/β [169, 297]. It was originally described as essential for type 1 IFN signaling in a human fibroblast cell line [326]. The study of TYK2 deficient patients highlights its role in different cytokine receptor expression and signaling [176, 185, 219]. IRF7 is a transcription factor that amplifies type I and III interferon genes upon viral infections [145, 208]. Forward genetic studies identify IRF7 as an essential factor in anti-influenza immunity [60].

6.7.2 Etiology

Homozygous or compound heterozygous null mutations in *STAT1* lead to complete unresponsiveness to IFNγ, IFNα/β, IFNλ, and IL27 because neither GAF nor ISGF can be formed [30]. Therefore, genes regulated by these transcription factors such as inducible NO synthetase and Mx proteins are not expressed upon stimulation with the respective interferons leaving patients susceptible to life threatening infections with mycobacteria and viruses (mainly herpes viruses). The clinical phenotype is milder if instead of null alleles, homozygous or compound heterozygous hypomorphic *STAT1* mutations are present [56]. According to the compositions of GAF and ISGF, mutations in *STAT2* that prevent measurable STAT2 protein expression leave responsiveness to IFNγ (and IL27) unaffected, but abolish response to IFNα/β (and IFNλ) [132]. Moreover, STAT2 deficiency is recently revealed to cause abnormal mitochondrial fission, linking the innate immunity to mitochondrial function [295].

All together, the following functionally aberrant *STAT1* mutation types have been found and can lead to very different clinical pictures: Dominant negative (Sect. 6.6), and null alleles (Sect. 6.7), hypomorphic (Sect. 6.7), and hypermorphic alleles (Sect. 6.10) (Table 6.2) [200], and alleles that to date do not fit into a clear functional and clinical picture [296]. These heterozygous *STAT1* mutations arise de novo and are

associated with decreased STAT1 expression, sometimes chronic mucocutaneous candidiasis, autoimmunity, and severe infections. A progressive loss of lymphocytes and lymphocyte function is a feature very different from the other forms. Even though the latter mutations are not recessive they are mentioned here because they can also facilitate viral infections that can be fatal. Furthermore, there is some limited, but remarkable correlation of the different clinical pictures with the localization of mutations within different STAT1 domains [30].

TYK2 deficiency (OMIM*611521) was first considered to be an AR genetic etiology of HIES based on the observation of a single patient [219]. The impaired IL12 and IFNα/β signaling in this patient accounted for his susceptibility to intracellular organisms and viruses. HIES could be attributed to impaired IL6 cellular responses. The identification and immunological investigation of additional patients changed our perception of TYK2 deficiency as a unique clinical entity that does not match with HIES [176, 185]. Recently, compound heterozygous mutation of *IRF7* (OMIM*616345) has been documented as cause of life-threatening influenza infection [61].

6.7.3 Clinical Manifestations

To date, only few patients with AR STAT1 and STAT2 deficiencies have been characterized. Therefore, it is unknown if these disorders have distinctive clinical features that are not shared by other immunodeficiencies. Patients with two null or hypomorphic *STAT1* alleles are susceptible to mycobacteria including those that are non- or weakly virulent in healthy individuals such as *Mycobacterium kansasii* or BCG and also to viral infections [30].

If the disorder is caused by *STAT1* null alleles the mycobacterial infections clinically resemble those found in complete IFNγ deficiency (Sect. 6.6). Multiple organs can be affected and blood cultures can be positive for mycobacteria. Such mycobacterial and viral infections are often life threatening early in life. HSV1 may cause lethal encephalitis and other viruses of the herpes group such as CMV may lead to severe infection. Remarkably, patients can fight other viral infections such as rhinoviruses, parainfluenza and live polio-vaccine indicating redundancy of anti-viral host defenses. In the case of hypomorphic *STAT1* alleles that allow for some STAT1 signaling the viral and mycobacterial infections tend to occur later in life and the clinical course is milder.

Complete STAT2 deficiency has been described first in a patient as the reason for severe disseminated vaccine strain measles complicated by hepatitis and severe pneumonitis [132]. In the brother of this patient, this deficiency was the likely reason for a fatal short illness due to a suspected viral infection. In relatives with the same homozygous deficiency, viral infections tended to be milder or were even unremarkable and only detectable by serology. These findings support again the notion of redundancy in anti-viral defenses. Recently, three STAT2-deficient patients (including the first reported patient) were evaluated in detail [295]. Two Albanian siblings presented with neurological problems after MMR vaccination. These patients also had underlying mitochondrial problems.

The first TYK2 deficient patient displayed the characteristics of HIES, i.e. high circulating IgE levels, atopy and predisposition to cutaneous staphylococcal infections [219]. Moreover, he was susceptible to clinical disease caused by BCG and nontyphoidal *Salmonella*, and recurrent viral infections.

The second TYK2 deficient patient did not display HIES features, however like the first one, he suffered from intracellular infections (BCG and *Brucella*) and recurrent viral infections [176].

A recent report, described in detail the clinical and immunological characteristics of all eight identified TYK2 deficient patients including the first two ones [185].

Altogether, TYK2 deficient patients demonstrate a phenotype similar to partial AR STAT1 deficiency with susceptibility to diseases caused by intracellular bacterial and mild viral infections. TYK2 deficiency also should be considered in cases of severe tuberculosis in children. It is now clear that HIES is not a characteristic feature of TYK2 deficiency.

Table 6.2 Genetic defects that cause impaired interferon type I and III responses

Genetic defect	Inheritance	Immunological phenotype	Clinical phenotype
Partial/complete STAT1 deficiency	AR	Impaired/abolished IFNα/β,γ,λ, IL27 responses	Intracellular bacterial (mycobacteria, salmonella) and viral diseases
Partial STAT1 deficiency	AD	Selectively impaired IFNγ responses	Selective intracellular bacterial diseases (MSMD)
Gain of STAT1 activity	AD	Enhanced IFNα/β,γ,λ, IL27 responses	CMC, other infections, autoimmunity, aneurysms, carcinomas
Complete STAT2 deficiency	AR	Impaired IFNα/β responses	Severe viral infections (disseminated vaccine-strain measles), mitochondrial defect
Complete TYK2 deficiency	AR	Impaired IFNα/β, IL12, IL23, IFNλ, IL10 responses	Intracellular bacterial (mycobacteria, salmonella) and viral diseases
Complete IRF7 deficiency	AR	Impaired type I and type III IFN responses	Severe influenza infection

Finally, AR IRF7 (F410V, Q421X compound heterozygous) deficiency is discovered as the underlying defect in a girl who developed severe primary influenza infection during pandemic H1N1 2009 influenza A virus [61]. The patient did not experience severe infections caused by other viruses.

6.7.4 Diagnosis

Clinical clues to differentiate mycobacterial disease in MSMD from such infections in otherwise healthy individuals and important differential diagnoses have already been described in Sect. 6.6. Severe viral and especially herpes group infections do also occur in T cell deficiencies and in disorders of TLR3 and its signaling pathway. Further genetic defects of anti-viral defenses will most probably be discovered in the near future. If both, viral and mycobacterial infections occur within one family and no T cell deficiency (including HIV) is present then AR STAT1 deficiency is a likely diagnosis [30]. STAT2 deficiency is even rarer than STAT1 deficiency [132]. It should be considered as a differential diagnosis if no other clue for an exclusive susceptibility to viral infections is detected.

In AR STAT1 deficiency, high serum levels of IFNγ can be found. In whole blood assays, monocytes do not respond to BCG and IFNγ by producing normal amounts of IL12. Furthermore, cells from patients with AR STAT1 or STAT2 deficiency do not or not sufficiently respond to IFNα/β in terms of forming ISGF and inducing transcription of genes such as *Mx* that are regulated by ISGF. The respective genetic defects should of course be confirmed by sequencing. Electron microscopy of muscle and fibroblasts from the affected STAT2-deficient patients revealed long mitochondria, suggesting defective mitochondrial fission [295]. The mitochondrial fission protein DRP1 (dynamin related protein 1) was inactive after abnormal phosphorylation pattern induced by STAT2 absence.

All TYK2 deficient patients displayed impaired cellular responses to IL12, IFNα/β, IL23, IL10 and IFNλ [185]. In contrast, TYK2 is redundant for signaling downstream of receptors specific to IFNγ, IL21, and IL27. All TKY2 deficient patients except the first one responded normally to IL6. The expression of exogenous wild-type *TYK2* in the first patient's cells did

not rescue IL6 hyporesponsiveness, an evidence against the role of *TYK2* mutation as a cause [185].

The mutant *IRF7* alleles fail to induce type I and type III interferons in pDCs. Moreover, increased influenza virus replication was documented in affected patient's iPSCs-derived pulmonary epithelial cells [61].

6.7.5 Management

In complete AR STAT1 deficiency, HSCT should be attempted. Response to anti-viral and anti-mycobacterial medication is poor in contrast to the partial form [30]. In this case, additional therapy of mycobacterial infections with IFNγ and prophylactic therapy with azithromycin as in other partial defects of the IFNγ/IL12 axis may be considered. It is not yet clear to what extent adaptive immunity can compensate for the defect in anti-viral defense in the course of life. Any possible dangerous viral infection especially herpes encephalitis should be prompted by adequate antiviral medication as early as possible. The same may be true for STAT2 deficiency. At least some live viral vaccines such as measles are probably contraindicated [132]. In case of contact, immunoglobulins with sufficient titers should be applied. TYK2 deficient patients have been managed with specific therapies directed against each microbial or viral infection.

6.8 Warts, Hypogammaglobulinemia, Infections, Myelokathexis (WHIM) Syndrome

6.8.1 Definition

The WHIM syndrome is very rare and comprised of warts, hypogammaglobulinemia, infections, and myelokathexis (OMIM*193670) [122, 342]. Myelokathexis is the retention of mature neutrophils in the bone marrow [353]. Most patients with WHIM syndrome carry heterozygous gain of function mutations in the gene coding for the chemokine receptor CXCR4 [141].

6.8.2 Etiology

CXCR4 (CD 184) is a G protein-coupled receptor, including seven transmembrane regions, an amino-terminal extracellular domain, and an intracellular carboxy terminus. It is coded by *CXCR4* gene (OMIM*162643) and expressed in the immune system and throughout the central nervous system [127]. The ligand of CXCR4, SDF1 (stromal cell-derived factor-1) or CXCL12, is produced by bone marrow stromal cells and a variety of other tissues. SDF1 interaction with CXCR4 plays a central role in bone marrow homing and trafficking of hematopoietic progenitor cells to the bone marrow [192, 303]. Many but not all WHIM cases have been linked to heterozygous mutations in CXCR4, all of which are clustered in the cytoplasmic tail of the receptor [127, 141]. Mutant receptors display gain-of-function properties leading to absent receptor desensitization, due to defective ligand-mediated receptor internalization and/or decreased phosphorylation of activated mutant CXCR4 [128, 173]. Increased responsiveness to SDF1 leads to pathological retention of post-mature leukocytes in the bone marrow (myelokathexis) [18, 290]. In mouse models with desensitization-resistant CXCR4 receptors, suppression of T and B lymphopoiesis and dysfunction of the immunological synapse were demonstrated [17, 168].

The mechanism for the susceptibility to human papilloma virus (HPV) infection is unknown. It is disproportional compared to other viruses. Moreover, an unusual Human Polyoma Virus has been detected in the skin of a WHIM patient (HPγ-10) [41]. WHIM patients show a significant decrease in plasmacytoid and myeloid dendritic cells [311], which may be important for antiviral immunity. Alternative to and independent of immunodeficiency it has been hypothesized that the mutant CXCR4 signalling directly stimulates keratinocyte transformation [59].

The absence of mutations in the *CXCR4* gene in some patients supports the view that WHIM

syndrome is genetically heterogeneous [18, 141]. Pathways linked to CXCR4 signalling and candidate genes in CXCR4 negative WHIM are GPCR Kinase-3 (GPK-3), Rac-2 (Rac-related C3 Botilinum toxin substrate 2) and Sphingosine-1 phosphatase receptor-5 (S1P5) [4].

6.8.3 Clinical Manifestations

HPV-induced warts may already appear in early childhood. While some individuals have relatively few or no warts, others are afflicted with extensive cutaneous verrucosis, including genital condyloma acuminata with dysplastic changes [122, 342].

Recurrent bacterial infections from infancy including pneumonia, sinusitis, otitis, cellulitis, periodontitis, and abscesses are caused by common pathogens. The clinical course is relatively benign, however, deaths from mycobacterial disease have been reported [81, 89, 127]. Malignancies comprise EBV positive B cell lymphomas, T-cell lymphomas, HPV induced vulvar, basal cell and oral squamous cell carcinomas [51, 153]. The overall cancer risk is estimated to be 30 % by the age of 40 years [19]. Finally, complex congenital heart defects (double aortic arch, tetralogy of Fallot) have been described infrequently [19].

6.8.4 Diagnosis

WHIM should be suspected in any patient with warts, leukopenia, neutropenia and hypogammaglobulinemia. Examination of bone marrow shows myeloid hypercellularity with morphologic abnormalities (Fig. 6.5) consistent with apoptosis (pycnotic, hypersegmented nuclei, and multiple small cytoplasmic vacuoles) [127]. Neutropenia in WHIM is severe, with absolute counts usually below 300/μL [82, 127]. During acute systemic

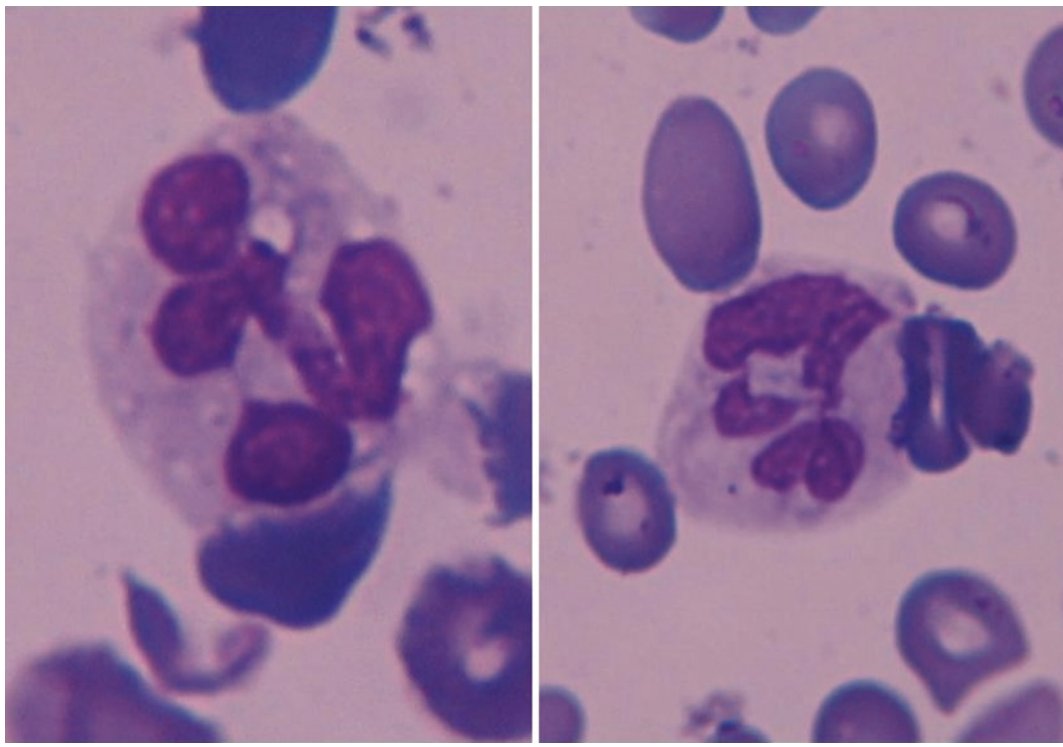

Fig. 6.5 Peripheral blood smear of a patient with WHIM syndrome. Polymorphonuclear cells showing hypersegmented nuclei with long filaments connecting nuclear lobes

infections, neutrophils can be recruited to the blood; even leukocytosis with neutrophilia is observed. Lymphopenia is less common than neutropenia. B lymphopenia has been described in several patients [13, 122] with marked reduction of $CD27^+$ memory B cells [128]. Hypogammaglobulinemia is variable and may affect all isotypes [13, 122, 128]. T lymphocyte subsets and in-vitro lymphocyte proliferation to mitogens are abnormal in some but not all patients [127, 342]. Verification of disease causing mutations in *CXCR4* (when present) confirms the diagnosis.

6.8.5 Management

Plerixafor (Mozobil) is a small molecule CXCR4 antagonist. It was originally designed to inhibit HIV entry into CXCR4+ CD4 cells and then licensed for stem cell mobilization in the context of stem cell transplantation. In phase I trials it has now been used in WHIM at dosages from 0.02/mg/kg s.c. to 0.24 mg/kg at 2–4 day intervals and resulted in significant and sufficient recruitment of neutrophils into blood [73, 214]. Administration of granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) also causes a rapid increase in the neutrophil count and may normalize bone marrow cytology [146, 340, 341]. Prophylactic antibiotics and regular infusions of intravenous immunoglobulin are non-specific but may reduce the incidence of bacterial infections.

Warts are usually resistant to local therapy. The high risk of malignant transformation of genital warts is of concern and requires careful monitoring [83]. In one WHIM patient, immunization with a quadrivalent HPV vaccine led to HPV specific humoral and cellular immunity [134]. To what extent WHIM patients can be protected by HPV and other vaccines is unknown.

6.9 Epidermodysplasia Verruciformis

(***EVER1 deficiency, EVER2 deficiency***)

6.9.1 Definition

Epidermodysplasia verruciformis (EV; OMIM*226400) is a rare, hereditary disorder with an extremely increased susceptibility to HPV infection affecting the skin. EV was described by dermatologists from Basel, Switzerland, Lewandowsky and Lutz in 1922 and was probably both the first description of a PID and the first evidence for the involvement of HPV infection in the development of skin cancer [197, 202, 245, 248]. The majority of cases (approximately 75%) is caused by mutations in the *EVER1* (*TMC6*) and *EVER2* (*TMC8*) genes [273]. Early development of widespread, refractory flat warts and pityriasis versicolor-like lesions are distinctive features. There is a specific susceptibility to β-HPV 3, 10 in plane warts, to β-HPV 5, 8 in skin carcinomas which emerge in over one-third of cases [202, 310].

6.9.2 Etiology

HPVs are small, non-enveloped double-stranded DNA viruses measuring about 55 nm in diameter [246], present in normal skin and are ubiquitous. EVER proteins are located in the endoplasmatic reticulum, forming a complex with zinc-transporter-1 (ZnT-1) [195]. A dysregulation of zinc-dependent transcription factors in keratinocytes might lead to their malignant transformation. A similar mechanism might be responsible for dysregulated T-cell activation, explaining EV in primary/secondary immunodeficiencies [194]. EV-like disease has been described in T-cell deficiencies such as SCID, RHOH, MST1/STK4 [1, 67, 68, 301, 346, 347] and secondary immunodeficiencies, e.g., HIV. In EV tumors, loss of EVER protein function may lead to increased transcription of the HPV genes E6 and E7 genes, which encode for the major oncoproteins responsible for the oncogenic potential of HPV. UV light is likely to be involved in the progression from benign warts to malignancy [256, 275]. EV is genetically heterogeneous, autosomal-dominant inheritance has also been described [213, 276].

6.9.3 Clinical Manifestations

EV patients are prone to a subset of HPVs, but not to other infections. There are two presenting conditions in EV [69]. First, disseminated, benign, plane warts (HPV3 and 10) begin during infancy and early childhood [158, 206]. The lesions start on the sun-exposed areas, are hypo- or hyperpigmented and may generalize to the limbs, neck, and trunk. The mucous membranes are rarely involved. The typical lesions are flat or presenting as pityriasis versicolor-like macules (Fig. 6.6). Second, there are malignant, verrucous lesions (HPV5 and 8), most frequently localized in sun-exposed areas, which develop in over one-third of cases after the second decade of life [202, 310]. Lesions converting to malignancy appear usually as actinic keratoses and are located mainly on the forehead [246]. Cancers develop slowly and are mainly locally destructive, but progressive extension and metastases have been observed in some patients [157, 203].

6.9.4 Diagnosis

HPVs can be detected by in situ hybridization or polymerase chain reaction on skin tissue specimens. The classic histologic presentation of EV is a verruca plana-type lesion with minimal hyperkeratosis and acanthosis [234]. The cells of the upper epidermis have a clear, blue-gray pale cytoplasm and a central pycnotic nucleus. Appearance, clinical course, histopathological findings of skin lesions, and molecular HPV typing lead to the right diagnosis. EV can be confirmed in approximately 75 % of all cases by mutational analysis of the *EVER1* or *EVER2* genes. If αHPV infections occur with lymphedema and anogenital dysplasia this is called WILD (warts, immunodeficiency, lymphedema, dysplasia) syndrome [186].

6.9.5 Management

A definitive therapy for EV has not been available up to now. Lesions are refractory to conventional therapies and complete regression of HPV associated lesions has never been observed. Various topical (5-Fluorouracil, imiquimod) and systemic (interferon (alfa-2a) combined with retinoids, cimetidine) therapies have been tried with variable results [25, 126, 206]. Surgical removal is used for localized malignant and large disfiguring benign lesions. Strict sun avoidance should be started once the syndrome is diagnosed. There is a life-long risk of cancer; however, it may be helpful and reassuring for the patient to point out that over 60 % of patients do not develop skin cancer.

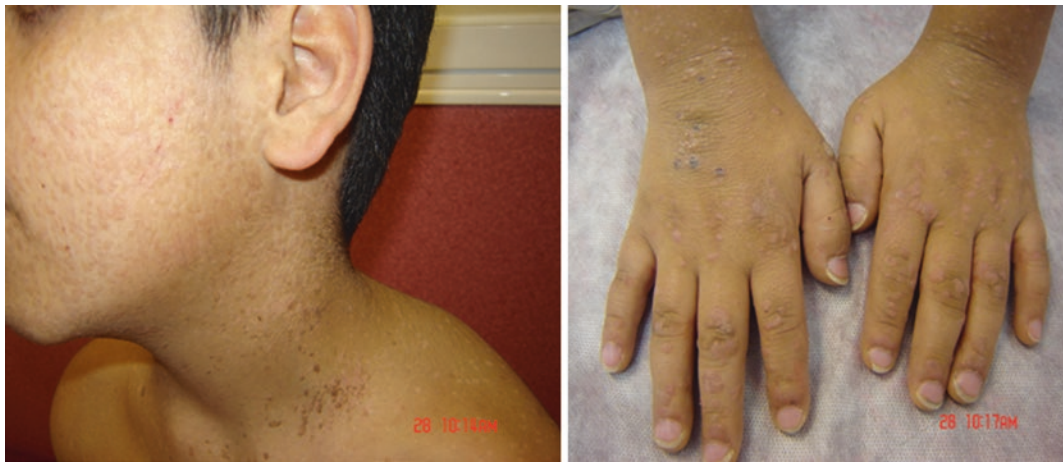

Fig. 6.6 Flat wart lesions and hypo/hyperpigmented (tinea versicolor-like) macules in a patient with epidermodysplasia verruciformis

6.10 Chronic Mucocutaneous Candidiasis

(***IL17RA deficiency, IL17F deficiency, IL17RC deficiency, STAT1 gain-of-function mutation, ACT1 deficiency***)

6.10.1 Definition

Fungal infections are a huge albeit still largely unappreciated problem affecting an estimated one billion people worldwide. Of these, *Candida* infections are amongst the most frequent causing both chronic mucocutaneous and acute systemic disease [39].

Chronic Mucocutaneous Candidiasis (CMC) is an umbrella term describing a clinical phenotype presenting as persistent or recurring, debilitating infections of the skin, nails and mucous membranes with the yeast *Candida*, mostly *albicans*, although alternative strains (*C. glabrata*, *C. kruseie*, *C. dubleniensis*) are increasingly seen. *Candida* is an opportunistic yeast colonising gastrointestinal and urogenital mucosa in about 30–50 % of healthy humans, but in permissive circumstances such as primary or secondary immune deficiencies, will cause disease even death (Fig. 6.7) [198, 254, 329].

Secondary CMC, usually presenting as oral thrush, can be precipitated by a range of recognised permissive factors (dentures, antibiotics, inhaled steroids, immunosuppressive drugs, diabetes, HIV/AIDS) and will resolve once these factors are eliminated. Interestingly, vulvovaginal candidiasis (VVC) is most frequently seen in otherwise healthy women, suggesting that in this condition, local protective mechanisms play a vital role [39, 198]

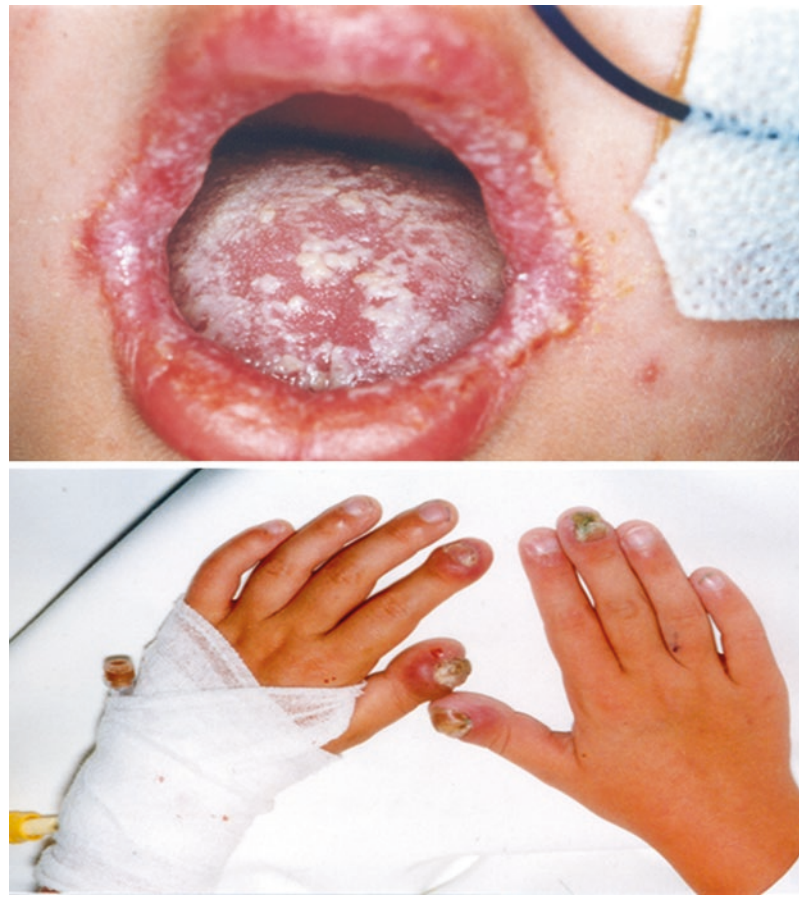

Fig. 6.7 Clinical presentation of chronic mucocutaneous candidiasis. Oral thrush and nail involvement in a child with the gain-of-function-STAT1 mutation (Courtesy of M. Abinun; Newcastle, UK)

Primary CMC is caused by inborn errors of immunity, resulting in PID and susceptibility to infection. CMC (especially oral *Candida* infection – thrush), may occur in the context of a conventional PID, defined by an overt immunological phenotype resulting in a broad susceptibility to a range of microorganisms including viruses, bacteria and fungi, when the underlying defect damages T cell immunity (e.g. in severe combined immune deficiency – SCID). In contrast, CMC can present as a non-conventional PID defined as selective susceptibilities to weakly pathogenic and/or opportunistic microorganisms, in this case specifically to the fungus *Candida* [254, 329].

6.10.2 Etiology

Accumulating evidence suggests that mucocutaneous fungal infections such as CMC are seen in patients with primary defects affecting innate and adaptive immune responses that activate the Th17 pathway. Interestingly, CMC patients, with the exception of CARD9 deficiency (see below) rarely if ever develop invasive fungal disease [329].

The innate immune system recognises a range of conserved fungal PAMPs, initiating a rapid, conserved response, which activates inflammatory cells, that have a dual role of eliminating the intruder and initiating the appropriate adaptive immune response. The latter is achieved by engaging host PRRs that bind to fungal PAMPs, triggering signalling pathways which result in targeted cytokine production, recruitment and polarization of relevant T, B and NK lymphocyte subsets [227]. Fungal PAMPs are recognised by several families of PRRs: The most important fungi in human pathology (*Candida*, *Aspergillus*, *Cryptococcus*) are recognised by TLR2, TLR4 and TLR9 and heterodimers containing TLR1 and TLR6 [227]. Genetic mutations of TLRs and their adaptors (MYD88, IRAK4, TLR3) have been linked to increased susceptibility to bacterial [260] and/or viral [288], but interestingly, not to fungal infections, although TLR1 and TLR4 polymorphisms have been associated with increased susceptibility to invasive fungal disease [228] and TLR3 to cutaneous candidiasis [226]. C-type lectin receptors (CLRS) are PRRs that recognise carbohydrate structures on fungal and other pathogens. Dectin1 binds β-1,3-glucan, activating the Syk tyrosine kinase via a downstream complex of the cytosolic proteins caspase recruitment domain-containing protein 9 (CARD9), Bcl-10 and MALT1 to the NF-κB which acts as a central regulator in the production of inflammatory cytokines in neutrophils, macrophages and dendritic cells as well as promoting IL23 production and subsequent Th17 cell induction [93]. Polymorphisms of dectin1 [106] and mutations of CARD9 [121] were reported to underlie CMC in certain patients. (*See* Sect. 6.11 *or more details*) Defects of other CLRs (dectin-2, mannose receptor), NLRs, RigI helicases, etc. have not as yet been associated with fungal disease in humans [227].

The adaptive immune response is triggered upon binding of the cognate antigen to the TCR of naive $CD4^+$ T cells, which are then initiated to differentiate into three effector lineages, depending on the local cytokine milieu provided by innate immune cells. The classical T helper type (Th1) cell is induced by IL12, regulated by the transcription factor T-bet and secretes IFNγ that promotes cell-mediated immunity, essential for dealing with intracellular microorganisms. Th1 cells were previously believed to be crucial in antifungal immunity but this role has now largely been taken over by Th17 cells [103, 271]. Th2 cells are induced by IL4, regulated by GATA3 and produce IL4, IL5 and IL13, which promote antibody production essential for protection against extracellular microorganisms. However, although fungi induce antibody production, humoral immunity is generally not protective [198]. Th17 cells develop in the presence of IL1β, TGFβ and IL6 which signals via STAT3 to induce expression of the Th17 lineage defining transcription factor retinoic acid-related orphan receptor (ROR)γt, while IL23 promotes further Th17 cell expansion and maintenance. Th17 cells secrete IL17A, IL17F and IL22 which promote cutaneous and mucosal immunity by activation of epithelial cells, granulopoesis, recruitment of neutrophils, production of chemokines and antimicrobial factors and are

Table 6.3 PIDs with increased selective susceptibility to mucocutaneous and invasive fungal infections

Genetic defect	Inheritance	Clinical phenotype
IL17F deficiency	AD	CMC, folliculitis
IL17RA deficiency	AR	CMC, folliculitis
IL17RC deficiency	AR	CMC
ACT1 deficiency	AR	CMC, blepharitis, folliculitis, and macroglossia
GOF-*STAT1* mutation	AD	Various fungal, bacterial, and viral (HSV) infections Autoimmunity (thyroiditis, diabetes, cytopenia) Enteropathy
CARD9 deficiency	AR	Invasive candidiasis infection Deep dermatophytoses *Exophiala spinifera Phialophora verrucosa*
RORC deficiency	AR	CMC, mycobacterial infections
AIRE deficiency	AR	CMC, Autoimmune Polyglandular Syndrome 1

believed to play a crucial role in fungal immunity [269]. IL17 is a dimeric molecule that is biologically active as a homodimer of the IL17A chain, a homodimer of the IL17F chain, or a heterodimer of an IL17A and an IL17F chain. Any of these dimers can signal through binding to IL17RA [269].

In recent years, several mutations affecting the innate and adaptive pathways of fungal immunity have been reported, confirming and increasing our understanding of fungal immunity, specifically the crucial role of the IL17 pathway (Table 6.3).

6.10.3 Clinical Manifestations

In 2011, Puel et al. [268] reported the first two "proof of concept" genetic aetiologies of CMC: AR deficiency in the IL17 receptor IL17RA and AD deficiency of the IL17 cytokine IL17F. IL17RA deficiency was complete, abolishing cellular responses to IL17A and IL17F homo and heterodimers. By contrast, IL17F deficiency was partial, with mutant IL17F-containing homo and heterodimers displaying impaired but not abolished activity. In 2015, AR mutations of IL17RC were added as a third proof-of-concept genetic aetiology of CMC [199].

AR IL17RA deficiency (OMIM*613953) was found in a patient who presented with neonatal *C. albicans* skin infection and subsequent *S. aureus* dermatitis. He was homozygous for a nonsense mutation in the *IL17RA* gene, resulting in the creation of a premature stop codon at the position that would prevent production of the extracellular domain of IL17RA. Consistent with this mutation, IL17RA was not detected on the surface of the patient's fibroblasts and PBMCs. In addition, when the patient's fibroblasts were stimulated with various concentrations of IL17A and IL17F homo or heterodimers, the patient failed to respond by production of IL6 or GROα. Transfection of the patient's fibroblasts with wild-type IL17RA restored responsiveness to IL17. The parents and siblings of the patients were heterozygous for the mutation and were healthy.

AD IL17F deficiency (OMIM*613956) was found in 5 of 17 kindreds who clinically all suffered with CMC and had a missense mutation of the *IL17F* gene. The mutated gene was also found in two asymptomatic family members suggesting incomplete clinical penetrance. This mutation replaced a highly conserved serine residue at position 65 with a leucine at a site predicted by computational analysis to be important for cytokine binding to its receptor. The mutation had no effect on the production of IL17F as a recombinant protein. Likewise, the mutant IL17F was able to form homodimers and heterodimers with IL17A. However, the mutant IL17F–containing homodimers or heterodimers had reduced binding to IL17RA on the surface of fibroblasts. IL17F homodimers also displayed much reduced induction of IL6 and GROα compared with wild-type IL17F homodimers, IL17A/mutant IL17F heterodimers, or IL17A homodimers. Thus, CMC in this kindred resulted from a mutation causing a hypomorphic, dominant-negative IL17F allele, which leads to production of IL17F homodimers and IL17A/IL17F heterodimers that

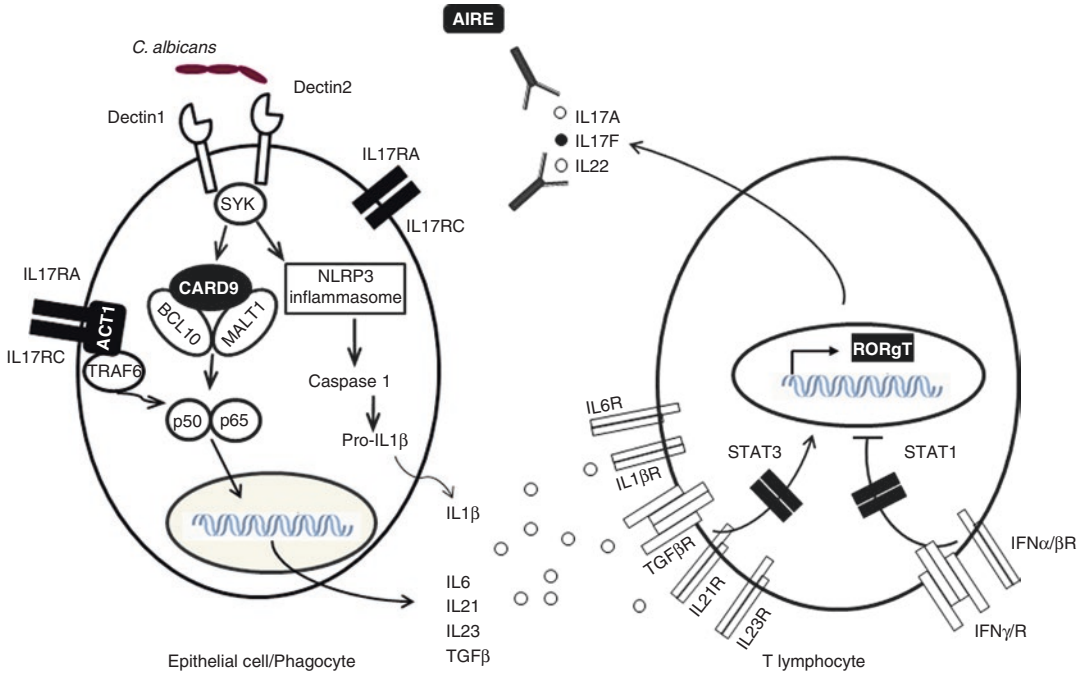

Fig. 6.8 Inborn errors of IL17 immunity underlie chronic mucocutaneous candidiasis. Mutated proteins are marked in *black*

have reduced binding to IL17RA and, hence, impaired bioactivity.

Patients were treated with courses of oral fluconazole with varying and temporary effect. Skin infections and dermatitis were treated with antibiotics.

These two mutations confirmed that human IL17 is essential for mucocutaneous immunity against *C. albicans* and definitely demonstrate the potential for disruption of the IL17 circuit to cause CMC (Fig. 6.8). Importantly, this puts into perspective recent efforts to target IL17 in the treatment of inflammatory disorders where potential adverse consequences, such as mucocutaneous infections must be considered [115].

AR IL17RC deficiency (OMIM*616445) was recently identified as a cause of isolated CMC [199]. Three children from unrelated kindreds displayed AR IL17RC deficiency due to homozygous mutations for different nonsense alleles that prevented expression of IL17RC on the cell surface. The defect was complete, abolishing cellular responses to IL17A and IL17F homo and heterodimers although the response to IL17E was maintained. These experiments of nature indicated that human IL17RC is essential for mucocutaneous immunity to *C. albicans* but is otherwise largely redundant.

AR ACT1 deficiency (OMIM*615527) was identified in 2013 by the same group caused by biallelic missense mutations in the adaptor protein ACT1 (TRAF3IP2) located in the SEFIR region [33]. This mutation impaired the homotypic interaction of ACT1 with the IL17 receptor abolishing responses to IL17A and IL17F in fibroblasts as well as to IL17E in leukocytes. It did not affect interactions with other proteins (HSP90, HSP70 or CD40) which are mediated by other domains of the ACT1 protein. Healthy individuals who were homozygous for a common missense polymorphism located in a different ACT1 domain (D10N) had impaired but not absent responses to IL17 cytokines. These findings demonstrated that human IL17A and IL17F depend on ACT1 to mediate protective mucocutaneous immunity although other ACT1-dependent IL17 cytokines seem to be largely redundant in host defense.

In the same year 2011, AD mutations in the coiled-coiled domain (CCD) of the *STAT1* (OMIM*614162) were first reported by van de Veerdonk et al. [324] in 14 patients from five families identifying two heterozygous mutations and Liu et al. [200] in 47 patients from 20 families identifying 12 heterozygous mutations. *GOF-STAT1* mutations in the DNA binding domain (DBD) have since been reported [308]. To date, 76 *GOF-STAT1* mutations in 274 patients in 167 kindreds from 40 countries have been reported [315], all with complete clinical penetrance but no obvious genotype-phenotype correlation [71, 220]. Unexpectedly, the molecular mechanisms found [200, 299] showed it to be a GOF mutation, unlike the previously reported loss-of-function AR and AD mutations underlying MSMD, salmonellosis and viral diseases [15]. GOF-STAT1 mutations both in the CCD and DBD have a gain-of-function effect by reducing the dephosphorylation of activated STAT1, leading to accumulation of phosphorylated STAT1 in the nucleus [200, 220] although enhanced initial hyperphosphorylation may also be contributing (unpublished data). Patients' PBMCs show reduced numbers of Th17 cells and markedly impaired Th17 cytokine production, specifically IL17A and IL22 [230]. IFNγ production has been reported as both normal [230] and decreased [323] but importantly, these patients are not particularly susceptible to intracellular microorganisms that provoke an IFNγ mediated Th1 protective immune response. The impaired *in vitro* Th17 cell proliferation and IL17 production in response to *Candida* stimulation is likely responsible for the CMC, but the mechanisms through which the GOF-STAT1 mutation decreases STAT3-dependent production of Th17 cytokines remain unknown. It is possible that the dominance of activated STAT1 shifts the immune response toward STAT1-dependent IL-7 inhibitors and away from STAT3-mediated induction of Th17 cell generation. Our recent studies demonstrate that the GOF-STAT1 mutation does not impair STAT3 phosphorylation, STAT3 nuclear translocation nor DNA binding but markedly reduces STAT3-induced gene transcription which may be responsible for the reduced STAT3-dependent Th17 production (unpublished data). Further understanding of the consequences of STAT1 hyperactivity on cell function is needed.

Patients with the GOF-STAT1 mutation make up the largest group of CMC patients although no genetic cause has yet been identified in about half of the remaining patients with chronic candidiasis [220]. The majority of CMC patients with the GOF-STAT1 mutation present with mucocutaneous infections with *Candida* as well as a range of other symptoms, which vary markedly from patient to patient. Clinical presentations may be reminiscent of HIES (skin abscesses, boils, dermatitis but not pneumatoceles) while other symptoms include mild to moderate (sometimes severe) bacterial and/or viral infections, hypothyroidism with or without autoantibodies, autoimmune hepatitis, keratitis, dental loss, cerebral aneurysms and oral/esophageal squamous cell cancer [269, 324]. Recent reports suggest that GOF-STAT1 mutations may be associated with a much broader clinical phenotype than initially appreciated including disseminated fusariosis, coccidioidomycosis, and histoplasmosis [286], recurrent viral infections [314, 324] and IPEX-like features including polyendocrinopathy, enteropathy and dermatitis [321]. Interestingly, in some (but not all) patients both *Candida* and bacterial infections seem to improve with age (personal observations).

6.10.4 Diagnosis

Diagnosis could be made based on the clinical phenotypes, including mucocutaneous candidiasis and above-mentioned findings.

6.10.5 Management

Treatment of CMC patients can be quite complex depending on symptoms. Most patients will require long-term oral antifungals such a fluconazole because of which *Candida* resistance is becoming an increasingly serious

problem. Some cases of non-responsiveness may be due to infection with two or more *Candida* strains with different sensitivities because of which regular culture monitoring is essential. Patients can respond well to short intermittent courses of antifungals rather than daily doses (e.g. 7 days every month) reducing the side-effects, particularly azole liver toxicity while not compromising effectiveness. In GOF-STAT1 CMC patients, sporadic reports of HSCT have reported a lethal outcome (possibly due to lack of engraftment) [5], as well as complete cure after [78, 143]. There are also reports of successful treatment [225] and long term follow-up [294, 343] with GM-CSF. Unfortunately, only symptomatic treatment is available for associated, often severe problems and the need for alternative etiological therapies is becoming obvious.

6.11 CARD9 Deficiency

6.11.1 Definition

Deep dermatophytosis is a severe and sometimes life-threatening fungal infection caused by dermatophytes. It is characterized by extensive dermal and subcutaneous tissue invasion and by frequent dissemination to the lymph nodes and occasionally, the central nervous system. The condition is different from common superficial dermatophyte infection and has been reported in patients with mutations in the intracellular adaptor molecule CARD9.

6.11.2 Etiology

The first report in 2009 [121] described a homozygous loss-of-function nonsense mutation in *CARD9* (OMIM*212050) in four patients from a large consanguineous family from Iran who had recurrent oral and/or vaginal candidiasis as well as tinea corporis and dermatophytosis. The mutation (Q295X) resulted in a premature stop codon in the coiled-coil domain of CARD9 and lack of CARD9 expression. Seventeen additional patients from eight unrelated Tunisian, Algerian, and Moroccan families were subsequently identified [191] with clinical features of deep dermatophytosis of whom four died. No other severe infections, fungal or otherwise, were reported in the surviving patients. Two new autosomal recessive mutations of *CARD9* with complete clinical penetrance were identified in all patients (*Q289X* in 15 patients and *R101C* in 2 patients). An additional patient with chronic invasive *Candida* meningo-encephalitis was found to be compound heterozygote for two previously undescribed *CARD9* mutations (c.214G>A and c.1118G>C) [93]. Dectin1 deficiency was reported in a single family with CMC and dermatophyte infections [106], although with the allele prevalence in the healthy population of 3–8 % it has been characterized as a polymorphism and a risk factor rather than a PID.

6.11.3 Clinical Manifestations

CARD9 is a crucial adaptor protein, which acts as a central regulator in the production of inflammatory cytokines in neutrophils, macrophages, and dendritic cells as well as promoting IL23 production and subsequent Th17 cell induction (see above). Thus, CARD9 deficiency results in impaired production of cytokines required for IL17 T-cell differentiation and/or maintenance leading to increased susceptibility to fungal infections. More importantly, mutations in the *CARD9* gene were found to result in the loss of protein expression in myeloid cells (neutrophils and monocytes) where it is most abundant resulting in lack of monocyte-derived cytokines and impaired neutrophil killing in response to fungal infections predisposing the patient to life-threatening systemic, cerebral and invasive *Candida* and dermatophyte infections [93]. The predisposition to CNS candidiasis may be enhanced by the persistence of *Candida* within monocytes that act as a vehicle for fungal dissemination and facilitate crossing into the CNS through the blood brain barrier (the "Trojan horse" hypothesis) [329].

6.11.4 Diagnosis

Diagnosis will be based on clinical suspicion, confirmed by genetic testing.

6.11.5 Management

CARD9 deficiency is a serious condition so intense systemic anti-fungal treatment with or without surgery will depend on clinical presentation and patient response. Long term antifungal prophylaxis is indicated in most patients.

6.12 Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy

6.12.1 Definition

CMC is a clinical hallmark of Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy/Autoimmune Polyendocrinopathy Type 1 (APECED/APS1) (OMIM*240300), a rare AR disease caused by an underlying mutation of the Autoimmune Regulator (*AIRE*) gene, which regulates expression of ectopic antigens in the thymus, thus promoting deletion of self-reactive T lymphocytes and preventing autoimmunity.

6.12.2 Etiology

To date, more than 60 *AIRE* mutations have been reported, spreading throughout the length of the gene. AIRE promotes expression and presentation of tissue-specific antigens (which are normally not expressed in the thymus) in medullary thymic epithelial cells (mTECs), resulting in deletion of self-reactive thymocytes [10]. There is also evidence that AIRE influences the development of natural regulatory T cells [190, 283]. The role of AIRE in peripheral tolerance induction is still a matter of hot debate as although *AIRE* is expressed in peripheral lymphoid tissue, detection of the AIRE protein has been more elusive [10]. Recent evidence suggests that peripheral tolerance induction is mediated by a BM derived cell that is not a dendritic cell [116]. An abstract from a recent conference demonstrates that AIRE is expressed in synovial tissue from patients with rheumatoid arthritis, possibly as an attempt to control inflammation [233]. Our own work suggests that AIRE may have a role in regulating the function of tolerogenic dendritic cells (unpublished data).

6.12.3 Clinical Manifestations

APECED/APS1 is characterized by a clinical triad of CMC, hypoparathyroidism and Addison disease (adrenocortical failure), usually (but not always) presenting in early childhood with CMC often being the first clinical symptom to appear, frequently followed by hypoparathyroidism presenting as seizures due to hypocalcemia. In many patients, additional organ-specific autoimmunity develops over the years including diabetes mellitus, gonadal atrophy, hypothyroidism, autoimmune hepatitis etc., caused by organ-specific autoreactive lymphocytes and antibodies [258].

6.12.4 Diagnosis

The underlying cause of CMC in these patients has long been a mystery that could not be explained by the underlying gene mutation, particularly as it was shown that APECED/APS1 patients have normal or even increased IL17A production in response to *Candida* stimulation [230]. The riddle was recently elegantly resolved when the existence of neutralizing autoantibodies to Th17 cytokines (IL17A, IL17F and IL22) were reported, explaining the candidiasis in APECED/APS1 in the context of autoimmunity. Puel et al. [270] analysed the plasma of 33 patients with APECED, 29 of whom had CMC, and found specific and neutralizing IgG autoantibodies against IL17A (67%), IL17F (94%), and IL22 (91%). All patients had autoantibodies against at least one of Th17 cytokines, including rare patients without CMC. Kisand et al. [178] evaluated 162 patients with APECED and found neutralizing autoantibodies against IL17A (41%), IL17F (75%), and IL22 (91%). Interestingly, these patients do not produce autoantibodies to any other cytokines, including IL1b,

IL6, IL 23, and IL26, except IFNs type 1, while antibodies to Th17 cytokines were not found in a range of other autoimmune diseases [178, 270]. IFN type 1 antibodies have only been reported in thymoma patients, a minority of whom may also develop anti-Th17 antibodies associated with CMC [178]. It is not clear why neutralizing autoantibodies to IFN type 1 do not result in increased susceptibility to viral infections, although it is currently believed that the abundance of IFN type 1 production by all cells may be able to override the neutralizing effect of autoantibodies. Surprisingly, mouse models of APECED/APS1 with targeted disruptions of the *AIRE* gene (*AIRE* knock-outs) do not develop autoimmune disease and do not regularly produce autoantibodies to Th17 cytokines implying that the mouse model may not convincingly represent human disease [171]. The specificity and sensitivity of Th17 cytokine autoantibodies in APS1/APECED patients makes them a valuable diagnostic tool that has already found its way to clinical practice [179], particularly as genetic testing for *AIRE* mutations is not readily available given that mutations scan the whole gene. These findings provided more evidence of the role of IL17 in protection against CMC.

6.12.5 Management

Treatment of APECED/APS1 patients focuses primarily on substitution therapy for the failing endocrine organ function, although severe cases may require serious immunosuppressive therapy [258]. Biological treatments aimed at reducing autoantibody production by eliminating B lymphocytes with rituximab (anti-CD20) have had variable success (personal communication, Dr Mario Abinun). Long-term local and/or oral anti-fungal treatment and prophylaxis is needed in most patients.

6.13 RORC Deficiency

6.13.1 Definition

To date, five genetic etiologies of CMC have been reported of which *IL17RA*, *IL17RC* and *ACT1* are AR while *IL17F* and *GOF-STAT1* mutations are AD. Recently a novel, biallelic mutation of the transcription factor retinoic acid-related orphan receptor (*ROR*)*C* in humans was reported to underlie impairment of immunity to both *Candida* and Mycobacterium (OMIM*616622) [238].

6.13.2 Etiology

Inborn errors of human IL17A/F or IFNγ are each associated with a specific set of infections. Inborn errors of IL17A/F underlie CMC (see above) while inborn errors of IFNγ underlie MSMD that is characterized by selective susceptibility to weakly pathogenic mycobacteria. *RORC* is the master regulator of IL17 cells in humans, but was previously not known to influence IFNγ production. However, in seven individuals from three kindreds who suffered with both candidiasis and mycobacteriosis, biallelic *RORC* loss-of-function mutations were found resulting in lack of functional RORγ and RORγT isoforms and lack of IL17A/F producing cells [238]. This finding was consistent with the CMC seen in these patients, but unexpectedly, leukocytes from these RORγ and RORγT deficient individuals also displayed defective IFNγ responses to Mycobacterium, which reflected profoundly defective IFNγ production by circulating γδ T cells and $CD4^+$ $CCR6^+$ $CXCR3^+$αβ T cells. Collectively, these data demonstrate that human *RORC* plays a surprising dual role in host defense in that both mucocutaneous immunity to *Candida* and systemic immunity to Mycobacterium require RORγ, RORγT or both.

6.13.3 Clinical Manifestations

Seven children from three kindreds presented with unusual combinations of infectious diseases without a known genetic cause. One patient died at 6 years of age from disseminated BCG. Two other children, 7 and 4 years of age, from another family had similar clinical presentations but survived. A fourth child form another family presented with disseminated BCG at 16 months. Another three children had mycobacterial disease. Importantly, 6/7 children also suffered with

CMC of varying severity. Patients had mild lymphopenia, small thymus, lack of palpable axillary and cervical lymph nodes and absence of MAIT and type 1 NKT cells in peripheral blood, consistent with the phenotype of *Rorc-/-* mice.

6.13.4 Diagnosis

Diagnosis was made by whole exome sequencing combined with genome-wide linkage analysis that identified three different biallelic, loss of function mutations of the *RORC* gene. All unaffected family members were either heterozygous or homozygous for the wild-tye (WT) allele confirming an AR pattern of inheritance.

6.13.5 Management

Patients were treated as per current protocols for mycobacterial infection and prophylaxis as well as for mucocutaneous candidiasis.

6.14 Monocyte/Dendritic Cell Deficiencies

(***AD GATA2 deficiency, AR IRF8 deficiency***)

6.14.1 Definition

The mononuclear phagocyte system (MPS) contains populations of ontogenically distinct but functionally related cells including blood monocytes, dendritic cells (DCs) and tissue macrophages [162]. They are found in almost all tissues, including peripheral blood and are often typified as antigen presenting cells, however; DCs and macrophages are also effectors of homeostasis and inflammation [135]. The MPS deficiency is often overlooked in an individual's susceptibility to infections [62]. The identification of individuals with monocyte and DC deficiencies related to single gene defects has provided the chance to study the developmental ontogeny of MPS compartment and the non-redundant role of its components in infection resistance and immune surveillance.

6.14.2 Etiology

Autosomal dominant GATA2 (AD GATA2) deficiency (OMIM*614172) and autosomal recessive IRF8 (AR IRF8) deficiency (OMIM*614894) underlie the development of monocytopenia and DC deficiency as different clinical syndromes.

GATA2 is a key transcription factor required for the development and maintenance of hematopoietic stem cells (HSCs). It interacts with other transcription factors that specify early lineage commitment and is expressed in monocytes, mast cells and mature megakaryocytes [37, 211]. Most of *GATA2* mutations appear to cause loss of function of the mutated allele leading to haploinsufficiency, however, it is also possible that these mutants have a dominant negative action, as reported for T354M variant [63, 131, 149]. Insufficient GATA2 expression forces HSCs to enter cell cycle and differentiate, thus reducing self-renewal capacity [63, 77]. Different types of mutations have been identified but no clear correlation between genotype and phenotype can be ascertained.

IRF8 is one of the nine members of the IRF family of transcription factors that bind to IFN-stimulated response elements (ISRE) and regulate the expression of genes stimulated by IFNα/β [209, 319]. IRF8 is expressed in macrophages and DCs and plays role in development and function of myeloid cells [318]. AD IRF8 mutation underlie the development of MSMD (Sect. 6.6). AR IRF8 deficiency is caused by homozygous K108E mutation reported in one patient and causes a distinct phenotype [133]. K108E mutation resulted in loss of nuclear localization and of transcriptional activity of IRF8, together with higher levels of ubiquitination/sumoylation and enhanced proteosomal degradation [284].

6.14.3 Clinical Manifestations

GATA2 deficiency underlies different clinical syndromes. Loss of DCs, monocytes B and NK

cells (DCML deficiency) [84]; monocytopenia with susceptibility to *Mycobacteriuma avium* complex (monoMAC syndrome) [149]; familial myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) [131] and hereditary lymphedema with MDS (Emberger syndrome) [247]. The diverse manifestations of GATA2 deficiency and its natural history have been recently documented in two large cohorts [85, 300]. The disease presents an extended age range of onset with more than 90 % of penetrance in different families. Most patients have unremarkable childhood vaccination and infection histories [63]. From an infectious perspective, general warts and non-tuberculous mycobacterial infections are the most common manifestations. Affected patients are also prone to infections with some bacteria, herpes viruses (EBV, HSV, VZV) and fungal elements including invasive aspergillosis, disseminated histoplasmosis and mucosal candidiasis [300].

Impaired immune surveillance and defective antiviral immunity probably underlie the increased incidence of solid tumors [63]. HPV-induced squamous carcinoma, EBV-related mesenchymal tumors, breast cancer, desmoids tumor and schwannoma have been reported [85, 300].

GATA2- deficient patients are at increased risk of developing familial MDS/AML [131].

MDS/AML is reported in about 85 % of the affected patients and in 30–50 % of these patients it is the presenting feature [85, 217, 300]. The acquisition of secondary genetic abnormalities in the transformation of GATA2 mutation to MDS/AML is documented [131, 247]. Monosomy 7, somatic *ASXL1* mutation and trilineage dysplasia are risk factors for development of AML in GATA2-deficient patients [339].

Up to 20 % of patients with *GATA2* mutation develop lymphedema that is unilateral and progressive (Emberger syndrome). Sensorineural hearing loss is an additional feature of this syndrome. It has been demonstrated that GATA2 is essential for endothelial cell maintenance and lymphatic vessel valve development [174, 175]. Some studies associated the development of lymphedema and the presence of N-terminal frameshift mutations or large deletions [300].

Interestingly, pulmonary alveolar proteinosis (PAP) is a characteristic feature of GATA2 mutation that could be documented in about 20 % of patients [300]. So, GATA2 deficiency could be accounted as a secondary cause of anti-GM-CSF negative PAP. (*See* Sect. *6.15 for more details*)

About half of the patients with GATA2 mutation develop autoimmune features dominated by panniculitis that is seen in 30 % of them [63, 300]. Severe Treg deficiency and increased B cell populations ($CD38^{-}CD21^{-}$) involved in autoimmune processes may trigger this susceptibility [23, 85]. Additional important clinical features of GATA2 deficiency are thromboembolic events seen in 25 % of the patients and risk of preterm labor in pregnant mothers having *GATA2* mutation [300].

AR IRF8 deficiency is reported in an infant presenting with severe disseminated BCG infection, oral candidiasis, severe respiratory viral infection and striking myeloproliferation [133].

6.14.4 Diagnosis

At first, most GATA2-deficient patients have normal leukocyte numbers and differentials in the peripheral blood. However, attrition of hematopoietic progenitors with advancing disease represents the characteristic hematologic and immunologic phenotype [62].

The loss of GATA2 causes an intrinsic progenitor cell defect that results in a complete absence of multi-lymphoid progenitors (MLPs) and a relative depletion of granulocyte–macrophage progenitors (GMPs) [23, 62].

Symptomatic patients have very low numbers of circulating monocytes and no detectable $CD1c^{+}$, $CD141^{+}$ and plasmacytoid DCs in the peripheral blood [23]. B and NK lymphocytopenia are frequently documented and $CD4^{+}$ lymphocytopenia and neutropenia are seen in about half of patients [255, 300]. The bone marrow progressively loses function in many patients, acquires new cytogenetic abnormalities and transforms to MDS/AML [85, 300].

GATA2 deficiency is also associated with markedly elevated serum levels of Fms-like

tyrosine kinase 3 ligand (Flt3L), an important factor in DC development [23]. Serum Flt3L levels show a biphasic pattern, where Flt3L becomes progressively elevated but then declines as MDS develops [85]. Serial measurements of Flt3L may be useful to assess disease evolution. Absence of $CD14^+$ and $CD16^+$ circulating monocytes, $CD11c^+$ conventional DCs and $CD123^+$ plasmacytoid DCs, in the presence of neutrophilia, characterize AR IRF8 deficiency. The single patient reported also had normal number of B cells, T cells (however anergic) and NK cells [133, 284]. Functionally, a severe impairment of IL12 and IFNγ induction was observed in PBMCs stimulated with BCG or mitogens [133].

6.14.5 Management

A watch and wait policy is acceptable for many GATA2-deficient patients, however it is a trend to transplant in early stages, before the development of severe end organ damage or leukemia [63, 148]. Initial treatment of GATA2 deficiency must focus on control of infections and management of pulmonary disease. It is suggested to vaccinate children against HPV, to be cautious for herpesviruses infections, and to use prophylaxis against Nontuberculous mycobacteria [148]. Serial monitoring of peripheral blood counts every 3–6 months is useful and annual BM examination for morphology with cytogenetics is advisable [63, 148]. Monitoring of Flt3L levels as a probable marker of disease progression is recommended [85]. Patients with hypogammaglobulinemia and abnormal antibody responses will benefit from immunoglobulin replacement [58].

HSCT has been performed on several GATA2-deficient patients and has a good outcome [70, 300]. HSCT reverses the infectious, hematopoietic and pulmonary disease seen in GATA2 deficiency [123, 300]. Given the high incidence of relapse and rejection after nonmyeloablative HSCT, a myeloablative regimen may be the first choice [124].

The AR IRF8 deficient patient received cord-blood stem cell transplantation [133].

6.15 NK Cell Deficiencies

(***MCM4 deficiency***)

6.15.1 Definition

Natural killer (NK cells) are part of the innate immune system cells exert antiviral and antitumor surveillance functions [330]. Compared to B and T lymphocytes, NK cells do not possess antigen–receptor rearrangement and do not require pre-activation in order to recognize and lyse target cells. NK cells also produce ample amounts of cytokines, which enable them to modulate immune responses. Genetic defects of human NK cells may affect their development, function, or both [165]. Inborn errors of NK cell development could be categorized into either those that affect multiple hematopoietic lineages or those that are specific to NK cells. The first group is not the matter of this section and has been reviewed elsewhere [165, 239]. Some cases of selective quantitative circulating human NK cell deficiencies with specific susceptibility to viral infections have been reported [24, 99, 104]. However, the mechanisms that control NK cell development in human subjects remain unclear.

The only identified selective human NK cell deficiency is caused by mutation in *MCM4* encoding the minichromosome maintenance complex component 4 (MCM4) [120, 152].

The underlying immunodeficiency in some other PIDs (GATA2 deficiency, γc and JAK3 deficiencies) is also confounded with NK cell deficiencies that are discussed in the related sections.

6.15.2 Etiology

MCM4 is a highly conserved DNA helicase that is required for DNA replication and cell proliferation [26]. Patients with autosomal recessive MCM4 deficiency from an Irish traveler community presented with a developmental syndrome including selective NK cell deficiency. The studied patients shared the same splice defect, probably because of a founder effect [120, 152].

MCM4 deficiency (OMIM*60998) contributed to a developmental defect in transition of $CD56^{bright}$ to $CD56^{dim}$ NK cells, as evidenced by the lack of $CD56^{dim}$ NK cells in the peripheral blood and the preservation of the small $CD56^{bright}$ NK cell population [120, 152].

Moreover, patients' fibroblasts contained high numbers of DNA breaks and showed cell-cycle abnormalities [120]. The accumulation of chromosomal aberrations, potentially accounts for the loss of $CD56^{dim}$ NK cell population [165].

6.15.3 Clinical Manifestations

Patients displayed growth retardation, increased chromosomal breakage, adrenal insufficiency and, lymphoma (in one case) [120, 152]. From an infectious side, the patients had unusual susceptibility to herpes viruses [120].

6.15.4 Diagnosis

The constellation of clinical data leads to the provisional diagnosis of MCM4 deficiency. Patients have normal numbers of B and T cells, but very few circulating NK cells [165]. Adrenal function tests should be performed. Mutation analysis makes the definitive diagnosis.

6.15.5 Management

Directed therapy to control and prevent herpes viruses is recommended. Herpes virus susceptibility and genomic instability make the affected patients at greater risk to develop malignancies; lifelong surveillance seems wise.

6.16 Pulmonary Alveolar Proteinosis

6.16.1 Definition

Pulmonary alveolar proteinosis (PAP) is characterized by alveolar accumulation of surfactant because of defective surfactant clearance by alveolar macrophages [35].

Three main categories of PAP have been defined: idiopathic, secondary and genetic.

GM-CSF and its receptor play critical roles in the pathogenesis of PAP.

The idiopathic form of PAP is caused by anti-GM-CSF autoantibodies and is in the range of PIDs that are caused by anti-cytokine antibodies [40, 180]. Secondary PAP is often related to hematologic malignancies and immunosuppressive therapies or encountered in the setting of defined PIDs such as ADA deficiency, lysinuric protein intolerance and GATA2 deficiency [35, 125, 253, 300]. Genetic PAP, the most severe form, results from mutations in the GM-CSF receptor and is reviewed here [28].

6.16.2 Etiology

The GM-CSF receptor is composed of the binding α chain, coded by *CSF2RA*, and the common β chain, coded by *CSF2RB*, which is also used by IL3 and IL5 receptors [38]. Depending on the GM-CSF concentration, the receptor signaling occurs through either NF-kB or STAT5-regulated pathways [130]. Pulmonary GM-CSF is required to stimulate the terminal differentiation of alveolar macrophages; however the precise mechanisms remain poorly understood [316].

Homozygous mutations of *CSF2RA* (OMIM*300770) and *CSF2RB* (OMIM*614370) have corresponded to the development of PAP [305].

6.16.3 Clinical Manifestations

The onset of clinical disease is insidious, with a subacute progressive dyspnea [305]. Adult-onset cases are also reported [309]. PAP patients are susceptible to pulmonary and extrapulmonary infections frequently caused by opportunistic infections [293].

6.16.4 Diagnosis

Diagnosis of PAP is begun by computed tomography (CT) scan and confirmed by staining of

broncho-alveolar lavage fluid for periodic acid-Schiff-positive inclusions in the macrophages [212]. In these patients, alveolar and serum concentrations of GM-CSF are elevated and anti-GM-CSF antibodies are absent [305].

6.16.5 Management

In mild disease, supportive treatment including whole lung lavage may be sufficient [79, 304]. In severe disease, lung transplantation is curative [151].

6.17 Isolated Congenital Asplenia

6.17.1 Definition

Congenital asplenia is often associated with complex visceral defects as part of heterotaxy syndromes [156, 280]. The causative mutations have been identified in various genes controlling left-right laterality [20, 351]. In contrast, isolated congenital asplenia (ICA; i.e., in the absence of heterotaxy or cardiac anomalies) was first thought to be rare and sporadic [224]. Studies of case reports and rare national surveys suggested probable autosomal dominant, as well as spontaneous, occurrences [119, 205]. Recently, heterozygous mutations in *NKX2-5* (OMIM*600584) and *RPSA* (OMIM*271400) have been identified as the underlying cause of ICA in humans [34, 183].

6.17.2 Etiology

Using mouse models of spleen morphogenesis to help filter the exome sequencing data of a single family with ICA led to the discovery of a heterozygous missense mutation in *NKX2-5* working in a dominant-negative fashion [183]. Pbx1, a prime regulator of the organogenesis of the spleen, governs spleen development through transactivation of the *Nkx2-5* gene product (Nkx-2) [22]. Moreover, both Pbx1 and Nkx-2 control spleen growth by repression of CDK inhibitor p15Ink4b [193]. Finding of a *NKX2-5* mutation as a possible cause of human ICA reinforces the central role of PBX target genes in the development of spleen.

The exome analysis of several ICA kindreds revealed heterozygous mutations in *RPSA* as a common underlying defect, identified in about one-third of the studied families [34]. *RPSA* encodes ribosomal protein SA (RPSA), a component of the small subunit of the ribosome [21]. RPSA is ubiquitously expressed and is involved in pre-rRNA processing [235].

This finding establishes an indispensable role for RPSA in human spleen development; nevertheless, the underlying mechanisms required to be clarified.

6.17.3 Clinical Manifestations

Asplenic patients are exposed to life-threatening bacterial infections. The most frequent pathogens in patients with ICA are encapsulated bacteria, with *Streptococcus pneumonia* as the leading infectious agent [205, 263]. The infections associated with ICA can be fatal in childhood but tend to improve with age [205].

6.17.4 Diagnosis

ICA can be diagnosed, based on the results of ultrasonography or the presence of Howell-Jolly bodies in blood smears. The absence of other developmental defects is obligatory. Definitive diagnosis is made by sequencing of the pertinent genes.

6.17.5 Management

Antibiotic prophylaxis and immunizations against *S. pneumoniae* and *Haemophilus influenzae* type b (Hib) are recommended [267]. Though breakthrough infections after vaccine failure have been documented [328]. Periodic determination of antibody titers to reevaluate the need for booster doses seems rational. Infectious episodes should be rapidly identified and aggressively treated using intravenous antibiotics.

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Autoinflammatory Disorders

7

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7.1 Introduction

Autoinflammatory disorders are a group of diseases that are characterized by recurrent or continuous, generalized inflammation where no infectious or autoimmune cause can be detected [110, 158]. The term was first used for the Mendelian inherited periodic fever syndromes (Table 7.1).

The concept of autoinflammatory disorders has expanded and now at least 25 separate genes are implicated in the monogenetic diseases (infevers, http://fmf.igh.cnrs.fr/ISSAID/infevers) as well an increasing number of polygenic and multifactorial diseases. (*See Table 1.6 and Fig. 1.13 for updated classification of autoinflammatory disorders*).

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This chapter will mainly focus on the Mendelian inherited autoinflammatory diseases as knowledge in the field has expanded considerably and many of the polygenic and multifactorial diseases are discussed in the rheumatologic and gastroenterology literature. As yet there is not complete consensus on which polygenic and multifactorial diseases are classed as autoinflammatory and this will probably change in the coming years. Autoinflammatory diseases are a consequence of dysregulation of the innate rather than the adaptive immune system. The relationships between adaptive and innate immunity are complex but a classification of immunological diseases according to the extent to which these two systems are involved was proposed by McGonagle and McDermott in 2006 [160] (Fig. 7.1). A new definition of autoinflammatory diseases "clinical disorders marked by abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition" was introduced in 2010 and thus highlights the importance of the innate immune system [126].

Common symptoms during attacks of autoinflammatory diseases are malaise, fever, skin rash, arthritis/arthralgia, abdominal pain and CNS manifestations. The patients also often have an intense inflammatory reaction during the attacks with elevated white cells counts and biochemical markers of inflammation. Onset of the disease is generally in childhood or adolescence but almost 10 % present as adults (http://www.printo.it/eurofever/). The patients are usually

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Table 7.1 Characteristics of the hereditary periodic fevers

Periodic fever syndrome	Gene	Mode of inheritance	Predominant population	Usual age at onset	Potential precipitants of attacks	Distinctive clinical features	Typical duration of attacks	Typical frequency of attacks	Characteristic laboratory abnormalities	Treatment
FMF	*MEFV* Chromosome 16	Autosomal recessive (dominant in some families)	Eastern Mediterranean	Childhood/ early adulthood	Usually none, Occasionally menstruation, fasting, stress, or trauma	Short severe attacks Erysipelas-like erythema	½–3 days	Variable	Marked acute phase response during attacks	Colchicine (Anti-IL-1 therapies in resistant cases)
TRAPS	*TNFRSF1A* Chromosome 12	Autosomal dominant	Northern European, but reported in many ethnic groups	Childhood/ early adulthood	Usually none	Prolonged symptoms	More than a week (may be very prolonged)	Variable (may be continuous)	Marked acute phase response during attacks Low levels of soluble TNFR1 when well	Anti IL-1 therapies Etanercept, High-dose corticosteroids
MKD/ HIDS	*MVK* Chromosome 12	Autosomal recessive	Northern European	Infancy	Immunizations, infections	Diarrhoea and lymphadenopathy.	3–7 days	1–2 monthly	Elevated IgD and IgA, acute phase response, and mevalonate aciduria during attacks	Anti-IL-1 therapies, Anti-TNF therapies
FCAS	*NLRP3* Chromosome 1	Autosomal dominant	Northern European	Childhood	Exposure to cold environment	Cold-induced fever, arthralgia, rash, and conjunctivitis	12–24 h	Depends on environmental factors	Acute phase response during attacks; to a lesser extent when well	Cold avoidance, Anti-IL-1 therapies
MWS	*NLRP3* Chromosome 1	Autosomal dominant	Northern European	Neonatal/ infancy	Marked diurnal variation, Cold environment, but less marked than in FCAS	Urticarial rash, Conjunctivitis Sensorineural deafness	Continuous (often worse in the evenings)	Often daily	Varying but marked acute phase response most of the time	Anti-IL-1 therapies
CINCA/ NOMID	*NLRP3* Chromosome 1	Sporadic	Northern European	Infancy	None	Urticarial rash, Aseptic meningitis, deforming arthropathy, sensorineural deafness, mental retardation	Continuous	Continuous	Varying but marked acute phase response most of the time	Anti-IL-1 therapies

PAPA	*PSTPIP1* Chromosome 15	Autosomal dominant	Very few families reported. Northern European	Childhood	None	Pyogenic arthritis, pyoderma gangrenosum, and cystic acne	Intermittent attacks with migratory arthritis	Variable (may be continuous)	Acute phase response during attacks	Anti-TNF therapies
Blau's syndrome	*NOD2* Chromosome 16	Autosomal dominant	None	Childhood	None	Granulomatous polyarthritis, iritis, and dermatitis	Continuous	Continuous	Sustained modest acute phase response	Corticosteroids, Anti-TNF therapies Methotrexate
FCAS2/ NAPS12	*NLRP12* Chromosome 19	Autosomal dominant	Very few families reported – possibly more from Carribean	Infancy	Exposure to cold environment	Urticarial rash, sensorineural deafness, fever, abdominal pain	5–10 days	~ monthly	Variably elevated	Not well established NSAIDS, Corticosteroids Antihistamines, Anti-IL-1 therapies
DIRA	*IL1RN* Chromosome 2	Autosomal recessive	Very few families reported from various ethnicities	Neonatal	None	Fetal distress, pustular rash, joint swelling, oral mucosal lesions	Continuous	Continuous	Sustained acute phase response	Anti-IL-1 therapies
Majeed Syndrome	*LPIN2* Chromosome 18	Autosomal recessive	Very few families reported Middle Eastern kindreds	Early childhood	None	Multifocal sterile osteomyelitis, dyserythropoietic anemia, and neutrophilic dermatosis	Continuous bone inflammation, fevers for 3–4 days	Continuous, fevers every 1–2 weeks	Sustained modest acute phase response	NSAIDs, Corticosteroids, Anti IL-1 therapies
DITRA	*IL36RN* Chromosome 2	Autosomal recessive	Very few families reported – possibly more in North Africa	Variable from infancy to adulthood	Pregnancy and infections reported	Repeated flares of sudden onset generalised pustular psoriasis	Highly variable	Highly variable	Acute phase response during attacks	Unclear (Anti-TNF and IL-1 therapies)
CANDLE/ PRAAS/ NNS/JMP	*PSMB8* PSMA3, PSMA4, PSMB9 and POMP also described Chromosome 6	Autosomal recessive	Caucasian, Japanese and Asian kindreds reported	Infancy	None	Progressive partial lipodystrophy,	Continuous	Continuous	Varying but marked acute phase response most of the time	Unclear (JAK inhibition?)

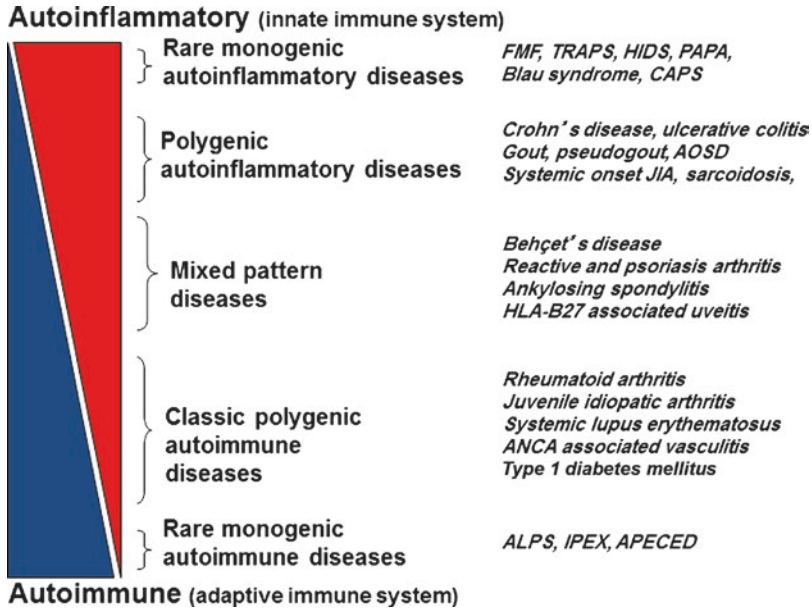

Fig. 7.1 Autoinflammatory versus autoimmune immunological diseases (Adapted with permission from [160])

symptom-free between attacks but may have subclinical inflammation.

Although the autoinflammatory syndromes have only been identified as such during the last few decades, perhaps the earliest clinical description is found in William Heberden's 1802 Commentaries on History and Care of Disease (London: T. Payne): 'Pains which are regularly intermittent, the fits of which return periodically as those of an ague; such as I have known in the bowels, stomach, breast, loins, arms and hips, though it be but seldom that such parts suffer in such a manner'. Over the last two decades the clinical descriptions have become more refined as underlying genetic causes have been identified. The first disease to have a gene isolated was Familial Mediterranean fever with the identification of pyrin mutations in 1997. Since then mutations in at least another 24 genes have been implicated in monogenetic autoinflammatory diseases with advances in understanding of their pathophysiology although there are still many unanswered questions.

Autoinflammatory diseases can be classified according to the mode of inheritance (Table 7.1). Familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD) also known as hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) and mevalonic aciduria (MVA), deficiency of the interleukin-1 receptor antagonist (DIRA), deficiency of the IL-36 receptor antagonist (DITRA), Majeed syndrome and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome are largely autosomal recessive diseases. Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA), Blau syndrome and the cryopyrin-associated periodic syndromes (CAPS), are inherited in an autosomal dominant pattern. The concept of autoinflammatory diseases has expanded from initially including only hereditary syndromes to also encompassing non-Mendelian inherited diseases. There is still no agreement as to which of these syndromes will be included. The following diseases are often regarded as non-Mendelian autoinflammatory: periodic fever, aphtous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA), systemic onset juvenile idiopathic arthritis (SoJIA), adult-onset Still's disease (AOSD), chronic

recurrent multifocal osteomyelitis (CRMO), Behçet's disease (BD) and Schnitzler's syndrome. The role of Crohn's disease (CD) as an autoinflammatory disease or immunodeficiency is not yet settled. Apart from PFAPA, CRMO and Schnitzler's syndrome the polygenic/multifactorial diseases will only be discussed briefly.

The study of autoinflammatory diseases has given us insights into the innate immune system. Pattern recognition molecules (PRMs) are a group of molecules responsible for sensing danger signals and are involved in the first line of defense; they are highly conserved and can be seen in plants and insects. The extracellular Toll-like receptors (TLRs) were discovered in 1992. A few years later, the intracellular Nod-like receptors (NLRs) were found [93, 111] and since several other PRMs have been characterized such as Rig1 like receptors (RLRs) and C-lectin receptors (CLR). Two NLRs; Nod-like receptor family pyrin domain containing 3 (NLRP3, also known as NALP3, cryopyrin and CIAS1) and nucleotide-binding oligomerization domain protein 2 (NOD2) have been shown to be pivotal in autoinflammatory diseases [155, 238] but others have also been described, including NLR family CARD domain-containing protein 4 (NLRC4). The NLRP3 inflammasome can be activated by microbial toxins, bacterial RNA, uric acid and ATP [159]. Although, the development in the field is remarkable, much still remains to be learned regarding pathogenesis and treatment of autoinflammatory disorders.

The focus has so far mainly been on the NLRP3 inflammasome and IL-1β, but other mechanisms are also involved in autoinflammation including type I interferons and NF-κB as well as defective regulatory mechanisms with unopposed signaling [53].

The awareness and knowledge of autoinflammatory diseases is important. Patients with these diseases need to be recognized and diagnosed [122] as well as evaluated for the risk of AA amyloidosis, the main long-term risk. They should also receive appropriate treatment, with the aim of preventing episodes, inflammation and AA amyloidosis as well as improving length and quality of life.

It is often a challenge to investigate the patient with a suspected autoinflammatory disease. As in most areas of medicine, the mainstay is a good clinical case history and physical examination, in particular during episodes. Many conditions can mimic autoinflammatory diseases. Occult or recurrent infections (for example frequent viral infections, malaria, brucellosis, and *Borrelia recurrentis*) are important differential diagnosis as well as malignant diseases and atypical autoimmune diseases. Immunodeficiencies including cyclic neutropenia have to be considered. It is crucial to ascertain if there is a marked inflammatory response during attacks as this is a hallmark of systemic autoinflammatory disease. It is especially important to cover family history and ethnicity in detail. A patient diary is often valuable. The clinical picture will give a clue as to which hereditary periodic fever syndrome might cause the symptoms but there are overlaps in the clinical presentation of the different diseases. Furthermore, there are many patients with a probable autoinflammatory disease whose signs and symptoms do not fit with any of the known diseases. The understanding of these "undifferentiated" disorders need to be improved.

A proportion of patients with clinical signs and symptoms suggesting a specific autoinflammatory disease, but with no mutation found with conventional Sanger sequencing has been found to have somatic mosaicism. Most reports have been in CAPS (*NLRP3*), but somatic mosaicism has also been found in a handful of other autoinflammatory diseases.

The increased knowledge of many autoinflammatory diseases in combination with the development of cytokine inhibitors has prompted potential for better treatment.

7.2 Familial Mediterranean Fever

7.2.1 Definition

Familial Mediterranean fever (FMF; OMIM*249100) is an ancient disease but was only described as a clinical entity as recently as 1945

[220] and it was given the name FMF in 1958 [98]. FMF is the most common of the hereditary autoinflammatory diseases worldwide and prevalence of FMF has been estimated to be 1 in 250 to 1 in 500 among non-Ashkenazi Jews and 1 in 1000 in the Turkish population. The disease is mainly found in populations from the eastern Mediterranean area (especially non-Ashkenazi Jews, Armenians, Turks and Arabs). FMF can be found in other ethnic groups around the Mediterranean Sea but at a lower incidence [7, 133, 135]. It has been proposed that the only possible explanation for the high frequency of *MEFV* mutations in populations in the eastern Mediterranean area is that heterozygous carriers have a survival advantage compared to non-carrier, possibly due to an increased resistance to an undetermined infection [157]. The disease is uncommon in other ethnic populations. However, a clinical understanding of the disease has become increasingly important in other parts of the world, partly due to emigration from the eastern Mediterranean area. The disease usually presents in children or adolescents, 50 % has onset before the age of 10 years and 90 % before the age of 20 years.

7.2.2 Etiology

FMF is an autosomal recessive inherited disease caused by mutation in the MEditerranean FeVer (*MEFV*) gene (OMIM*608107) on chromosome 16. FMF was the first of the autoinflammatory diseases where a gene defect could be found (1997) [78, 112]. Initially, five mutations were described and they are still the most frequent (80–90 %). Thus far more than 300 variants have been described mostly encoding substitutions (fmf.igh.cnrs.fr/ISSAID/infevers/). Mutations in both alleles are found in only 2/3 of clinically classic cases. The reason for this is not known but mutations in another gene or in the promoter region could be explanations. *MEFV* codes for a protein, pyrin ("relation to fever") also called marenostrin ("our sea"), which is mainly expressed in granulocytes, monocytes and synovial fibroblasts. The structure and function of pyrin have not yet been characterized in detail, although it is clearly of importance for regulation of the innate immune system and subtle abnormalities of leucocyte function have been reported in FMF. The putative 781 amino acid protein has sequence homologies with a number of proteins of apparently disparate function and cellular localization. Recent work suggests that pyrin is not primarily a nuclear protein, but interacts via its N-terminal death domain with microtubules and the actin cytoskeleton, consistent with a role in directed cell migration and by the C-terminal domain to activate IL-1β and NF-κB. There are two possible mechanisms for this action of pyrin (Fig. 7.2). In the sequestration hypothesis it is believed that native pyrin has an inhibitory effect on the cryopyrin (NLRP3) inflammasome by competitive binding of ASC and pro-caspase-1 as well as binding of caspase-1 [37, 184]. The pyrin inflammasome hypothesis suggests that pyrin can form an inflammasome by binding to ASC and another adaptor protein in order to cleave pro-caspase-1 and activate IL-1β [35].

Members of the death-domain superfamily play important roles in the assembly and activation of apoptotic and inflammatory complexes through homotypic protein-protein interactions. Proteins with pyrin domains are involved in inflammation, apoptosis, and NF-κB signaling and have been implicated in pathways in CAPS as well. A recent study indicates that pyrin is activated by pathogen-mediated modifications of Rho GTPases, a small G protein that is induced by toxins from bacteria like *Clostridium difficile*, *Vibrio parahemolyticus* and *C. botulinum* [260]. This mechanism may explain the survival advantage of individuals that are heterozygous for *MEFV* in the eastern Mediterranean area.

7.2.3 Clinical Manifestations

The symptoms of FMF are self-limiting (12–72 h) recurring attacks of fever and serositis. The most frequent manifestation besides fever is peritonitis (80 %). The abdominal pain can resemble appendicitis and 40 % patients undergo laparoscopy before the FMF diagnosis is made. Pleuritis is seen in about 15–30 % of the patients [209] and is usually one-sided with painful breathing. Acute

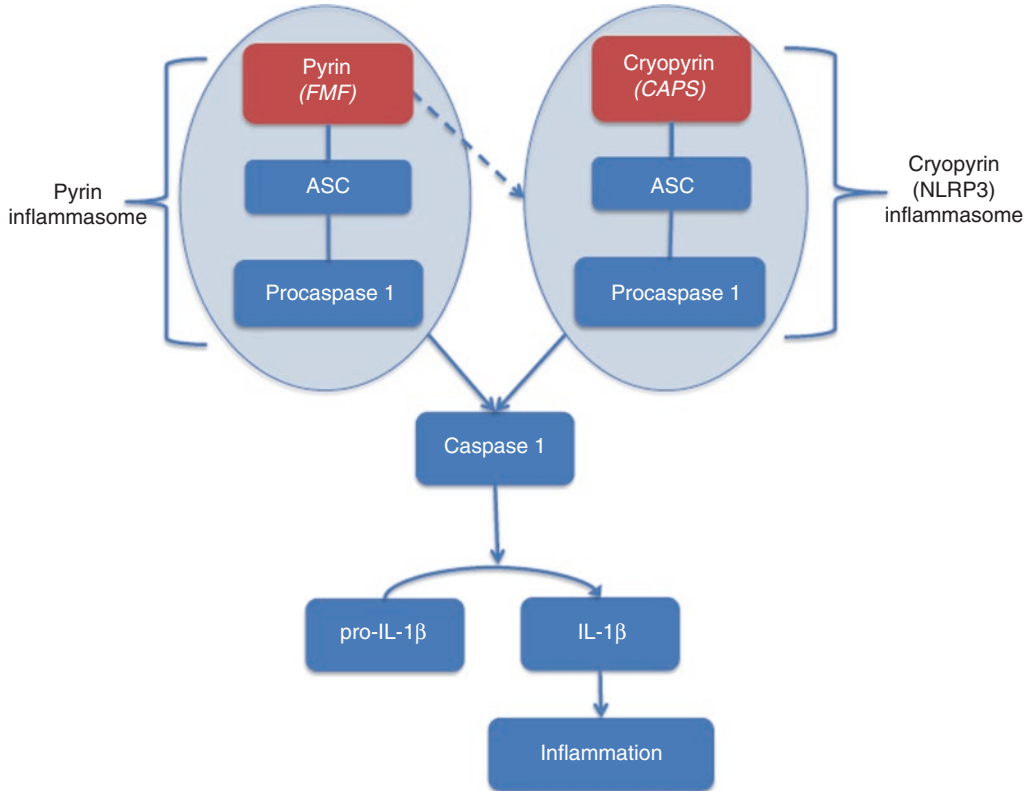

Fig. 7.2 Cryopyrin inflammasome and the pyrin inflammasome in cryopyrin-associated periodic syndromes (CAPS) and familial Mediterranean fever (FMF)

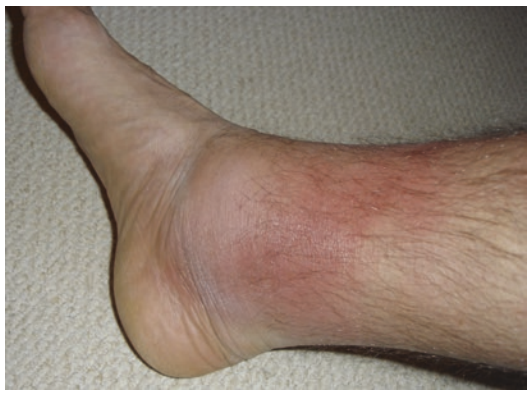

Fig. 7.3 Erysipelas-like erythema in a patient with FMF

arthritis is also common, usually affecting one or a few large joints (ankle, knee, hip or the sacroiliac joints). The arthritis is usually non-erosive but it may in rare cases be chronic and erosive. Pericarditis and orchitis can also occur but are rare. An erysipelas-like erythema during attacks is seen in about 25 % of pediatric patients [180]. The erythema is often associated with arthritis and is usually located between the knee and ankle, on the dorsum of the foot, or in the ankle region (Fig. 7.3). Polyarteritis nodosa and Henoch-Schonlein purpura are associated with FMF [243].

There is a short but marked inflammatory response during an attack indicated by an increase in CRP, ESR and serum amyloid A protein (SAA). Studies have shown that subclinical inflammation is common between attacks [65, 138], which might also affect the patients' quality of life [177].

The main risk of FMF is development of renal AA amyloidosis, which may lead to end-stage renal failure. SAA is the precursor of amyloid deposits in FMF. SAA levels rise during attacks and usually normalize in attack-free periods [244]. However, in a significant proportion of

patients, SAA levels are not normalized [65, 138]. The level of increased SAA with which there is no risk for development of amyloidosis has not been established. The *MEFV* mutation M694V and the SAA1 genotype are risk factors for amyloidosis [34, 85, 147, 265]. Interestingly, the country of residence is for unknown reasons an independent risk factor with the highest risk for those in Armenia, Turkey or Arabic countries [242]. Analysis of SAA might be a tool in diagnosing as well as monitoring FMF [17]. Patients with amyloidosis as the presenting or only manifestation of disease (phenotype II) exist but are uncommon [13, 243].

Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) is an extremely rare autosomal dominant disease [156]. The disease is distinct from FMF, but is caused by a mutation in *MEFV*. Manifestations include episodes of fever, dermatitis, arthralgia, myalgia and myositis.

7.2.4 Diagnosis

The diagnosis is made on the basis of clinical criteria. The Tel Hashomer criteria [148] are often used to make the diagnosis (Table 7.2). A set of criteria for childhood FMF has been proposed [261] (Table 7.3). However, these criteria have shortcomings, especially in countries with a low prevalence of FMF were the specificity is limited [131]. The diagnosis should be considered in patients with ethnicity from the eastern Mediterranean with recurrent inflammatory episodes. A diagnostic trial with colchicine treatment is part of the investigation in patients with atypical symptoms. Genetic investigation can in atypical cases verify the diagnosis but a negative mutation analysis cannot rule out the disease since *MEFV* positive mutations in both alleles are only seen in 2/3 of patients with classical FMF.

Table 7.2 Simplified criteria set for diagnosis of familial Mediterranean fever (FMF), "Tel Hashomer criteria"

Major criteria
1–4. Typical attacks
1. Peritonitis (generalized)
2. Pleuritis (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)
4. Fever alone
5. Incomplete abdominal attack
Minor criteria
1–2. Incomplete attacks involving one or more of the following sites
1. Chest
2. Joint
3. Exertional leg pain
4. Favorable response to colchicine

The requirements for diagnosis are ≥1 major criteria or ≥2 minor criteria. Typical attacks are defined as recurrent (≥3 of the same type), febrile (≥38 °C) and short (lasting between 12 h and 3 days)

Table 7.3 Yalçinkaya set of criteria for the diagnosis of familial Mediterranean fever (FMF) in childhood

1. Fever (axillary temperature >38 °C, duration of 6–72 h, 3 attacks)
2. Abdominal pain (duration of 6–72 h, 3 attacks)
3. Chest pain (duration of 6–72 h, 3 attacks)
4. Oligoarthritis (duration of 6–72 h, 3 attacks)
5. Family history of familial Mediterranean fever

Diagnosis is definite, if two or more criteria are satisfied

7.2.5 Management

The disease is treated prophylactically with life long colchicine [59, 90, 267]. Most patients will be symptom-free and the risk of amyloidosis is reduced from 25–40 % to less than 1 %. However, colchicine is not effective in acute attacks. Children usually need a higher dose per kilogram than adults do [123]. Colchicine can sometimes, especially in higher doses, give gastrointestinal side effects. A temporary reduction in the colchicine dose and reduced intake of lactose can relieve the gastrointestinal symptoms. Cohort studies suggest that colchicine in pregnancy is safe and should be continued. Failure to respond to colchicine should prompt a careful review of compliance but cytokine (mostly IL-1 and to a lesser extent TNF) inhibitors have been used with success in therapy resistant cases [30, 37, 94, 167, 179, 211]. Acute FMF attacks can be treated with non-steroid anti-inflammatory drugs (NSAID). Corticosteroids do not have an effect on the classical manifestations but are effective in

protracted myalgia, a rare vasculitic complication of FMF [140]. Arthritis that becomes chronic can be treated as juvenile idiopathic arthritis or rheumatoid arthritis.

7.3 Mevalonate Kinase Deficiency

(***Hyperimmunoglobulinemia D and periodic fever syndrome, Mevalonic aciduria***)

7.3.1 Definition

Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS, OMIM*260920) was defined in 1984 [248] and was given its name because of increased IgD and periodic fever. Mevalonic aciduria (MVA, OMIM*251170) is a more severe disease with mental retardation and dysmorphic features in addition to similar symptoms as for hyperimmunoglobulinemia D and periodic fever syndrome (HIDS). It later turned out that both diseases are caused by a defect in the same enzyme (mevalonate kinase). The name mevalonate kinase deficiency (MKD) is now used for the both diseases, but is most often used to describe the periodic fever syndrome historically known as HIDS. MKD is an uncommon inborn error of the cholesterol biosynthesis. There are only a few hundred and less than one hundred patients known with HIDS and MVA, respectively. Most patients with HIDS are from Europe, in particular from the Netherlands and France. A common founder of the most frequent variant V377I may explain this geographical bias [222].

7.3.2 Etiology

MKD is autosomal recessive inherited and caused by a mutation in the mevalonate kinase (*MVK*) gene (OMIM*251170) located on chromosome 12 [61, 107]. The mutation leads to reduced activity of mevalonate kinase. This enzyme is part of the cholesterol, farnesyl and isoprenoid biosynthetic pathway (Fig. 7.4). In MVA, mevalonate kinase activity is almost zero [104] and in

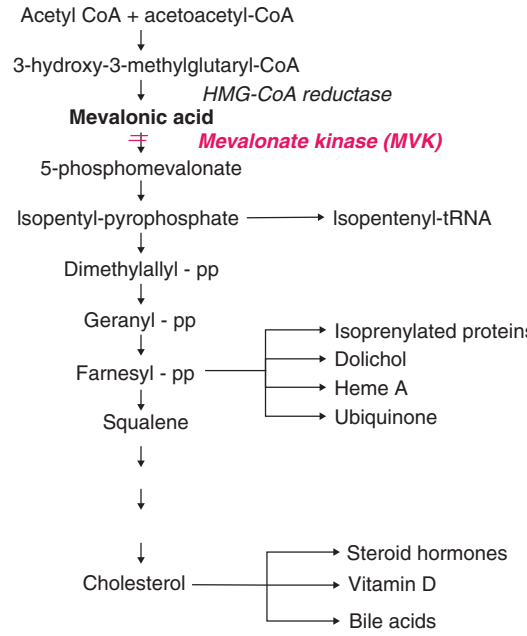

Fig. 7.4 Defect in the cholesterol biosynthesis in mevalonate kinase deficiency (MKD)

HIDS 1–10 % of normal levels [61, 107] resulting in an accumulation of mevalonic acid. In MVA mevalonic acid is continuously very high, while in HIDS it is normal between attacks and increases only moderately during attacks. There are about 60 known disease-causing mutations (http://fmf.igh.cnrs.fr/infever). HIDS is associated with a "severe" and a "mild" mutation (the most common being 1129G>A (V377I)), in contrast with MVA which is associated with two "severe" mutations. The activity of the V377I is temperature-dependent, leading to decreased activity with increasing temperature [106], which might partly explain the recurrent attacks seen in HIDS. The reason why mutations in *MVK* lead to an autoinflammatory disease is still not clear. There have been discussions as to whether the attacks are caused by an increase of mevalonate or a decrease of compounds further down the pathway (Fig. 7.4). The first hypothesis seems unlikely as an attempt to reduce mevalonate production in a patient with MVA has led to disease exacerbation [104]. Animal and *ex vivo* studies support the notion that the lack of isoprenoid triggers an IL-1β response, but the relevance of these studies need to be further explored. In any case

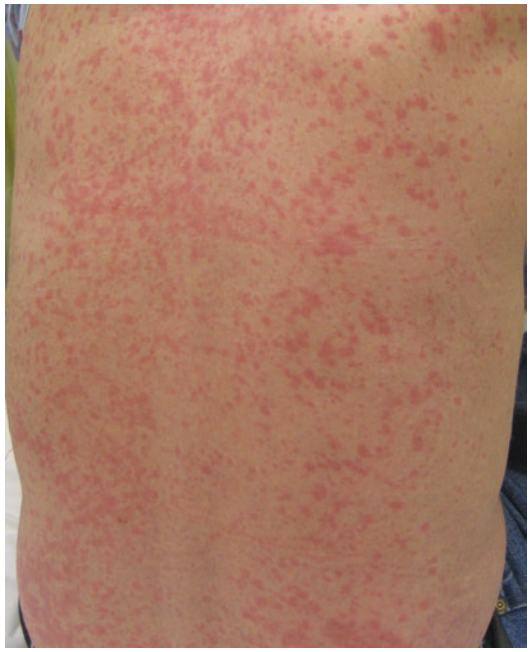

Fig. 7.5 Rash seen in a patient with hyper-IgD syndrome (HIDS) (Courtesy of A. Simon; Nijmegen, the Netherlands)

there seems to be an agreement that IL-1β has a central role in HIDS, which is supported by the clinical experience of treating patients with IL-1 blockade [246]. Another study also suggests that decreased lymphocyte apoptosis in MKD is important for the pathogenesis of MKD [21].

7.3.3 Clinical Manifestations

A continuous spectrum of clinical presentations is seen from the more benign HIDS to the severe MVA. The symptoms usually start appearing before the age of 1 year [79] and are characterized by episodes of fever and inflammation that recur every 2–8 weeks and last 3–7 days [62, 247]. Other common symptoms during attacks are skin rash, cervical lymphadenopathy, arthritis/arthralgia, diarrhea and abdominal pain (Fig. 7.5). Sometimes there are headache, and oral or genital ulcers. Retinitis pigmentosa and intermittent neutropenia have been described. The disease typically ameliorates somewhat in early adult life. Attacks in patients with HIDS can be triggered by vaccination and stress. MVA is characterized by the same inflammatory symptoms as HIDS but also by dysmorphic features, neurologic symptoms, mental retardation and failure to thrive [104].

7.3.4 Diagnosis

MKD is diagnosed by mutational analysis of the *MVK* gene. The diagnosis is supported by decreased enzymatic activity of mevalonate kinase or increased urine concentration of mevalonate [119, 246]. In HIDS, mevalonate is slightly elevated during attacks, but not during attack-free periods. It is important that the laboratory is able analyze urine mevalonate at low concentrations. Methods used for detecting aminoaciduria are not always sufficiently sensitive for analyzing the low but significantly raised levels of mevalonate in HIDS during attacks. This problem is not encountered in MVA where mevalonate is continuously very high. Acute phase reactants increase during episodes. IgD and IgA are increased in 80% of the patients both during and between attacks. The reason for the polyclonal rise in IgD and IgA is not known and does not seem to be disease specific as an increase is seen in many other inflammatory diseases including FMF and PFAPA.

7.3.5 Management

The clinical course in MKD is variable and the treatment often needs to be tailored for the individual patient. A treatment algorithm with a step-wise approach has been proposed as a tool to support clinical decisions [246]. Many patients are treated, on demand or continuously, with NSAID and/or corticosteroids [235]. Several other anti-inflammatory agents (e.g. colchicine, statins and thalidomide) have been tried without significant effect [246]. A number of case series indicate that anakinra is the most effective biological agent in MKD, with complete or partial effect in the majority of patients [235]. A smaller proportion of patients respond to etanercept, and patients that do not respond to anakinra might very well respond to etanercept or vice versa [235, 246]. Recently, a patient was reported to respond to alendronate treatment with normalization of all clinical and

laboratory abnormalities related to MKD [33]. A few patients with MVA have been treated successfully with hematopoietic stem cell transplantation (HSCT) [12, 173]. The severity of the disease seems to diminish during adulthood [64].

7.4 Tumor Necrosis Factor Receptor-Associated Periodic Syndrome

7.4.1 Definition

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS; OMIM*142680) was formerly known as familial Hibernian fever due to the heredity factor and the predominance of Irish ancestry in the first cases described [256]. The disease was renamed TRAPS when it was discovered that it was caused by a mutation in the TNF receptor gene 1 [158]. TRAPS is probably the most frequent autosomal dominant hereditary autoinflammatory disease. However, it is still an unusual disease with an estimated prevalence in Europe of approximately one per million [139].

7.4.2 Etiology

TRAPS is caused by a mutation in the tumor necrosis factor receptor superfamily 1A (*TNFRSF1A*) gene (OMIM*191190) that encodes for the TNF receptor 1 (=55 kD TNF receptor). The gene for the disease, located on chromosome 12, was found in 1999 [158]. To date more than 100 different disease-causing mutations have been found in TRAPS (http://fmf.igh.cnrs.fr/ISSAID/infevers/). Two mutations, c.362G>A (R92Q) and c.224C>T (P46L), are regarded as polymorphisms or associated with a milder phenotype [195] and occur in 2 and 10 % of Caucasians and Africans, respectively. In the initial description of TRAPS it was found that there was a shedding defect of the TNF receptor, which led to decreased concentration of soluble TNF receptor in serum [158]. However, this is only true for some of the TRAPS mutations and this is probably not related to the pathogenesis. A new theory is that there is misfolding of the extracellular domain of the mutant TNF receptor 1 leading to retention in the endoplasmatic reticulum and that TRAPS may result from the consequences of the abnormally retained TRAPS mutant TNF receptor 1 [28, 149] giving rise to intracellular stress and production of reactive oxygen species.

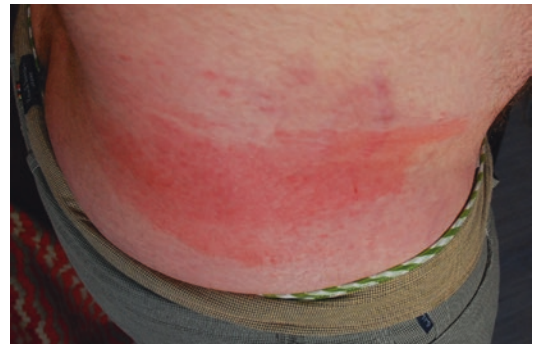

Fig. 7.6 Rash seen in a patient with TRAPS

7.4.3 Clinical Manifestations

TRAPS is characterized by long episodes (>1 week) of fever accompanied by abdominal pain, arthralgia, myalgia, skin rash, arthritis, pleuritis, conjunctivitis and periorbital edema (Figs. 7.6 and 7.7) [137]. The clinical symptoms and severity are variable. The median age of onset is 4 years but the range is wide (2 weeks to 50 years). The attacks last an average of 10 days but the duration varies from several days to more than a month. The myalgia is often migratory with an overlying rash.

7.4.4 Diagnosis

The diagnosis of TRAPS is suspected in patients with recurring long attacks (>1 week), myalgia with an overlying erythematous rash, ocular manifestations and a family history suggesting autosomal dominant inheritance. Acute phase reactants are increased during attacks. Reduced soluble TNF receptor levels are seen in many but not all patients. The symptoms of TRAPS are

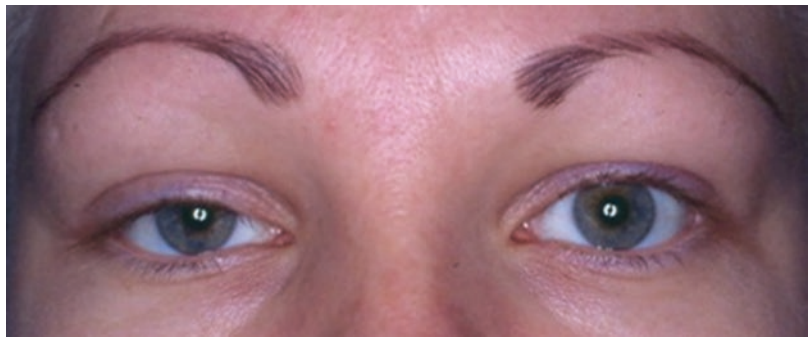

Fig. 7.7 Periorbital edema seen in a patient with TRAPS (Courtesy of T. Pettersson; Helsinki, Finland)

very variable and the diagnosis is based on DNA analysis. Somatic mosaicism, including gonosomal mosaicism, has recently been reported [206]. It is still not settled how to interpret patients with signs and symptoms of autoinflammatory disorder who have the polymorphisms (or low penetrance mutations) R92Q and P46L.

7.4.5 Management

Steroids are effective in treating TRAPS but unacceptably high doses are often required. IL-1 blockade is the current treatment of choice in patients requiring biologics [235]. Etanercept, a TNF blocking agent, has been used with some success, although not in all cases [40, 235]. Infliximab, a humanized mouse antibody to TNF, seems to be ineffective and paradoxal inflammatory reactions have been observed [63, 115].

7.5 Cryopyrin-Associated Periodic Syndrome

(***Chronic infantile neurological cutaneous articular syndrome, Muckle-Wells syndrome, Familial cold autoinflammatory syndrome***)

7.5.1 Definition

Until recently this were regarded as three distinct autosomal diseases: Chronic infantile neurologic cutaneous and articular syndrome (CINCA, OMIM*607115) also known as neonatal-onset multisystem inflammatory disease (NOMID), Muckle-Wells syndrome (MWS, OMIM*191900), and familial cold autoinflammatory syndrome (FCAS, OMIM*120100), They have now been linked to mutations in the same gene, however, and are regarded as a clinical continuum [3]. The name cryopyrin-associated periodic syndrome (CAPS), used for all three conditions, indicates that the same protein, cryopyrin, is affected in these diseases. They are all rare. It appears that MWS is more common in Europe and FCAS in North America [3].

7.5.2 Etiology

All three diseases are caused by a mutation in the NLR family, pyrin domain containing 3 (*NLRP3*) gene (OMIM*606416), The gene is located on chromosome 1. The gene for FCAS and MWS was found in 2001 [101] and for CINCA/NOMID in 2002 [5, 71]. In total more than 100 disease-causing mutations are known today (http://fmf.igh.cnrs.fr/ISSAID/infevers/). Some of the mutations are associated with part of the syndrome but overlaps are common [172]. The gene codes for a protein, cryopyrin, which is mainly expressed in neutrophiles, monocytes and chondrocytes. Cryopyrin forms a complex known as the NLRP3 inflammasome (= cryopyrin inflammasome), together with ASC and cardinal [155, 238]. This cleaves pro-caspase-1 to active caspase-1, which in turn activates IL-1β

(Fig. 7.2). The mutations in CAPS give rise to a gain-of-function of the NLRP3 inflammasome. However, the understanding of the role of the mutated cryopyrin is still unclear. There are conflicting data regarding apoptosis and regulation of nuclear factor kappa B (NF-κB) in CAPS. Not all patients with the clinical picture of CAPS (especially in CINCA but also in MWS) have a germline mutation in *NLRP3*, but somatic mosaicisms have been found in some of these patients [170, 232].

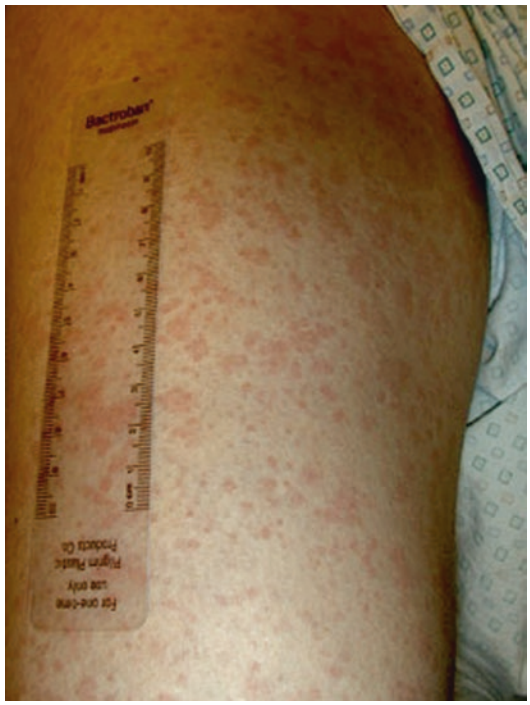

Fig. 7.8 Urticaria-like rash seen in a patient with familial cold autoinflammatory syndrome (FCAS) (Courtesy of H. Hoffman; California, USA)

7.5.3 Clinical Manifestations

Although these diseases have been classified as three different diseases they often have overlapping symptoms such as fever, urticaria-like rash, arthritis/arthralgia and an acute inflammatory reaction. FCAS and MWS are often associated with an autosomal dominant pattern of family history. The diseases can be regarded as a continuum with FCAS as the mildest form, MWS as the intermediate and CINCA as the most severe. There are overlap forms of CINCA/MWS and MWS/FCAS.

FCAS was first described in 1940 [127]. FCAS is characterized by cold-induced attacks of fever associated with urticaria-like rash, arthralgia and conjunctivitis (Figs. 7.8 and 7.9) [103]. The symptoms usually start before the age of 6 months. The average delay between cold exposure and symptoms is 2–3 h and the episode usually lasts less than 24 h. This is in contrast to the more common cold urticaria where the symptoms develop soon after cold exposure. The risk of developing amyloidosis is lower than MWS.

MWS was first described in 1962 [169]. The syndrome is characterized by episodic attacks with urticaria-like rash, fever, malaise, conjunctivitis, arthralgia and progressive sensorineural hearing loss [48, 60]. The duration of the attacks is longer (24–72 h) than in FCAS. The disease usually manifests itself during childhood but hearing loss usually begins in adolescence. About 25 % of patients will develop AA amyloidosis [1].

CINCA was first described in 1981 [190] and NOMID in 1983 [95]. It later turned out to be the same disease and the terms CINCA/NOMID are used interchangeably. In addition to fever, the

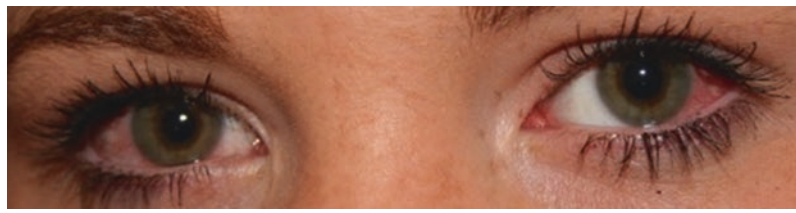

Fig. 7.9 Conjunctivitis in a patient with familial cold autoinflammatory syndrome (FCAS)

clinical spectrum includes the triad of cutaneous, neurological and articular symptoms. The non-pruritic urticaria-like skin rash usually develops in the neonatal period or in early infancy. The neurological symptoms, which vary considerably between patients, can include chronic aseptic meningitis, papilledema with optic-nerve atrophy, uveitis, seizures, cerebral atrophy, mental retardation and sensorineural hearing loss [191]. The articular manifestations differ from juvenile idiopathic arthritis by being a deforming arthropathy with bony overgrowth especially affecting the knees but also ankles, elbows, wrists and hands [191]. There is chronic inflammation with increased ESR, CRP and SAA but flares occur at irregular intervals. About 1/5 of untreated patients will not survive through to adulthood.

7.5.4 Diagnosis

The diagnosis is made on the basis of clinical criteria, see Table 7.1. Overlaps between the diseases are common and the phenotype can vary even within a family. A germline mutation in *CIAS1* is found, using conventional mutation analysis, in only about half of all cases of CINCA/NOMID [3], but somatic mosaicism seems common in "mutation negative CAPS patients" [170, 232].

7.5.5 Management

For many years, the treatment of CAPS was mainly supportive. Steroids, disease modifying anti-rheumatic drugs (DMARD) and anti-TNF therapy were used with some effect. However, a number of case reports and studies have shown substantial success in treating CAPS with IL-1 blocking agents [89, 96, 102, 136, 235]. Recovery of hearing in a patient with MWS has been reported after treatment with anakinra [166].

7.6 Blau Syndrome

(***Pediatric granulomatous arthritis, Early onset sarcoidosis***)

7.6.1 Definition

Sarcoidosis is a granulomatous multisystem disease that mainly affects patients between 20 and 40 years of age. The symptoms in adults usually involve the triad of lung, lymph node and eye manifestations. In the pediatric population two distinctive forms have been identified [204, 217]. School-aged children and adolescents have clinical manifestations similar to the adults involving lungs and lymph nodes. Young children (<5 years) usually have the triad of arthritis often causing camptodactyly, uveitis and dermatitis resulting in a characteristic tan colored rash. This syndrome is usually referred to early onset sarcoidosis (EOS, OMIM*609464). Blau syndrome (OMIM*186580), a rare autosomal dominant inherited disease with granulomatous inflammation [18, 114], was described in 1985 and the symptoms are almost identical to early onset sarcoidosis [100, 164, 204]. Sporadic early onset sarcoidosis (without a family history of the syndrome) has been shown to be the same disease as Blau syndrome [124, 125, 201]. The name pediatric granulomatous arthritis (PGA) has been proposed for both Blau syndrome and early onset sarcoidosis [203], but it has not been widely accepted. Instead, Blau syndrome is now often used for both the familial and sporadic form.

7.6.2 Etiology

Blau syndrome is caused by a mutation in the nucleotide-binding oligomerization domain protein 2 (*NOD2*) (also known as caspase recruitment domain family 15 (*CARD15*)) gene (OMIM*605956) on chromosome 16 [162]. The two most prevalent mutations are, c.1000C>T (R334W) and c.1001G>A (R334Q) [200, 203, 255]. About 20 disease-causing mutations have up today been reported (infevers, http://fmf.igh.cnrs.fr/ISSAID/infevers). The location of the mutations in Blau syndrome is in the NACTH region in contrast to Crohn's disease where mutations are found in the LRR region. The mechanism for the disease is not fully known but it is

probably involved in regulation of apoptosis and in the innate immune response to bacterial lipopolysaccharide via activation of NF-κB [201]. In Blau syndrome, there is a gain-of-function of the mutated protein in contrast to Crohn's disease where there is a loss-of-function. Studies have shown that the same mutations are found in EOS as in Blau syndrome [124, 125, 200]. These mutations are not found in older children and adults with sarcoidosis.

7.6.3 Clinical Manifestations

The dermatitis is a cutaneous eruption of small papules often described as a tan colored rash. The rash has also been described as an ichthyosis-like exanthema. This kind of rash is rarely seen in the adult form of sarcoidosis. The dermatitis can be intermittent in contrast to sarcoidosis in adults. The joint symptoms include synovitis and tenosynovitis, which often are polyarticular. Camptodactyly can develop. The most important morbidity is due to the uveitis. About 1/3 of the patients develop moderate to severe visual impairment. Bilateral panuveitis is common uveitis type and is often complicated by band keratopathy, glaucoma, and cataract formation [200].

The clinical manifestations associated with Blau syndrome are expanding [202]. In addition to the three core symptoms (arthritis, uveitis and dermatitis), fever, subcutaneous nodules, erythema nodosum, large-vessel vasculitis (early onset Takayasu disease), and several other symptoms can appear [200, 202].

7.6.4 Diagnosis

The diagnosis is supported by the clinical criteria including the core symptoms (dermatitis, arthritis, uveitis), non-caseating granulomas and onset before 5 years of age. The diagnosis can be confirmed by DNA analysis. Most patients (34/45) which are *NOD2* mutation positive have the classical triad [200]. Asymptomatic individuals with *NOD2* mutation have been reported [200]. Most, but not all patients, with the classical triad have a disease-causing mutation [125, 200, 255]. These disease-causing mutations can also give rise to atypical forms of Blau syndrome [215]. Somatic mosaicisms have been reported in patients with Blau syndrome [52, 161]

7.6.5 Management

Steroids have been used for treatment but relapses are common after withdrawal. Steroid sparing agents may be required. Case studies has shown variable efficacy with anti-TNF therapy [202]. IL-1 blocking agents seem to be largely ineffective but case reports have shown efficacy [224].

7.7 Pyogenic Arthritis, Pyoderma Gangrenosum and Acne Syndrome

7.7.1 Definition

Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome (OMIM*604416) is an autosomal dominant inherited disease characterized by pyogenic arthritis, pyoderma gangrenosum and acne [144]. The disease is only known in a few families [43, 144, 198, 231].

7.7.2 Etiology

PAPA was mapped for a disease locus on chromosome 15 in 2000 [257, 264]. The disease was found, 2 years later, to be caused by a mutation in the proline serine threonine phosphatase interacting protein 1, (*PSTPIP1*) gene (OMIM*606347) on chromosome 15 [258]. Eleven different mutations have been associated with PAPA to date. The mechanism by which these cause inflammation is not known. However, the PSTPIP1 protein binds to pyrin, the protein affected in FMF, and may cause inflammation in the same pathway of the innate immune system as FMF [225].

7.7.3 Clinical Manifestations

The first manifestation to appear, between 1 and 16 years of age, is usually oligoarticular pyogenic arthritis [258]. The arthritis, often erosive, can start spontaneously but sometimes after a mild trauma. Usually the joint symptoms will be less pronounced with age. Acne develops later, often at puberty. The acne is often severe and cystic. Pyoderma gangranosum-like ulcerative lesions occur in some patients. Other manifestations include sterile abscesses at injection sites and pancytopenia after administration of sulfa-containing drugs. The penetrance of the disease seems to be variable and some mutation-positive family members are symptom free [56].

7.7.4 Diagnosis

The diagnosis is made on clinical criteria. The disorder should be suspected if there is a familial appearance suggesting autosomal dominant inheritance. The diagnosis can be confirmed with DNA analysis.

7.7.5 Management

There is no established treatment for this rare disorder. PAPA is only partly responsive to treatment with oral and intraarticular steroids. Case series have shown variable results on anti-TNF treatment [43, 56, 66, 226] as well as anti-IL-1 treatment [56, 58, 218, 258]. The treatment is usually more effective against the arthritis than the skin manifestations.

7.8 NLRP12 Associated Periodic Fever Syndrome

7.8.1 Definition

NLRP12 associated periodic fever syndrome (NAPS12) or familial cold autoinflammatory syndrome 2 (FACS2; OMIM*611762) is an exceptionally rare autosomal dominant disease first described in 2008 causing episodes of fever with variable associated symptoms with some reports of sensorineural deafness and cold induced symptoms [118].

7.8.2 Etiology

The nonsense and splice site mutations identified in the NLR family, Pyrin domain-containing 12 (*NLRP12*) gene (OMIM*609648) appear to reduce the inhibitory effect of the protein on NF-κB signaling [8].

7.8.3 Clinical Manifestations

Patients presented in infancy or the neonatal period with a syndrome with some features of cold induction, fever, arthralgia and myalgia, urticaria and sensorineural deafness. The first cases reported were from two unrelated families from the Caribbean and subsequent cases have been reported [23, 118, 252].

7.8.4 Diagnosis

The diagnosis is made on clinical criteria. The disorder should be suspected if there is a pattern of autosomal dominant inheritance and NLRP3 is wild type. The diagnosis can be confirmed with DNA analysis.

7.8.5 Management

There is no established treatment for this rare disorder.

7.9 Deficiency of ADA2

7.9.1 Definition

The deficiency of ADA2 (DADA2) or monogenetic polyarteritis nodosa (PAN) vasculopathy

(OMIM*615688) was described independently in 2014 by two groups [171, 270]. The clinical spectrum is wide and so far not well established. Manifestations include childhood systemic and local polyarteritis nodosa (PAN), recurrent fever, mild immunodeficiency, livedo racemosa and early-onset stroke.

7.9.2 Etiology

The syndrome is caused by recessive loss-of-function mutations in the cat eye syndrome chromosome region, candidate 1 (*CECR1*) gene (OMIM*607575), encoding adenosine deaminase 2 (ADA2) [171, 270]. The mutations cause reduced activity of ADA2 in plasma. The ADA2 protein is produced by myeloid cells and is thought to be a growth factor for endothelial cells as well as leucocytes. ADA2 deficiency may induce proinflammatory cells leading to inflammation and vasculopathy.

In contrast, overexpression of ADA2 due to gain-of-function mutation in *CECR1*, causes Cat Eye Syndrome (CES), a congenital malformation syndrome [45].

7.9.3 Clinical Manifestations

The manifestations of DADA2 are heterogeneous and the two initial case-series had different inclusion criteria. In the study by Navon Elkan et al, patients were recruited mainly from familial cases (Georgian Jewish) of PAN [171]. All the Georgian Jewish patients were homozygous for a mutation encoding p.Gly47Arg substitution.

In the study by Zhou et al., patients with recurrent fevers, livedo racemosa, mild immunodeficiency and early-onset stroke were included [270]. Six patients were compound heterozygous for eight different *CECR1* mutations. The patients with immunodeficiency had hypogammaglobulinemia/low IgM levels, recurrent bacterial and viral infections, varying degrees of lymphopenia

The three patients with PAN phenotype in this study also had homozygous p.Gly47Arg substitution.

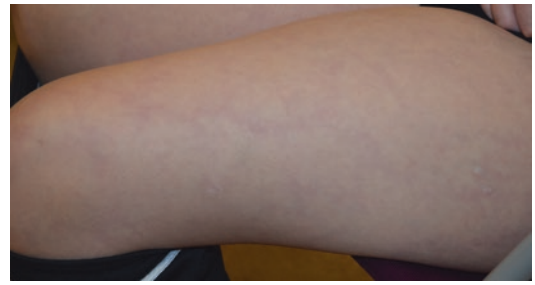

Fig. 7.10 Livedo racemosa seen in a patient with deficiency of ADA2 (DADA2)

7.9.4 Diagnosis

The diagnosis is based on clinical criteria including recurrent fever, early onset stroke, livedo racemosa (Fig. 7.10) and features of PAN. The suspicion should be especially high if there is a pattern of autosomal recessive inheritance. The diagnosis can be made by measurement of ADA2 in serum and it is confirmed with DNA analysis.

7.9.5 Management

Treatment with anti-TNF agents [171] had positive results. A few patients underwent HSCT and they are reported to have normalized their ADA2 activity and to have improved clinically [249, 250]. ADA2 replacement treatment or fresh-frozen serum could also be a possible short-term treatment option.

7.10 STING-Associated Vasculopathy with Onset in Infancy

7.10.1 Definition

The acronym SAVI (STING-Associated Vasculopathy with Onset in Infancy) (OMIM*615934) was proposed in 2014 for an autosomal dominant disorder, characterized by early-onset systemic inflammation with elevated inflammatory markers, severe cutaneous vasculopathy and lung disease [145].

7.10.2 Etiology

The syndrome is caused by a gain-of-function mutation in the transmembrane protein 173 (*TMEM173*) gene (OMIM*612374) (encoding the stimulator of interferon genes, STING) leading to an induction of type I interferon signaling [145]. SAVI is now included among the type I interferonopathies.

7.10.3 Clinical Manifestations

So far only about ten cases have been published [39]. The patients described by Liu et al ($n=6$), had onset of symptoms before the age of 2 months [145]. All had rash on cheeks, ears, nose, and digits. The symptoms of these areas worsened with time and included scarring of the ear cartilage, perforation of the nasal septa and severely affected digits. Biopsies of affected areas show vascular inflammation of the capillaries. All had fever (mostly recurrent low-grade), systemic inflammation and failure to thrive. All six had pulmonary manifestations including adenopathy, reduced lung function and interstitial lung disease.

7.10.4 Diagnosis

The disease should be considered in a child with very early onset (<2 months of age) of rash at the typical locations, fever, failure to thrive, systemic inflammation and lung involvement. The diagnosis can be confirmed with DNA analysis.

7.10.5 Management

There is no established treatment. Corticosteroids, DMARDS and biologics had no or limited effect. Treatment with JAK inhibitor (blockade of interferon signaling) is a possible option.

7.11 Deficiency of the IL-1 Receptor Antagonist

7.11.1 Definition

Deficiency of the IL-1 receptor antagonist (DIRA) or osteomyelitis, sterile multifocal, with periostitis and pustulosis (OMPP) (OMIM*612852) is an extremely rare autosomal recessive disease characterized by a neonatal onset of a pustular rash, multifocal osteitis and periarticular soft-tissue swelling.

7.11.2 Etiology

DIRA is a model of the consequences of unregulated activity of IL-1α and β in humans. It is caused by missense or deletion mutations in the interleukin 1 receptor antagonist (*IL1RN*) gene (OMIM*147679), which encodes the IL-1 receptor antagonist (IL-1Ra). Mutations in both alleles result in either complete absence or dysfunction of IL-1Ra and thus unopposed binding of IL-1α and β to the IL-1 receptors [4, 196].

7.11.3 Clinical Manifestations

The disease has been reported in only a handful of families of various ethnicities living in Northern Europe and Central America. The disease presents in the immediate neonatal period with a pustular rash, joint swelling, multifocal osteitis of the ribs and long bones, heterotopic ossification and periarticular soft-tissue swelling [4, 113, 143, 196].

7.11.4 Diagnosis

The diagnosis is made on clinical criteria. The disorder should be suspected if there is a pattern of autosomal recessive inheritance. The diagnosis can be confirmed with DNA analysis.

7.11.5 Management

Treatment is replacement of IL-1R antagonist with its recombinant form, anakinra [4].

7.12 Majeed Syndrome

7.12.1 Definition

Majeed Syndrome (OMIM*609628) was first reported in 1989 as an autosomal recessive syndrome, characterized by chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia and in some cases neutrophilic dermatosis [151].

7.12.2 Etiology

The disease was found to be due to mutations in the Lipin2 (*LPIN2*) gene (OMIM*605519) on chromosome 18 in 2005 [73]. Lipin2 is widely expressed in the liver, the kidneys, the gut, and lymphoid tissues, including the bone marrow. Lipin2 protein is thought to play role in lipid metabolism although its exact function and how mutations may cause an inflammatory phenotype is not established.

7.12.3 Clinical Manifestations

The disorder has been described in only a handful of children. Disease onset is usually in the neonatal period and attacks consist of several days of fever, severe pain, and the appearance of periarticular soft tissue swelling. Long-term complications of growth retardation and flexion contractures are well recognized.

7.12.4 Diagnosis

The diagnosis is made on clinical criteria. The disorder should be suspected if there is a pattern of autosomal recessive inheritance. The diagnosis can be confirmed with DNA analysis.

7.12.5 Management

There have been reports of modest benefit from NSAIDs and corticosteroids. Recent case reports suggest IL-1 blockade with anakinra (IL-1RA) and canakinumab is more effective although the long-term effect on dyserythropoesis is not yet known [99]

7.13 Deficiency of IL-36 Receptor Antagonist

7.13.1 Definition

Deficiency of IL-36 receptor antagonist (DITRA) or generalized pustular psoriasis (GPP) (OMIM*614204) is an autosomal recessive disease, characterized by recurrent episodes of a generalized sterile pustular rash accompanied neutrophilia, a marked acute phase response and fever.

7.13.2 Etiology

The disorder is due to mutations in IL-36 receptor antagonist (*IL36RN*) (OMIM*605507) on chromosome 2 and was identified in 2011 [152, 176]. To date 14 nonsense or deletion mutations have been described. Loss of the IL-36R antagonist is thought to result in unregulated signaling by IL-36 α, β, and γ via the Il-36 receptor. IL-36R antagonist is expressed in keratinocytes and a mouse model supports a central role of IL-36 signaling in psoriatic disease [20].

7.13.3 Clinical Manifestations

This extremely rare disease was initially reported in kindreds from North Africa and Japan with

recurrent episodes of a generalized sterile pustular rash accompanied neutrophilia, a marked acute phase response and fever. Age at onset varied from childhood to the sixth decade. Episodes could be precipitated by stress, pregnancy or drugs and they could be life threatening [69, 152, 176].

7.13.4 Diagnosis

The diagnosis is made on clinical criteria. The disorder should be suspected if there is a pattern of autosomal recessive inheritance. The diagnosis can be confirmed with DNA analysis.

7.13.5 Management

There is no established treatment for this rare disorder. Acitretin has been used with variable effect. There is one report of benefit from anakinra [205] and treatment with TNF blockade and cyclosporine have improved some patients [183].

7.14 Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature

7.14.1 Definition

The acronym CANDLE (Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature) (OMIM*256040), also known as Autoinflammation Lipodystrophy and Dermatosis Syndrome (ALDO) or Nakajo-Nishimura Syndrome (NNS), was proposed in 2010 for an autosomal recessive disease, characterized by early onset, fevers, delayed physical development, microcytic anemia, recurrent annular lesions, swollen violaceous eyelids, thick lips, progressive lipodystrophy and arthralgia [240]. Therefore it could also be named as Joint contractures, Muscular atrophy, microcytic anemia, and Panniculitis-induced lipodystrophy (JMP) syndrome. The acronym proteasome-associated autoinflammatory syndrome (PRAAS) is also used as an umbrella term.

7.14.2 Etiology

The syndrome was initially described as due to substitution mutations in proteasome subunit beta type 8 (*PSMB8*) gene (OMIM*177046) on chromosome 6. Most patients are homozygote but in some cases mutations in other proteasome genes have been found [24]. *PSMB8* encodes the inducible β5i subunit of the immune proteasome. Proteasomes are ubiquitously expressed and are involved in proteolysis, generating antigenic peptides for class I MHC presentation and maintenance of cell homeostasis. It is suggested that failure of proteolysis leads to accumulation of damaged proteins, increased cellular stress and increased interferon (IFN) signaling. Cytokine profiling and analysis of the transcriptome was consistent with dysregulation of the IFN pathway in four children [2, 11, 83, 128].

Recent studies have shown that mutations in other proteasome genes (*PSMA3*, *PSMA4*, *PSMB9* and *POMP*) may also cause the disease [24]. These genes encode other subunits of the proteasome (PSMA3, PSMA4, PSMB9 and POMP). The inheritance is diallelic, but in the case of mutations in *POMP* autosomal dominant.

7.14.3 Clinical Manifestations

CANDLE was initially described in four patients with early onset, fevers, delayed physical development, microcytic anemia, recurrent annular lesions, swollen violaceous eyelids, thick lips, progressive partial lipodystrophy and arthralgia. Skin biopsies demonstrated a perivascular and interstitial infiltrate comprising mature neutrophils and atypical mononuclear cells of myeloid lineage [240]. Nakajo-Nishimura syndrome (NNS) was first described in Japan in 1939 as secondary hypertrophic osteoperiostosis with pernio and is characterized by partial lipomuscular atrophy, clubbing, a pernio-like, heliotrope-like, or nodular erythema-like rash, periodic fever and joint contractures. More than 20 cases have been reported with evidence for a common founder [11]. Joint contractures, muscle atrophy, microcytic anemia and panniculitis-induced childhood

onset lipodystrophy (JMP) syndrome was described in 2010 in three adults from a Portuguese kindred and another from Mexico [83]. It is possible that the muscle involvement and joint contractures may be later onset complications of progressive disease in untreated or partially treated patients who survive beyond childhood.

7.14.4 Diagnosis

The diagnosis is made on clinical criteria including characteristic skin histology. The disorder should be suspected if there is a pattern of autosomal recessive inheritance (N.B. autosomal dominant inheritance if the mutation is in *POMP*). The diagnosis can be confirmed by DNA analysis.

7.14.5 Management

Treatment attempts, including anti-TNF agents and the interleukin-6 (IL-6) receptor blocker tocilizumab, were only partially effective [146]. There is an ongoing clinical study (ClinicalTrials.gov Identifier: NCT01724580) of Janus Kinase (JAK) inhibitors with the aim of reducing IFN gamma-inducible protein 10 production.

7.15 Very Early Onset Inflammatory Bowel Diseases

(***IL-10 deficiency, IL-10Rα deficiency, IL-10Rβ deficiency, NFAT5 haploinsufficiency, ADAM17 deficiency***)

7.15.1 Definition

Very early onset of inflammatory bowel disease (VEO-IBD) is very rare and presents with severe enterocolitis and perianal manifestations. Extra-intestinal manifestations include recurrent fever, and often folliculitis and arthritis. The disease is autosomal recessive disease (OMIM*613148 and #612567), caused by mutations in *IL10RA* (OMIM*146933), *IL10RB* (OMIM*123889) or *IL-10* (OMIM*124092) genes [87, 88]. Recently, haploinsufficiency of *NFAT5* (OMIM*604708) has also been reported in a case with autoimmune enterocolopathy and infections [22]. Mutations in *ADAM17* gene has also been reported in two siblings of a family with inflammatory skin and bowel disease [19].

7.15.2 Etiology

There is a defect of the IL-10 axis either by loss-of-function of one of the two receptors (IL10 receptor α-chain, or IL10 receptor β-chain) or less commonly IL10. IL10 is a major anti-inflammatory cytokine that can be induced in response to colonic colonization. Decreased IL10 signaling causes a dysregulated proinflammatory cytokine response that affects macrophage activation [219].

7.15.3 Clinical Manifestations

Children develop severe inflammation in the colon and the perianal region with onset before the age of 3 months. These symptoms can be accompanied by recurrent fever, increased inflammatory markers, infections, folliculitis, arthritis, aphthous lesions. Some develops B-cells lymphoma. The patients are in a hyperinflammatory state.

7.15.4 Diagnosis

The disease should be thought of in a child with very early onset (<3 months of age) of severe inflammatory bowel disease with perianal fistules [245, 263]. Signs of autoimmunity are absent.

7.15.5 Management

Early onset inflammatory bowel disease is a severe disease and mainly refractory to standard immunosuppressant treatments. HSCT has been used as a curative treatment in small case series [68].

7.16 Autoinflammation and PLCγ2-Associated Antibody Deficiency and Immune Dysregulation

7.16.1 Definition

Autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation (APLAID; OMIM*614878) is an autosomal dominant extremely rare disease, only described in one family [268]. The disease has the uncommon combination of immunodeficiency and autoinflammation.

7.16.2 Etiology

The APLAID are caused by gain-of-function mutations in the phospholipase Cγ2 (*PLCG2*) gene (OMIM*600220). The enzyme phospholipase Cγ2 (PLCγ2) is involved in several immunological pathways and the pathway involved in APLAID is not completely understood. Activation of the NLRP3 inflammasome through Ca2+ signaling may, however, be part of the pathogenesis [36].

In contrast, another disease caused by different mutations (deletions) in the *PLCG2* gene is the PLCγ2-associated antibody deficiency and immune dysregulation (PLAID) syndrome [175].

7.16.3 Clinical Manifestations

The autoinflammatory signs and symptoms of APLAID include recurrent blistering skin lesions, interstitial pneumonitis with bronchiolitis, ocular inflammation and arthralgia. The immunodeficiency is characterized by recurrent sino-pulmonary infections.

PLAID has a different phenotype with very early-onset cold induced urticarial rash, and signs of autoimmunity instead of autoinflammation. Autoimmune features (thyroiditis, vitiligo and autoantibodies) are found in a high frequency of the patients.

7.16.4 Diagnosis

The diagnosis is made on the clinical phenotype in combination with low concentrations of IgA and IgM, and can be confirmed by DNA analysis. No autoantibodies are found. In both diseases, patients had low- or normal serum IgA and IgM levels, poor responses to pneumococcal vaccine and reduced class-switched B-cells [165].

7.16.5 Management

There is no established treatment for this rare disorder.

7.17 Sideroblastic Anemia, Immunodeficiency, Fevers, and Developmental Delay

7.17.1 Definition

Sideroblastic anemia, immunodeficiency, fevers, and developmental delay (SIFD; OMIM*616084) is an early onset disease caused by autosomal recessive loss-of-function mutations in tRNA nucleotidyl transferase, CCA-adding, 1 (*TRNT1*) gene (OMIM*612907) described in 2013 [259].

7.17.2 Etiology

TRNT1 codes for an enzyme essential for maturation of both nuclear and mitochondrial transfer RNAs. The mutations lead to metabolic defects in both the mitochondria and cytosol [38]. The mechanisms are not fully known.

7.17.3 Clinical Manifestations

The main features are severe anemia combined with recurrent non-infectious fever episodes. Most patients have B-cell lymphopenia and/or hypogammaglobulinemia. Recurrent sinopulmonary infections distinct from the recurrent fever episodes are common. Sensorineural hearing

loss, cardiomyopathy, and central nervous system abnormalities are seen in some patients.

7.17.4 Diagnosis

The diagnosis is made on clinical phenotype, and can be confirmed by DNA analysis.

7.17.5 Management

The mortality is, due to multiorgan or cardiac failure, high. There is no established treatment. Treatment with HSCT has been reported to be successful in one case.

7.18 Aicardi-Goutieres Syndromes

7.18.1 Definition

Aicardi-Goutieres Syndromes (AGS) have recently been included among the autoinflammatory diseases due to the pathogenic mechanism with increased INF type I production. AGS are discussed in detail in neurologic literature and will only be discussed briefly. AGS was initially described as an early onset progressive brain disease with pleocytosis in CSF and with basal ganglia calcifications. Beside neurologic and cognitive defects the patients may have cutaneous manifestations such as chilblain and livedo reticularis. Seven types of the syndrome have already been identified in association with type I interferonopathies [46, 47, 142] (Table 7.4).

7.18.2 Etiology

The mechanisms underlying various disease phenotypes associated with Aicardi-Goutieres syndromes have not been clearly understood. Meanwhile mutations in at least seven different genes (*TREX1*, *RNASEH2A*, *RNASEH2B, RNASEH2C, SAMHD1, ADAR*, and *IFIH1*) can cause AGS (Table 7.4). All the gene products are involved in DNA and RNA metabolism. The defect causes accumulation of nucleotides that promotes intracellular stress and results in increased type I interferon production.

7.18.3 Clinical Manifestations

Recent studies have shown that mutations in these genes may have a wide phenotype distribution, ranging from severe neurological impairment to mild cutaneous disease, systemic autoinflammation, and autoimmunity [142]. Progressive encephalopathy, intracranial calcifications, cerebral atrophy, leukodystrophy, hepatosplenomegaly are the main characteristics of Aicardi-Goutieres syndromes. Details of clinical and laboratory findings of each disease are presented in the Table 7.4.

7.18.4 Diagnosis

The diagnosis of the Aicardi-Goutieres syndrome could be made based on clinical phenotype of the patients. The main laboratory findings are thrombocytopenia, elevated hepatic transaminases, and chronic CSF lymphocytosis.

7.18.5 Management

Treatment is symptomatic and supportive, which would be done based on clinical phenotypes of disease. As some patients suffer from seizure, anticonvulsant drugs can be recommended. Special dietary advice might also be needed.

7.19 Other Monogenic Autoinflammatory Disorders

7.19.1 CARD14 Mediated Psoriasis

Most cases of psoriasis are sporadic but familial cases are described. CARD14 mediated psoriasis (CAMPS; OMIM*602723) is an autosomal dominant disease, characterized by early onset

Table 7.4 Characteristics of different types of Aicardi-Goutieres syndrome [189]

Disease	Inheritance	OMIM*	Associated features	Genetic defect	OMIM*
TREX1 deficiency (AGS1)	AR, AD	225750	Progressive encephalopathy intracranial calcifications, cerebral atrophy, leukodystrophy, hepatosplenomegaly, thrombocytopenia, elevated hepatic transaminases, CSF lymphocytosis	*TREX1*	606609
RNASEH2B deficiency (AGS2)	AR	610181	Progressive encephalopathy Intracranial calcifications, cerebral atrophy, leukodystrophy, hepatosplenomegaly, thrombocytopenia, elevated hepatic transaminases, CSF lymphocytosis	*RNASEH2B*	610326
RNASEH2C deficiency (AGS3)	AR	610329	Progressive encephalopathy, intracranial calcifications, cerebral atrophy, leukodystrophy, hepatosplenomegaly, thrombocytopenia, elevated hepatic transaminases, chronic CSF lymphocytosis	*RNASEH2C*	610330
RNASEH2A deficiency (AGS4)	AR	610333	Progressive encephalopathy, intracranial calcifications, cerebral atrophy, leukodystrophy, hepatosplenomegaly, thrombocytopenia, elevated hepatic transaminases, chronic CSF lymphocytosis	*RNASEH2A*	606034
SAMHD1 deficiency (AGS5)	AR	612952	Progressive encephalopathy, intracranial calcifications, Cerebral atrophy, leukodystrophy, hepatosplenomegaly, thrombocytopenia, anemia, elevated lactates, chronic CSF lymphocytosis, skin vascularitis, mouth ulcers, arthropathy	*SAMHD1*	606754
ADAR1 deficiency (AGS6)	AR	615010	Progressive encephalopathy, intracranial calcification, severe developmental delay, leukodystrophy	*ADAR1*	146920
AGS7	AD	615846	Progressive encephalopathy, intracranial calcification, severe developmental delay, leukodystrophy	*IFIH1*	606951

CSF cerebrospinal fluid, *XL* X-linked, *AD* autosomal dominant, *AR* autosomal recessive

plaque psoriasis or generalized pustular psoriasis [121]. It has sometimes been described as an autoinflammatory disease with local inflammation [9]

The disease is caused by mutations in the caspase recruitment domain family member 14 (*CARD14*) gene (OMIM*607211) [121]. The gene encodes CARD14 that activates NF-κB. The mutated *CARD14* is a gain-of-function mutation that further activates NF-κB. CARD14 is mainly expressed in the skin. In addition, some other rare *CARD14* variants may cause psoriasis [120].

CAMPS was initially described in only two families with early onset of plaque psoriasis and one sporadic case with generalized pustular psoriasis [121]. In contrast to many autoinflammatory disorders there is no acute phase response or fever. A recent large study could not confirm an association with familial psoriasis vulgaris but with generalized pustular psoriasis [16].

The disease should be suspected in a child with early onset generalized pustular psoriasis or plaque psoriasis. The diagnosis can be confirmed with DNA analysis.

The treatment is similar to the standard therapy for moderate to severe psoriasis.

Interestingly, mutations in *CARD14* are found in a few patients with early onset familial pituriasis rubra pilaris [80]. CAMPS and familial pituriasis rubra pilaris seems to share a similar pathophysiology and might be part of a clinical spectrum.

7.19.2 Haploinsufficiency of A20

Haploinsufficiency of A20 (HA20) or familial Behcet-like autoinflammatory syndrome (AISBL) (OMIM*616744) is a newly described disease in six families [269]. The manifestations are similar to Behçet's disease but the symptoms starts at an early age. Manifestations include oral and genital ulcers, arthritis/arthralgia, and ocular inflammation. Positive pathergy test have been described in a patient. Some patients develop autoantibodies, but autoimmune diseases seem to be rare. The disease is inherited in an autosomal recessive pattern. HA20 is caused by loss-of-function mutations in TNF alpha induced protein 3 (*TNFAIP3*) gene (OMIM*191163). *TNFAIP3* encodes A20, which is a negative regulator of the NF-κB pathway. Cells from patients have an activation of the NLRP3 inflammasome with increased secretion of active IL-1 and IL-18. Treatment with IL-1 inhibition in one patient was effective.

7.19.3 Episodic Fevers, Enteropathy, and MAS due to NLRC4 Hyperactivity

Recently two groups independently showed [31, 199] that early onset inflammatory disease with features similar to macrophage activation syndrome (MAS) was caused by a mutation in NLR family, CARD domain containing 4 (*NLRC4*) gene (OMIM*606831). The disease is very rare and these two papers described one patient and one family, respectively. The symptoms were fever and loose stool. The patients had increased inflammatory markers, hyperferritinemia, increased serum Il-18, hypertriglyceridemia, pancytopenia and splenomegaly. The disease seems to be partially responsive to IL-1 blockade.

A milder form (FCAS-like features) also with mutations in *NLRC4* have described [129].

7.19.4 TNFRSF11A-Associated Disease

In 2014, three patients with TRAPS-like symptoms (long recurrent fever episodes and abdominal pain) were found to have mutations in the tumor necrosis factor receptor superfamily member 11a (*TNFRSF11A*) gene (OMIM*603499) [117]. The gene codes for the receptor activator of NF-κB (RANK). The pathogenesis is unclear.

7.19.5 Histiocytosis-Lymphadenopathy plus Syndrome

Histiocytosis-lymphadenopathy plus syndrome (OMIM*602782) is a disease associated with histiocytosis and lymphadenopathy, caused by

homozygous or compound heterozygous mutation in the *SLC29A3* gene (OMIM*612373). Some other features such as cutaneous, cardiac, joint contractures, and/or endocrinopathy and deafness could also be seen.

7.19.6 Cherubism

Cherubism (OMIM*118400) is a rare condition, leads to prominence of the lower portion in the face, caused by heterozygous mutation in the *SH3BP2* gene (OMIM*602104).

7.19.7 Spondyloenchondro-Dysplasia with Immune Dysregulation

Spondyloenchondrodysplasia with immune dysregulation (SPENCDI; OMIM*607944) is an autosomal recessive disorder, characterized by skeletal dysplasia, metaphyseal changes and neurologic involvement [25, 197]. SPENCDI is caused by homozygous or compound heterozygous mutation in the *ACP5* gene (OMIM*171640). SPENCDI is characterized by skeletal dysplasia, metaphyseal changes, neurologic involvement, in addition to immune dysregulation [25, 197]. Recurrent bacterial and viral infections, intracranial calcification, SLE-like autoimmunity, inflammatory myositis, hemolytic anemia, and thrombocytopenia have also been reported in SPENCDI.

7.20 Multifactorial/Polygenic Autoinflammatory Diseases

7.20.1 Periodic Fever, Aphtous Stomatitis, Pharyngitis and Cervical Adenitis Syndrome

Periodic fever, aphtous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome is an acronym for the most important features of the disease i.e. Periodic Fever, Aphthae, Pharyngitis and cervical Adenitis. The first description of the syndrome was made in 1987 and the acronym, PFAPA, was established 2 years later [153, 154].

The prevalence of PFAPA syndrome is not known and the incidence has rarely been studied. In Norway the incidence has been estimated to 2.3 per 10 000 children up to 5 years of age [77]. The disease is much more common than the monogenic autoinflammatory diseases in many parts of the world, with the exception of areas with high prevalence of FMF [126]. Since the first definitions of PFAPA were established, the condition has been diagnosed, not only in children below 5 years of age, but also in older children and adults [32, 182].

PFAPA has been regarded as a non-hereditary condition [181]. However, during the years, many clinicians have experienced that one of the parents or a more distant relative had similar symptoms as a child. Familial clustering has recently been supported in the Eurofever registry, in addition to previous case series and reports [42, 212, 239]. It is only now, when children adequately diagnosed with PFAPA have children of their own that an increased familial occurrence can be investigated prospectively. A familial clustering with a non-Mendelian inheritance indicates that PFAPA is a polygenetic condition [178]. However, environmental factor(s) and multifactorial aetiology cannot be excluded, in particular when the favourable outcome of tonsillectomy is taken into account.

When a cohort of PFAPA patients was analysed for predominant mutations in classical monogenic periodic fever syndromes (i.e., *MEFV*, *TNFRSF1A*, *NOD2*, and *NLRP3*), the frequency of genetic variance was the same as in the general population [49]. Furthermore, screening for a number of autoinflammatory genes and genes coding for human inflammasomes did not detect any disease causing variants [57]. The R92Q mutation in the *TNFRSF1A* gene is regarded as polymorphism and when associated with disease the phenotype shows high rate of spontaneous resolution and amelioration of the recurrent fever episodes similar to that of PFAPA [187]. In a study from 2013 patients with PFAPA syndrome were found to have *NLRP3* variants in a significantly higher frequency than expected, but this was not confirmed in a follow-up study

[57, 130]. It has been proposed that mutations in the *SPAG7* gene could be the cause of PFAPA. However, no such conclusion can be drawn, as the child with the *SPAG7* mutation did not even fulfil the criteria of PFAPA [14].

The etiology of PFAPA remains unknown, but recent studies have shed new light on the pathophysiology. Studies of blood cell during flares demonstrate increased absolute neutrophil count as well as decreased absolute lymphocyte- and eosinophil counts [27, 130]. There are also indications that three key aspects of neutrophil function are altered in children with PFAPA, most prominently during febrile episode, including apoptosis, priming and generation of an intra-cellular oxidative burst [229]. Studies of whole blood gene expression and serum cytokines during flares indicate an activation of pro-inflammatory cytokines including IL-1β, IL-18 and IL-6 as well as an activation of INF-γ related cytokines including IP-10/CXCL10 and MIG/CXCL9 [26, 130, 228]. The question of an increased inflammatory activation between febrile episodes has yet to be resolved due to conflicting data [76, 227, 228]. Taken together the present knowledge suggests an activation of both the innate and the adaptive immune system, the latter with a likely Th-1 response [214].

The diagnosis is based on recognition of the clinical features of PFAPA. The classical criteria include periodic febrile attacks with disease onset before the age of 5 years, pharyngitis, cervical adenitis and aphthae (Table 7.5) [237]. These criteria do not exclude other conditions and needs to be further developed to improve the specificity.

The most useful discriminatory features of the disease are that the attacks are regular and appear together with signs of delineated by the acronym (including exudative tonsillitis) [84, 178]. At some phase of the disease the episodes typically occurs with an interval specific for each child, however this regularity may vanish over time [178]. The duration of febrile attacks are 3–7 days with an interval of 2–8 weeks [154, 181, 233, 237]. The fever is accompanied by pharyngitis, cervical adenitis and/or oral aphthae (Fig. 7.11). Some children have additional symptoms during the episodes including mild stomach ache, leg pain as well as nausea and vomiting [237]. Inflammatory parameters (CRP and SAA) increase markedly during attacks but normalize between attacks. The children feel well between the attacks and the symptoms usually disappear within a few years [154, 181, 237]. A clinical observation suggests that children with PFAPA syndrome have fewer viral infections than other children of the same age [237]. When the recurrent episodes disappear they seem to get viral infections at a frequency comparable to their peers.

A sometimes challenging differential diagnosis is the much more uncommon cyclic neutropenia whose exclusion is included in the classical criteria. In cyclic neutropenia, the blood neutrophils characteristically oscillate with a 21-day periodicity. When the diagnosis cannot be excluded on

Table 7.5 Diagnostic criteria used for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome

1. Regularly recurring fevers with an early age of onset (<5 years of age)
2. Symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs:
Aphthous stomatitis
Cervical lymphadenitis
Pharyngitis
3. Exclusion of cyclic neutropenia
4. Completely asymptomatic interval between episodes
5. Normal growth and development

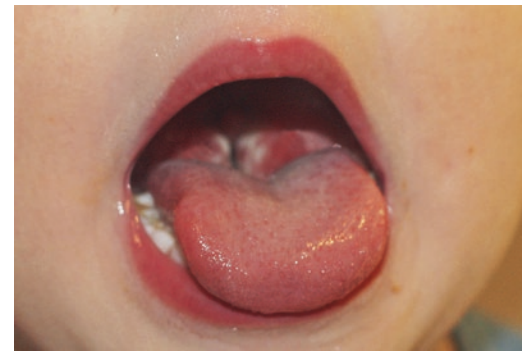

Fig. 7.11 Excudative pharyngitis in a boy with periodic fever, aphtous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome

clinical grounds, molecular analysis for the neutrophil elastase gene (*ELANE*) or repeated neutrophil counts during several weeks is recommended [50]. Recurrent infections also need to be considered, at least at the start of the disease. These include repeated streptococcal infections, and viral infections associated with tonsillitis and significant inflammation such as adenovirus. The occurrence of oral aphtae can be helpful in discriminating PFAPA from streptococcal tonsillitis. PFAPA also need to be distinguished from hereditary periodic fevers. The diagnosis should be challenged in children that fulfil the criteria if they show additional signs and symptom suggestive of monogenic hereditary periodic fevers including rash, conjunctivitis, thoracic pain, severe abdominal pain as well as episodes triggered by exercise and cold exposure [84, 213].

The treatment is mainly supportive with reduction of symptoms using primarily NSAIDs. Corticosteroids usually abort an attack within a few hours [237]. We use steroids only to postpone a febrile episode that occurs at an unsuitable time for the child, whereas others treat each episode with corticosteroids [236]. However, in a significant proportion of patients, corticosteroids shorten the interval between attacks. Colchicine has been evaluated in a few patients and need to be further investigated [234]. Tonsillectomy showed resolution of the disease in 80–90 % of cases in the initial case series [81]. These results have been repeated in a small randomised controlled trail and were supported in a Cochrane Review [29, 82]. The benefits and risks with tonsillectomy has to be assessed for the individual child, bearing in-mind the age of the child, the likely time to resolution the intensity and frequency of the episodes, as well as the quality of life and functioning of the child. One small case series indicates that PFAPA flares are responsive to IL-blockade, which has to be further evaluated [228].

7.20.2 Systemic Onset Juvenile Idiopathic Arthritis

Systemic onset juvenile idiopathic arthritis (SoJIA; OMIM*604302) is one of the categories of juvenile idiopathic arthritis (JIA) [188]. SoJIA represents 5–10 % of all JIA patients. It is the most severe category and it is a potentially fatal disease. The diagnosis of SoJIA is made on clinical criteria [188]. They include arthritis with daily fever of at least 2 weeks' duration. The typical fever pattern is fever once or twice per day followed by normal temperature and improved general condition. During the fever there is often a salmon pink evanescent skin-rash (Fig. 7.12). Generalized lymph node enlargement, hepatomegaly, splenomegaly and serositis are often present. Autoantibodies are not associated with SoJIA in contrast with several of the other categories of JIA. The etiology of SoJIA is unknown and is considered as multifactorial. However, in Saudi Arabia 5 families have been described with monogenic autosomal-recessive form of systemic JIA associated with mutation in laccase domain–containing 1 (*LACC1*) [254].

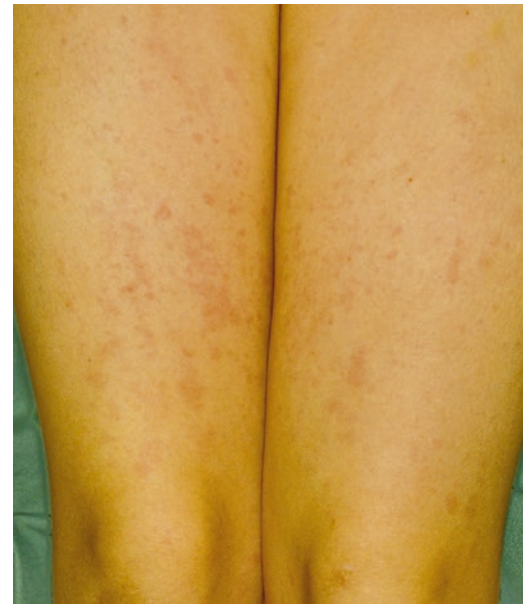

Fig. 7.12 Rash in a patient with systemic onset juvenile idiopatic arthritis (SoJIA)

Corticosteroids have been the first line of treatment and methotrexate was often used as a steroid-sparing agent. Anti-TNF treatments are generally less effective for SoJIA than other categories of JIA. A study in 2005 showed that genes involved in IL-1β processing are activated

in SoJIA [185]. Furthermore, the same study showed good results in treating patients with anakinra. Several studies has shown efficacy using IL-1 blocking agents [150, 193, 207], mainly as second line treatment. One study also showed good efficacy when anakinra was used as first line treatment [251]. The levels of IL-6 are increased in SoJIA and correlates with fever and systemic features. Studies has shown efficacy with IL-6 blockade [51, 266].

7.20.3 Adult-Onset Still's Disease

Many of the features of adult-onset Still's disease (AOSD) are similar to SoJIA [186]. AOSD is characterized by a wide variety of symptoms including intermittent fever, evanescent salmon-pink rash, arthritis, sore throat, polyserositis, lymphadenopathy, and splenomegaly. Several criteria set have been developed for AODS and the most used was developed by Yamaguchi [262]. The clinical course and severity have also a wide spectrum. Corticosteroids are used in most patients with good effect but high doses might be needed. Methotrexate can be used as a steroid-sparing agent. TNF inhibitor agent can be effective in refractory cases but are less effective than in rheumatoid arthritis [6]. Recent case-series has shown better efficacy using IL-1 blockage [86] and IL-6 blockage [41].

7.20.4 Chronic Recurrent Multifocal Osteomyelitis

Chronic recurrent multifocal osteomyelitis (CRMO; OMIM*259680) is characterized by recurrent non-bacterial osteomyelitis with or without low-grade fever [67, 75]. CRMO is a problematic diagnostic term as it is unclear how it relates, for example, to patients with a single lesion or chronic non-recurrent disease [75]. In recent years, the term chronic non-bacterial osteomyelitis (CNO) has been proposed as a unifying term that encompasses different disease progressions and number of lesions [168]. In the pediatric literature CRMO and CNO are often used interchangeably [75]. The acronym SAPHO stands for synovitis, acne, pustulosis, hyperostosis, and osteitis and is often used in adult literature [174] as it is commonly associated with arthritis and skin lesions. SAPHO and CRMO show a considerable overlap. We will mainly adhere to the term CRMO in this section.

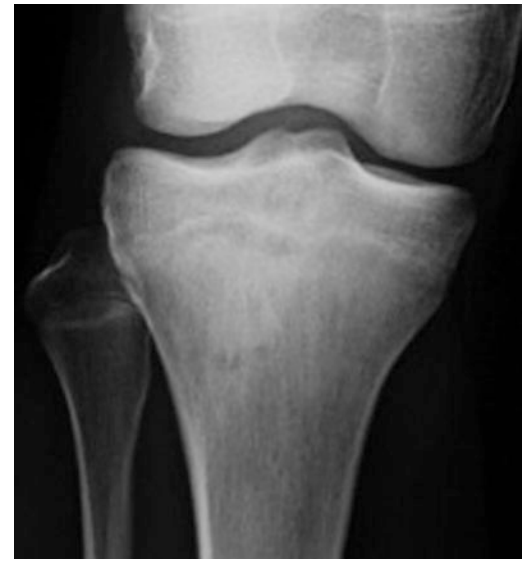

Fig. 7.13 An osteomyelitic lesion in tibia in a patient with chronic recurrent multifocal osteomyelitis (CRMO)

In addition to pustulosis palmoplantaris and psoriasis [15, 116, 141], CRMO can be associated to Sweet syndrome and IBD. There are evidences that CRMO and SAPHO can develop into ankylosing spondylitis [230, 253]. Inflammatory disorders are common in first-degree relatives (up to 50%) [74].

The diagnosis of CRMO is made on clinical criteria including no response to antibiotics and typical radiologic findings (Fig. 7.13) [216]. The location of the bone lesions are typically in the metaphyses of long bones but may also occur in the mandible, sternum, clavicle and vertebrae [108, 116] [216]. In SAPHO the osteomyelitic lesions are more often located in the anterior chest wall then it's the case in CRMO.

The etiology is unknown, but there is evidence that genetic factors may be involved due to affected family members and a report of a susceptibility gene located on chromosome 18 [91]. There seems to be

an alteration in expression of cytokines with a decrease in the anti-inflammatory cytokines IL-10 and IL-19 and an increase in the pro-inflammatory IL-20 [105]. Several monogenic diseases, with features of CRMO, have recently been discovered. Three syndromes (Majeed syndrome, PAPA and DIRA) are discussed earlier in this chapter. Interestingly diseases similar to CRMO are also seen in animals. Mutations in *PSTPIP2* cause a murine form, chronic multifocal osteomyelitis (CMO), of CRMO [72]. Canine hypertrophic osteodystrophy (HOD) is a disorder, with features similar to human CRMO that occurs especially in Weimarans [210].

The severity and the numbers of osteomyelitic lesions (1– >20) vary considerably. There are no controlled treatment trials and treatments are based on smaller case-series. The first line of treatment is often NSAID but short courses of oral corticosteroids are often needed. If failure DMARDS (methotrexate and sulfasalazine/salazopyrin) and biologics (TNF and IL-1 blockade) will be effective in many cases [97]. Bisphosphonates (pamidronate) has also been successfully used [163].

7.20.5 Crohn's Disease

Crohn's disease (OMIM*266600) is an IBD, characterized by an often relapsing transmural, granulomatous inflammation. It is sometimes associated with arthritis and skin manifestations. The disease is associated with *NOD2* mutations [109]. However, the mutations have a different location than in Blau syndrome and are probably associated with a loss-of-function in contrast to Blau syndrome where a gain-of-function is seen. There are conflicting results regarding the role of the *NOD2* mutations in the pathogenesis of CD [192, 194].

7.20.6 Behçet Disease

Behçet Disease (BD; OMIM*109650) is a chronic relapsing multisystemic inflammatory disease that has been suggested to be included among the autoinflammatory syndromes [92] even if some features, such as HLA association, resemble an autoimmune condition. The disease is mainly found in populations around the "Silk Route". The hallmarks of BD are recurrent oral and genital ulcerations, uveitis, and heterogeneous skin lesions (folliculitis or erythema nodosum) [208]. Other manifestations include musculoskeletal, gastrointestinal and neurological symptoms. Some patients have a pathergy phenomenon.

The classification criteria from 1990 are often used [44]. Mutations in the *MEFV* gene, responsible for FMF, are found in a high frequency in BD [241] but there are no increases in *MVK*, *NLRP3* or *PSTPIP1* mutations [132]. The treatment depends on the severity and organs involved. Treatment may include corticosteroids, colchicine, azathioprine, thalidomide and biologics (TNFα or IL-1 inhibition) [10].

7.20.7 Schnitzler Syndrome

This was first reported in 1974 and is characterized by a chronic urticarial like rashes (Fig. 7.14), a monoclonal immunoglobulin M (IgM) immu-

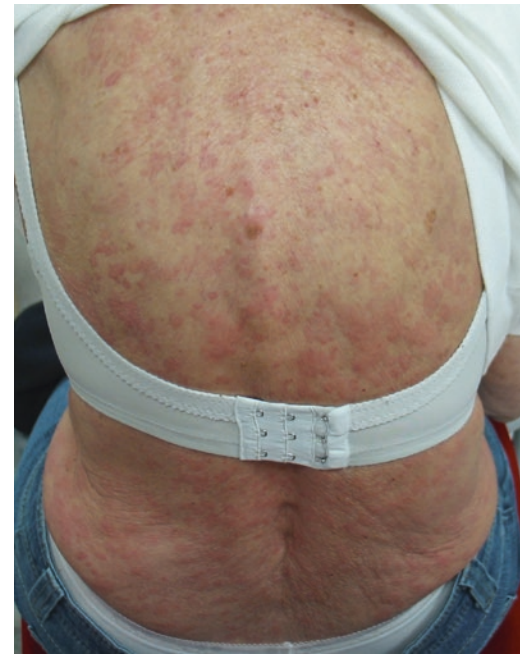

Fig. 7.14 Chronic urticarial-like rash seen in a patient with Schnitzler's syndrome

nopathy and systemic inflammation usually presenting as fever [221]. The median age at onset is 51 years and there is a slight male preponderance. The monoclonal protein appears central to the pathogenesis although the mechanism remains unclear. About a fifth of patients eventually progress to overt plasma cell malignancy. Chemotherapy has been used in the past but does not appear to relieve the syndrome and should only be used for conventional hematological indications. The treatment of choice of Schnitzler's is IL-1 blockade [54, 55, 134].

7.20.8 "Undifferentiated" Autoinflammatory Disorders

Many patients with suspected autoinflammatory disease do not fit in any of the above-mentioned syndromes. This is a diagnostic and treatment challenge. Only a few percent of patients in this category have been found to have an "autoinflammatory" mutation [70, 223]. It is important to follow these patients, in particular regarding the risk of renal amyloidosis, the severe complication of autoinflammatory diseases. It might be advisable to follow creatinine, SAA and check for proteinuria. In case of persistent inflammation a therapeutic trial with anti-inflammatory agents (colchicine, corticosteroids or biologics) should be considered.

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Complement Deficiencies

8

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8.1 Introduction

The complement system is an essential part of innate immunity, with vital interconnections with the adaptive immune system. Complement was discovered shortly before 1900, when it was recognized as a heat-labile component in serum that "complemented" the bacteriolytic effect of antibodies [81]. Today, around 50 components have been described, comprising molecules present in the fluid phase as well as on the cell surface, involved in complement activation, regulation, and cellular effects [118]. Conventionally, complement is viewed as a first line of defense against microbial particles, essential for the recognition and elimination of foreign structures of pathogenic origin, but also of damaged self-cells or cell debris. Although the innate immune effect is the obvious task of the complement system, additional functions within a broader sense of defense have now also been recognized as complement dependent [85, 118]. The complement system has several interconnections with the adaptive immunity, e.g. via bridging antibody recognition to complement-dependent opsonization and lowering the threshold for antigenic B-cell stimulation [23] and regulating T cells [74, 89]. The complement response has crosstalk connections with the Toll-like receptor-dependent signaling [52, 167] and with the coagulation and kallikrein-kinin systems

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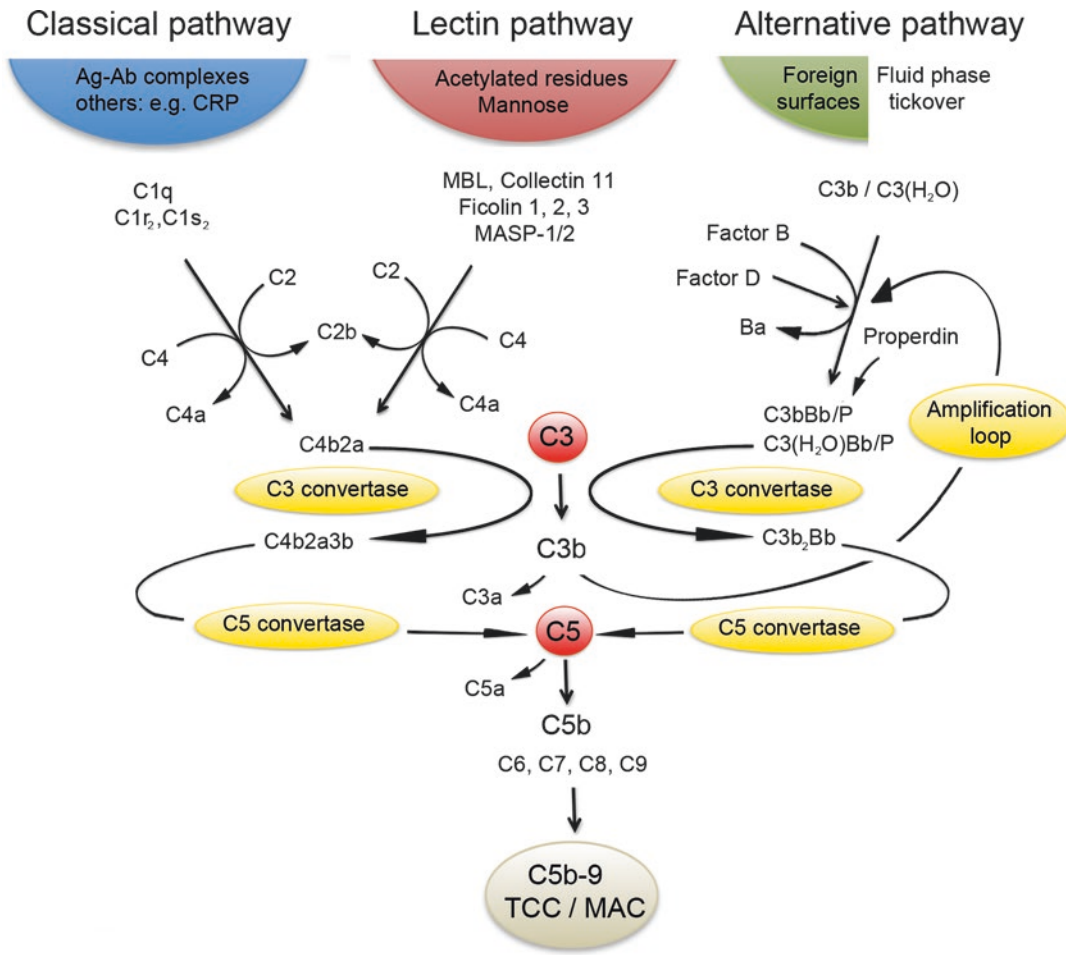

Fig. 8.1 Complement activation pathways

[43, 62, 94]. Complement activation has also been shown to be involved in embryonic and synaptic development [119, 144] and tissue regeneration [93, 145].

The complement system is activated via the classical, lectin or alternative pathway (Fig. 8.1), which are all initiated by different structures and by different mechanisms [159, 160]. The system is based on the recognition of molecular patterns that lead to the formation of enzyme complexes with proteolytic activity that cleave complement components in a cascade-like manner. The formation of C3- and C5-convertases is central in the cascade. These convertases cleave the components C3 and C5, respectively, leading to the key effects of complement activation. Effector molecules are produced throughout the cascade, leading to opsonization for enhanced phagocytosis (C3b, iC3b and C4b) [35], generation of pro-inflammatory peptides (C3a and C5a) [78], direct lysis of cells (C5b-9) [51] and co-stimulation of B-cell activation (C3d) [23].

Complement activation is a continuously ongoing process, in which principally all surfaces exposed to complement are prone to trigger activation. These potentially harmful effects are, on healthy host cells, efficiently counteracted by an array of fluid-phase and membrane-bound regulators. Most regulators are focused at the convertase formation and at the degradation of C3b [170].

Complement proteins are primarily produced in the liver by hepatocytes and constitutively

Table 8.1 Characteristics of primary complement deficiencies

Complement components	Deficiency[a]	Gene	Inheritance	Associated features
Classical pathway	C1q	*C1QABC*	AR	SLE, Rheumatoid disease, Infections
	C1r	*C1R*	AR	SLE, Rheumatoid disease, Infections
	C1s	*C1S*	AR	SLE, Rheumatoid disease, Infections
	C4	*C4A*, *C4B*	AR	SLE, Rheumatoid disease, Infections
	C2	*C2*	AR	SLE, Vasculitis, Polymyositis, Infections
Lectin pathway	MBL	*MBL2*	AR	Pyogenic infections
	Ficolin 3	*FCN3*	AR	Recurrent infections
	Collectin 11	*COLEC11*	AR	3MC syndrome
	MASP-2	*MASP2*	AR	Pyogenic infections, SLE
	MASP-3	*MASP1*	AR	3MC syndrome
Alternative pathway	Factor D	*CFD*	AR	Neisserial infection
	Properdin	*PFC*	XL	Neisserial infection
C3	C3	*C3*	AR	Recurrent pyogenic infections, Glomerulonephritis
Terminal pathway (Membrane attack complex)	C5	*C5*	AR	Neisserial infections, SLE
	C6	*C6*	AR	Neisserial infections, SLE
	C7	*C7*	AR	Neisserial infections, SLE, Vasculitis
	C8a	*C8α*	AR	Neisserial infections, SLE
	C8b	*C8β*	AR	Neisserial infections, SLE
	C9	*C9*	AR	Neisserial infections, SLE
Regulatory proteins	C1 inhibitor	*C1NH*	AD	Hereditary angioedema
	Factor I	*CFI*	AR	Recurrent pyogenic infections
	Factor H	*CFH*	AR	Hemolytic-uremic syndrome, Membranoproliferative glomerulonephritis[b]
	MCP	*CD46*	AR	Hemolytic-uremic syndrome, Glomerulonephritis
	DAF	*CD55*	AR	Paroxysmal nocturnal hemoglobinuria
	CD59	*CD59*	AR	Hemolysis pyogenic infections
	PIGA	*PIGA*	XL	Paroxysmal nocturnal hemoglobinuria
	CR3	*ITGB2*	AR	Pyogenic infections

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked, *SLE* systemic lupus erythematosus
[a]Deficiency implies both complete genetic deficiency and genetic variants (polymorphisms) that predispose to the associated features
[b]Similar manifestations are seen with genetic variants of factor I, CD46, CD55, factor B, and C3

secreted in plasma, or induced by inflammatory cytokines during the acute-phase response, but local synthesis of complement proteins by resident or infiltrating cells is pivotal to drive the inflammatory processes. Some proteins, like C1q, C7 and factor D, are mainly produced extrahepatically, e.g. C1q by macrophages and factor D by adipose and renal cells [100].

Complement deficiencies, acquired or hereditary, have been recognized for almost all of the known components of the complement system (Table 8.1). Acquired deficiency may be caused by infections or immune-complex disorders. Most inherited deficiencies of complement components are expressed in an autosomal recessive pattern. One exception is properdin deficiency,

which is inherited in an X-linked manner [47], and another one is C1 inhibitor (C1INH) deficiency, which is a dominant trait [95]. A complement gene defect may give rise to a dysfunctional protein or to a complete absence of the protein. Parents of patients with a complete deficiency of a complement component are usually heterozygotes for the mutation, resulting in approximately half-normal levels of the protein [162]. Half-normal levels of several complement factors, e.g., components of the terminal pathway [164], usually suffice to exhibit normal complement effects, but family studies are needed to identify affected family members [45]. (*See Table 1.7 and Fig. 1.14 for updated classification of complement deficiencies*).

Most of the inherited deficiencies are uncommon, but there are various ethnic and geographical influences on the prevalence of these deficiencies. For example, C9 deficiency is the most common complement deficiency in Japan, where it may occur in up to 0.1 % of the population [36], while it is rare in the Western countries. On the other hand, C2 deficiency has a frequency of up to 0.01 % in the Western countries, but it is extremely rare in Japan [113, 114]. It has been estimated that the prevalence of a hereditary complete complement component deficiency is 0.03 % in the general population, excluding deficiency of mannan-binding lectin (MBL), which is present in homozygous form in as much as 5–25 % of the general population [137, 152], depending on how the deficiency is defined.

Primary complement deficiencies are in particular associated with an increased susceptibility to recurrent and invasive bacterial infections and with autoimmune disorders [9]. Deficiency of C1INH, the main inhibitor of the classical and lectin pathways of complement activation, leads to angioedema. However, this is primarily a result of an increased generation of bradykinin caused by decreased inhibition of the kallikrein-kinin system [18], and therefore is not to be regarded as a real complement deficiency disease.

Patients with a deficiency of an early complement component in any of the activation pathways, which leads to decreased activation of C3, often manifest with recurrent pyogenic infections, principally with encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenza* type-b. This is primarily because opsonization of micro-organisms followed by phagocytosis is a main host defense against these organisms [114]. For deficiencies of the terminal complement components (C5-9), recurrent systemic neisserial infections are the dominant manifestations, because the clearance of these bacteria is highly dependent on C5b-9-mediated lysis [28]. However, the severity of the neisserial infections in these patients is usually mild. Properdin deficiency usually leads to severe neisserial infections.

Autoimmune systemic lupus erythematosus (SLE)-like diseases are typically seen with classical pathway component deficiencies, in particular with C1q deficiency [156]. Nine out of ten C1q-deficient patients suffer from SLE or SLE-like disease [126]. The frequency is especially high also in C1r/s- and C4-deficient patients. This highlights the importance of the classical pathway in the clearance of apoptotic cells, tolerance, and processing immune complexes.

Newly discovered mutations within two genes of the lectin pathway were recently connected to a developmental disorder connected to the Malpuech, Michels and Mingarelli-Carnevale (3MC) syndrome [22, 119, 134]. This is the first evidence that a human deficiency of a complement component can lead to a developmental disorder.

Although complement deficiencies are uncommon in the general population, individuals with such deficiencies frequently suffer from serious and often life-threatening diseases, which need specific therapy, including vaccines and easy access to antibiotics. Therefore, patients with recurrent or invasive bacterial infections, certain kidney diseases, familial autoimmune disease or angioedema, should always be tested for complement deficiencies [162].

Screening tests for complement component deficiency have traditionally included functional hemolytic tests for the classical (CH50 test) and alternative pathways (AH50 test, also called AP50 test). These assays utilize sensitized sheep erythrocytes and rabbit erythrocytes, respectively, for

complement activation. The amount of serum necessary for 50% erythrocyte lysis is determined. Low levels of CH50 or AH50 necessitate additional evaluation. If both CH50 and AH50 are low or absent, one or more of the common and terminal components (C3, C5, C6, C7, C8, and C9) may be missing. If the CH50 is low or absent but the AH50 is normal, a classical/lectin pathway component may be missing, whereas if the AH50 is low or absent but the CH50 is normal, an alternative pathway component may be missing [162].

Recently, a novel enzyme-linked immunoassay (ELISA) has been developed for separately revealing deficiencies of classical, lectin or alternative pathway components [129]. This is an enzyme-linked immunoassay, measuring the function of complement based on selective binding of classical pathway components to surface-bound IgM, lectin pathway components to mannan and alternative pathway components to lipopolysaccharide (LPS). The read-out is common for the three pathways, namely detection of polymerized C9. From this functional complement screening test it can be deduced which components might be deficient; e.g. an MBL defect will be revealed by a low lectin pathway activity, a C2 defect will show low activity in both the classical and the lectin pathway, C3 or C5-C9 deficiencies will result in low activity in all three pathways. An advantage with this screening system is that properdin deficiency consistently shows low alternative pathway activity, which is not always the case with the hemolytic AH50 assay.

Measurement of the fragments formed during the enzymatic reaction cascade is another useful technique for evaluating the complement system activity [104]. For instance, C4a, C4d and C4bc are used for the determination of classical or lectin pathway activation, Ba, Bb and the convertase C3bBbP are measured for evaluating alternative pathway activation, C3a, iC3b, C3bc and C3dg to detect C3 activation, and finally C5a and soluble C5b-9 to determine terminal pathway activation [162]. Importantly, activation fragments must be specifically detected in the presence of the corresponding native proteins. This is usually accomplished by using monoclonal antibodies binding to neoepitopes exclusively exposed in cleaved fragments or complexes formed subsequent to complement activation [104].

Individual components of the complement system can be measured by immunochemical methods, including immunoprecipitation assays such as nephelometry, turbidimetry, radial immunodiffusion and radio- and enzyme-immunoassays [162]. In certain cases, functional assays are required for further evaluation, despite the presence of normal amounts of component protein detected by immunochemical assays [112].

Although effective management for complement deficiencies is restricted, most complement-deficient patients will undoubtedly benefit from a correct diagnosis [136]. In case of some complement inhibitor deficiencies, like C1INH and factor H, it is crucially important to make the diagnosis, since these are potentially life-threatening diseases that can be effectively treated.

If a complement deficiency is identified, management focuses on the associated disease, such as infection or autoimmunity. Prevention of infections by vaccination and immediate treatment with appropriate antibiotics are crucial. In some of these patients, antibiotic prophylaxis may be considered, and special attention should be given to vaccination against encapsulated organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria* species. Also early recognition and management of autoimmune diseases are necessary [162]. In case of C1INH deficiency, prophylactic treatment can be required, as well as acute treatment with C1INH concentrate.

In 2007, the first complement inhibitor, eculizumab (Soliris®), was approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) [60]. The inhibitor is a humanized monoclonal antibody prepared on the IgG2/4 chimeric backbone, targeting C5 and preventing its cleavage; i.e. C5a is not released and the lytic C5b-9 complex is not formed. Eculizumab is now also approved for the treatment of atypical hemolytic uremic syndrome (aHUS) [50]. In aHUS, kidney transplantation may also be considered along with the symptomatic treatment, primarily for those with mutations in the membrane cofactor protein (MCP).

8.2 Deficiencies of Classical Pathway Components *(C1q/C1r/C1s Deficiencies, C4 Deficiency, C2 Deficiency)*

8.2.1 Definition

The classical pathway is, in general, activated by clusters of IgG or IgM, whose Fc regions are bound by the recognition molecule C1q. C1q has a hexameric structure, which exhibits low affinity for monomeric IgG but binds much stronger to aggregated IgG [77]. There is an IgG subclass difference in activation, i.e. IgG3 is the most reactive, followed by IgG1 and IgG2. C1q does not bind to IgG4 [11]. C1q also does not bind to free IgM, but antigen-bound IgM exposes new sites in the CH3 domain for C1q recognition and complement activation [111]. Although the antigen-bound IgG/IgM is viewed as the traditional target for C1q binding and classical pathway activation, C1q is a pattern recognition molecule, and a growing number of structures are now acknowledged as C1q ligands. These ligands include pentraxins (C-reactive protein) [2], abnormal endogenous proteins (prions, β-amyloloid fibers) [131], structures associated with cell death (phosphatidylserine, DNA) [108, 109] and glycosaminoglycans/proteoglycans [38, 53].

While not every ligand will activate complement, C1q binding may induce clearance of particles via direct opsonization, implicated especially in the removal of apoptotic cells [103, 155]. The majority of C1q forms a calcium-dependent C1 complex with $C1r_2$ and $C1s_2$ [169]. Upon activation, a conformational change within C1q occurs, which leads to enzymatic cleavage and thereby activation of the serine protease C1r, and this in turn cleaves and activates the serine protease C1s. C1s cleaves C4 into C4a and C4b, with C4b covalently attaching to the adjacent activation site (e.g. a cell coated with antibodies) and the small C4a fragment diffusing into the fluid phase. C2 associates with C4b and is cleaved by C1s into C2a and C2b. The C2a and C4b form on the target cell surface the classical pathway C3 convertase (C4bC2a), which cleaves C3 into C3a and C3b. C3a is released into the fluid phase as an anaphylatoxin and C3b is deposited on the target cell where it serves as an opsonin [capable of binding to the complement receptor (CR)1 on phagocytes and erythrocytes] or is further cleaved to iC3b as another opsonin [capable of binding to the CR3 receptor (CD11b/CD18) on phagocytes]. Moreover, C3b interacts with C4bC2a to form the C5 convertase of the classical pathway (C3bC4bC2a).

The surface-bound C3b is also a trigger for direct alternative pathway activation, which underlines the importance of the classical pathway for initiating an activation that subsequently is amplified within the alternative pathway. Even when the trigger of complement activation is solely dependent on the classical or lectin pathway, a large fraction of C3 cleavage can actually arise from an amplification loop within the alternative pathway. This pathway is initiated spontaneously by a certain amount of constant hydrolysis of the C3 thiol-ester bond, thus rendering $C3(H_2O)$, which is "C3b-like" and binds factor B [55]. All three complement activation pathways (classical, lectin and alternative pathway) share the same terminal C5-C9 activation sequence (Fig. 8.1).

Complement deficiencies within the classical pathway have highlighted the importance of this pathway in the elimination of pyogenic encapsulated bacteria, especially *Streptococcus pneumoniae* and *Haemophilus influenzae* strains. Classical pathway activation effectively opsonizes these bacteria for phagocytosis by myeloid cells. Furthermore, classical pathway deficiencies increase the susceptibility for autoimmune disorders, especially for SLE or an SLE-like disease; this is particularly evident for C1q deficiency [141]. The mechanism for this increased susceptibility is not yet fully understood, but lack of C1q leads to impaired clearance of immune complexes and apoptotic cells, thereby increasing the exposure of autoantigens (the waste-disposal hypothesis) to the immune system [92]. The importance of C1q for the maintenance of B-cell tolerance against self-antigens and C1q-dependent cytokine response may also play a role in the pathogenesis of SLE upon C1q deficiency [156, 165].

8.2.2 Etiology

Classical pathway deficiencies (C1, C4, and C2) are inherited in an autosomal recessive pattern. Deficiencies of C1 and C4 are rare, and the genetics are complex, involving multiple genes for each component. C1q (encoded by *C1QA*, OMIM*120550, *C1QB*, OMIM*120570 and *C1QC* OMIM*120575), C1r (*C1R*, OMIM*613785), and C1s (*C1S*, OMIM*120580) are required for C1 function. Thus, if any one of these subunits is missing, the functional complex cannot form. Deficiency of C1q is either due to a failure in synthesis or to the synthesis of a nonfunctional low-molecular weight C1q [88]. Twelve causative mutations within *C1QABC* have been described, in 64 confirmed cases from 38 families (2011) [126]. Fourteen cases of C1r and C1s deficiency have been reported (2010) [88]. The C1r and C1s genes are closely linked, and patients deficient in C1r are usually low in C1s as well [88]. C4 exists in humans in two forms, C4A (acidic) and C4B (basic), encoded by two adjacent coexisting genes (*C4A*, OMIM*120810 and *C4B*, OMIM*120820). All four alleles must be deleted or defective to cause total C4 deficiency [125]. Moreover, both genes may be present in up to seven copies and contain numerous polymorphisms. Complete C4 deficiency is extremely rare and has only been described in 28 cases (2010) [88].

C2 deficiency (*C2*, OMIM*613927) is the most common classical pathway component deficiency, with an incidence of 1 homozygous case per 20,000 in Western white populations [114]. C2 deficiencies are classified into two types: type I representing absence of C2 synthesis and type II representing failure in protein secretion [67]. Nine out of ten cases are of type I, with a majority caused by a 28-bp deletion in exon 6 [146].

8.2.3 Clinical Manifestations

Patients with a deficiency of an early classical pathway component (C1, C4, or C2) are predisposed to infections with pyogenic encapsulated bacteria, but the infections are usually milder than those observed in patients with a deficiency of properdin, C3, or a terminal component. A study of 40 C2-deficient patients in Sweden reported 57 % of them to have invasive infections, of which 30 % had repeated infections [68]. Most significant, deficiencies of classical pathway components are frequently associated with the development of autoimmune syndromes, particularly SLE. Individuals with total deficiency of any component of the C1 complex or C4 display a higher occurrence of SLE and usually more severe manifestations of the disease compared to a deficiency of C2 [88]. The onset is in general early, and the female to male ratio in C1/C4 deficiency is 1:1, in contrast to deficiency of C2, in which the epidemiology of SLE has a later onset and with a female predominance. Of the 64 described cases of C1q deficiency, 88 % exhibited SLE or SLE-like disease [126].

The corresponding fractions of patients with SLE in C1s/r and C4 deficiency are 57 % and 75 %, respectively [114]. Also partial C4 deficiency is associated with the disease, primarily regarding C4A. Homozygous C4A deficiency is up to 5 times more prevalent in the SLE patient cohort compared to the healthy population [88]. Approximately 10 % of the C2-deficient subjects develop SLE [114]. The highly significant relation between classical pathway deficiencies and the development of an SLE-like disease underline the critical function of the classical pathway, primarily connected with the clearance of immune complexes and apoptotic cells [9]. C2 deficiency is also associated with an increased prevalence of atherosclerosis and cardiac disease [68].

8.2.4 Diagnosis

Classical pathway deficiency can be detected by the traditional CH50 assay, based on hemolysis of sensitized sheep erythrocytes, or by the novel ELISA screening assay for all pathways [129]. An absence or a decrease of CH50 in the presence of normal AH50 indicates that at least one of the early components of the classical pathway is missing or low [115]. Complete deficiencies of

C1q, C1r or C1s will induce a low classical pathway activity, but a normal lectin and alternative pathway activity in the ELISA screening test. A complete deficiency of C4 or C2 will lead to a low classical and lectin pathway activity, whereas the alternative pathway activity will be normal.

The identification of the missing component follows from the recovery of complement activity in either of these tests by the addition of a purified component, by immunochemical tests, or by gene sequencing of the component in question.

8.2.5 Management

Treatment of patients with complement deficiencies is based on treatment of the clinical manifestations. Identification of autoimmune diseases in patients with deficiencies of early components of the classical pathway is necessary, anti-inflammatory therapies should be used for management of the autoimmune disease. Recurrent infections in these patients should be managed with appropriate antibiotic therapy and vaccination [162]. Allogenic Hematopoietic stem cell transplantation (HSCT) has recently been applied for a few number of patients with C1q deficiency that were resistant to medical therapy to cure SLE [107]. While autoimmune disease is often the dominant clinical picture, death is most often due to infection. Therefore, education and strategies to ensure ready access to medical care and antibiotics is critical. Furthermore, studies suggest an important role for complement in atherosclerosis, and aggressive management of cardiac risks is important.

8.3 Deficiencies of Lectin Pathway Components *(MBL Deficiency, MASP-2 Deficiency, MASP-3 Deficiency, Ficolin 3 Deficiency, Collectin 11 Deficiency)*

8.3.1 Definition

The overall structure of the lectin pathway (Fig. 8.1) is similar to that of the classical pathway, and both pathways share C4 and C2 during downstream activation. The pattern recognition molecules of the lectin pathway comprise five lectins capable of initiating activation: mannan-binding lectin (MBL), ficolin 1, 2 and 3 (also termed M-, L-, H-ficolin) and collectin 11 (also termed collectin kidney 1) [24, 25, 54, 58]. Collectin 11 is the most recently characterized member of the complement-activating lectins, but has until now only been shown to activate complement *in vitro* [58, 90]. Currently, the data describing in which context and to what extent collectin 11-dependent opsonization and activation is significant, are limited.

Activation of the lectin pathway is initiated by any of these lectins binding specific carbohydrate structures (MBL) or patterns of acetyl groups (ficolins). Analogously to C1s/C1r in the classical pathway, serine proteases are associated to the recognition molecules of the lectin pathway. These proteases are termed MASP-1, MASP-2 and MASP-3. MASP-2 is ubiquitous for any lectin pathway activation; it becomes activated after lectin binding and cleaves both C4 and C2 [3, 56]. Recent data suggest MASP-1 to be equally important for lectin pathway activation, acting as a crucial activator of MASP-2 [56]. MASP-1 is not able to cleave C4 but has been indicated to substantially contribute to C2 cleavage [56]. Currently, the relevance of MASP-3 in complement activation is not clear [22]. The cleavage of C2 and C4 results in the formation of a C3 convertase (C4bC2a), which is identical to that of the classical pathway. The same is true for the subsequent downstream events.

8.3.2 Etiology

Deficiency of MBL (*MBL2*, OMIM*154545) is predominantly caused by one of three SNPs in exon 1 of the *MBL2* gene, coding for the allelic variants referred to as B, C and D, with A being wild-type MBL [40, 87, 91, 147]. Any of these mutations affect the essential assembly of a functional MBL oligomer from MBL monomers [39, 40]. There are also additional SNPs in the promoter region of *MBL2* that affect the serum MBL

level [39, 40]. These variants of *MBL2* are quite common, and thus, MBL deficiency is seen in many populations. MBL deficiency is not a complete deficiency but is related to a serum "cut-off" value, often <100 ng/mL (normal levels range from 0.5 to 5 μg/mL). Referring to this value, approximately 10 % of Caucasians are MBL deficient, and up to 30 % exhibit levels below the normal range [124, 151]. Thus, MBL deficiency is one of the most common protein deficiencies in humans. It has been claimed that the genetic evolution of *MBL2* represents heterosis, implying that there is an advantage of being heterozygous [57]. According to this concept, a complete deficiency of MBL might increase infection susceptibility, whereas high levels of the protein may lead to host tissue damage caused by excessive complement activation ("the double-edged sword") [99].

In contrast to MBL, deficiencies in the ficolins and in collectin 11 are rare. The ficolin genes are polymorphic, since both ficolin 1 (*FCN1*, OMIM*601252) and ficolin 2 (*FCN2*, OMIM*601624) present polymorphisms in the promoter and structural parts that affect the serum levels, but no cases of complete ficolin 1 or 2 deficiency have been described to date. In 2009, a complete ficolin 3 (*FCN3*, OMIM*604973) deficiency was described in a patient suffering from recurrent severe pulmonary infections [101]. A frameshift mutation (*FCN3 + 1637delC*) in exon 5 of *FCN3* caused a complete ficolin 3 deficiency in the homozygous patient. The allele frequency of this mutation was reported to be about 0.01 [101, 102]. Collectin 11 (*COLEC11*, OMIM*612502) is highly conserved, and the function within the complement system is to date largely unknown. Recently, two reports by Sirmaci *et al*. and Rooryck *et al*. linked mutations within the *MASP1* (OMIM*600521) and *COLEC11* genes to developmental disorders classed in the 3MC syndrome [119, 134]. Mutations within the well-conserved carbohydrate recognition domain of *COLEC11*, with premature termination or deletion of exon 1–3, were found in seven families. Collectin 11 was further linked to embryonic development in zebrafish, in which a functional loss of collectin 11 leads to craniofacial abnormalities that could be rescued by injection of human collectin 11 mRNA [119].

MASP1 codes for the three splice variants MASP-1, MASP-3 and MAP44, the latter lacking the serine protease domain. Mutations within the exon specific for MASP-3 have been suggested to be causative for the 3MC syndrome, found in six families. *MASP1* was also linked to the embryonic development in the zebrafish [119]. MASP-2 (*MASP2*, OMIM*605102) deficiency was first described in 2003 by Stengaard-Pedersen *et al*. in a patient with non-functional lectin pathway as a result of a homozygous missense mutation (p.D120G) in exon 3 of *MASP2* [142]. Later studies have shown MASP-2 deficiency to be fairly common, caused by several different polymorphisms, of which the frequent p.D120G has an allelic frequency of 0.01–0.04 in Caucasians [13, 153].

8.3.3 Clinical Manifestations

Deficiency of MBL generally increases the risk of any type of infection but is mostly related to an increased frequency of pyogenic infections, including pneumococcal infection and sepsis, particularly in neonates/infants or in patients undergoing immunosuppressive treatment. The increased risk in infants can be explained by the "window" period from 6 to 18 months of life, in which the mother's antibodies have disappeared and the levels of those of the child are still insufficient, resulting in reduced immune defense. Normally, MBL deficiency is not associated with an increased incidence of infections, but MBL may be of importance as a redundancy protein in immunosuppressed patients, e.g. those treated with cytostatics, irradiation for malignancy or after HIV infection. MASP-2 deficiency is associated with an increased susceptibility to infection and autoimmunity disease [142]. Lung infections and cystic fibrosis have been reported in patients with MASP-2 deficiency, but homozygous mutations are also found in the healthy population [37, 106, 153]. Ficolin 3 deficiency has been described in one patient suffering from

recurrent respiratory disease and in two premature infants with severe necrotizing enterocolitis [101, 127]. A deficiency in the lectin pathway may lead to autoimmune diseases [114], but may also modify the progress of a disease to be more benign, as seen in rheumatoid arthritis patients [41], or to be more serious, as seen in cystic fibrosis [42]. A 2- to 3-fold increased incidence in MBL deficiency has been reported in patients with lupus erythematosus [75]. Some studies have shown that MBL deficiency is related to cardiovascular disease, in which a deficiency might be either beneficial or detrimental [105, 121]. Thus, at present, any conclusion with respect to the clinical consequences of MBL deficiency can hardly be drawn.

Whole exome sequencing has revealed a link between mutations within the *MASP1* gene and the cause of the 3MC syndrome [134]; this was later extended also to mutations within the *COLEC11* gene. Patients with the 3MC syndrome experience a spectrum of developmental disorders, of which the most common are growth and mental retardation, facial dysmorphism (e.g. hypertelomerism, cleft lip and palate, high arched eyebrows) and hearing loss [154]. Complement has, in experimental animal models, been implicated in embryonic development [4, 143, 157], but this is the first link in humans in which mutations within complement genes are related to the pathogenesis of a developmental disorder.

8.3.4 Diagnosis

MBL-dependent activation of the lectin pathway can be assessed by a screening ELISA [129]. MBL deficiency and MASP-2 deficiency will cause low lectin pathway activity, whereas classical and alternative pathway activities will be normal. Moreover, a functional assay of MBL binding and capacity to activate C4 has also been described, in which the amount and function of later complement components are not of importance [112]. Further analysis includes immunochemical quantitation of MBL and genotyping of MBL and MASP-2.

8.3.5 Management

Patients with recurrent infections may benefit from antibiotic prophylaxis and immunization with a polyvalent pneumococcal vaccine [162]. Purified MBL for therapeutic use as a substitution therapy is under development [158], but the indications for such treatment remains at the moment unclear.

8.4 Deficiencies of Alternative Pathway Components (*Factor D Deficiency, Properdin Deficiency*)

8.4.1 Definition

In contrast to the classical and lectin pathways, the alternative pathway is triggered primarily not by the exposure of molecular patterns of pathogenic or damaged cells, but instead by any surface that lacks sufficient complement activation regulation. The trigger of the alternative pathway is C3b and C3(H_2O), the latter being a C3b-like molecule that at a slow rate is produced in plasma by spontaneous hydrolysis of native C3 (a process termed "C3 tick-over") (Fig. 8.1) [110]. Once C3b/C3(H_2O) is exposed on surfaces or in the fluid phase, respectively, it associates with factor B, which subsequently is cleaved by factor D into Ba and Bb. Ba is released into the fluid phase, and Bb forms, together with C3b/C3(H_2O), the C3 convertase of the alternative pathway C3bBb [27]. Analogous to the C4b2a, C3bBb cleaves C3 into fluid phase-released C3a and surface-deposited C3b. C3b of any origin (classical, lectin or alternative pathway) triggers further alternative pathway activation. In this way, the alternative pathway is responsible for a potent amplification of complement activation, referred to as the "amplification loop" [55, 82]. Alternative pathway activation/amplification is efficiently counteracted by membrane-bound and fluid-phase regulators present at or in close proximity to host cells, of which a majority is focused at the level of convertase formation and C3b degradation. Properdin is a positive regulator of the alternative

pathway, as it acts by stabilizing the C3bBb complex. The properdin-stabilized C3bBbP has a 10-fold higher stability than C3bBb [26]. Properdin has been proposed to be a pattern recognition molecule of the alternative pathway, suggested to bind directly to surfaces (e.g. to LPS) and attract C3b, thereby triggering alternative pathway activation [76, 139]. This may explain the increased susceptibility to neisserial infection in cases of properdin deficiency. An alternative pathway C5 convertase is formed when C3b associates to C3bBb, thus activating the terminal pathway as in the classical and lectin pathways.

8.4.2 Etiology

Early alternative pathway deficiencies of factor D (*CFD*, OMIM*134350) and properdin (*CFP*, OMIM*300383) are rare. No factor B (*CFB*, OMIM+138470) deficient individuals have been found to date. Total homozygous deficiency of factor D has been described in three families [5, 59, 140], of which two were defined at the molecular level [5, 137]. Properdin deficiency is found more frequently than factor D deficiency. The properdin gene is located on the X-chromosome, therefore the properdin deficiency is generally present only in males, whereas female carriers typically have half of the normal plasma level [32]. Properdin deficiency is classified into three types [135]; type I representing complete absence in protein, type II with diminished protein levels (typically 1–10% of normal levels) but still functionally active and type III presenting with properdin in normal levels but not functional. Type I is the most frequent phenotype of properdin deficiency, predominantly caused by frameshift mutations and premature stop codons, leading to transcription of a truncated protein, which is rapidly degraded [32].

8.4.3 Clinical Manifestations

Alternative pathway component (properdin, factor D) deficiency is associated with severe, fulminant infections by *Neisseria gonorrhoeae* or *N. meningitidis*, with a high mortality rate [32]. All index patients in factor D-deficient families presented with *Neisseria meningitides* infection [140]. Properdin deficiency is significantly linked to meningococcal disease, the risk of fulminant and fatal meningococcal infection was estimated to be 250 times higher in the type I-deficient patients compared to the general population [31]. The disease is often seen with sepsis, and the lethality is higher in deficient patients compared to patients with normal properdin levels [31]. The deficiency of alternative pathway components is not associated with autoimmune diseases [9].

8.4.4 Diagnosis

The traditional AH50, based on the lysis of rabbit or guinea pig erythrocytes, has been used for screening of alternative pathway-component deficiencies but is hampered by not always detecting properdin deficiency. This problem does not occur with the ELISA screening assay [129]. A defect in alternative pathway components (factor B, factor D or properdin) will yield low alternative pathway activity with normal classical and lectin pathway activity. Alternative pathway components can be further evaluated by functional and immunochemical tests, and by gene sequencing.

8.4.5 Management

Patients with alternative pathway-component deficiencies should be vaccinated with the tetravalent meningococcal vaccine, particularly important in properdin-deficient persons [136]. Early antibiotic treatment is mandatory.

8.5 Deficiency of Complement Component C3

8.5.1 Definition

Present at approximately 1.3 mg/mL in blood, complement component 3 (C3) is the most abundant complement protein in plasma. C3, together with factor B and MASP, is thought to be among

the most ancient complement proteins [166]. By displaying a variety of conformations and fragments, it exerts multiple functions in the cascade, including alternative pathway activation, convertase formation, opsonization (C3b/iC3b), stimulation of inflammatory cells (C3a), and B-cell stimulation (C3d).

Recent crystal structure determination of native C3, C3c [66] and C3b in complex with factor B and D [33] has led to new insights into this complex component. Native C3 is a rather inert molecule, consisting of an alpha-chain and a beta-chain held together with a disulfide bond [122]. Upon proteolytic cleavage by a C3 convertase, C3a is split from the alpha chain. The remaining C3b undergoes a major conformational change that leads to the exposure of a previously hidden reactive thioester. In the vicinity of a surface, this thioester mediates the covalent attachment of C3 to hydroxyl groups or amines, whereas in the absence of an accepting surface, it hydrolyzes within fractions of a second [49]. Surface-bound C3b is able to interact with factor B in an alternative pathway C3 convertase as well as with complement receptors (CR) 1, 3, and 4. Following surface attachment, C3b is prone to inactivation by factor I, in which case the alpha chain is cleaved into iC3b, which has even higher affinity for the important CR3 phagocytic receptor. iC3b can then be further degraded to C3c and C3dg [19]. Apart from being proteolytically activated, C3 can adopt a C3b-like conformation through the spontaneous hydrolysis of the thioester of fluid phase C3. C3(H_2O) still retains C3a in the alpha chain but has C3b-like functions, including alternative pathway C3 convertase formation and receptor interactions [49].

8.5.2 Etiology

C3 (encoded by *C3* OMIM*120700) deficiency is rare, only described in 27 cases (2011) [22]. C3 is inherited in an autosomal pattern, and C3 deficiency is a recessive trait [162]. Acquired C3 deficiency occurs in factor H or factor I deficiencies, or in the presence of C3 nephritic factor, due to consumption of native C3 [162].

8.5.3 Clinical Manifestations

Primary and secondary deficiencies of C3 result in severe, recurrent pyogenic infections because of ineffective opsonization of pathogens [15, 120]. C3 deficiency is most problematic early in life. A more developed antibody-dependent response against pyogenic bacteria renders adults less dependent on complement opsonization, and therefore, C3 deficiency is less challenging later in life compared to early in childhood [9].

In C3-deficient patients, the cause of infection is mainly Gram-negative bacteria such as *Neisseria meningitidis*, *Enterobacter aerogenes*, *Haemophilus influenzae* and *Escherichia coli* [79]. Many patients with C3 deficiency may also develop membranoproliferative glomerulonephritis without systemic features of SLE [9]. Impaired antibody responses, including abnormal IgG switch and reduced production of IgG2 and IgG4 is seen in many C3-deficient patients [9].

8.5.4 Diagnosis

C3 can be measured functionally and quantitatively. In the screening tests for complement activity, it will show reduced classical, lectin and alternative pathway activity.

8.5.5 Management

Patients with C3 deficiency may benefit from early or prophylactic antibiotic therapy and vaccination. Autoimmune diseases should also be identified and treated in these patients.

8.6 Deficiencies of Terminal Pathway Components *(C5-9 Deficiencies)*

8.6.1 Definition

The terminal pathway starts with the cleavage of C5, a process common to all three pathways, which results in the products C5a and C5b [162].

C5b initiates the formation of the terminal C5b-9 complement complex (TCC) by subsequently binding C6 and C7. If there is a lipid membrane close to this event, C5b-7 will insert and subsequently engage C8 and one or more C9 molecules. This membrane complex is also frequently termed the membrane attack complex (MAC) and can lyse certain microorganisms, such as *Neisseria* species, and any target cell not protected by regulatory proteins [63, 83]. In sublytic doses, C5b-9 will induce cell activation and is important for host cell signaling [14, 150]. If there is no lipid membrane present, C5b-7 may bind the soluble regulator proteins vitronectin and clusterin. C8 and C9 then bind to this complex to form the soluble form of TCC (sC5b-9), which can be detected as activation product in the fluid phase. C5a, generated irrespective of the fate of C5b-9, is an anaphylatoxin and a potent chemotactic factor that can trigger activation of inflammatory cells to release vasoactive mediators [63]. Two C5a receptors have been described, the C5aR1 (CD88) and the C5aR2. The deleterious inflammation of an overactive or inadequately regulated complement system is to a large degree mediated by the proinflammatory effect of C5a [78].

8.6.2 Etiology

Deficiencies of terminal complement components C5 (*C5*, OMIM*120900), C6 (*C6*, OMIM*217050), C7 (*C7*, OMIM*217070), C8 (*C8*A, OMIM*120950, *C8B*, OMIM*120960 and *C8G*, OMIM*120930), and C9 (OMIM*120940) are all inherited in an autosomal recessive manner [162]. Deficiencies within components of the terminal complement complex are rare, except for C9 in the Japanese population, in which this deficiency is detected in approximately one in every thousand subjects [36, 64], caused by a premature stop codon due to point mutations [163]. C9 deficiency is uncommon in Western countries. C8 is an oligomeric protein made up of one α, one β, and one γ subunit. A deficiency of the γ subunit has currently not been described. Deficiency of C8 instead depends on mutations in α or β subunits. Mutations within C8α are predominantly present in the African and Hispanic populations, whereas mutations within C8β have only been described in Caucasians [116].

8.6.3 Clinical Manifestations

Terminal complement component deficiencies typically lead to recurrent systemic infections by *Neisseria gonorrhoeae* or *N. meningitidis*, because the bactericidal function of C5b-9 is important in the defense against neisserial infections. The risk of neisserial infection is estimated to be 7000–10,000 higher in C5-9-deficient patients compared to complement-sufficient patients [29]. It has been claimed that the meningococcal serogroups W and Y are particularly common in C5-9-deficient patients [29, 120], but this idea has later been challenged [30]. The neisserial infection is usually milder in C5-9-deficient patients and rarely fatal, which might be linked to lower levels of released endotoxin, correlating positively with the level of TCC [10]. In addition to the lack of TCC, there is an important biochemical distinction in C5 deficiency compared to a deficiency in C6-9 in the inability of C5-deficient subjects to generate C5a. Regardless of this distinction, the incidence of systemic bacterial infection is in more than 95 % of the cases caused by *Neisseria* spp. due to the lack of TCC. Today it is accepted that no association exists between terminal complement components and autoimmune disease [9, 164], although there are some isolated cases of autoimmune findings in patients with a deficiency of the terminal components [114].

8.6.4 Diagnosis

In patients with terminal component deficiencies classical, lectin and alternative pathway activities are low in functional complement screening tests. The components can further be measured by functional or immunochemical methods. C8 is made up of 3 chains, which are encoded by different genes. As C8 requires all 3 chains to be

functional in the C5b-9 complex, assays that measure only the C8 protein can be misleading, whereas the functional assay is diagnostic [162].

8.6.5 Management

Patients with terminal complement component deficiencies may benefit from vaccination with the polyvalent meningococcal vaccine. Early antibiotic treatment is essential, but long-term antibiotic treatment is not usually needed [162].

8.7 Deficiencies of the Soluble Regulatory Proteins *(C1 Inhibitor Deficiency, Factor I Deficiency, Factor H Deficiency)*

8.7.1 Definition

The complement response is considered to occur rapidly and locally. Activation of the complement system is therefore tightly controlled through the action of complement inhibitors. Negative regulators are present both in the fluid phase and as membrane-attached molecules (please see Sect. 8.8 for more details), aimed to inhibit fluid-phase complement activation as well as activation at the surface of host cells. Many fluid-phase regulators are attracted to host cells via interaction with carbohydrate structures. Complement regulators exist at all levels of the complement system: initiation, C3b processing, convertase assembly and stability, half-life of anaphylatoxins and assembly of the terminal C5b-9 complex [170]. C1INH is an inhibitory protein that regulates the classical pathway by covalently attaching to $C1r_2$-$C1s_2$, disassembles C1r and C1s from C1q and stops activation of the classical pathway [130, 168]. If not inhibited, one single activated C1s molecule can cleave numerous molecules of C4. Thus, deficiency of C1INH leads to uninhibited cleavage of C4 and as a consequence, to consistently low C4 concentrations in the circulation. C1INH also blocks active sites of MASPs and thereby prevents excessive activation of the lectin pathway [20]. C1INH deficiency is usually regarded as a complement disease, since the diagnosis is based on C1INH and C4 levels. However, the pathophysiology is caused by an uncontrolled generation of bradykinin due to insufficient C1INH-dependent inhibition of the kallikrein-kinin system [18].

C3b is a key hub for complement regulation due to its potency to amplify complement activation via the alternative pathway C3 convertase. Several regulators are focused on C3b and on the C3 convertases. Regulators control the C3 convertase formation through two different approaches, either by competitive binding/displacing factor B/Bb and C2/C2a from the C3 convertase (decay acceleration), or by serving as a cofactor for the degradation of C3b/C4b by the proteolytic protein factor I (cofactor activity). C4b-binding protein (C4BP) and factor H are potent soluble inhibitors of classical/lectin pathway and alternative pathway, respectively. Both inhibitors have decay acceleration and cofactor activity. Factor I degrades C3b into iC3b, C3c, and C3dg, and similarly cleaves C4b in the presence of associated cofactors. Soluble fluid-phase regulators of the TCC include vitronectin and clusterin. They both bind to C5b-7 in plasma and render the subsequent fluid-phase sC5b-9 complex water soluble [150]. The effect of the potent anaphylatoxins C3a and C5a is controlled by carboxypeptidase N, which cleaves off the C-terminal arginine, thereby preventing or lowering the effect of C3a/C5a on their corresponding receptors [7]. The principle of complement inhibition is not unique for host cells but has also been adopted by many microorganisms, which recruit soluble host regulators to evade complement binding and subsequent microbe elimination [84].

8.7.2 Etiology

Hereditary C1INH deficiency (OMIM*106100) is inherited via an autosomal dominant trait [95], which affects about 1:50,000 persons [72]. Nearly 200 mutations (2009) in the C1INH gene (*C1INH*, OMIM*606860) have been reported [17]. C1INH deficiency is typically caused by heterozygous mutations, and although one report

has demonstrated homozygosity [6], it is generally thought that complete C1INH deficiency is incompatible with life.

Deficiencies of factor I (*CFI*, OMIM*217030) and factor H (*CFH*, OMIM*134370) are inherited as autosomal recessive traits, and complete deficiency of any of these factors is rarely seen [137]. There is at present no report of a complete C4BP deficiency [137]. Heterozygous mutations within factor H, factor I or factor B are associated with the development of atypical hemolytic-uremic syndrome (aHUS). These mutations rarely result in hypocomplementemia because the excessive complement activation is, in general, not systemic but predominantly localized to the glomerular and arteriolar endothelial cells of the kidney [73]. In aHUS, factor H and other regulatory proteins are not necessarily deficient, but of certain predisposing phenotypes contributing to abnormal complement regulation. Most of the heterozygous factor H mutations in aHUS cluster within the C-terminus of the protein (domains SCR19 and SCR20) [21], a region that is critical to control activation of complement on cell surfaces but not required to regulate complement activation in plasma [48, 70]. Currently, about 50 % of patients with aHUS are carrying heterozygous mutations in one of the genes encoding complement control proteins. Factor H and factor I mutations cause up to 30 % and 10 % of the cases, respectively [161].

Homozygous and heterozygous mutations within factor H are also associated with membranoproliferative glomerulonephritis type II (MPGN2) and age macular degeneration (AMD). The development of AMD is strongly associated with a polymorphism in short consensus repeat (SCR) domain 7 (His402) of factor H, and factor H-dependent development of MPGN2 is related to mutations impairing secretion of factor H [21].

There are an additional five factor H related genes (*CFHR1–5*) located downstream of the factor H gene *CFH* on chromosome 1q31.3. Their products [complement factor H-related (CFHR) plasma proteins] all bind C3 and can differently modulate the effect of factor H and/or inhibit complement activation. Deletion of *CFHR3*/*CFHR1* (OMIM*134371 and OMIM*605336) is associated with the development of factor H autoantibodies, implicated in a form of aHUS termed DEAP HUS (Deficiency of CFHR plasma proteins and Autoantibody Positive form of Hemolytic Uremic Syndrome) [69, 138]. This syndrome is clinically similar to aHUS but typically arises in adulthood.

Carboxypeptidase N is encoded by two genes (*CPN1*, OMIM*603103 and *CPN2*, OMIM*603104). No complete deficiency has been reported. One patient, heterozygous for two mutated *CPN1* alleles showed 20 % carboxypeptidase N activity [96]. This patient suffered from episodic angioedema [96]. The maximum frequency of homozygosity for the more severe variant, presumingly coding for an enzyme variant with no or little activity, was estimated to be about 1/30 000 [12].

8.7.3 Clinical Manifestations

Deficiency for any one of these inhibitors results in extensive complement utilization, leading to an inappropriate inflammatory response, damage to self-tissue, and depletion of C3 or other components downstream of the missing control protein [162].

Heterozygous deficiency of C1INH results in hereditary angioedema (HAE), which is characterized by recurrent episodes of facial (Fig. 8.2), truncal, and extremity edema that spontaneously subsides in 1–3 days [8]. The patient may have life-threatening laryngeal edema and in some patients swelling of the bowel wall results in severe colicky abdominal pain, nausea, and vomiting that mimics acute abdominal syndromes [46, 132]. Symptoms usually arise spontaneously, but in some patients, they may be triggered by mild trauma, estrogens, drugs such as angiotensin-converting enzyme inhibitors, or possibly by psychological stress [1, 34]. Also in HAE, chronic activation of the complement system, leading to depletion of classical pathway proteins, may result in appearance of autoimmune disorders, specifically SLE [114]. Acquired C1INH deficiency is a rare condition, usually

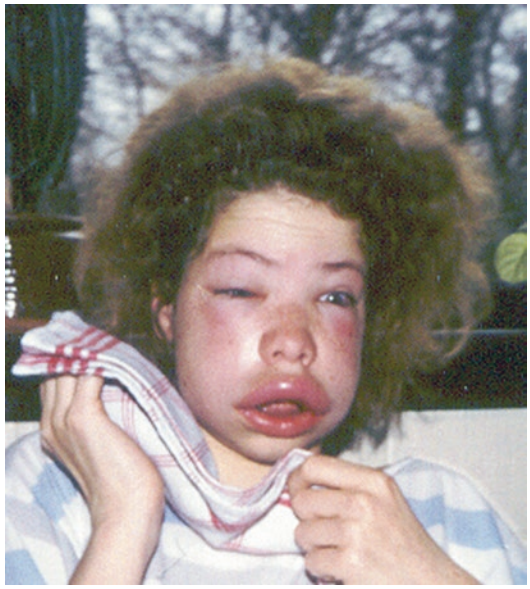

Fig. 8.2 Hereditary angioedema patient during an angioedema attack (Obtained with permission from the Netherlands Organization of Patients with HAE-QE)

presenting after the 2nd decade of life, and is often related to underlying conditions such as autoimmune and lymphoproliferative disorders with the presence of anti-C1INH autoantibodies [95, 133].

Homozygous and heterozygous factor H deficiency is commonly associated with either aHUS, MPGN2 or AMD [21]. aHUS is characterized by hemolytic anemia, thrombotic microangiopathy and acute renal failure. If untreated, aHUS is a life-threatening progressive disease. Homozygous factor H or factor I deficiencies, or presence of a C3 autoantibody (C3-nephritic factor, C3NeF) stabilizing the alternative pathway C3-convertase, may cause complete secondary C3 deficiency through C3 consumption, which in turn predisposes patients to bacterial infections [116]. MPGN2 and partial lipodystrophy are also seen with C3NeF [86]. MPGN2 is characterized by deposition of complement-containing dense deposits in the glomerular basement membrane of the kidney. AMD has a similar pathophysiology as MPGN2, but AMD manifests in the eye by deposition of drusen between the retinal pigment epithelium and Bruch's membrane [21].

A subgroup of aHUS patients showing persistent activation of the alternative pathway was found to carry mutations in the gene encoding factor B. Functional analyses demonstrated that the aHUS-associated factor B mutations are gain-of-function mutations that result in enhanced formation of the C3bBb convertase, or increased resistance to inactivation by complement regulators [44].

8.7.4 Diagnosis

Diagnosis of HAE can be made by measuring the plasma concentration of C4 and C1INH, which is strongly decreased in type I HAE, as well as the functional plasma C1INH activity, which is decreased in both type I and type II HAE (type II is a functional defect) [45, 72]. The quantity of C1INH protein is assessed immunochemically (in type I HAE usually <30% of mean normal adult level). Gene sequencing can make further distinction.

Plasma levels of regulatory proteins, such as factor H and factor I, can be measured immunochemically. When complement consumption is not apparent, gene analysis is needed as direct proof of a deficiency and may be required to exclude or confirm a diagnosis of familial or recurrent aHUS.

8.7.5 Management

HAE patients have been successfully treated with replacement of C1INH by infusion of intravenous fresh frozen plasma or C1INH concentrate, especially at the time of attacks [72, 97, 162]. The androgens stanazolol and danazol are used for prevention of episodes of HAE. These anabolic steroids increase the circulating levels of normal functional C1INH in HAE [71]. Another class of agents used for prophylaxis is the antifibrinolytic agents such as tranexamic acid and aminocaproic acid, which act by blocking plasmin generation. Although their efficacy is less than that of attenuated androgens, some view that the incidence of side effects is also less than that of the androgens.

Treatment for aHUS and AMD caused by aberration in complement regulation or gain-of-function mutations in factor B or C3 implies strategies to correct the increased activation.

Plasma exchange to remove factor H autoantibodies and overly active factor B/C3 or plasma transfusions to replace the missing or defective soluble regulatory components (factor H and factor I) have been tried in several patients with aHUS, and was successful in some of these patients [161]. In late 2011, eculizumab was approved for treatment of aHUS in the USA and Europe [128]. Eculizumab has been shown to improve overall clinical outcome, including improved renal function, and to reduce thrombotic microangiopathy in aHUS patients [128]. Adverse effects by eculizumab treatment are increased risk of neisserial infections, similar to what is seen in terminal pathway-deficient patients. Therefore, all patients receiving eculizumab are routinely vaccinated against *N. meningitidis* [128].

In general, curative treatment of a congenital complement deficiency is only possible with liver transplantation, which is, however, not a preferred therapy. In case of factor H deficiency, renal transplantation often ends in relapses of HUS. There are a few reports of both successful and unsuccessful combined liver/kidney transplantation for patients with factor H mutations [65, 117, 123]. Extensive plasma exchange before operation has shown to reduce complications and improve survival of the transplanted organs [65, 123].

8.8 Deficiencies of Membrane Regulatory Proteins and Complement Receptors *(MCP Deficiency, DAF Deficiency, CD59 Deficiency, PIGA Deficiency, CR3 Deficiency)*

8.8.1 Definition

In addition to the soluble regulators of complement activation also membrane-anchored regulators protect host cells from complement activation. As such, CR1 (CD35), MCP (CD46) and decay-accelerating factor (DAF, CD55) are all membrane regulators at the level of convertase assembly and stability. DAF and MCP exhibit decay acceleration and cofactor activity, respectively, whereas CR1 does both. CD59 is the membrane regulator of the terminal pathway. CD59 binds C8 and C9 and so prevents insertion of C8 and C9 into the C5b-9 complex, thereby protecting host cells against lysis.

Many effector functions of complement activation products require interaction with specific receptors. CR1, CR3 (CD11b/CD18), and CR4 (CD11c/CD18), together with the complement receptor of the immunoglobulin family (CRIg), are important receptors for binding C3b-opsonized particles. By means of these receptors, opsonized particles are bound, engulfed, and eliminated by phagocytosis. Erythrocytes, which are incapable of phagocytosis, clear immune complexes (IC) and other agents from the bloodstream by binding C3b-tagged particles via CR1 on their surface and transporting them to the liver and spleen for removal and degradation by tissue macrophages [16]. CR3 is the main integrin on neutrophils and monocytes, and its expression increases following complement activation and cell stimulation via the C5aR1 (CD88) [98]. CR3 binds iC3b even better than C3b. CR2 (CD21) is expressed on B lymphocytes, binds C3d with the highest affinity and acts as a co-receptor for B-cell activation, thereby enhancing responsiveness toward antigens [23]. The biological effects of the anaphylatoxin C3a are mediated by binding to the C3aR, and of C5a to the C5a receptors C5aR1 and C5aR2.

8.8.2 Etiology

Deficiencies of MCP (*MCP*, OMIM*120920), DAF (*CD55*, OMIM*125240), and CD59 (*CD59*, OMIM*107271) are inherited as autosomal recessive traits. Mutations in MCP are associated with aHUS, about 10–15 % of the patients with aHUS carry heterozygous MCP mutations [161].

PNH is an acquired clonal stem cell disorder characterized by hemolysis, cytopenias, infections, and venous thrombosis. Somatic mutations of the phosphatidylinositol glycan class A gene (*PIGA*, OMIM*311770) in hematopoietic stem cells disturb the lipid anchorage of several surface membrane proteins in descendent hematopoietic cells [148]. In addition to somatic PIGA mutations, germline mutations have also been reported in patients with PNH [149]. The complement

regulatory proteins DAF and CD59 are dependent on this lipid anchorage and are therefore not expressed on affected cells. A heterozygous germline mutation, together with a somatic deletion within the *PIGT* (OMIM*610272), which is another essential gene in lipid anchorage, was recently also associated with the development of PNH [80].

8.8.3 Clinical Manifestations

Deficiency in any complement membrane regulator results in an uncontrolled extensive complement activation and inflammatory response, as seen in aHUS and PNH.

DAF and CD59 are linked to the outer leaflet of the erythrocyte membrane by means of a phospho-inositol-glycan moiety [61]. In case of a defect in the synthesis of this anchor, the erythrocytes are highly susceptible to complement-mediated cell lysis, leading to autologous hemolytic attacks, hemolytic anaemia and hemoglobinuria in PNH patients [9]. Lack of DAF and CD59 also affects platelets; PNH patients are therefore often seen with thrombocytopenia and recurring thrombosis.

Leukocyte adhesion deficiency type 1 (LAD-I) is caused by a genetic defect in CD18, implying that CR3 (CD11b/CD18) and CR4 (CD11c/CD18) are not expressed. This leads to a reduced phagocytosis of particles opsonized with iC3b, and thus to increased susceptibility to infections. The site of infection is predominantly skin and mucosal surfaces [113].

8.8.4 Diagnosis

The level of MCP (CD46) expression can be tested on blood cells by flowcytometry. When complement consumption is not apparent, gene analysis is needed as direct proof of a deficiency and may be required to exclude or confirm a diagnosis of familial or recurrent aHUS.

More than 20 different mutations in MCP have now been identified in patients with aHUS. Many of these mutants have been functionally characterized and have helped to define the pathogenic mechanisms leading to aHUS development. Over 75 % of the reported mutations cause a reduction in MCP expression due to homozygous, compound heterozygous or heterozygous mutations.

Diagnosis of PNH and LAD-I is made by flowcytometric measurement of DAF/CD59 and CD18, respectively. Definite diagnosis is established by mutation analysis.

8.8.5 Management

PNH patients are today symptomatically treated with the C5-blocking antibody eculizumab. This treatment has successfully replaced the need for repeated blood transfusions [60]. Patients treated with eculizumab should receive neisserial vaccine for the known increased risk of such infections when the terminal pathway is non-functional.

Due to the membrane-bound nature of MCP, plasma exchange does not work in the MCP mutation group, but these patients have a better prognosis than patients with factor H mutations On the other hand, renal transplantation is a particularly viable therapy specifically for aHUS patients with MCP mutations [162].

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Other Well-Defined Immunodeficiencies

9

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9.1 Introduction

Our knowledge about primary immunodeficiency diseases (PID) is rapidly growing, which leads to periodic revisions of classification of PID. Although the International Union of Immunological Societies (IUIS) Expert Committee has recently modified the classification of PID, and replaced the section of "Other well-defined immunodeficiencies" with "Combined immunodeficiencies with associated or syndromic features" [211], we prefer to keep the term as it was. (*See* Table 1.8 and Fig. 1.15 *for updated classification of other well-defined immunodeficiencies*).

A defect of the immune system could be affecting adaptive immunity – as in combined immunodeficiencies – or innate immunity as in defects of phagocytes and the complement system. However, in some immune defects, in spite of "*well described*" presenting clinical features, the underlying pathogenesis is still elusive. On the other hand in some PID, "*immunodeficiency*" is not the only major finding. In fact, the immune deficiency can be variably mild or even absent in some patients, for which we can not always state a clear justification.

The disorders categorized as "other well defined immunodeficiencies", usually necessitate a collaborative team for management, because

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apart from susceptibility to infections, these patients are usually affected by other organ system dysfunction. A subset of these disorders is associated with genomic instability. They share some features including the high risk of cancer, facial anomalies, antibody deficiency, and neurodegeneration. For example, Wiskott-Aldrich syndrome is an X-linked hereditary thrombocytopenia, with other manifestations of autoimmunity and eczema, while non immune aspects of the autosomal dominant hyper-IgE syndrome are skeletal deformities and pneumatocele formation.

This chapter tries to provide a concise review on this collection of '*other well defined*' PID, starting with a number of diseases, associated with DNA repair defects.

A number of inter-related molecular pathways have evolved to prevent and repair the accumulation of mutations in DNA, occurring secondary to exogenous damage from ionising or ultraviolet radiation, chemicals, or from byproducts of normal endogenous cellular physiological processes, such as generation of free radicals and errors occurring during meiosis, in order to maintain chromosomal structural integrity and prevent mutagenesis or cell death. Different repair pathways address the different forms of DNA damage that occur, including replacement of nucleotides and repair of single or double strand breaks or cross-linked DNA.

Three specialized cellular developmental programs, which are utilized during development of T and B lymphocytes require repair of targeted DNA damage, namely: – generation of lymphocyte antigen receptors, – immunoglobulin isotype switching, and – somatic hypermutation.

Many DNA repair networks use pathway-specific proteins and enzymes. However, several proteins have multiple roles, and function in combination, to help detect or repair different types of DNA damage. These repair pathways are ubiquitous, but some are also used by the developing lymphoid system to repair DNA that has been damaged in a targeted way during lymphocyte antigen receptor generation, immunoglobulin isotype switching or somatic hypermutation. Defects in these proteins and enzymes may lead to defective adaptive immunity. The extent to which immunity is impaired is dependent on the role of any particular protein or enzyme in repairing DNA, and the role that the particular repair pathway has in maintaining genomic integrity, and specifically the role of the protein in one of the three cellular lymphocyte developmental processes.

DNA double-strand breaks (DSBs) can generate harmful mutations that predispose to proliferation of damaged cells. Such damage provokes breakage sensing, signal transduction and effector function, leading to cell cycle-checkpoint arrest and/or apoptosis of the cell. Repair proteins are recruited to damaged sites and bind in a highly ordered sequence to the DNA break, and to the surrounding chromatin. The MRE11–RAD50–nibrin (MRN) complex is the initial sensor of DSB damage which tethers damaged DNA ends and activates ataxia telangiectasia mutated (ATM) protein – the central component of the signal transduction pathway which responds to DSBs. Following ATM activation, several DNA-repair and cell-cycle-checkpoint proteins, including H2AX, MDC1 and nibrin, are activated, leading to cell cycle arrest and DNA repair. H2AX is phosphorylated to form γ-H2AX, which activates the cascade of repair-protein relocalisation. MDC1 stabilises the MRN complex to the adjacent chromatin at the site of the break and coordinates assembly of other checkpoint and repair proteins, including the E3 ubiquitin ligase RNF168, to the surrounding chromatin.

Bloom syndrome protein unwinds secondary DNA structures that impede replication fork progression in homologous recombination and occur during the normal replicative stress generated by the intense proliferation experienced by lymphocyte precursors during development. Bloom syndrome protein interacts with proteins that resolve DNA crosslinking, some of which are mutated in Fanconi's anaemia. Bloom syndrome protein also interacts with ataxia telangiectasia mutated (ATM) protein, and with MLH1, a protein involved in DNA-mismatch repair. Other enzymes involved in mismatch repair include DNA ligase I (LIG1).

Specific repair pathways are utilized during lymphocyte development. During lymphocyte

antigen receptor development, over 10^{15} genetically diverse cells are generated, each with a unique receptor that recognizes a unique antigen–MHC combination. Receptors are created by breaking, stochastically resorting and joining DNA sequences encoding the antigen-capture region of the receptor, by adapting the non-homologous end joining DNA-repair mechanisms that maintain genome stability. Recombination is a site-specific event that occurs at the T-cell receptor (TCR) α-, β-, γ- and δ-chain loci, and the B-cell receptor (BCR) immunoglobulin heavy (IgH), and immunoglobulin k or λ light (IgL) chain loci. Recombination occurs between component variable (V), junction (J), and for TCRβ, TCRδ and BCR IgH loci, diversity (D) gene segments. The fused VJ or VDJ coding sequence is subsequently joined to a constant region segment through RNA splicing. Two lymphocyte specific recombination-activating gene proteins (RAG1 and RAG2) introduce site-specific DNA-DSBs at conserved noncoding DNA sequences adjacent to the points at which recombination occurs, either side of the segments to be rearranged. A hairpin intermediate structure is formed at the coding sequence ends which is processed by artemis, after it has been activated by Ku70–Ku80 and DNA-PKcs. The final ligation is made by the XRCC4–LIG4–C-XLF complex.

Optimal antibody responses with high antigen affinity require maturation of the antibody repertoire, which occurs in the germinal centers of secondary lymphoid organs following antigen- and T-cell-driven activation. During the somatic DNA arrangement process known as isotype switching, the IgH constant region of the BCR encoded by Cμ, switches to a downstream constant region encoded by Cα, Cγ or Cε. Activation-induced cytidine deaminase (AID) induces DNA-DSBs to initiate isotype switching. AID selectively deaminates cytosine to uracil, which is subsequently removed by Uracil DNA glycosylase (UNG), to produce an abasic site. This is cleaved by one of the base excision–repair enzymes to create a DNA single-strand break (SSB). The DNA mis-match repair proteins MSH2–MSH6 recognize uracil at uracil:guanine mismatched bases, and create a further SSB. If a particular uracil is on the complementary strand to a previous SSB, a DSB results, enabling isotype switching to occur. PMS2 converts AID- and UNG-induced SSBs into the DSBs required for isotype switching. DSBs induced during isotype switching are repaired using the non-homologous end joining pathway.

Isotype switching and somatic hypermutation both occur in germinal centers, although they can occur independently: – IgM can be mutated in the absence of isotype switching. Somatic hypermutation introduces random mutations into the BCR variable region, which leads to minor conformational changes of the antigen receptor. B cells that consequentially acquire a BCR with high antigen affinity are positive selected. Somatic hypermutation, initiated by AID, is achieved by RNA editing of cytosine to uracil residues in the variable region. The DNA mismatch repair proteins, MSH2–MSH6, recognize AID-induced uracil/guanine residues, and recruit the exonuclease EXO1 and DNA polymerase h (POLH) resulting in guanine: cytosine to thymidine: adenosine transversions. The non-homologous end joining pathway is not utilized during somatic hypermutation, but the MRN complex is involved in DNA cleavage at AID-induced abasic sites.

A growing number of genetic defects in the DNA-repair pathways have been identified in patients with primary immunodeficiency. As most of these proteins are involved in ubiquitous DNA repair processes, defects lead not only to immunodeficiency, but also impairment of other tissue repair, and most diseases are therefore syndromic, with manifestations beyond the immune system.

9.2 Ataxia-Telangiectasia

9.2.1 Definition

Ataxia telangiectasia (AT) is a rare systemic autosomal recessive disorder (OMIM*208900) caused by mutations in *ATM* [51], manifest by progressive cerebellar ataxia, oculocutaneous telangiectasia, gonadal sterility, postnatal growth

Table 9.1 Similarities and dissimilarities of AT, ATLD, NBS, BS, and ICF

Finding	A-T	ATLD	NBS	BS	ICF
Neurological defect	Ataxia	Ataxia	None	None	Some cases
Telangiectasia	Present	Absent	Absent	Absent	Rare
Muscular pathology	Fasciculation	Fasciculation	None	None	Hypotonia
Chromosomal translocations	7/14	7/14	7/14	SCE	1/16/9
Microcephaly	Absent	Absent	Present	Present	Absent
Typical facies	Absent	Absent	Bird like	Bird like	Various
Malformation	Absent	Absent	Present	Absent	Absent
Metal retardation	Absent	Absent	Some cases	Absent	Some cases
Malignancies	Present	Not reported	Present	Present	Not reported
Respiratory infections	Present	Not reported	Present	Present	Present
Skin abnormalities	Present	Not reported	Present	Some cases	Some cases
Serum alpha-fetoprotein	Elevated	Normal	Normal	Normal	Normal
Serum immunoglobulin	Low	Normal	Low	Low	Low

AT ataxia-telangeictasia, *ATLD* ataxia-telangeictasia-like disease, *NBS* Nijmegen breakage syndrome, *BS* Bloom's syndrome, *ICF* immunodeficiency, centromeric region instability, facial anomalies syndrome, *SCE* sister chromatin exchange

retardation, a high incidence of predominantly lymphoid tumors and variable, often progressive immunodeficiency.

9.2.2 Etiology

Mutations in Ataxia-Telangiectasia Mutated (*ATM*, OMIM*07585), located on 11q22-23 and encompasses 66 exons is associated with AT. The estimated incidence of ataxia telangiectasia is 1 in 20,000 to 100,000 live births [252].

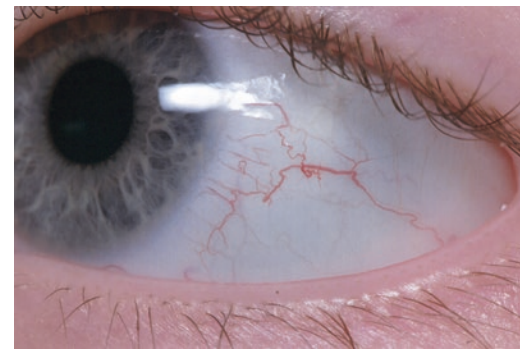

Fig. 9.1 Bulbar telangiectasia on the conjunctivae of a patient with ataxia telangiectasia (Adapted with permission from the Bubble Foundation UK)

9.2.3 Clinical Manifestations

The majority of children are healthy in infancy and begin walking normally, but are slow to develop further, with difficulty standing still without wobbling (Table 9.1). Patients usually present to neurologists with cerebellar ataxia before telangiectasia appear. As the disease progresses, patients develop dysarthria, with complex movement disorders, and become wheelchair reliant. Abnormal eye movements develop, particularly oculomotor apraxia. Most never attain normal speech due to problems with articulation, and speech is slow with misplaced emphasis placed on single words or syllables. Swallowing difficulties develop over time. Telangiectasias appear mainly on bulbar conjunctivae between 3 and 5 years of age (Fig. 9.1), and exposed areas of the skin, particularly the external ear, nose, face, and neck. Other skin manifestations include café-au-lait macules and hypopigmented patches.

Immunodeficiency occurs in approximately 70% of patients. Recurrent sinopulmonary infection may be a presenting feature, sometimes concomitant with raised IgM and low or absent IgG [185]. Sinopulmonary infection may be associated with recurrent aspiration, common

over the age of 10 years, which can lead to chronic lung disease [150] The incidence of infection is variable and more common when null mutations are present on both ATM alleles [79, 239]. Antibody responses to bacterial antigens are generally reduced, particularly those directed against carbohydrate polysaccharide antigens [226]. However, opportunistic infection is extremely unusual. Lymphocytic interstitial pneumonitis has rarely been described [257].

From 10 years of age, the incidence of malignancy is 1 % per year, and around 10–20 % of patients with ataxia telangiectasia will develop malignancy [195], (85 % of which are lymphomas and acute leukemias).

9.2.4 Diagnosis

Diagnosis is based on clinical features as described above, and laboratory features. Serum alpha-fetoprotein is invariably raised, although the level does not correlate with disease severity. Laboratory immunological abnormalities include immunoglobulin deficiency, particularly absence or marked reduction of IgA and IgG2; raised IgM has been described. Humoral immune deficiency becomes more severe with increasing age in some individuals, but recurrent sinopulmonary infection is exacerbated by recurrent aspiration with increasing neuromuscular incordination. Poor polysaccharide antibody responses are common, such as those derived against pneumococcal antigen. Lymphocytopenia also occurs, but is generally not progressive [49, 145].

Cytogenetic analysis reveals spontaneous abnormalities, including chromosomal breakage, translocations, and rearrangements particularly involving the immunoglobulin and T lymphocyte receptor gene loci on chromosomes 7 and 14 (chromosome 7/14 translocation).

The diagnosis of radiosensitivity is difficult, slow and confined to a few laboratories. Sensitivity to ionising radiation may be demonstrated using a clonogenic survival assay during which fibroblasts are irradiated with increasing doses of ionizing radiation. The percentage survival of cells is assessed after a specific time period (usually 3 weeks) and compared with normal control cells. An alternative method exposes cells to increasing doses of ionizing radiation, followed by staining for γ-H2AX foci which are present at the site of DSBs but disappear over time, as the damage is repaired. Persistence of γ-H2AX foci indicates impairment of repair mechanisms. Genetic analysis of *ATM* at chromosome 11q22 will confirm the diagnosis.

Newborn screening for severe combined immunodeficiency by quantitative analysis of T-lymphocyte receptor excision circle DNA episomes in the neonatal blood spot has detected some patients with ataxia telangiectasia in the newborn period [160].

9.2.5 Management

Treatment is supportive. Median survival is currently 25 years. Prophylactic antibiotics may be used for those with recurrent bacterial infection – rarely immunoglobulin substitution may be required. Treatment of those patients that develop malignancy is extremely challenging, as tumors are often aggressive, and all ataxia telangiectasia cells are extremely vulnerable to damage by chemotherapeutic agents that cause DNA-DSB. Death may caused by extreme sensitivity to chemotherapy for malignancy [25]. The incidence of late complications following radiotherapy may be higher in some affected patients. Reduced intensity regimens have been used [195] in treating malignancy in some cases [124, 158, 227]. Hematopoietic stem cell transplantation (HSCT) has been offered to some patients, although adverse effects from the chemotherapy can be fatal [100]. A successful outcome may cure the malignancy [266], but neurological deterioration is unlikely to be halted. Novel approaches to treatment currently in development are the use of antisense oligonucleotides to correct splicing, frameshift and missense mutations to convert absent or unstable protein to partially or fully functional protein, or the use of ribosomal read-through agents to surmount premature termination codons, and permit normal

protein expression [80]. Female *ATM* heterozygotes harbor an increased risk of breast cancer [195]. Heterozygosity for *ATM* may also confer increased risk of other malignancies [217], and sensitivity to chemotherapeutic agents or radiation [198, 294].

9.3 Ataxia Telangiectasia-Like Disorder

9.3.1 Definition

Ataxia telangiectasia-like disorder or ATLD (OMIM*604391) is an extremely rare form of DNA repair defect [93, 256].

9.3.2 Etiology

Ataxia telangiectasia-like disorder, caused by mutations in *MRE11A* (OMIM*600814) on chromosome 11q21, is extremely rare, with few patients reported [66, 90, 140, 165, 189, 202, 241, 265].

9.3.3 Clinical Manifestations

Whilst the clinical features are similar to those found in patients with ataxia telangiectasia, progressive cerebellar ataxia is later in onset and also of slower progression than in patients with ataxia telangiectasia (Table 9.1). Additionally, telangiectasia is absent. Lymphoid tumors have not been reported, although poorly differentiated lung adenocarcinoma has been described. A few patients are microcephalic [165].

9.3.4 Diagnosis

Immunoglobulin levels are normal, although antigen-specific antibodies have been reported as deficient, particularly those derived against pneumococcal polysaccharide antigen. Defective immunoglobulin isotype switching has been reported.

9.3.5 Management

Treatment is supportive.

9.4 Nijmegen Breakage Syndrome

9.4.1 Definition

Nijmegen breakage syndrome (OMIM*251260) is a rare autosomal recessive disorder of DNA-DSB repair, was first described in 1981 in a Dutch patient [286]. It is due to mutations in *NBN* (OMIM*602667) on chromosome 8q21 [286].

9.4.2 Etiology

Whilst the exact incidence is unknown, many Nijmegen breakage syndrome patients are ethnically from Eastern Europe, particularly Poland and Czech and Slovak republics where the prevalence of the founder mutation (657del5) ranges from 1/154 to 1/190 and the incidence is estimated to be 1/95,000 live births [270].

9.4.3 Clinical Manifestations

Nijmegen breakage syndrome is characterized by progressive severe microcephaly and a "bird-like" face (Fig. 9.2), intrauterine growth retardation and short stature (Table 9.1). Most patients have severe microcephaly, with occipito-frontal circumference significantly below the third percentile [286]. Microcephaly is pre-natal in 75 % of cases, develops during early infancy in the remaining patients and is progressive, associated with a decline in cognitive skills giving rise to mild to moderate mental retardation by 7–10 years of age. Associated with this are abnormal facies with a sloping forehead, receding mandible, prominent mid-face, long nose, and upward slant of the palpebral fissures. The characteristic facial features become more prominent as the microcephaly progresses. Other malformations occuring in 50 % of patients include clinodactyly

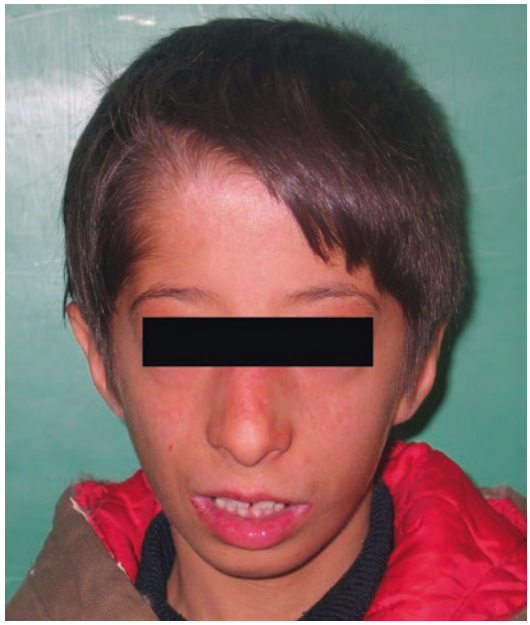

Fig. 9.2 Typical facial appearance of a patient with clinical diagnosis of Nijmegen Breakage syndrome. A similar appearance, described as bird-like facies, may be present in other DNA repair defect syndromes as in Bloom's syndrome or DNA ligase 4 deficiency

and syndactyly, gastrointestinal tract atresia or stenosis, choanal atresia, cleft lip and palate, hydronephrosis, and hip dysplasia. Hypergonadotropic hypogonadism is common in males and ovarian dysgenesis and premature ovarian failure occurs in females [50]. Café-au-lait spots and depigmented skin lesions are common, and cutaneous non-caseating granulomas have been rarely described [272, 298].

Immunodeficiency is common. Many affected individuals experience recurrent upper and lower respiratory tract infections including pneumonia, bronchitis, sinusitis, otitis media, and mastoiditis [183]. Bronchiectasis is the second leading cause of death in patients with Nijmegen breakage syndrome. Opportunistic infections have not been reported but there is generalized immune dysfunction such as autoimmune thrombocytopenia and hemolytic anemia more frequently than expected [183, 206].

Patients have a predisposition to malignancy, particularly of the reticulo-endothelial system [207]. Malignancy is the leading cause of death for these patients – 40% develop malignancy before 20 years of age [183]. Most are lymphomas, but there are rare instances of glioma, rhabdomyosarcoma, and medulloblastoma [52, 67, 103]. There is an increased risk of malignancy in heterozygous carriers [188, 230, 302].

9.4.4 Diagnosis

Diagnosis is determined on clinical and laboratory features, but a definitive diagnosis requires genetic confirmation, as other radiosensitive disorders can mimic Nijmegen breakage syndrome. Severe microcephaly is the prominent feature associated with mild retardation and characteristic facial features. Laboratory features include absent or low levels of one or more immunoglobulin classes or IgG subclasses in up to 80% of patients [107]. Most patients demonstrate T and B lymphocytopenia, with a reduction in class-switched memory B lymphocytes [75, 168, 210]. Most patients have reduced *in vitro* proliferative responses to mitogens.

As in ataxia telangiectasia, the characteristic laboratory abnormality in Nijmegen breakage syndrome is chromosome instability and radiosensitivity. Chromosomal breakage, translocations, and rearrangements, especially chromosome 7/14 translocations are common (Fig. 9.3). Sensitivity to ionizing radiation can be demonstrated using a clonogenic survival or γ-H2AX assay, with sensitivity comparable to that observed in patients with ataxia-telangiectasia. Similar karyotypic abnormalities can be seen following exposure to DNA-crosslinking agents, such as mitomycin C, as found in Fanconi anemia [97]. Immunoblotting and molecular genetic testing are required to confirm the diagnosis. The 657 del 5 mutation of *NBS1* is present in 85% of cases in the United States. In patients with an appropriate ethnic background, targeted sequencing simplifies the task of genetic confirmation in many cases.

9.4.5 Management

There is no specific treatment for Nijmegen breakage syndrome. Subjects should be evaluated

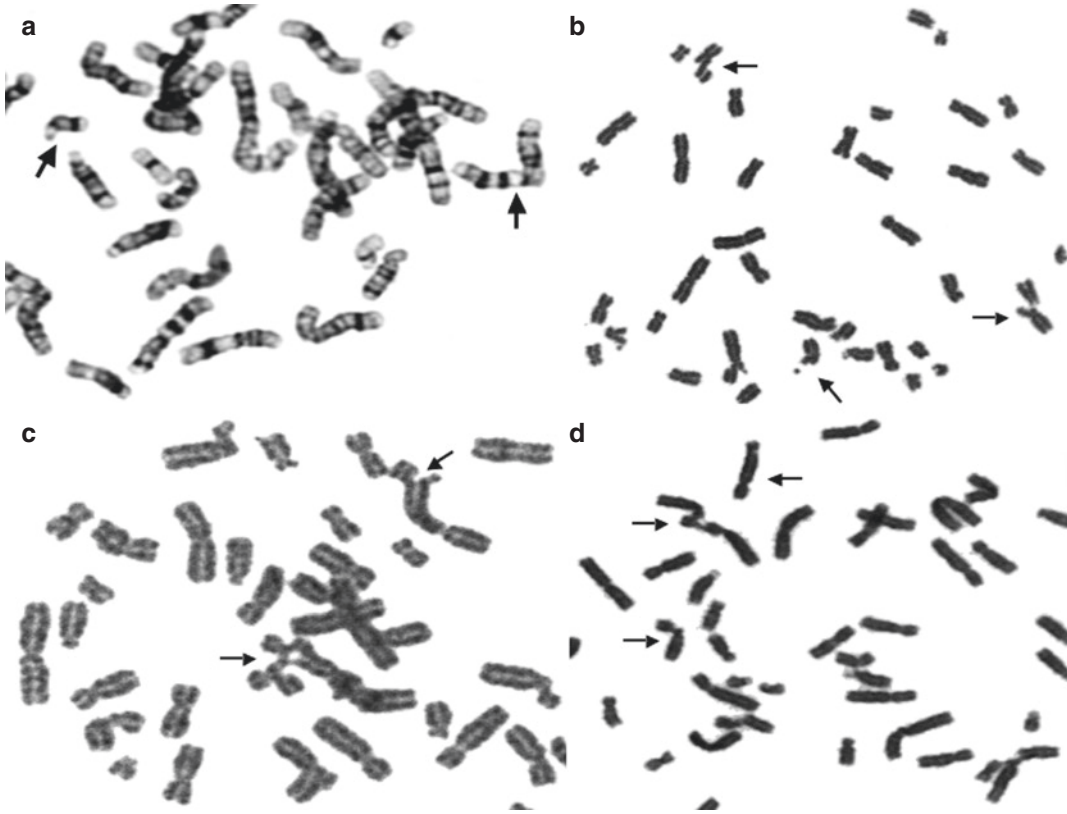

Fig. 9.3 Karyotype from a patient with Nijmegen Breakage syndrome. (**a**) Chromosome t(7;14) rearrangement (*arrows*). (**b**) chromosomal breakage following exposure to 50 centiGray ionising radiation (*arrows*). Karyotype from a patient with Fanconi anemia. (**c**) Multiradial formation (*arrows*) after culture for 72 h following exposure to mitomycin C at 0.32 mg/mL for 60 min. (**d**) Chromosome breakage (*arrows*) following lymphocyte culture with diepoxybutane (DEB) for 72 h (Adapted with permission from the Bubble Foundation UK)

for immunodeficiency and treated with antibiotic prophylaxis and immunoglobulin replacement where appropriate. Increasing numbers of patients with severe immunodeficiency or resistant or secondary malignancy, have successfully undergone HSCT with reduced-intensity conditioning regimens, although may remain at increased risk of developing secondary malignancies [5].

Patients have a high risk of developing malignancy, predominantly lymphomas [207]. The increased sensitivity to ionising radiation and chemotherapy complicates treatment of malignancies [17, 76], but reduced intensity regimens have led to successful treatment with reduced toxicity [25]. Life expectancy is reduced because of the risk of developing malignancies or severe infections.

9.5 RAD50 Deficiency

9.5.1 Definition

One patient has been reported with Nijmegen Breakage Syndrome-like features, which was due to mutation in another gene rather than *NBN* [18].

9.5.2 Etiology

In that patient with Nijmegen Breakage Syndrome-Like Disorder (OMIM*613078), compound heterozygous mutations in *RAD50* (OMIM*604040) was detected, which is one of the components of the MRN complex, were found [18].

9.5.3 Clinical Manifestations

The clinical features comprised pre-natal growth failure with microcephaly, poor post-natal growth and 'bird-like' facies. Speech delay was also noted; moderate psychomotor retardation, with mild spasticity and a non- progressive ataxic gait have persisted. Cutaneous features included multiple cutaneous pigmented naevi and hypo-pigmented areas. There was no significant infectious history. At latest follow-up, aged 23 years, there was no evidence of myelodysplasia or lymphoid malignancy.

9.5.4 Diagnosis

Lymphocyte numbers, proliferations to mitogens and immunoglobulin levels were normal. Chromosomal instability with 7:14 translocations was noted and there was lymphocyte sensitivity to ionizing radiation. In this individual, one mutation created a premature stop codon, the other led to an abnormally large polypeptide [281].

9.5.5 Management

In this one patient, the phenotype of RAD50 deficiency more closely resembles that of Nijmegen Breakage Syndrome than ataxia telangiectasia, unlike MRE11 deficiency. Although immunodeficiency was not reported in this patient, given the function of RAD50 in the MRN complex in TCR and BCR formation and CSR, it is possible that immunodeficiency will be a feature in other patients. Our current knowledge would suggest that treatment should be symptomatic.

9.6 Radiosensitivity, Immunodeficiency, Dysmorphic features and Learning Difficulties (RIDDLE) Syndrome

9.6.1 Definition

Radiosensitivity, immunodeficiency, dysmorphic features and learning difficulties (RIDDLE) syndrome (OMIM*611943). To date, only two patients have been reported in the literature with Radiosensitivity, immunodeficiency, dysmorphic features and learning difficulties (RIDDLE) syndrome (OMIM*611943) [71, 243].

9.6.2 Etiology

RIDDLE syndrome is due to mutations in RNF168 (OMIM*612688) on chromosome 3q29, coding for a ubiquitin ligase.

9.6.3 Clinical Manifestations

The first patient presented with mild facial dysmorphism, short stature, learning difficulties and mild motor abnormalities. No oculocutaneous telangiectasia were reported. The second patient presented with short stature and microcephaly. There was no history of learning difficulties and schooling was normal. Conjunctival telangiectasia were present and the patient exhibited a mild wide-based gait. Recurrent sino-pulmonary infections were documented. In early adulthood he developed progressive interstitial lung disease from which he subsequently died.

9.6.4 Diagnosis

An isolated low serum IgG level was noted in early childhood, with normal IgM and IgA and normal T- and B-lymphocyte numbers documented in the first patient. In the second, serum IgA was low, but IgG and IgM were normal. Alphafetoprotein was raised in the second patient. B-lymphocytes from the patient demonstrated increased use of microhomology across the Sm-Sa and Sa-Sg3 switch regions, with a reduced frequency of mutations and insertions; findings that are similar, although less severe, to those found in LIG4 deficiency, and suggestive of abnormal class switch recombination [213]. Somatic hypermutation was normal.

Cells from both patients exhibited radiosensitivity to ionizing radiation, with reduced survival of

fibroblasts in the colony survival assay and in the second patient, persistence of radiation-induced γ-H2AX foci was demonstrated. Biallelic nonsense mutations in *RNF168*, coding for a ubiquitin ligase – important in the formation of chromatin ubiquitinylation – were subsequently reported in the first patient [242], and a homozygous nonsense mutation was reported in the second.

There is some clinical and biochemical overlap with this syndrome and ataxia-telangiectasia. RNF168 has a role in organising chromatin to facilitate long-range NHEJ, which appears essential for CSR, but not VDJ recombination.

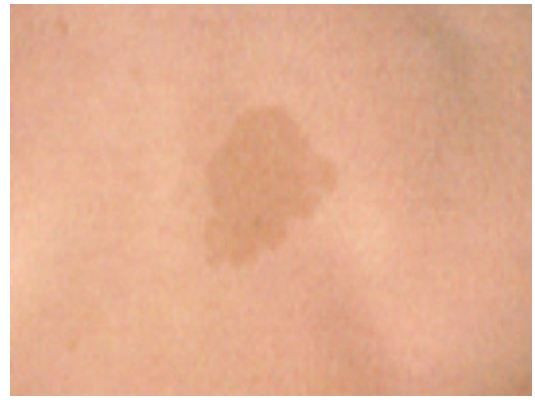

Fig. 9.4 Hyper-pigmented skin patch on the torso of a patient with Bloom syndrome (Adapted with permission from the Bubble Foundation UK)

9.6.5 Management

The first patient was treated with replacement immunoglobulin from early childhood and was well at time of publication of the report.

9.7 Bloom Syndrome

9.7.1 Definition

Bloom syndrome (OMIM*210900) is an autosomal recessive disorder, which is rare, most commonly found in the Ashkenazi Jewish population.

9.7.2 Etiology

Bloom syndrome is due to defects in *BLM* (OMIM*604610) on chromosome 15q26.1, which encodes RecQL3 DNA helicase, critical in suppressing crossover formation between sister chromatids and resolving Holliday junctions during DNA replication [285].

9.7.3 Clinical Manifestations

Bloom syndrome is characterized by proportionate pre- and post-natal growth deficiency, photosensitive, telangiectatic, hypo- and hyper-pigmented skin (Fig. 9.4), predisposition to malignancy and chromosomal instability (Table 9.1). There is an increased incidence of diabetes mellitus. Immunodeficiency, although common, is variable and generally not severe [74, 133, 269]. Life-threatening infection may rarely occur [99].

9.7.4 Diagnosis

Low concentrations of one or more immunoglobulin isotypes are the most frequently found immunological abnormality [133, 143, 269]. However, impaired T-lymphocyte proliferation, diminished CD4+ T- lymphocyte numbers and impaired function are also described [259].

Cytogenetic analysis reveals a characteristic increase in sister-chromatid exchange (Fig. 9.5). The Bloom syndrome protein has no role in VDJ recombination [14, 131], and only a minor role in CSR, although microhomology-mediated end joining was observed at Sm-Sg3 switch regions, possibly implicating BLM in the resolution phase of CSR [15].

T- and B-cell-receptor recombination occurs in the thymus and bone marrow, respectively. Early lymphocyte progenitors undergo successive stages of lineage commitment, generating a functional lymphocyte receptor repertoire. Between critical developmental stages of VDJ rearrangement of the T-cell b- and a-chain, and B-cell IgH and IgL chain, the lymphocyte

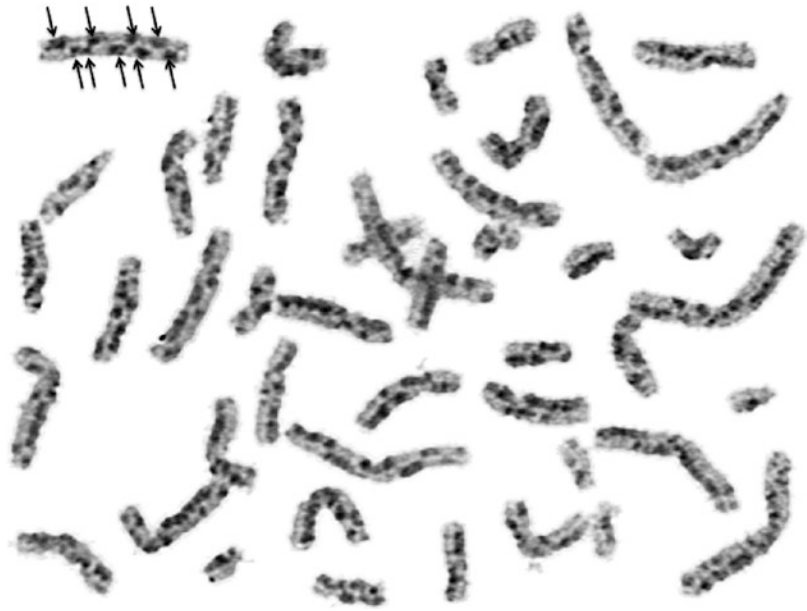

Fig. 9.5 Karyotype from a patient with Bloom syndrome. A large increase in the number of sister chromatid exchanges (*arrows*) are visible (Adapted with permission from the Bubble Foundation UK)

precursors undergo intense proliferation. During this phase, cells experience the normal replicative stress of proliferating cells, and in doing so, accumulate abnormal replication intermediates, normally resolved by Bloom syndrome protein.

9.7.5 Management

Treatment is symptomatic – prophylactic antimicrobial agents may be administered if the symptoms warrant treatment, and surveillance for development of malignancy should be performed.

9.8 Dyskeratosis Congenita

9.8.1 Definition

Dyskeratosis congenita (DKC) is a rare genodermatosis with multisystem complications, caused by inherited defects in the telomerase complex [24]. It is characterized by cutaneous poikiloderma, nail dystrophy, and premalignant oral leukoplakia. Patients have a significant risk for developing aplastic anemia, myelodysplasia and malignancies.

9.8.2 Etiology

Dyskeratosis congenita is a rare systemic disorder due to defects in one of nine proteins that are key to chromosome telomere maintenance.

DKC is a genetically heterozygous disorder. X-linked recessive (OMIM*305000), and an autosomal dominant (OMIM*127550) subtypes, which are due to defects in the enzyme telomerase [174, 275], are among well-known forms of DKC. However, several autosomal recessive subtypes and some more autosomal dominant subtypes have already been described. Details of known subtypes of DKC are presented in the Table 9.2.

Eukaryotic chromosomes end with tandem repeats of simple sequences. These GC rich repeats allow telomere replication and stabilize chromosome ends [108]. Each round of DNA replication in the senescent cells would result in the shortening of one of the two daughter DNA molecules [109]. Telomerase is an enzyme that protects against progressive shortening of the chromosomes at each successive cell division [109, 118]. It is a ribonucleoprotein which consists of a nucleolar protein named dyskeratin [123], a reverse transcriptase (TERT) and an RNA template that dictates the synthesis of the G-rich strand of telomere terminal repeats.

Table 9.2 Subtypes of Dyskeratosis congenita with bone marrow failure and dysfunctional telomere maintenance [211]. (published under the CC-BY license)

Pathogenesis	Inheritance	OMIM*	Associated features	Genetic defect	OMIM*
Dyskerin deficiency	XL	305000	Intrauterine growth retardation, microcephaly, nail dystrophy, recurrent infections, digestive tract involvement, pancytopenia, reduced number and function of NK cells. A severe phenotype with developmental delay and cerebellar hypoplasia is known as HHS	*DKC1*	300126
NHP2 deficiency	AR	613987	Pancytopenia, sparse scalp hair and eyelashes, prominent periorbital telangiectasia, hypoplastic/dysplastic nails	*NOLA2* (*NHP2*)	606470
NHP3 deficiency (NOP10 deficiency)	AR	224230	Pancytopenia, sparse scalp hair and eyelashes, prominent periorbital telangiectasia, hypoplastic/dysplastic nails	*NOLA3* (*NOP10*, *PCFT*)	606471
RTEL1 deficiency	AD/AR	615190	Pancytopenia, sparse scalp hair and eyelashes, prominent periorbital telangiectasia, hypoplastic/dysplastic nails. May present as HHS	*RTEL1*	608833
TERC deficiency	AD	127550	Reticular hyperpigmentation of the skin, dystrophic nails, osteoporosis premalignant leukokeratosis of the oral mucosa, palmar hyperkeratosis, anemia, pancytopenia. May present as HHS	*TERC*	602322
TERT deficiency	AD/AR	613989	Reticular hyperpigmentation of the skin, dystrophic nails, osteoporosis premalignant leukokeratosis of the oral mucosa, palmar hyperkeratosis, anemia, pancytopenia. AD version is milder than the AR version which can resemble HHS	*TERT*	187270
TINF2 deficiency	AD	613990	Reticular hyperpigmentation of the skin, dystrophic nails, osteoporosis premalignant leukokeratosis of the oral mucosa, palmar hyperkeratosis, anemia, pancytopenia. May present as HHS	*TINF2*	604319
TPP1 deficiency	AD/AR		Reticular hyperpigmentation of the skin, dystrophic nails, osteoporosis leukoplakia of the oralmucosa, carcinoma, leukemia palmar hyperkeratosis, anemia, pancytopenia. May present as HHS	*ACD*	609377
DCLRE1B deficiency	AR	616353		*DCLRE1B/SNM1/APOLLO*	609686
PARN deficiency	AR	616353		*PARN*	604212

XL X-linked, *AD* autosomal dominant, *AR* autosomal recessive, *HHS* Hoyeraal- Hreidarsson syndrome, *NHP* nuclear protein family A member, *RTEL1* regulator of telomere elongation, *ACD* adrenocortical dysplasia homolog

In addition, three other proteins: GAR1, NHP2 and NPO10 are associated with dyskeratin in the core nucleoprotein formation.

The defect in telomerase function or activity results in accelerated telomerase shortening in DC cells and is associated with increased loss of cells by replicative cell senescence particularly from tissues that need constant renewal such as the dermatologic and hematopoietic systems [174].

The genetic defect for the X-linked form is located on Xq28 and associated with the *DKC1* gene (OMIM*300126), that is translated into a 514 amino acid protein, dyskeratin. It is a core protein in the structure of active telomerase since it is associated with the H/ACA class of small nucleolar RNAs and is associated with telomerase RNA (hTR), which contains an H/ACA consensus sequence. Furthermore, it has a pseudouridylation activity (guiding the conversion of uracil to pseudouracil in ribosomal RNA) that is an essential step in ribosomal biogenesis, in some mammals like mice [223]. The latter is not established in humans however.

The autosomal dominant DKC is due to mutations in the telomerase RNA component (*TERC*, OMIM*602322) gene [275]. TERC is a 451 nucleotide RNA and consists of four structural domains: the pseudoknot domain, CR4-CR5 domain, the H/ACA domain and the CR7 domain. The pseudoknot and CR4-CR5 domains together with reverse transcriptase enzyme are required for its catalytic function while the H/ACA and CR7 domains are for TERC RNA accumulation. Several mutations in TERC have been found in several of the TERC domains. All of these mutations result in reduced telomerase activity either due to RNA stability/accumulation or catalytic defect. Furthermore it is seen that patients with autosomal dominant DKC have a greater risk of malignancies and the greater severity in disease activity in successive generations [276]. A number of patients with aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria (PNH), and myelodysplasia (MDS) have mutations in TERC too [274, 296].

The other protein component of the telomerase is reverse transcriptase (TERT), a class of DNA polymerase that uses RNA templates for replication. Heterozygous mutations of TERT have been revealed in some autosomal dominant forms of DKC [12]. Mutations in TERC have also been found in the autosomal-dominant form of the inherited bone marrow failure syndrome and in a subset of patients with aplastic anemia and myelodysplasia [277].

Høyeraal-Hreidarsson syndrome [129, 130] is an X-linked multisystem disorder [1] characterized by severe growth retardation, bone marrow failure, neurological abnormalities and immunodeficiency [23]. Knight et al. revealed that HH is a severe variant of DKC with mutations in dyskeratin gene [142] and other studies confirm that this syndrome is a genetic telomerase defect [254, 295].

Female patients with HH have been reported with a severe phenotypic variant of the autosomal recessive form of DKC due to a novel homozygous TERT mutation. In two unrelated consanguineous families has also been detected [58, 163].

9.8.3 Clinical Manifestations

The classical clinical presentation is characterized by a triad of oral leukoplakia, reticular pigmentation, particularly of the upper torso, and nail dysplasia. There is an increased risk of bone marrow failure, myelodysplasia and acute myeloid leukemia, as well as squamous cell carcinomata of the head and neck or of anogenital malignancy. Neurodevelopment is generally normal. The age at onset, and the severity of symptoms is variable, ranging from mild phenotypic features with normal bone marrow function to early onset barrow failure associated with the classical triad of symptoms.

Hoyeraal Hreidarsson syndrome (OMIM*300240) is a severe form of DKC, associated with cerebellar hypoplasia and presenting in early childhood. Severe developmental delay, growth failure and early bone marrow failure are all features of this phenotype [129, 163].

Revesz syndrome also presents in early childhood [215]; patients have bilateral exudative retinopathy as well as the typical features of DKC with significant developmental delay. Intracranial calcification and sparse, fine hair have also been described.

9.8.4 Diagnosis

Diagnostic investigations include measurement of telomere length, which in patients with DKC are abnormally short compared to age-matched controls. Mutation analysis of the nine genes implicated in patients with DKC will confirm the diagnosis.

9.8.5 Management

Treatment is symptomatic, and patient-specific. HSCT is curative for marrow failure, myelodysplasia or acute leukemia. For patients with no suitable donor, androgen treatment may help bone marrow failure. Other malignancies should be treated as indicated. Careful follow-up is required to monitor the development of significant clinical features requiring intervention.

9.9 Rothmund-Thomson Syndrome

9.9.1 Definition

Rothmund-Thomson syndrome (OMIM*268400) is another rare autosomal disorder, associated with DNA repair defects.

9.9.2 Etiology

Rothmund-Thomson syndrome is a rare autosomal disorder caused by mutations in *RECQL4* (OMIM*603780) on chromosome 8q24.3 encoding RECQL4, a DNA helicases that acts as an ATP-dependent DNA helicase, related to the Bloom helicase and important in DNA replication and maintaining genome stability through base excision repair.

9.9.3 Clinical Manifestations

Rothmund-Thomson syndrome is characterized by poikiloderma, sparse hair and eyelashes, small stature, skeletal and dental abnormalities, cataracts, and an increased cancer risk particularly osteosarcoma and hematological malignancy. Whilst the skin is typically normal at birth, the rash, which manifests as erythema, swelling, and blistering on the face which spreads to the buttocks and extremities, characteristically develops between 3 and 6 months of age and evolves over years to chronic reticulated hypo- and hyperpigmentation, punctate atrophy, and telangiectases. Immunodeficiency is rarely reported [65].

Recently, rapid bone marrow failure involving the myeloid, lymphoid, and erythroid lineages has been reported in murine models with multipotent progenitor cells lacking RECQL4, associated with increased replicative DNA damage and failed cell-cycle progression [233].

9.9.4 Diagnosis

The diagnosis is clinical, and confirmed by genetic analysis. Patients with Rothmund-Thomson syndrome usually have alopecia of the head and eyebrows, while their skin lesions are usually seen in sun-exposed areas. Skeletal manifestations, cataracts, and predisposition to malignancy in Rothmund-Thomson syndrome are also distinguish it from other immunodeficiency diseases with skin involvement such as poikiloderma with neutropenia (OMIM*604173). (*See* Sect. 4.15 *for more details*)

9.9.5 Management

Management is supportive and includes use of barrier sunscreens to prevent skin cancer. One patient has been treated successfully with HSCT [33].

9.10 Other Well Defined Immunodeficiencies with DNA Repair Defects

(***DNA ligase IV deficiency***, ***Cernunnos-XLF deficiency***, ***XRCC4 deficiency***, ***DNA PKcs deficiency***, ***DNA ligase I deficiency***, ***Fanconi anemia***, ***PMS2 deficiency***, ***MCM4 deficiency***)

9.10.1 Definition

In addition to above-mentioned diseases, there are some other DNA repair defects associated with immunodeficiencies. Some of them have already been explained in other chapters. DNA ligase IV deficiency (OMIM*606593) and Cernunnos-XLF deficiency (OMIM*606593) are rare radiosensitivity disorders with very few patients reported, which share many clinical features. (*See* Sect. 2.3 *for more details*)

One patient with primordial dwarfism was reported (OMIM*616541) to have a homozygous missense mutation in *XRCC4* gene (OMIM*194363), which encodes for a protein that is part of the LIG4-Cernunnos/XLF-XRCC4 complex. Whilst the cells demonstrated sensitivity to ionizing radiation, no information was available on an immunophenotype [231]. More patients have subsequently been described, and although clinical immunodeficiency has not been described [21, 61, 179, 221, 231], biochemical immunological abnormalities have been reported in one patient [113].

DNA PKcs deficiency due to mutations in *PRKDC* gene (OMIM*600899) is a very rare disorder with ionizing radiation sensitivity.

One patient has been reported with compound missense mutations in *LIG1* (OMIM*126391) [20, 284].

Fanconi anemia (OMIM*603467) is a clinically heterogenous autosomal recessive or X-linked disorder, due to abnormalities in one of fifteen proteins important in DNA inter-strand cross-linking repair.

PMS2 deficiency (OMIM*276300) due to mutations in the *PMS2* gene (OMIM*600259), encoding the PMS2 component of the mismatch repair machinery, was also described as B cell-intrinsic CSR deficiency [209].

MCM4 deficiency (OMIM*609981) or natural killer cell and glucocorticoid deficiency with DNA repair defect (NKGCD) is due to mutations in the *MCM4* gene (OMIM*602638) [101]. (*See* Sect. 6.15 *for more details*)

9.10.2 Etiology

DNA ligase IV deficiency and Cernunnos-XLF deficiency are due to mutations in *LIG4* and *NHEJ1*, respectively.

Fanconi anemia is estimated to affect 1:360,000 births [251], but particular genotypes are more common in specific populations, notably Ashkenazi Jews, Spanish Gypsies, and black South Africans [43, 147, 177].

9.10.3 Clinical Manifestations

DNA ligase IV deficiency or LIG4 deficiency was initially described in a clinically and developmentally normal patient who developed T cell acute lymphoblastic leukemia, exhibited disproportionately severe cytopenia following treatment, and died following an extreme reaction to radiotherapy, including marked and prolonged cytopenia, severe desquamation and radiation-induced encephalopathy [216]. Several LIG4-deficient patients have subsequently been described [232]. Microcephaly with 'bird-like' dysmorphism, developmental delay, growth failure, lymphocytopaenia, hypogammaglobulinaemia and marrow hypoplasia are predominant features [178, 194]. Radiosensitive-SCID with microcephaly and growth delay is a recognized presentation, as well as the Omenn syndrome variant [36, 112]. Large B cell lymphomas have been reported, not always associated with Epstein-Barr virus, as well as T cell acute lymphoblastic leukemia [16, 85, 263].

Patients with cernunnos-XRCC4-like Factor (C-XLF) deficiency, due to mutations in *NHEJ1* were described after *LIG4* deficiency [3, 35]; the clinical and immunological phenotype is similar, with T and B lymphocytopenia, with a normal number of NK cells [59]. Microcephaly with 'birdlike' dysmorphism and developmental delay is characteristic, and patients classically experience recurrent viral, bacterial and opportunistic infection – autoimmune cytopenia has also been described [41]. To date, lympho-reticular malignancy has not been described.

The patient with *PRKDC* deficiency first presented at 5 months of age with classical symptoms of recurrent oral candidiasis and lower respiratory tract infections, and a T-B-NK+ SCID phenotype. Microcephaly was not present and there was no developmental delay [268]. The second patient had a markedly different phenotype. Although there were features of T-B-NK+ SCID,

as in the first patient, there were significant other morphological anomalies including pre-natal growth failure, microcephaly, facial dysmorphism with prominent forehead, wide nasal bridge, long philtrum with thin upper lip, small chin, low-set ears with overfolded helices, overlapping fingers, and postaxial polysyndactyly of the right foot. Additionally he had micropenis. The patient suffered severe developmental delay and intractable seizures [292].

Clinical features of DNA ligase I deficiency, overlapping with those of Bloom syndrome and ataxia telangiectasia, include pre- and post-natal growth retardation, developmental delay with normal cognitive development, facial dysmorphism with elf-like features, and photosensitivity. Immunodeficiency manifested as recurrent sinopulmonary infections from early childhood, with evolving IgA deficiency, relative hypogammaglobulinemia of IgG and normal IgM. An evolving neutropenia and lymphocytopenia with poor proliferative response to mitogens was described. In adolescence, the respiratory status deteriorated. There was no development of secondary sexual characteristics. Centripetal patchy cutaneous venous dilatation appeared, and there were some bulbar conjunctival telangiectasia. Hepatosplenomegaly developed associated with lymphocyte infiltration of the portal tract, suggesting lymphoma. The patient developed a severe cutaneous herpes zoster infection and died from pneumonia in early adulthood. Two further siblings, unrelated to the index case, have subsequently been identified, presenting with features consistent with severe combined immunodeficiency (*personal communication with A. Worth*). Additional features included multicystic dysplastic kidneys and severe anemia. One patient successfully underwent HSCT. LIG1 forms a complex with nibrin, and both molecules colocalise at replication factories to repair DSBs by homologous recombination at stalled replication forks [267]. Thus, defects in *LIG1* may be associated with failure to repair DNA damage during lymphocyte proliferation, rather than failure to complete NHEJ during TCR and BCR formation.

Fanconi anemia is characterized by bone marrow failure, and other anomalies including skeletal, renal, cardiac and gastrointestinal defects, skin hypo-pigmentation and predisposal to malignancy, particularly leukemia or head and neck squamous carcinomas [9, 220]. Whilst most immunological manifestations relate to bone marrow failure, some patients present in infancy or early childhood with significant or prolonged infections, more consistent with immunodeficiency [180]. Features that suggest a diagnosis of Fanconi Anemia include a history of parental consanguinity or family history of anemia, physical abnormalities or cancer.

9.10.4 Diagnosis

Diagnostic laboratory features for DNA ligase IV deficiency and Cernunnos-XLF deficiency include the immune-phenotype described above, in association with the characteristic clinical findings. In addition to T and B lymphocytopaenia, many patients with either syndrome have normal or raised IgM, and low IgA and IgG, often with impaired specific antibody responses. Both LIG4 and cernunnos-XLF have a role in class switch recombination, as well as VDJ recombination. Moderate impairment of VDJ recombination is observed in *LIG4*- and *NHEJ1*-deficient fibroblast VDJ recombination assays with an almost normal frequency of coding and signal joint formation but marked infidelity of coding and signal joint formation. Patients with *LIG4* and *NHEJ1* mutations also have altered resolution of CSR junctions, with greater use of microhomology at Sμ-Sα junctions [203]. Radiosensitivity can be demonstrated by exposing fibroblasts to ionizing radiation, and measuring survival, or by measuring γH2AX foci, which accumulate at the site of DNA-dsb, and disappear as the breaks are resolved. In cell lines deficient in *LIG4* or *NHEJ1*, γH2AX foci persist when they have resolved in normal cells.

The first patient with *PRKDC* deficiency had a homozygous three-nucleotide deletion and homozygous missense mutation in *PRKDC*.

Fibroblasts were sensitive to ionising radiation, with a DSB-repair defect comparable to that seen in artemis-deficient cells. The coding joints showed long stretches of palindromic nucleotides, and an end-joining assay demonstrated an increase in the use of microhomology, which was similar to that seen in artemis-deficient cells. A profound DSB-repair defect in the second patient was demonstrated using the γH2AX assay, which was distinctively different from that seen in artemis or LIG4 deficiency. A compound missense mutation and an exon deletion were uncovered in *PRKDC*.

An assessment should include a complete blood and differential count, and a bone marrow aspiration, biopsy, and cytogenetic evaluation, renal and urological assessment, including an ultrasound to rule out renal dysplasia, hydronephrosis, and/or genitourinary or reproductive tract malformations. An otological examination to assess for hearing loss or structural ear abnormalities should also be performed. Laboratory assessments include a diepoxybutane or mitomycin C chromosome fragility test of blood lymphocytes. Fibroblasts can be used to identify the Fanconi anemia complementation group and mutation analysis determines and/or confirms the initial complementation group result and identifies the specific causative gene. Fifteen genes associated with Fanconi anemia have been identified to date, of which 14 are inherited in an autosomal recessive fashion, and 1 (*FANCB*) is X-linked. Although cells from patients generally show hypersensitivity to agents that cause DNA inter-strand crosslinks, a few also demonstrate sensitivity to ionising radiation [175]. Whilst most of the Fanconi Anemia proteins form a core ubiquitin ligase complex, the FAND2-FANCI heterodimer is ubquitinated by this complex, and subsequently co-localises to chromatin with other DNA repair proteins, including the MRN complex [180]. Fanconi anemia proteins do not have direct a role in lymphocyte receptor development or modification. The effects on immunity more likely result from the effects of inter-strand DNA crosslinks occurring during cellular development, which lead to bone marrow failure.

9.10.5 Management

Treatment is supportive, and includes anti-viral and anti-bacterial prophylaxis. Many patients will require immunoglobulin replacement. Autoimmunity should be treated as appropriately, and for autoimmune cytopenias, steroids, rituximab and high-dose immunoglobulin (2 g/kg) may be required. Lympho-reticular malignancies are particularly difficult to treat, as they are often aggressive, and yet patients are intolerant of the chemotherapy. HSCT has been tried, particularly for patients with marrow hypoplasia or severe recurrent infection. Reduced intensity regimens seem best tolerated. Patients will need to be carefully followed in the future to monitor for late sequalae, and, in particular, the development of secondary malignancies.

Two patients with *PRKDC* deficiency demonstrate heterogeneity in presentation of these rare defects. The first patient underwent successful HSCT from an HLA-identical sibling. The second patient succumbed to neurological complications. Treatment should be supportive, and HSCT should be considered in selected cases.

Treatment of DNA ligase I deficiency should be symptomatic with prophylactic antimicrobials. The role of HSCT has yet to be determined.

Management of patients with Fanconi Anemia requires multi-disciplinary input. Whilst most patients develop bone marrow failure, the age at onset is extremely variable, even within families. Patients are at high risk of developing myelodysplasia or acute myeloid leukemia. Close monitoring is required to assess possible onset of myelodysplasia or leukemia and identify cytogenetic abnormalities that require immediate intervention. HSCT is currently recommended to cure marrow aplasia, and prevent or cure progression to myelodysplasia or leukemia. Patients with Fanconi Anemia have an extremely high risk of developing squamous cell carcinoma of the head and neck. From the age of 10 years, it is recommended to obtain a thorough examination from an ear, nose and throat specialist, oral surgeon or

other doctor experienced in head and neck cancer detection, bi-annually. Human Papilloma virus vaccination should be given to both boys and girls, to possibly prevent squamous cell carcinoma associated with the Human Papilloma virus. Unfotunately, successful treatment with HSCT does not prevent the occurrence of head and neck squamous cell carcinoma, and may increase the risk of such tumors developing. Carriers of autosomal recessive Fanconi Anemia are asymptomatic, except those who carry mutations in *FANCD1* (*BRCA2*), who have an increased risk of hereditary breast and ovarian cancer [128, 280].

9.11 Immunodeficiency, Centromeric Instability, Facial Dysmorphism Syndrome

(***ICF1***, ***ICF2***, ***ICF3***, ***ICF4***)

9.11.1 Definition

Immunodeficiency, Centromeric Instability, Facial Dysmorphism (ICF) Syndrome is a rare autosomal recessive disease. Few individuals with ICF1 (OMIM*242860), ICF2 (OMIM*614069), ICF3, and ICF4 have been reported.

9.11.2 Etiology

ICF syndrome is due to mutations in *DNMT3B* (ICF1) (OMIM*602900) [117], *ZBTB24* (ICF2) (OMIM*614064) [62], *CDCA7* (ICF3) (OMIM*609937), and *HELLS* (ICF4) (OMIM*603946) [261].

9.11.3 Clinical Manifestations

The dysmorphic facial features are variable and often mild (Table 9.1). Typically, patients exhibit a broad flat nasal bridge, hypertelorism, and epicanthic folds. Other features less often described include micrognathia, macroglossia and low-set ears. Delayed psychomotor development is apparent in some patients.

The immunodeficiency is variable, but commonly leads to severe recurrent infections, most commonly presenting in early childhood [240, 287]. Although severe respiratory infections are common, many infections are suggestive of impaired T lymphocyte function. Many patients present with agammaglobulinemia, despite the presence of B lymphocytes [116].

9.11.4 Diagnosis

ICF syndrome is characterized by agammaglobulinemia or hypoglobulinemia in the presence of B lymphocytes and pathognomic DNA rearrangements of the centromere-adjacent heterochromatic region of chromosomes 1 and/or 16 (and occasionally chromosome 9) in mitogen-stimulated lymphocytes, detected during routine cytogenetic examination of metaphase chromosomes [264]. Immunological investigations include enumeration of the lymphocyte phenotypes and assessment of immunoglobulin levels. The diagnostic test for ICF syndrome is standard metaphase chromosome analysis of peripheral blood which exhibit the characteristic changes (Fig. 9.6), namely:

- whole-arm deletions and peri-centromeric breaks of chromosomes 1 and 16 (and sometimes chromosome 9)
- multibranched chromosomes containing three or more arms of chromosomes 1 and 16 joined at the centromere
- occasional isochromosomes and translocations with breaks in the vicinity of the centromere.

It is unclear how the chromosomal changes lead to the immunodeficiency. The heterochromatic region DNA rearrangements exhibit DNA hypomethylation. At least four genes are responsible for the disease – *DNMT3B*, *ZBTB24 CDCA7* and HELLS.

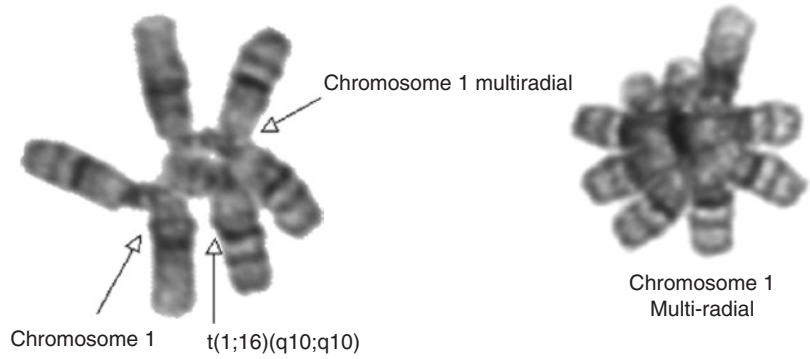

Fig. 9.6 Chromosome 1 from a patient with ICF, which shows multibranching, translocation, and decondensation of heterochromatic regions adjacent to the centromeres

9.11.5 Management

Initial management is symptomatic. Prophylactic immunoglobulin replacement should be administered. In view of the co-existent T lymphocyte immunodeficiency, ant-pneumocystis and antifungal prophylaxis may be administered. Death is commonly from opportunistic or pulmonary infections and the prognosis is particularly poor in children with intractable diarrhea and failure to thrive. Allogeneic HSCT has been successfully performed for ICF syndrome [98].

9.12 Hyper-IgE Syndrome

(***STAT3 deficiency***)

9.12.1 Definition

'So went Satan forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown.' With this citation from the book of Job 2:7, Davis, Schaller, and Wedgwood coined the term Job's syndrome in 1966 [60]. They reported two red-haired, fair-skinned girls who had frequent sinopulmonary infections, severe dermatitis, and recurrent staphylococcal skin infections that were remarkable for their lack of the features of classical inflammation, including warmth, hence the term 'cold' abscesses. The syndrome was further defined and clarified by Buckley et al., who noted similar infectious problems in two boys with severe dermatitis, characteristic facies, and elevated IgE levels, leading to the term Buckley's syndrome [39]. Following this report, elevated levels of IgE and a defect in neutrophil chemotaxis were identified in the two girls from the initial report, showing that Job's syndrome and Buckley's syndrome represented the same condition [125]. This syndrome is now often referred to as Hyper-IgE syndrome (OMIM*147060).

To date the Hyper IgE Syndrome has been recognized as multi-organ dysfunction characterized by both immunologic and non-immunologic manifestations and classically presenting with the clinical triad of (i) recurrent (cold) skin abscesses, (ii) recurrent (typically cyst forming) pneumonia, and (iii) elevated IgE (>10-times the upper limit of the norm) [110].

9.12.2 Etiology

In 2007, heterozygous mutations in the gene encoding the Signal Transducer and Activator of Transcription 3 (STAT3) (OMIM*102582) were found to underlie most cases of the autosomal dominant form of HIES (AD-HIES) [126, 173].

Minegishi et al., have shown that the observed mutations have a dominant-negative effect on the healthy allele and hence impair STAT3 signaling [173].

STAT3 plays a central role in signal transduction induced by multiple cytokines, including IL-6, IL-10, IL-11, IL-17, IL-21 and IL-22. As a consequence cell types requiring a stronger STAT3 signal, including but not limited to e.g. the Th17

cells, are defective, explaining the multisystem involvement of this primary immune deficiency.

Cytokines are important mediators of cell activation, differentiation, and migration, acting through binding to their cytokine receptors, which are expressed on the respective immune cells. Most cytokine receptors are composed of several transmembrane proteins, some of which change their conformation upon ligand binding allowing the phosphorylation of tyrosine kinases such as the Jaks and Tyk2, which are associated with the cytosolic part of the cytokine receptor. The phosphorylated Jaks then in turn phosphorylate the Signal Transducers and Activator of Transcription (STATs). Two phosphorylated STATs form one homo- or heterodimer, which translocates into the nucleus and binds to genomic DNA to initiate cytokine-specific downstream gene expression.

9.12.3 Clinical Manifestations

HIES is a multisystem disease with variable clinical manifestations (Table 9.3). Affected individuals may have some, but not all the features of HIES, depending on the age at which they present. AD-HIES typically first manifests with a neonatal rash and affects the immune system, connective tissue, skeleton, and dental development, with variations in severity. The rash typically starts on the face and scalp in the first few weeks of life, and is usually pustular and eczematoid [44, 83]. Biopsies show eosinophilic infiltrates and bacterial cultures typically grow *Staphylococcus aureus*. The rash often persists throughout childhood, but can be controlled with antistaphylococcal therapies, consisting of antibiotics, topical antiseptics such as diluted bleach, or both [208]. Abscesses are often caused by *Staphylococcus aureus*, and have been described as being "cold", indicating the lack of tenderness and warmth, typically seen with boils of that size. It is a typical observation in these patients that due to the lack of STAT3 (first named "APRF", acute phase response factor) signaling, the severity of infections or inflammation is not appreciated by the patient, e.g. due to abrogated IL-6 signaling.

Table 9.3 Clinical manifestation of Hyper IgE syndrome (STAT3 deficiency)

Immunologic (% frequency)	Non immunologic (% frequency)
Newborn rash (81) Boils (87) Recurrent pneumonias (87) Eczema (100) Mucocutaneous candidiasis (83) Peak Serum IgE >2,000 IU/mL (97) Eosinophilia (93) Increased incidence of lymphoma	Characteristic face (83) Retained primary teeth (72) Minimal trauma fractures (71) Scoliosis >10° (68) Focal brain hyperintensities (70) Chiari 1 malformation (18) Craniosynostosis (unknown) Arterial aneurysms (unknown) Degeneration joint disease (Unknown)

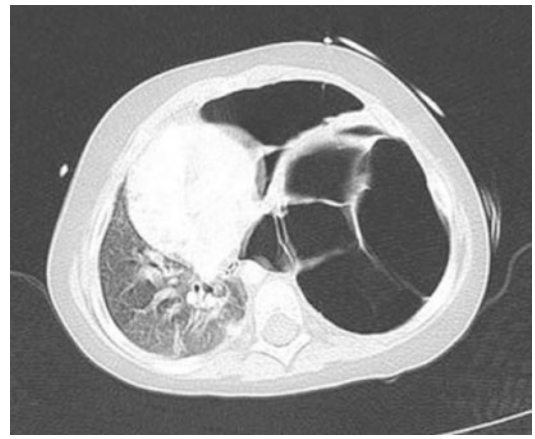

Fig. 9.7 Chest computed tomography showing enlarged pneumatoceles compressing heart and right lung

Pneumonia, often caused by *Staphylococcus aureus* or *Haemophilus influenza*, typically leave lung cavities (pneumatoceles) which are one of the life-limiting factors oft this disease. Pneumatoceles may be manifold or become huge as shown in Fig. 9.7. Similar to the variability seen with boils, the extent of pneumonia may be out of proportion to the systemic signs of illness (e.g. fever, malaise), leading to delayed diagnosis. Bronchoscopy may be needed to establish the specific bacterial diagnosis and also assists in clearance of copious but viscous pus. Pneumatocele formation and bronchiectasis

typically follow these pyogenic pneumonias. Structural parenchymal defects tend not to subside, but serve as sites for future infections [93, 110]. One of the most feared complications in this form of the hyper IgE syndrome is the colonization of these pneumatoceles with *Aspergillus fumigatus*: eradication is almost impossible, surgery is complicated, lung transplant often disapproved, and dissemination into the brain is a real threat.

Mucocutaneous candidiasis is common in HIES, typically manifesting as thrush, vaginal candidiasis and onychomycosis [110]. Much less frequently, disseminated histoplasmosis and cryptococcosis occur, typically in isolated non-pulmonary locations such as in the intestine or tongue [135].

STAT3-HIES has a characteristic facial appearance that develops during childhood and adolescence, characterized by asymmetry, broad nose, and deep-set eyes with a prominent forehead (Fig. 9.8) [37, 110].

Musculoskeletal abnormalities in HIES include scoliosis, minimal trauma fractures, osteopenia, hyperextensibility and degenerative joint disease [110]. Minimal trauma fractures occur in about half of individuals with HIES, and frequently involve the ribs and long bones. Osteopenia and osteoporosis also occur, but appear to be independent of the minimal trauma fractures. Osteoclast-mediated bone resorption is abnormal in HIES and likely relates to osteopenia and fractures [55, 152].

Most individuals with HIES fail to exfoliate their primary teeth normally, often requiring surgical extraction of some or all primary teeth to allow the secondary teeth to emerge normally [193]. Characteristic variations of the oral mucosa, tongue, roof of mouth and cheeks include central depressions of the tongue that may relate to *Candida* infections and central band-like protrusions of the palate [78].

HIES is associated with an increased rate of non-Hodgkin's lymphoma (NHL), the majority of which is B-cell origin and aggressive histology [151]. Several individuals responded to treatment and were apparently cured, but there was an increased mortality, which may in part be due to delayed diagnosis. Other reported malignancies have included Hodgkin's lymphoma, leukemia, and cancers of the vulva, liver and lung [200].

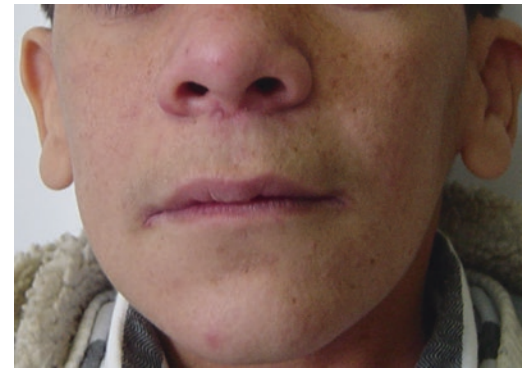

Fig. 9.8 Facial look of a patient with sporadic hyper IgE syndrome. Note the tickened skin, wide nose and perioral chilitis

9.12.4 Diagnosis

The diagnosis of STAT3 deficiency can be made based on a combination of clinical and laboratory findings. For this purpose a clinical HIES scoring system based on 19 clinical and laboratory findings has been developed to help with the diagnosis. In this scoring system more specific and objective findings are assigned more points. Scores of at least 40 points suggest HIES, whereas a score below 20 made the diagnosis unlikely. For intermediate values, no firm conclusion can be reached [111].

Further to this, an alternative scoring system to predict the presence of a mutation in STAT3 has been suggested [290].

This scoring system divided patients into three categories: (1) possibly mutant STAT3, with an IgE >1,000 IU/mL plus a weighted score of >30 of recurrent pneumonia, newborn rash, pathologic bone fractures, characteristic facies and high palate; (2) probably mutant, with these features and a lack of Th17 cells or a definite family history of HIES; and (3) definitely mutant, with these features and a dominant-negative heterozygous mutation in STAT3.

Characteristically IgE in serum is elevated, often > 10-times the normal value of age matched

control values, typical are IgE values between 20.000 and 100.000 IU. Newborns are supposed to have no IgE in serum, hence levels of a few hundred may already be diagnostic in these young patients, especially when there is a family history of autosomal-dominant hyper IgE syndrome and other causes for the IgE elevation such as helminth infections have been excluded.

The elevated IgE levels do not require specific therapy, they are polyclonal and not believed to be associated with pathology in patients with STAT3 deficiency.

STAT3 is a lineage defining transcription factor for the Th17 cell lineage, as RORγt is under its control. RORγt in turn controls the expression of IL17 and IL22, the two key interleukins of Th17 cells. In patients with defective STAT3 signaling, the development of this specific T cell subset was shown to be impaired [48, 157, 258], rendering the testing for the presence or absence of this T cell population *ex vivo* a diagnostic test for this type of the hyper-IgE syndrome.

In addition to the lack of the Th17 cell compartment, patients with STAT3 deficiency also have been described to have a Th2 cell deviation [244] and suffer from a specific antibody deficiency. Other than that, laboratory values such as the white blood cell count and other lymphocyte subsets, as well as functional tests such as lymphocyte proliferation or cytotoxicity or neutrophil degranulation and chemotaxis are not uniformly aberrant in this condition, which complicates the diagnosis.

9.12.5 Management

The therapeutic approach involves prevention and management of infections with long-term administration of systemic antibiotics and antifungals. Lung abscesses may require surgery but possible complications require close attention.

Bone marrow transplantation has been published in only four patients [105, 181]. One of these has died following transplant-related complications, but the other three are well and alive more than 12 years following transplant. The author hence encourages performing this procedure early enough in patients developing life-threatening complications such as lung cysts or lymphoma.

Recurrent lung and skin infections and chronic dermatitis are characteristic of Hyper-IgE syndrome. Therefore organ-specific treatment of complications is also needed.

With regard to the treatment of pneumonia, the choice of the antibiotic regimen is either guided by sensitivity testing (if available), or by empiric decision based on the knowledge of the frequent pathogens observed in patients with the hyper-IgE syndrome (see above). The management of pneumatoceles is difficult and requires specialist knowledge in tertiary referral centers used to manage patients with this condition. It always entails the collaborations with chest physicians and surgeons, as well as the pediatrician/internist. Recurrent lung infections with Staphylococcus (often leading to abscess formation) or Aspergillus are common. Prophylactic antibiotic therapy, TMP/SMX 160/400 mg or cephalexin 500 mg twice a day/dicloxacillin to prevent Staphylococcal infection is essential. Antifungal prophylaxis (fluconazole 100 mg weekly) has also been considered useful as cutaneous fungal infections are common. Pulmonary rehabilitation is recommended. The use of immunoglobulins may be considered if antibody deficiency is documented.

Treatment of the skin entails (i) the daily prophylactic administration of oral anti-staphylococcal antibiotics such as co-trimoxazole (ii) its topical decontamination with e.g. bleach-based or salt-based baths, or anti-septic ointments containing e.g. betadine, and (iii) in severe cases the use of topical or systemic corticosteroids as in severe atopic dermatitis. In selected cases the use of cyclosporine A has also shown benefit for severe skin disease. Treatment of eczema includes moisturizing on a daily basis and using low to mid potency steroid creams on the affected areas. Prednisone low dose (20 mg QD × 4–5 days) could be used in severe cases with weeping lesions. As these lesions are superimposed with *Staphylococcus aureus* antibiotic therapy is important. Small amounts of bleach added to the bath water, twice a week, can aid in clearing skin infection.

The possibility of fracture should be considered even with relatively minor trauma. Calcium

and vitamin D and biphosphonates may be prescribed. Children should be monitored carefully for scoliosis, and as necessary, retained primary teeth extracted if needed.

Mortality in Hyper-IgE syndrome has been due to pulmonary hemorrhage as a result of Pseudomonas pneumonia, invasive pulmonary aspergillosis and other complicated lung abcesses [77]. Embolectomy may be required. Coronary artery aneurysms have been reported [34]. Congenital patent ductus arteriosis also seen in association with Hyper-IgE syndrome should be treated using standard measures. There are rare reports of improvement of clinical indicators with administration of IFN-γ, however, evidence is not sufficient to consider this to be standard therapy.

9.13 DOCK8 Deficiency

9.13.1 Definition

Dedicator of Cytokinesis number 8 (DOCK8) deficiency (OMIM*243700) is an autosomal recessive immunodeficiency syndrome, which is characterized by a combined defect in humoral and cellular immunity [86, 299]. Many DOCK8-deficient individuals were initially diagnosed with an autosomal recessive form of the hyper-IgE syndrome (HIES). This syndrome overlaps phenotypically to some extent with the autosomal dominant form of HIES caused by *STAT3* mutations. Shared symptoms of DOCK8 and STAT3 deficiency include high serum levels of IgE, eczema, recurrent staphylococcal skin abscesses, frequent upper and lower respiratory tract infections, candidiasis, and hypereosinophilia. Individuals with STAT3 mutations may develop pneumatoceles, which are rarely seen in DOCK8-deficient patients. Mutations in STAT3 also often lead to non-immune symptoms involving dentition, bone and connective tissue. In contrast, DOCK8-deficient patients present frequently with allergies, severe and refractory cutaneous viral infections and sometimes with neurological symptoms. However, not all DOCK-patients demonstrate the full spectrum of this syndrome, especially in early childhood; therefore it can sometimes be difficult to distinguish between DOCK8 and STAT3 deficiency based on clinical presentation or laboratory results alone.

9.13.2 Etiology

DOCK8 is a member of the DOCK family of guanine nucleotide exchange factors (GEFs), which function as activators of small G proteins. Possibly DOCK8 is located at the cell membrane just downstream of the T cell receptor, mediating cellular activation to the cytoskeleton *via* CDC42, RAC1, and WASP [224]. DOCK8 is highly expressed within the immune system, especially in lymphocytes, suggesting crucial functions in these cell types and DOCK8 deficiency appears to impair the CD4+ and CD8+ T cell proliferative responses [148].

DOCK8 deficiency is an autosomal recessive trait, i.e. both *DOCK8* (OMIM*611432) alleles must be defective to develop a phenotype, as heterozygous parents of patients are reported to be normal. Hence most patients come from consanguineous parents and DOCK8 deficiency has no gender predilection.

The mutations in DOCK8 encompass large deletions, point mutations that alter splicing to cause nonsense mutations, inframe nonsense mutations, and small insertions and deletions that cause out-of-frame nonsense mutations [86].

9.13.3 Clinical Manifestations

All patients with DOCK8 deficiency had severe atopic dermatitis, often colonized with *Staphylococcus aureus*. Skin abscesses were documented in two thirds of the patients, not all of them lacking inflammation.

Allergies were seen in three quarters of the patients with food allergies in two thirds of the patients, and additional environmental allergies in the remainder; in addition, asthma was diagnosed in one third of the patients.

Upper respiratory tract infections are very prevalent (96%) in DOCK8-deficient individuals, leading to pneumonia in almost all patients, fol-

lowed by bronchiectasis formation in more than a third of cases. Pneumatoceles, however, were only documented in a singleton of 43 documented cases.

Susceptibility to viral infections is very characteristic for this primary immune deficiency: More than half of the patients (up to 60 %) suffer from severe and recurrent outbreaks of Herpes viruses including HSV, VZV, CMV and EBV. More than one third of the patients suffer from severe and recurrent outbreaks of Molluscum contagiosum. About 30 % of patients suffer from human Papilloma virus infections, and a few patients from fatal polyoma virus infection (JC virus infection causing PML). Candidasis was present in 70% of patients.

An ill-defined CNS involvement is further complicating the disease and leads to severe neurological impairment, often followed by death.

9.13.4 Diagnosis

Although developed for the autosomal-dominant phenotype of the Hyper-IgE syndromes (which later turned out to be STAT3 deficiency), the NIH scoring sheet [111] can also be used to diagnose other forms of this condition. A diagnostic cut-off of 40 points has been proposed for the autosomal-dominant variant, whereas almost all of the DOCK8 patients had more than 20 points. Hence, by lowering the diagnostic cut-off, the use of this scoring sheet can also be advised for the autosomal-recessive Hyper-IgE patients.

Additionally, CD4 T cells and CD8 T cells may be low during the first 10 years of life, this is not a universal finding in patients with DOCK8 deficiency. Moreover, the role of the Th17 cell compartment in this condition is still being debated. B cell numbers are mostly normal and NK cells are either lowish or may be slightly decreased. As expected in patients with a form of the Hyper-IgE syndrome, eosinophil counts are consistently elevated.

With regards to the immunoglobulin serum levels, IgE is always above 1000 IU, and other isotypes are also rather elevated with the exception of IgM which is often below 700 mg/dL.

9.13.5 Management

The treatment of choice in this condition is the HSCT [13, 19, 166, 248]. Four of the first five patients published are still alive and well, however, the author knows of additional patients who are performing exceptionally well after receiving a new bone marrow. While waiting for the perfect match, the management of *Molluscum contagiosum* is a therapeutical challenge. Following curettage, local injections of both IFNα and IFNγ have been tried with variable success.

9.14 PGM3 Deficiency

9.14.1 Definition

After the report of the first six families with PGM3 deficiency (OMIM*615816) [229], there seems to be a strong genotype-phenotype correlation with more severe mutations in *PGM3* (OMIM*172100) leading to a more severe impairment of the enzymatic function of the protein, leading to a more severe clinical phenotype. This phenotype is, however greatly variable in between families, leading from 35 y/o patients who suffer from immunologic, neurologic, and skeletal impairment to patients who succumbed in childhood due to their disease.

As two of the initial six families have, however, been published as Hyper-IgE families prior to the discovery of their genetic cause, the listing of this condition in the chapter of the hyper IgE syndromes seems plausible.

9.14.2 Etiology

PGM3 deficiency is a glycosylation disorder. PGM3 is a phosphoglucomutase involved in the production of UDP-GlucNAc, which UDP-GlucNAc is a central precursor of protein glycosylation. PGM3 mutations in patients with the Hyper-IgE syndrome are hypomorphic mutations leaving some protein present, albeit with reduced enzymatic activity [229]. As many proteins of the immune system are highly glycosylated, with the neutrophils being the most glycosylated white

blood cells, an ineffective glycosylation is likely to impair immunity. Other glycosylation disorders also have various degrees of immune dysfunction as part of their clinical phenotype [229].

9.14.3 Clinical Manifestations

The phenotype of PGM3 deficiency is still under observation following the first 17 patients only published in 2014 [229]. However, it becomes clear that there are aspects of the Hyper-IgE immunodeficiency syndrome (e.g., staphylococcal skin and chest infections, elevated IgE, and skin eczema), in addition to the congenital glycosylation phenotype. The latter specifically includes a neurologic and musculoskeletal impairment with mentally challenged children, myoclonus and hypotonia [301]. Moreover, although not seen in all patients, the renal impairment also seems to be part of the phenotype [297].

9.14.4 Diagnosis

As it is true for other glycosylation defects, laboratory findings vary in between patients. With the limited experience from the first 17 patients from six families we observed the following:

1. At one point in time there was a relative lymphopenia in all of the patients tested.
2. Within the lymphocyte compartment the CD4 cells were the most affected.
3. All patients had elevated serum IgE levels and eosinophilia.
4. All other immunoglobulin isotypes (IgG, IgA and IgM) were either normal or elevated.

In addition, T cell proliferation was normal following strong stimuli such as PHA, but reduced following stimulation with antigen-specific stimuli such as tetanus or PPD, but results depended on the glucose level provided in the culture medium.

Applying the NIH-HIES score PGM3-deficient patients scored 40 points and higher with the exception of one patient (27 points).

9.14.5 Management

As this condition has only recently been described, specific treatment is only currently being developed. The replenishing of the UDP-GlucNAc pool seems a plausible option and is currently being evaluated at the National Institutes of Health, Bethesda, Maryland. Whether a bone marrow transplantation will alleviate the immune-mediated features of the disease is unknown; the search for a suitable matched sibling donor may however, be complicated by the fact that *PGM3* is located on chromosome 6 and a crossover between the HLA locus and *PGM3* may not be present in siblings.

9.15 Comel Netherton Syndrome

9.15.1 Definition

Comèl-Netherton syndrome or Netherton syndrome (NETH, OMIM*256500) is a rare autosomal recessive disorder of the skin, hair and immune system. In 1964, Wilkinson [289], delineated the triad of congenital ichthyosis or Ichthyosis linearis circumflexa, Trichorrhexis invaginata and Atopy, as Netherton syndrome. Ichthyosis linearis circumflexa (ILC) was first described by Comel et al. in 1949 [56]. Trichorrhexis invaginata (TI) also known as bamboo hair had been described in 1958 by Dr. Netherton [182]. Trichorrhexis invaginata is considered to be pathognomonic, but may be difficult to detect. Patients also exhibit atopic manifestations including eczema-like rashes, atopic dermatitis, pruritus, hay fever, angioedema, urticaria, high levels of IgE in the serum, and hypereosinophilia [234].

9.15.2 Etiology

Chavanas et al. [46, 47] established their report in 2000, which clarified that mutations in *SPINK5* (OMIM*605010) and subsequent elimination/inactivation of the serine protease inhibitor LEKTI are the molecular cause of NETH. Other studies

confirmed it later [26, 153, 237]. This gene, 61 kb in size, consists of 33 exons and encodes a Kazal-type serine protease inhibitor [27, 68, 119]. This protein is highly expressed in thymus and mucous epithelia, and thereby termed LEKTI for Lympho-Epithelial Kazal-Type related Inhibitor. LEKTI may play a role in anti-inflammatory and/or anti-microbial protection of mucous epithelia. Furthermore, it has a critical role in the process of normal desquamation. Several proteases such as the stratum corneum trypsin-like serine protease [84] and stratum corneum chymotryptic enzyme [127], are thought to play a key role during this process. It could potentially be controlled by LEKTI, through the proteolysis of intercellular adhesion molecules and organization of lamellar body-derived lipid structures in the stratum corneum [134]. Lack of regulation of target serine proteases could lead to impaired proteolysis of membrane-bound receptors, premature secretion of lamellar body contents and disturbance in the formation of the intercellular lipid layers [89], that cause defective epidermal barrier. As *SPINK5* is highly expressed in the thymus [159], defective LEKTI expression might have an effect on T-cell differentiation, thus explaining the unbalanced Th2 immune response with markedly elevated IgE levels and the increased susceptibility to infections characteristic for NETH.

9.15.3 Clinical Manifestations

NETH may first appear as severe congenital generalized exfoliative erythroderma. Later, serpiginous scaling and migratory polycyclic erythematous patches surrounded by a doubled-edged scale (Ichthyosis linearis circumflexa) may become visible (Fig. 9.9). These are usually found in flexural areas of untreated patients and leave no atrophy, scarring or pigmentation [56, 136].

All patients had abnormal hair [136, 234]. Hair growth on the scalp, eyebrows and body may be sparse. Individual hairs are dry, straight, lusterless and brittle. Scalp hair grew to 1–3 cm before breaking; especially on the occipital area due to friction. This hair shaft abnormality usually develops during the infancy or early childhood and may improve with age. The eyebrows are particularly more preferential to examine microscopically showing the characteristic ball-and-socket appearance or Bamboo hair (Fig. 9.10).

The invagination is caused by the softness of the cortex in keratinized zone, probably because of the reduced number of disulfide bands. Scalp scaling (39 %), lichenified or eczematous changes (30 %), palm or sole involvement (16 %), pruritus (11 %), excess vellous hair (9 %), heat intolerance (7 %), and abnormal teeth or nails (5–7 %) are other ectodermal manifestations. Some percentages of the patients may have mental retardation, neonatal hypernatremia, decreased growth, and serum aminoaciduria [234].

9.15.4 Diagnosis

Trichorrhexis invaginata associated with congenital icthyosiform erythderma or ILC make the clinical diagnosis possible. Recurrent infections occur in 28–30 % of cases with NETH, of which chronic upper respiratory tract and staphylococcal skin infections are the most common [106, 234]. IgG abnormalities (both hypo and hyper IgG) are presented in 12 % [234]. Elevated levels of serum IgE (mean of 4,751 IU/mL in one series), positive skin test or RAST results, selective antibody deficiency to protein/polysaccharide antigens, associated with IgA-IgG_2 deficiency, and decreased delayed type hypersensitivity responses has been reported in isolated cases or series [108, 247]. An increased incidence of deep tissue infections has not been reported.

9.15.5 Management

Treatment is usually symptomatic and should be adjusted to the patient's needs. Topical emollients, keratolytics and corticosteroids may help. Low dose acitretin [120, 121] has been effective, but should be avoided in erythrodermic neonates, and its long-term use is limited due to its potential side effects. Topical calcineurine inhibitors [225, 249], tacrolimus and pimecrolimus creams, and topical calcipotriol [104] have been effective in some patients. These treatments should be given with caution because of their systemic absorption [8] via the dysfunctional skin barrier.

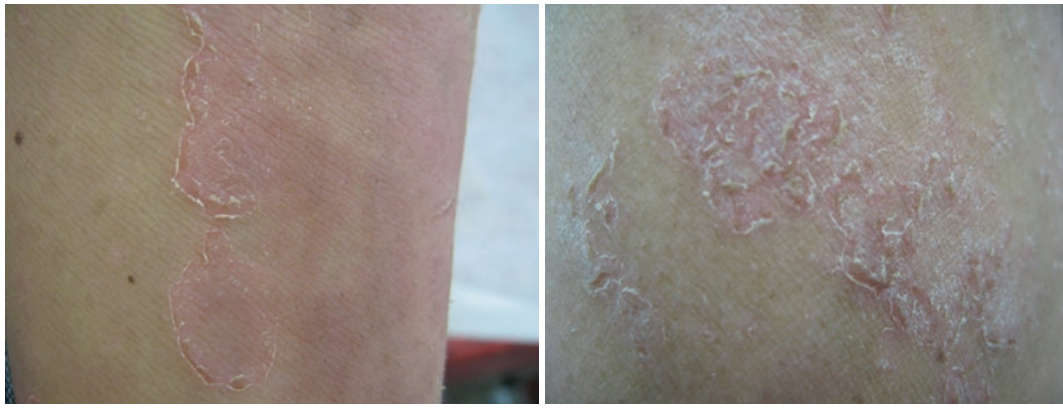

Fig. 9.9 Ichthyosis linearis circumflexa. Note the serpiginous scaling and erythematous patches surrounded by a doubled-edged scale (Courtesy of K. Balighi; Tehran, Iran)

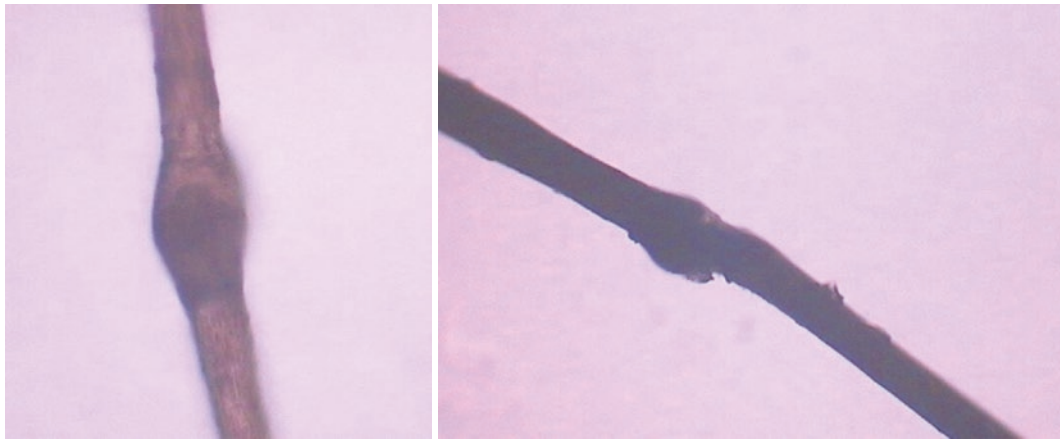

Fig. 9.10 Trichorrhexis invaginata; note the characteristic ball-and-socket appearance or Bamboo hair (Courtesy of K. Balighi; Tehran, Iran)

Ex vivo gene therapy studies suggest that *SPINK5* gene transfer may mediate localized correction of skin architecture inside and outside of the grafted area [73].

9.16 Other Forms of Hyper-IgE Syndrome

9.16.1 Definition

Several other defined single gene mutations have been described to result in syndromes with features of HIES as well as other abnormalities.

9.16.2 Etiology

A homozygous deleterious mutation in *TYK2* (OMIM*176941) was the first genetic defect published in a patient diagnosed with a Hyper-IgE syndrome due to his susceptibility to cutaneous staphylococcal infections and high serum concentrations of IgE [172]. However, this patient also had BCGitis and *Salmonella* infections. He also suffered from recurrent cutaneous herpes simplex virus reactivations. The report of this patient paved the way for the subsequent identification of STAT3 deficiency, which is the signaling molecule directly downstream of the

Janus kinase Tyk2. Since this initial report of a Tyk2-deficient patient who had a Hyper-IgE phenotype but additionally experienced BCGitis, which is not characteristic for the Hyper-IgE syndromes, there are also some other patients described with mutations in *TYK2*, who interestingly did not have a hyper-IgE phenotype, but an immunodeficiency characterized by the susceptibility to mycobacterial infections [146]. (*See* Sect. 6.7 *for more details*)

We and others have screened our cohorts of Hyper-IgE patients for additional patients with mutations in *TYK2*, but have failed to identify additional patients.

9.16.3 Clinical Manifestations

Minegishi et al. (2006) [172] described a 22-year-old Japanese male clinically diagnosed with autosomal recessive Hyper-IgE syndrome (HIES) (OMIM*243700). The patient had a history of susceptibility to various microorganisms, including virus, fungi, and mycobacteria. He had an episode of Bacille Calmette-Guerin (BCG) infection at age 22 months and non-typhi salmonella gastroenteritis at age 15 years. The patient had normal numbers of natural killer, B, and T cells, but the patient's cells showed defects in multiple cytokine signaling pathways. The patient's parents were consanguineous, suggesting a recessive hereditary disorder.

Woellner et al. (2007) [291] noted that the patient with TYK2 deficiency reported by Minegishi et al. (2006) had clinical features atypical for autosomal recessive HIES, including BCG lymphadenitis and non-typhi salmonella infection [172]. They suggested that TYK2 deficiency is clinically distinct from autosomal recessive HIES. In a response, Minegishi et al. (2007) proposed that TYK2 deficiency be categorized as a disease entity with characteristic features of both autosomal recessive HIES and Mendelian susceptibility to mycobacterial disease (MSMD; OMIM*209950) [171].

9.16.4 Diagnosis

The diagnosis of patients with TYK2 deficiency is not evidence based and relies on the clinical presentation.

9.16.5 Management

The management could be similar to management experience in other patients with primary immunodeficiencies such as antibiotic prophylaxis and the consideration of a more definite treatment by stem cell transplantation.

9.17 Wiskott-Aldrich Syndrome

9.17.1 Definition

Wiskott-Aldrich syndrome (OMIM*301000) is a rare X-linked disorder characterized by persistent microthrombocytopenia, eczema, cellular and humoral immunodeficiency, and an increased risk of autoimmune disease and hematologic malignancy [7, 250]. In 1937, Wiskott described three brothers with thrombocytopenia, bloody diarrhea, eczema and recurrent ear infections. Later in 1954, Aldrich demonstrated that this syndrome was inherited as an X-linked recessive trait. In the 1950s and 60s, the features of immunodeficiency were identified, and Wiskott-Aldrich syndrome (WAS) was added to the list of primary immunodeficiency diseases. WAS is caused by mutations in the gene encoding the Wiskott-Aldrich syndrome protein (WASP). The gene (OMIM*300392) resides on Xp11.22-23. The exact function of WASP is not fully elucidated, but it seems to function as a bridge between signaling and movement of the actin filaments in the cytoskeleton. Cloning of the *WAS* gene, has allowed the recognition of an attenuated form of the syndrome, X-linked thrombocytopenia (XLT), manifesting mainly with chronic or intermittent thrombocytopenia and small platelets, sometimes associated with mild eczema [271, 303].

9.17.2 Etiology

The *WAS* gene was identified by positional cloning in 1994 [69]. The gene consists of 12 exons encoding a 502 amino-acid intracellular protein (WASP) expressed exclusively in hematopoietic cells. WASP is a member of a family of proteins involved in the organization of the actin cytoskel-

eton [256]. The protein consists of several functional domains that regulate its activity and subcellular localization. These include a N-terminal EVH1 (Ena/VASP homology 1) domain, a GTPase-binding domain (GBD), a proline-rich region and a C-terminal verproline homology/cofilin homology/acidic region domain [169, 253]. Other members of this family include a more widely expressed neural tissue homologue of WASP (N-WASP), and two newly identified WASP family proteins referred to as WAVE 2 and WAVE 3. These molecules are similar to WASP in their C-terminal region [255].

To carry out vital functions, such as growth, endocytosisand exocytosis, cells have to rearrange their actin cytoskeletons. This process requires the activation of a group of small guanosine triphosphate (GTP)-binding proteins, which cycle between an active GTP-bound form and an inactive guanosine diphosphate (GDP)-bound form. These proteins are called Rho, Rac and Cdc42 and regulate the formation of different polarized actin structures such as stress fibers, lamellipodia, and filopodia [184]. Actin filament growth (F-actin) occurs by rapid monomer (G-actin) addition to the barbed leading end of a nucleated site. Member of the WASP family acts as scaffold to which many elements, including actin, bind, permitting the reorganization of the cytoskeleton. At rest, WASP and N-WASP are in a closed configuration controlled by several proteins. The WASP-interacting protein (WIP) constitutively interacts with the N-terminal region of WASP, inhibiting WASP effector activity. WASP is relieved after T cell receptor (TCR)-mediated activation that results in WIP phosphorylation [273]. This process allows WASP to be activated by Rho-family GTPases [228]. Binding of Cdc42 to GBD domain of WASP or N-WASP consent to these proteins to assume an open configuration and to bind at the C-terminal region the actin related protein 2/3 (Arp2/3) complex, leading to the nucleation of actin and thus controlling cell shape (Fig. 9.11). WASP and N-WASP represent key regulators of Arp2/3 molecular machine [235].

Many different *WAS* mutations that alter the protein binding to different GTPases have been identified, thus leading to defective cytoplasmic signaling and actin polymerization. Presumably, *WAS* mutations interfere with the proper signaling and growth of cells of the hematopoietic lineage, resulting in the platelet and immune defects observed clinically, although the exact mechanisms and defective pathways remain largely unknown. Studies have demonstrated that the Cdc42-WASP interaction is necessary for certain chemoattractant-induced T-cell chemotaxis [115]. Furthermore, it was shown that defective WASP function results in abnormal migration and motility in multiple key cellular components of the immune system and specifically, dendritic cells (DCs), myeloid cells, macrophages, natural killer (NK) cells, as well as both B and T lymphocytes [30, 40, 102, 154, 196, 197, 300].

Identification of WAS mutations in patients with WAS-XLT has provided powerful tools to confirm at a molecular level the diagnosis in symptomatic male subjects [70, 192, 250]. Villa et al. presented proof that mutations in WAS can result in X-linked isolated thrombocytopenia characterized by small-sized platelets [271].

According to the paper by Ochs and Thrasher, 158 unique *WAS* mutations were identified among a large cohort of patients with WAS/XLT [192]. Mutations of *WAS* gene results in 3 different phenotype: the classic WAS, characterized by thrombocytopenia-small platelets, eczema and recurrent infections; the milder XLT variant [271, 303], which can be intermittent; and congenital X-linked neutropenia [72]. The severity of the phenotype is largely dependent on the effect of the mutations at a protein level. Patients with mutations that allowed expression of normal-size mutated protein, even if in reduced quantity, were more likely to have XLT phenotype, whereas patients affected by mutations causing lack of protein expression or expression of a truncated protein were usually affected by classical WAS. In some cases genotype seemed not to correlate with phenotype, making it difficult to predict the clinical course [192].

It was shown that somatic mosaicism, resulting from spontaneous reversion of mutations responsible for WAS, may contribute to explain the inconsistent genotype/phenotype correlation found in some patients [11, 278, 279]. Back mutations can restore wild type sequence in selected cell population; moreover second-site

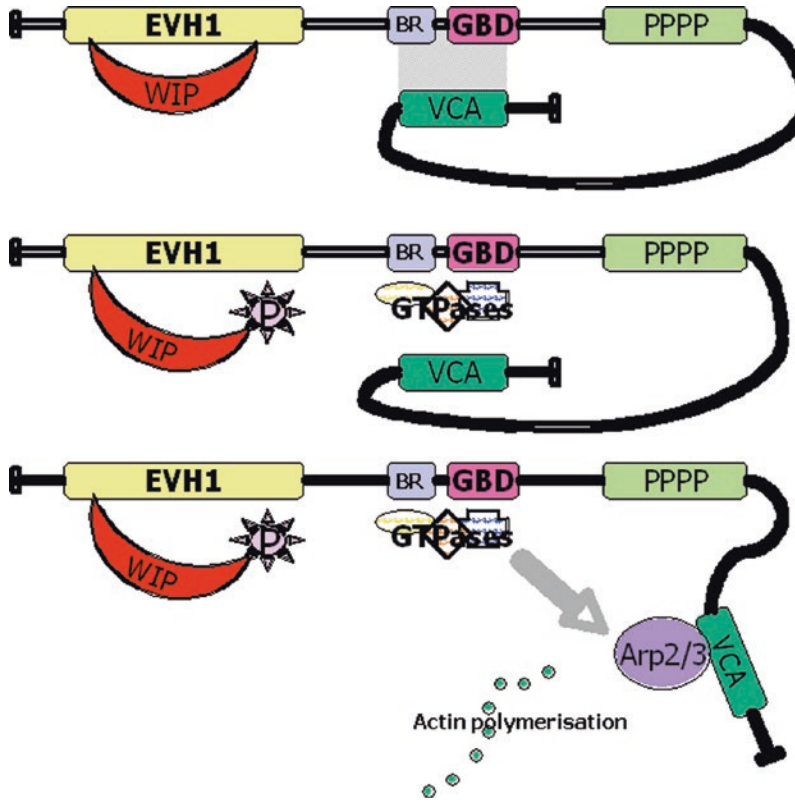

Fig. 9.11 Schematic representation of WASP and model of activation. In the inactive configuration, WASP is bound to WIP at the EVH1 domain and adopts an autoinhibited configuration in which the VCA domain interacts with the GBD and BR domains. T cell receptor (TCR)-mediated activation results in WIP phosphorylation, which allows WASP to be activated by Rho, Rac, Cdc42. After activation WASP assumes an open configuration and binds at the C-terminal region the Arp2/3 complex, leading to actin polymerization. *VCA* verproline cofilin homology domain, *GBD* GTPase-binding domain, *BR* basic region, *PPPP* proline-rich region, *Arp2/3* actin related protein 2/3

mutations can lead to compensatory changes. Reversion has been detected mainly in T lymphocytes, capable of restoring their function [144], and more recently also in NK cells [156].

9.17.3 Clinical Manifestations

WAS is a primary immunodeficiency disease involving both T and B lymphocytes. Platelets are also severely affected. In its classic form, WAS has a characteristic pattern of findings that include an increased tendency to bleed, caused by a significantly reduced number of platelets, eczema, and proneness to infection (Fig. 9.12). In addition, long-term observations of patients with WAS have revealed an increased incidence of malignancies, including lymphoma and leukemia, and an increased incidence of a variety of autoimmune diseases in many patients.

The clinical presentation of WAS varies from patient to patient. Some patients present with all three classic manifestations (thrombocytopenia and bleeding, immunodeficiency and infection, and eczema), other patients present only with low platelet counts and bleeding. The initial clinical manifestations of WAS may be present soon after birth or develop in the first year of life. The incidence of the classic WAS is estimated to be about four cases per one million live male births [250].

Thrombocytopenia and small platelet volume is a pivotal finding in patients affected by mutations in WAS gene. Only recently, precise Missense mutations identified within the Cdc42-

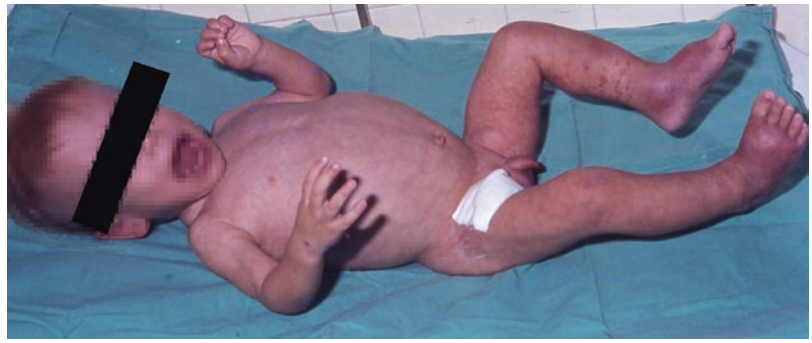

Fig. 9.12 A boy with Wiskott-Aldrich syndrome who suffered from vasculitis, intestinal bleeding and severe respiratory infections

binding site may not be associated with platelet abnormalities [40, 72]. Platelet counts can vary within different WAS/XLT patients and among individuals from the same family being as low as 5000/mm^3 or as high as 50,000/mm^3. Intermittent thrombocytopenia with consistently reduced platelet volume was described in 2 families and has been associated with unique missense mutations in WAS gene [186]. The mean volume of platelets in WAS patients is 3.8–5 fL, compared to 7.1–10.5 fL in individuals without WAS [191]. Platelet counts and volume usually increase after splenectomy, although these are still lower than in normal controls [155]. This suggests that spleen platelet turnover may play a role in determining thrombocytopenia. Platelets from WAS patients show indeed many functional and morphologic abnormalities. An alternative explanation is a decrease in platelet production since it has been shown that megakaryocyte differentiation is dependent upon the interaction of WASP with actin filaments [170].

Male infants affected by WAS usually present with bleeding, commonly bloody diarrhea, prolonged bleeding from circumcision, purpura, or unusual bruising. In a group of 154 patients, petechiae or purpura were found in 78 %, serious gastrointestinal bleeding (hematemesis or melena) in 28 %, epistaxis in 16 %, and intracranial bleeding in 2 % of patients [250].

Eczema is one of the characteristic findings. Atopic symptoms are frequently present, and a history of either mild or severe eczema was reported to develop in 81 % of patients [250]. When severe, it may be recalcitrant to therapy and persist into adulthood. The eczema may improve as the patient gets older, although serious complications such as secondary infection (e.g. cellulitis, abscess, and by *Herpes simplex virus*) or erythroderma can occur. Defective chemotaxis of dendritic and Langherhans cells seems to be responsible for the local generation of antigen-specific T cells and the development of eczema [262].

Because of the defective immunity, recurrent infections are frequent in classical WAS. Bacterial infections due to common organisms include otitis media, sinusitis, and pneumonia. Serious infections may also occur. Encapsulated organisms are frequent pathogens that may cause life-threatening complications, including meningitis, and sepsis. *Pneumocystis jiroveci* and viral infections, commonly *Herpes simplexvirus* or *Molluscum contagiosum*, may also become troublesome. Fungal infections, mainly caused by *Candida albicans* are observed in 10 % of patients [250].

The degree of the immune defect can be inconsistent among affected individual carrying different type of mutations and is largely dependent on protein expression. Both the cellular and humoral immune systems are affected. In classic WAS, serum IgM levels are moderately depressed and IgG levels are relatively normal, but IgA and IgE may be elevated. Typically, isohemagglutinin titers are low and antibody responses to several protein and polysaccharide antigens are depressed; in contrast, antibody responses to live vaccines are mostly normal [191, 250]. T cell proliferative responses to mitogens, immobilized anti-CD3 mAb [176], and to allogeneic cells [191] are impaired [57]. Lymphopenia may also

be found and is probably due to accelerated apoptosis of T cells [191, 214]. Abnormalities in the distribution of T cell subsets were identified, with an increased proportion of effector memory T lymphocytes among adults with WAS [204]. B-cell function seems to be also affected; EBV-transformed B cells from patients with WAS show reduced levels of F-actin and impaired actin polymerization [88]. Moreover Park et al. identified phenotypic abnormalities of B cells in patients with WAS [204]. A large proportion of circulating B cells failed to express CD21 and CD35, two complement receptors that are involved in antigen capture and presentation by B lymphocytes. This may compromise the ability to elicit and sustain adequate antibody responses and may also contribute to autoimmunity, since down-regulation of CD21 and CD35 has been reported in several autoimmune diseases in humans and in murine models of autoimmunity [187]. Besides, the same study report also on a decreased proportion of CD27+ post-germinal centre B cells and on the increased numbers of $CD10+CD27^{-}CD38^{bright}$ germinal centre B cell progenitors among WAS adults, suggesting a possible aberrant migration of patients' B cells due to underlying cytoskeletal defect.

WASP is also involved in innate immunity. NK cells from patients with WAS show a reduced accumulation of F-actin in the immunologic synapsis, therefore affecting also cytolitic NK function [102, 196]. Myeloid cells, macrophages, DCs and Langherans cells might also be affected by WAS mutations. Patients with WAS are unable to assemble podosomes in monocytes, macrophages, and DCs, resulting in a defect of adhesion and mobility [42].

Autoimmune disorders have been reported in 40 % of WAS patients [250]. Autoimmune manifestations include hemolytic anemia, vasculitis (including cerebral involvement), Henoch-Shönlein purpura, polyarthritis, renal disease and inflammatory bowel disease. Other less frequent autoimmune diseases include neutropenia, dermatomyositis, uveitis and recurrent angioedema. Development of autoimmune complications in patients affected by XLT is generally less frequent than in patients with WAS. IgA nephropathy, often causing chronic renal failure and requiring dialysis or renal transplantation, was described as a frequent complication in Japanese patients affected by XLT. A high serum concentration of IgM was reported to be a risk factor for autoimmunity or early death [82]. Based on recent findings, WASP seems to play an important role in the activation and suppressor function of natural CD4+CD25+ regulatory T cells (nTreg), and a dysfunction or incorrect localization of nTreg cells may contribute to the development of autoimmunity in WAS patients [2, 162].

Malignancies usually occur during adolescence or adulthood in patients affected by classic WAS and were reported in 13 % of patients with lymphoma, mainly EBV-positive B cell lymphoma, being the most frequent. WAS-associated malignancies have a poor prognosis [250]. Few cases of lymphoma were described also in XLT, but the exact incidence is unknown.

9.17.4 Diagnosis

Because of the wide spectrum of the clinical presentation, WAS/XLT should be considered in every male presenting with bleeding associated to congenital or early-onset thrombocytopenia and small platelets. A history or the presence of mild or severe eczema supports the diagnosis. Infections and immunologic abnormalities are more characteristic of WAS. A scoring system was established by Ochs et al. [190, 192] to better delineate markedly different clinical phenotypes (Table 9.4).

Sequencing analysis of WAS is essential for establishing final diagnosis and for identifying female carriers and performing prenatal diagnosis. X-inactivation studies in WAS carrier females have shown that the normal X chromosome is generally used as active X chromosome in all hemotopoietic cell lineages [288]. Protein expression studies by flow cytometry [138], using suitable anti-WASP antibody, are also important to assess the effect of *WASP* mutations and it might also assist in estimating, carefully, the severity of the disease.

Table 9.4 Clinical phenotypes associated with mutations of the *WAS* gene [192]

	WAS	XLT	IXLT	XLN
Phenotype				
Thrombocytopenia	Yes	Yes	Intermittent	No
Small platelets	Yes	Yes	Yes	No
Eczema	Yes	Possible	No	No
Immune deficiency	Yes	Possible (mild)	No	No
Infections	Yes	Possible (mild)	No	Typical for neutropenia
Autoimmunity and/or malignancies	Frequent	Possible	No	No
Congenital neutropenia	No	No	No	Yes
WAS mutations	Nonsense; frame shift	Missense (exons 1–3); inframe deletions or insertions	Missense	Missense in Cdc42-binding site
WAS protein expression	Absent or truncated	Present, reduced quantity	Present, normal quantity	Present

WAS Wiskott-Aldrich syndrome, *XLT* X-linked thrombocytopenia, *IXLT* intermittent XLT, *XLN* X-linked neutropenia

9.17.5 Management

Patients with thrombocytopenia may require intravenous immunoglobulin (IVIG) and/or corticosteroids [64]. If bleeding occurs, platelet and/or red blood cell transfusions may be required. As a general rule platelet transfusions should be avoided unless bleeding is serious in order to prevent sensitization. All blood products need to be irradiated and should be negative for cytomegalovirus. Splenectomy effectively stops bleeding tendency by increasing platelet numbers, although it might increase the risk of septicemia. Therefore, if performed, requires lifelong antibiotic prophylaxis.

In case of infections, prompt and selective antimicrobial therapy is essential. It is also important to search for a bacterial, viral or fungal etiology. Prophylactic treatment with IVIG may be beneficial in patients with classical WAS because of the abnormal antibody responses to multiple antigens. Eczema is managed in the usual fashion, with careful attention to skin care, moisturization, and appropriate (route and potency) steroid therapy. If autoimmune phenomena develop, high doses of IVIG, systemic steroids or more aggressive immunosuppression may correct the problem. Autoimmune hemolytic anemia might respond to anti-CD20 (rituximab) treatment. Surveillance for malignancy is an important aspect of care.

Bone marrow transplantation may be curative if an appropriate histocompatible donor is available [91]. Moreover, outcome of bone marrow transplantation in WAS patients showed 70 % 5-year survival rate for all patients who received transplants. When a matched sibling donor is unavailable, umbilical cord blood stem cell transplantation has been used. If bone marrow transplantation is successful, hematological and immunologic defects are corrected and eczema resolves.

Successful results recently achieved by the use of gene therapy in severe combined immunodeficiencies and other primary immunodeficiency disorders [92, 199] has encouraged the development of similar strategies also for WAS. Several preclinical studies were performed with promising *in vitro* results both for human and murine cells [45, 81, 141, 164, 245, 246]. Recent clinical trials suggest that gene therapy (GT) for WAS may be feasible and effective but the use of gamma-retroviral vectors may associate with a remarkable risk for leukemogenesis [32]. Human stem cell gene therapy for WAS based on lentiviral vector gene transfer into stem cells may offer a safety advantage and may open new avenues for GT in WAS, in particular, and PIDs in general [4, 293].

Long-term prognosis in patients with classic WAS is poor without appropriate treatment. The life expectancy was originally reported to be 3.5 years, and now over 11, although survival continues to increase over time [250]. Incidence of malignancies, especially lymphomas, increase substantially during the third decade of life in classic WAS. The cause of their death has remained similar over the years. Most patients died from complications of bleeding, infection, or malignancy. Median survival of 25 years is reported for patients who undergo splenectomy, and even longer for patients who undergo successful bone marrow transplant. Patients with XLT have a more favorable prognosis, with the majority reaching adulthood.

9.18 WIP Deficiency

9.18.1 Definition

WASP-interacting protein (WIP) deficiency (OMIM*614493) is a novel PID characterized by clinical and hematological features of WAS and mutation in WIPF1 (OMIM*602357) gene which encodes WIP but affected individuals have normal WAS gene sequence and messenger RNA level in T cells, and undetectable of both WASP and WIP [63]. WIP deficiency should be suspected in patients with WAS phenotype in whom *WAS* sequence and mRNA expression are normal [149].

9.18.2 Etiology

In T lymphocytes, WASP is complexed with the WIP which stabilizes WASP and prevents its degradation. Thus, the absence of WIP due to mutation of *WIPF1* may result in insatiability and complete degradation of WASP [149]. Lymphocytes of $WIP^{-/-}$ mice fail to proliferate and to secrete IL-2 despite normal lymphocyte development [10]. In addition, these cells show defective F-actin polymerization upon TCR ligation. Studies in mice suggest WIP is important for immunological synapse formation.

9.18.3 Clinical Manifestations

WIP was first described as a PID by Lanzi et al. in a female patient who presented with a WAS phenotype in early infancy and was found to have wild type WAS sequences [149]. The index patient was a female offspring of consanguineous Moroccan parents. Her female sibling had suffered from vesicular and ulcerative skin lesion and died of sepsis in early infancy. The index patients also presented with vesicular and ulcerative lesions on the skin and oral mucosa, eczematous rash, failure to thrive and recurrent infections. Hematological findings included thrombocytopenia and normal platelet volume and she had no bleeding tendency. She developed infections by RSV and rotavirus and acute hepatitis of unknown etiology [149]. Immunological analyses revealed T lymphopenia, impaired T cell proliferation and NK cell function, and elevated serum IgE level. PCR analyses showed borderline WIP mRNA level and no detectable WIP in T cell blasts. Genomic DNA sequencing revealed a c.1301C>G homozygous stop codon mutation in WIPF1. She underwent unrelated HSCT by using cord-derived stem cells at 4.5 months age.

9.18.4 Diagnosis

There are several overlapping and intervening clinical and laboratory findings in patients with WAS and WIP deficiency. These include eczematoid skin lesions, recurrent infection, T lymphopenia, thrombocytopenia, impaired T cell proliferation and NK cell function, however, in contrast to WAS, platelet volume appears to be normal in WIP deficiency and affected individuals have no bleeding tendency. Neither WASP nor WIP can be detected in T cell blasts of patients with WIP deficiency. Genetic data now suggest that WIP deficiency is an autosomal PID cause by mutations in WIPF1, located on chromosome 2.

Diagnosis of WIP deficiency requires analyses of both WAS and WIP genes and analyses of the expression of WAS and WIP.

9.18.5 Management

Appropriate management of infectious complications including immunoglobulin therapy is critical in patients with WIP deficiency. HSCT may result in complete recovery.

9.19 Hepatic Veno-Occlusive Disease with Immunodeficiency

9.19.1 Definition

The syndrome of immunodeficiency in association with hepatic veno-occlusive disease was first reported in 1976 Mellis and Bale who described five Australian infants in three families of Lebanese origin who had hepatic veno-occlusive disease (VOD), hypogammaglobulinemia and recurrent infections including *Pneumocystis jiroveci*. Lymph nodes histology showed absence of germinal centers and plasma cells [167]. The term VODI (veno-occlusive disease with immunodeficiency) has been proposed to describe this novel primary immunodeficiency disorder (OMIM*235550) [218]. Hepatic VOD had previously been known only to be associated with ingestion of pyrrolizine alkaloids (for example in bush teas or contaminated grains), as an important complication of stem cell transplantation, or to occur in association with cytotoxic drug use [222] and HIV infection [38]. VOD is probably a misnomer since the pathogenesis involves dysfunction of hepatic sinusoidal endothelial cells leading to sinusoidal congestion with the descriptor sinusoidal obstruction syndrome being more accurate [222]. The few reports of VOD in patients with primary immunodeficiencies [122, 236, 238] may represent another cause of VOD, complications of stem cell transplantation or intercurrent infection or unrecognized cases of VODI. Since the original description by Mellis and Bale [167], further VODI patients have been reported by Etzioni et al. [87] (2 non-consanguineous Lebanese siblings) and 1 non-consanguineous baby reported from Spain by Manzanares Lopez-Manzanares [161]. The reports from Roscioli et al., 2006 [218], Roscioli et al., 2009 [219], Cliffe et al. [53], document 21 Australian children of Lebanese background (15 from consanguineous families) and 2 unrelated non-consanguineous Italian children. Wang et al. [282] reported a Californian child of Hispanic background also included in the Cliffe report [53]. Eight 8 Arabic children from a large consanguineous family were reported by Ganaiem et al. [96]. The author is aware of at least one additional unpublished case of a Lebanese baby girl bringing to 40 the number of published or unpublished reports of VODI to date. Two thirds of these cases occurred in consanguineous families. Key clinical features are bacterial and opportunistic infections including *Pneumocystis jiroveci* infection, mucocutaneous candidiasis, enteroviral or cytomegalovirus infections, hepatomegaly or evidence of hepatic failure not explained by other factors in the affected individual or a first degree relative, onset before age 12 months (almost always before 6 months) with a family history consistent with autosomal recessive inheritance.

9.19.2 Etiology

Roscioli et al. [218] studied members of 5 affected families and using homozygosity mapping localized VODI to chromosome 2q36.3-37.1 and showed the causative gene to be *SP110* (OMIM*604457), a putative transcriptional factor which encodes the promyelocytic leukemia (PML) nuclear body protein [28]. *SP110* is in the SP100 gene family. It exists in three isoforms and encodes a 713-residue protein that has structural features consistent with a role in transcriptional regulation, including a nuclear localization signal; SP100-like dimerization, plant homeobox, bromo and LXXLL-type nuclear hormone domains and Sp100/AIRE-1/NucP41/75 domains (SAND) [28].

All 6 pathogenic *SP110* alleles identified to date are located in the *SP100*-like domain and all are associated with reduced expression of SP110 protein [53]. In all studies which have been performed in families recruited in Lebanon the muta-

tion identified was the exon 5 single base pair deletion, c.642del, producing a stop codon. A single consanguineous Australian family of Lebanese Christian background had an exon 2 deletion, c.40del which also results in a stop codon. All other Australian families of Lebanese origin who have been studied to date had the c.642 deletion [218]. A large Arabic family had an exon 4 deletion c.373del producing a stop codon [53, 96]. A single Italian patient was found to be homozygous for a 7-bp tandem duplication in exon 4, c.319_325dup, causing a frame-shift mutation, p.(Ser109Trpfs), with the introduction of a premature stop codon 5 codons 3′ of the mutation. Another Italian child was homozygous for an allele with a duplication of the final base of exon 5, c.667+1dup, resulting in a frameshift, with the introduction of a premature stop 4 codons 3′ of the mutation, resulting in nonsense-mediated mRNA decay. A single Hispanic patient recruited in Los Angeles had the only pathogenic missense mutation identified so far. A homozygous dinucleotide insertion/deletion missense mutation NM_080424.2 (SP110):c.78_79delinsAT was identified. While *SP110* mRNA was present in the patient's cells, SP110 protein levels were markedly reduced probably as a result of degradation of the normal length mutant protein [282]. Penetrance appears to be complete. Mutation analysis has not been reported for the patient reported from Spain in 1992 [161].

VODI is a rare disease and only 40 cases having been identified to date. However, in Sydney, Australia, where 21 of these patients have been identified the disease appears to be common among families reporting Lebanese descent and it can be estimated that there is one affected family per 10,000 members of the population self-identifying as having a Lebanese background. The carrier frequency in non-consanguineous members of this community can thus be estimated to be about 1:30. However, the c.642del mutation was not identified in 50 unaffected Lebanese controls recruited in Sydney [218]. Most Lebanese parents are 1st or second generation Australians making it unlikely that the high frequency and carrier rates represent a founder effect. In any case, two different mutations have been identified in the Australian families, and one of these has been found in at least two families in Lebanon. If the incidence of VODI in the Sydney Lebanese community was reflected in the population of Lebanon eight cases per year could be expected in that country. Only five patients with VODI are known to have been identified in Lebanon since Etzioni et al. reported a family from southern Lebanon almost 30 years ago [87]. No reports have emanated from the large communities of Lebanese background in North and South America.

The principle features of VODI are hypogammaglobulinemia, predisposition to opportunistic infections and susceptibility to develop hepatic VOD. At least three patients have had demyelinating leukodystrophy which did not appear to be explained by CNS infection. Thrombocytopenia and pancytopenia also observed at presentation and improve if the patient survives the presenting illness. The mechanisms by which deficiency of the SP110 protein leads to the manifestations of VODI, including liver and neurological disease are poorly understood. B cell numbers in VODI patients are normal but they fail to develop germinal centers or mature into plasma cells. Lymphopenia is an infrequent feature and T cell subset numbers and proliferative responses are usually normal. However, numbers of memory T and B cells are reduced. Intracellular T cell production of the cytokines interferon-γ, interleukin (interleukin)-2, IL-4 and IL-10 is reduced [218]. This is consistent with the observation that EBV-transformed VODI B cell lines when compared to controls have reduced levels of IL-10 mRNA and of IL-10 protein in their supernatants [29]. Reduced production of CD27 mRNA may explain the reduced numbers of memory B cells. VODI B cells are skewed away from more mature B cells towards transitional B cells [53]. There may thus be a role for SP110 in differentiation of naïve B cells; SP110 may also be required for the survival of effector B cells [53]. There is evidence that B cells from VODI patients have a defect in isotype switching. An intrinsic impairment of VODI B cells in T cell dependent responses is evident from the finding that immunoglobulin production by VODI B cells in

response to stimulation with CD40 ligand and IL-21 is markedly reduced [53].

The cause of the hepatic VOD is unknown but liver dysfunction is frequently observed to improve with control of the presenting infection, instigation of intravenous immunoglobulin (IVIG) and commencement of cotrimoxazole prophylaxis, an observation which suggests that liver disease it may be precipitated by the inflammatory state associated with infection events. However the unique occurrence of characteristic hepatic changes in VODI suggests that the genetic disorder predisposes to these developments.

Table 9.5 Clinical features reported in VODI patients

Interstitial pneumonia
Hepatic VOD
Hepatomegaly and liver dysfunction without VOD
Thrombocytopenia
Chronic diarrhoea and failure-to-thrive
Haemophagocytosis
Neurological syndromes
Cerebral, spinal leukodystrophy
SIAHD
Microcephaly
Developmental delay
Cerebral palsy
Porencephalic cysts
Cerebral infarction

9.19.3 Clinical Manifestations

The age at presentation was less than 6 months in 37 of the 38 children for whom this information is available. Presentations were with respiratory distress and/or hepatosplenomegaly and liver dysfunction (Tables 9.5 and 9.6). When serum immunoglobulin levels have been measured hypogammaglobulinemia was always present. *Pneumocystis jiroveci* was identified in about

Table 9.6 Features in 21 children with VODI recruited in Sydney, Australia

Feature	Number with feature	Number evaluable	%
Lebanese family	11 families	11	100
Consanguinity	8 families 15 children	11 21	73 71
Presentation by age 6 months	19	21	90
Definite PCP	8	21	38
Definite or probable PCP	13	21	62
Hepatic veno-occlusive disease (sinusoidal obstruction syndrome)	10	21	48
Thrombocytopenia at presentation	6	7	86
Hypogammaglobulinemia, Igs or evident at PM	20	20	100
Normal B cell numbers	12	12	100
Normal T cell numbers	11	12	91
Clinical evidence of T cell dysfunction	11	21	55
T cell subset abnormalities	1	11	9
Reduced proliferative response to PHA or ConA	2	8	25
Neurological abnormalities	7	21	33
SCID phenotype	1	21	5
Total Deaths	20	21	95
Deaths prior to IVIG + TMP-SMX (Mean age at death in months)	10 (4)	10	100
Deaths on IVIG + TMP-SMX (Mean age at death in months)	10 (62)	11	91

Modified from Cliffe et al. [54] and personal communication with M. Wong
ConA concanavalin A, *Igs* immunoglobulins, *IVIG* intravenous immunoglobulin, *PCP Pneumocystis jiroveci* pneumonitis, *PHA* phytohemagglutinin, *PM* post mortem, *TMP-SMX* cotrimoxazole

half of the babies with respiratory presentations. Several infants were identified because of a family history. Consanguinity was present in 8/11 Australian families with Lebanese background (*Roscioli, 2006* [218] *and personal communication with M. Wong*), in the large cohort identified in Jerusalem [96] and in some patients identified in Lebanon [87].

Hepatic VOD may be evident as hepatomegaly, ascites, jaundice and liver dysfunction and can be confirmed by the finding of an abnormal portal vein wave form or reversal of portal blood flow on ultrasonography, or by liver biopsy. Thrombocytopenia is usually present. Some patients have had liver enlargement and evidence of liver dysfunction without firm evidence of VOD, possibly because investigations were done early in the evolution of the hepatic VOD process.

Infections include *Pneumocystis jiroveci* pneumonitis (PCP), enteroviral infections, and mucocutaneous candidiasis (Table 9.7). Diarrhea and vomiting are very frequent findings, usually due to viral infection (Table 9.5).

Table 9.7 Infections reported in VODI

Pneumocystis jiroveci pneumonia
Mucocutaneous candidiasis
CMV hepatitis
Rotavirus infections
Enteroviral infections

Neurological abnormalities were found in 13 of 35 patients for which this information is available (Table 9.6). A 6 year old girl of consanguineous Lebanese parents presented at age 3 months with VOD and PCP and, after an apparent complete recovery, remained well for 6 years while receiving prophylactic cotrimoxazole and IVIG. At age 6 she developed a slowly evolving hemiparesis and improved on appropriate treatment after identification of toxoplasma on brain biopsy. She went on to have a matched sibling HSCT, but died of graft versus host disease, progressive VOD and hemophagocytic syndrome. Another boy of similar background and presentation developed quadriparesis probably due to a demyelinating process. No evidence of infection was found and progression was arrested with the use of high dose corticosteroids. This boy later developed a seizure disorder and was found to have an extensive cerebral leukoencephalitic process. This was also not progressive but was complicated by inappropriate secretion of antidiuretic hormone. He died at age 6 years (Fig. 9.13). Several patients have been reported to be microcephalic, to have developmental delay, cerebral palsy or porencephalic cysts. Evidence of cerebral

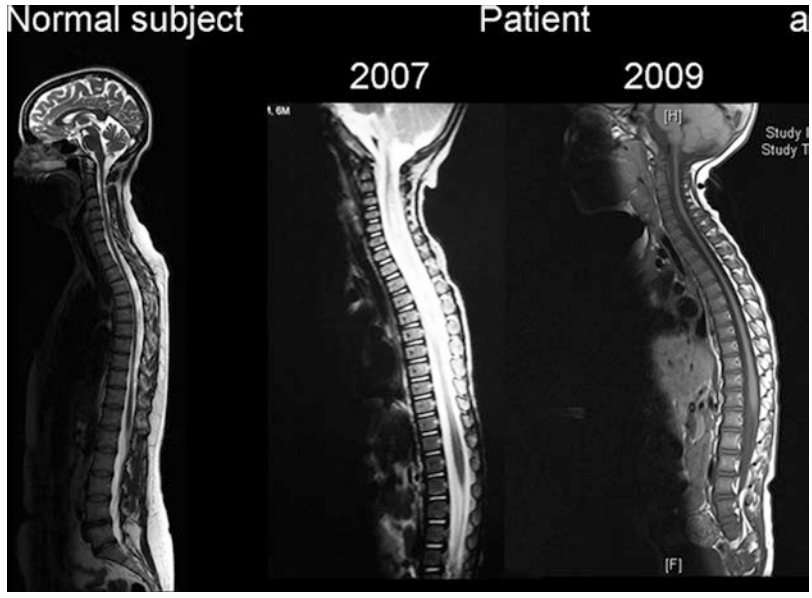

Fig. 9.13 MRI images obtained from a 2 year old boy who had an episode of spinal cord demyelination, and who represented with fitting in December, 2009. (**a**) Spinal views: the process improved over 2 years, apparently spontaneously, but functional improvement was limited; (**b**) Serial MRI images over on month showing evolution of the leukoencephalitic process

infarction was present in 4 of 7 children with neurological abnormalities.

9.19.4 Diagnosis

Diagnostic criteria for research purposes proposed by Roscioli et al. [218] were (1) hypogammaglobulinemia; (2) clinical evidence of T cell dysfunction such as *Pneumocystis jiroveci* infection or mucocutaneous candidiasis; (3) biopsy evidence of VOD not explained by iatrogenic factors in the affected individual or a first degree relative; (4) onset prior to the age of 12 months; and (5) a pattern of disease consistent with autosomal recessive inheritance. The validity of these criteria was later confirmed [53]. In practice, a diagnosis of hepatic VOD has not always been necessary when a baby presents with opportunistic infection and is found to have hypogammaglobulinemia, hepatomegaly and liver function abnormalities in a setting of a Lebanese background and consanguinity.

Thrombocytopenia is usually present at the time of diagnosis of VOD and improves as the VOD improves. Neutropenia or pancytopenia has sometimes been present. Hematological abnormalities improve if the child survives the presenting illness.

Lymphopenia is infrequently found and B cell and T cell numbers and lymphocyte subset analysis are usually normal. In the Australian series of 21 patients lymphopenia and marked reduction in T cell numbers (*personal communication with M. Wong*) were found in a single patient. Immunoglobulin levels are reduced (although one 4 month old patient had had earlier evidence of production of IgM and IgA). In the one patient studied in the newborn period hypogammaglobulinaemia was evident from birth [96]. T cell function as evidenced by proliferative responses to T cell mitogens such as phytohemagglutinin is usually normal. Memory T and B cell numbers are reduced. Intracytoplasmic production and/or secretion of interleukin (IL)-2, IL-4 and IL-10 is reduced. NK cell numbers are normal.

An infant with hepatomegaly will be expected to have hyperbilirubinemia and evidence of hepatocellular dysfunction including reduced serum albumin and coagulation abnormalities. Renal function is usually normal at presentation. Cerebrospinal fluid may show increased protein in the absence of other evidence of an infection process.

In the setting of VOD, abdominal ultrasound studies will show liver enlargement and ascites. Doppler studies may show reversal of portal blood flow. In an infant presenting with respiratory distress chest X-ray may show perihilar or diffuse interstitial changes of PCP. If neurological abnormalities are present, MRI of brain and spinal cord should be undertaken with contrast although it can be difficult to distinguish infection processes from non-infective leukoencephalitis.

Lung biopsy usually is not necessary, liver function testing and ultrasonography usually being adequate in the clinical context. Liver biopsy taken early after presentation is likely to show the features of sinusoidal obstruction syndrome with distinct areas of dilated sinusoids filled with red blood cell plugs, especially in centrilobular zones (Fig. 9.14). There may be extravasation of erythrocytes into the perisinusoidal space consistent with sinusoidal wall rupture [222]. If the presenting VOD does not improve early, fibrosis may be evident in centrilobular areas and later more extensively. When children have died within weeks of presentation in early infancy, changes of VOD have invariably been found at autopsy. Lung biopsy is unlikely to be required for a diagnosis of *Pneumocystis jiroveci* infection which can usually be made with broncho-alveolar lavage.

9.19.5 Management

In the absence of an animal model of SP110 deficiency exploration of pharmacological strategies to correct the cellular defect in VODI has not been possible and there is no known strategy to correct the effects of lack of SP110 function. Gene therapy has not been attempted. The Sydney experience suggests that early control of PCP of other infections and the commencement of IVIG will see early resolution of VOD in most infants. Matched sibling bone marrow transplantation has been undertaken in 2 Sydney patients, one in early

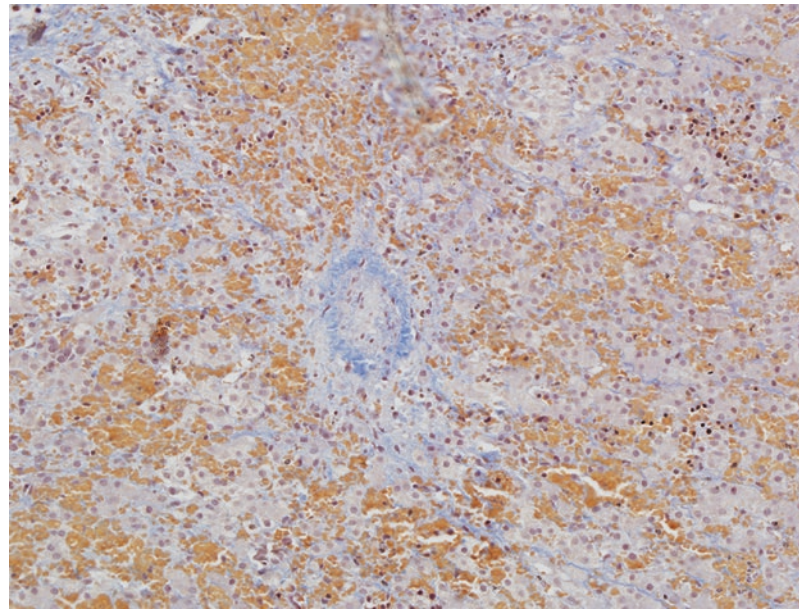

Fig. 9.14 Liver biopsy showing central vein occlusion, peri-venular fibrosis, zone 3 fibrosis and hepatocyte dropout from a girl who presented at age five months with hepatomegaly and ascites (Picro-trichrome stain, 100×)

infancy and one at age 6 years, with fatal outcomes. The risk of recurrence of hepatic VOD in the post transplant period is not surprising given the fact in other HSCT settings there is a very significant risk of VOD. Five members of a large Arabic family underwent HSCT from a matched sibling or family donor between age 2 and 15 months [96]. Two died within 6 weeks, but three survivors with stable mixed chimerism were 11–140 months post-transplant at the time of reporting. The two deaths were associated with recurrence of severe VOD. Both these patients received two alkylating agents, busulphan and thiotepa, as part of their conditioning regimen.

Immediately on a diagnosis of VODI all children should receive IVIG and cotrimoxazole prophylaxis and trough IgG levels should be maintained over 6 g/L. Patients who manifest recurrent mucocutaneous candidiasis should receive antifungal prophylaxis such as itraconazole.

Most children who have received IVIG early after diagnosis have recovered from their presenting illness although some have gone on to develop chronic liver failure. IVIG and prophylaxis for PCP appear to reduce the risk of infection but do not prevent neurological sequelae or other opportunistic infections. Of 7 patients who have had HSCT 3 have survived for at least 11 months post HSCT although one has ongoing seizures and severe attention deficit hyperactivity disorder 12 years post HSCT [96]. Seven of the 40 known patients are alive from 1 to 20 years after diagnosis, 3 after HSCT in early infancy [96]. Only 3 of 27 patients of Lebanese background have survived, 2 females have survived to their third decade, albeit with neurological sequelae (*personal communication with M. Lin*, Cliffe, 2012 [53]); the only surviving members of the large Arabic family with the c.373del exon 4 mutation have had successful HSCT. The two Italian patients with frameshift mutations and the Hispanic patient with a missense mutation are the only other long term survivors, suggesting that the patients with single base pair deletions (all Lebanese or other Arabic patients to date) may have a worse prognosis.

9.20 POLE Deficiency

(***POLE1 deficiency***, ***POLE2 deficiency***)

9.20.1 Definition

In 2012 a group of French investigators reported 11 members of a large consanguineous family

who exhibited mild Facial dysmorphism, Immunodeficiency, Livedo, and Short stature "FILS syndrome" (OMIM*615139) [201]. This phenotype was associated with homozygous genomic mutation in the DNA polymerase ε 1 (*POLE1*; OMIM*174762) [132].

POLE2 deficiency has very recently been described due to mutation in *POLE2* gene (OMIM*602670) in the child of related Saudi parents and is associated with a more severe block in B-cell development than POLE1 [95].

9.20.2 Etiology

Genome-wide homozygosity mapping in the 14 patients in the affected French FILS pedigree followed by sequencing of candidate genes with functions related to cell division or cell growth revealed a homozygous nucleotide substitution at position 3 in intron 34 (g. G4444 + 3 A > G) in the *POLE1* gene. Exome sequencing in one of the patients confirmed the mutation and demonstrated no other mutations in the homozygosity region. All (asymptomatic) parents tested were heterozygous for the mutation which was absent from control populations and databases. POLE1 from homozygous affected subjects was found to be predominantly in a form lacking exon 34. Wild type POLE1 transcripts from T lymphoblasts of patients were about 90 % reduced compared to healthy subjects. T lymphocytes from patients have impaired proliferation in response to anti-CD3 and IL-2 stimulation. T lymphoblasts and B lymphocytes from a lymphoblastoid cell line were predominantly in G1-phase with reduced numbers in S-phase. Similar findings were made in chondrocyte and osteoblast cell lines. When wild type POLE1 expression was restored using lentiviral transduction the cycle abnormalities were corrected. POLE1 expression is high in B cells, osteoblasts and chondrocytes correlating with the clinical phenotype.

The function POLE2 is not known, but is thought to involve protein-protein interactions, including dimerization with POLE1 [95].

9.20.3 Clinical Manifestations

The key clinical and immunological features of the patients, reported by Pachlopnik Schmid et al. [201], are summarized in Table 9.8. The patients had mild facial dysmorphism with malar hypoplasia and a high forehead. Livedo on the cheeks and limbs was almost always present and often noticed from birth. Telangiectasia was observed to develop over time. Patients were born at term with a normal gestational weight and length. Growth impairment was observed during early childhood resulting in varying degrees of short stature at skeletal maturity. Head circumference was usually normal. Bone dysplasia with limb pain was seen in 3 of 14 patients in whom lacunar bone lesions, cortical thickening, and modeling defects at the long bone diaphyses were found. One of these demonstrated metaphyseal striae.

A propensity to recurrent bacterial infection was evident from early infancy with recurrent upper and lower respiratory tract infections reported. Two patients had bronchiectasis and recurrent *S. pneumonia* meningitis was reported. There were two deaths reported in the cohort, one from pneumonia at age 2 [201]. The second report on POLE1 deficiency was a daughter of non-consanguinious Palestinian parents. The patient was suspected to have chromosome instability syndrome, while she manifested growth retardation, microcephaly, developmental delay, dysmorphic features, poikiloderma, and immunodeficiency associated with pancytopenia, and myelodysplasia [260].

As shown in Table 9.8, the salient immunological feature is defective production of antibodies to polysaccharide antigens. There is no known propensity to allergy, malignancy or opportunistic infection.

Clinical evolution of the patient with POLE2 deficiency was more severe than for patients with *POLE1* mutations [95].

9.20.4 Diagnosis

Diagnosis is based on the presence of the features shown in Table 9.8 and, in view of the rarity of the disorder should be confirmed by genotyping [201].

Table 9.8 Clinical and immunological features of FILS (POLE1 deficiency)

Feature	Number with feature	Percent	Number evaluable
Short stature	12	92	13
Facial dysmorphism	12	92	13
Telangiectasia	Increasing frequency with age		
Livedo	12	92	13
Bone disease	3	21	14
Death in presumed affected individual	2	14	14
Male infertility	0	0	1
Reduced IgG	1	8	13
Reduced IgA	4	31	13
Reduced IgM	13	100	13
Reduced IgG antibody to PPS	8	100	8
Reduced isohemagglutinin titer	9	100	9
Reduced antibody response to polio vaccine	0	0	7
Lymphopenia	2	18	11
Reduced memory B cells ($CD27^+/CD19^+$)	9	100	9
Reduced switched memory B cells ($\delta^-CD27^+/CD19^+$)	9	100	9
Reduced T cell proliferative response to PHA	8	62	13
Reduced NK cells	1	9	11

Adapted from Pachlopnik Schmid et al. [201]
PHA Phytohamagglutinin, *PPS Pneumococcal polysaccharide*

9.20.5 Management

The immune function abnormalities in many of the patients reported are consistent with a diagnosis of specific antibody deficiency. FILS patients treated with IVIG therapy experience significant improvement in frequency of respiratory tract infections (*personal communication with G. de Saint Basile*). Bone marrow transplantation will usually not be indicated and would be unlikely to benefit the non-immunological components of the phenotype.

9.21 Defects of Vitamin B12 and Folate Metabolism

(***Transcobalamin 2 deficiency***, ***SLC46A1/PCFT deficiency***, ***MTHFD1 deficiency***)

9.21.1 Definition

There is a new entity of "defects of vitamin B12 and folate metabolism", consists of transcobalamin 2 deficiency, SLC46A1/PCFT deficiency, MTHFD1 deficiency.

Transcobalamin 2 deficiency (OMIM*275350) is an autosomal recessive disorder, caused by homozygous or compound heterozygous mutation of the *TCN2* gene encoding transcobalamin 2 (OMIM*613441) [114].

Hereditary folate malabsorption or SLC46A1/PCFT deficiency (OMIM*229050) is an autosomal recessive disorder, caused by homozygous or compound heterozygous mutation in the *SLC46A1* (*PCFT*) gene (OMIM*611672) [212].

Heterozygous mutations in the trifunctional protein expressed by *MTHFD1* (OMIM*172460) has been recently reported to cause MTHFD1 deficiency (OMIM*601634) with phenotype of combined immunodeficiency.

9.21.2 Etiology

Few metabolic diseases are known to cause immunodeficiencies. These include adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) deficiency which may result in variable degrees of combined immunodeficiencies, transcobalamin 2 deficiency which result in neutropenia [137], functional methionine synthase Deficiency causing lymphopenia [304] and a SCID phenotype resulting from deficiency in the protoncoupled folate transporter [31] Heterozygous mutations in the trifunctional protein expressed by MTHFD1 has been recently reported to cause a SCID phenotype.

9.21.3 Clinical Manifestations

Transcobalamin 2 deficiency is characterized by early onset megaloblastic anemia, pancytopenia, and failure to thrive. Methylmalonic aciduria, recurrent infections, vomiting, and diarrhea could also be seen [114].

SLC46A1 or PCFT deficiency is characterized by signs and symptoms of folate deficiency. Patients with SLC46A1 deficiency suffer from megaloblastic anemia, diarrhea, infections, and neurologic deficits [212].

The patient with MTHFD1 deficiency presented early in life with *Escherichia coli* urinary tract infection and later on developed *Pneumocystis jiroveci* pneumonia. Other associated features were megaloblastic anemia, hemolytic-uremic syndrome, sensorineural deafness and convulsions.

9.21.4 Diagnosis

The patient with MTHFD1 deficiency showed severe panlymphopenia with poor T lymphocyte proliferation and hypogammaglobulinemia [139, 283]; serum vitamin B12 and folate levels were normal and the biochemical profile was significant for elevated homocysteine and slightly low methionine. Methylcobalamin production by patient fibroblasts was decreased compared with control cells.

9.21.5 Management

Treatment with cobalamin supplementation results in clinical improvement; however, mental retardation and neurologic abnormalities could be expected in untreated patients [114]. In SLC46A1 deficiency, treatment with folate supplementation is recommended. The patient with MTHFD1 deficiency was treated with intravenous immunoglobulins and trimethoprim/sulfamethoxazole. She showed partial immune-reconstitution characterized by improvement in the absolute lymphocyte count, serum immunoglobulins and T-lymphocyte proliferation after initiation of folate and hydroxocobalamin therapy.

9.22 Hennekam-Lymphangiectasia-Lymphedema Syndrome

9.22.1 Definition

Hennekam-lymphangiectasia-lymphedema syndrome 1 (HKLLS1) is an autosomal recessive disorder (OMIM*235510), characterized by lymphangiectasia and lymphedema with facial abnormalities and dysmorphic features [6].

9.22.2 Etiology

HKLLS1 is caused by homozygous or compound heterozygous mutation in the *CCBE1* gene (OMIM*612753) [6].

9.22.3 Clinical Manifestations

Lymphangiectasias, lymphedema, and facial dysmorphism are common features of Hennekam-lymphangiectasia-lymphedema syndrome. The dysmorphic features include a flat nasal bridge, hypertelorism, and small mouth. Other characteristics of the syndrome include mental retardation and cognitive impairment [94]. Decreased immunoglobulin lever has been reported in this syndrome, while T- and B- cell numbers could be low.

9.22.4 Diagnosis

The diagnosis suspicious should be made according to the clinical characteristics of the syndrome. Presence of both lymphangiectasias, especially in the gut, and lymphedema could help in differentiation of Hennekam-lymphangiectasia-lymphedema syndrome from other primary lymphatic dysplasias and isolated intestinal lymphangiectasia [22, 94].

9.22.5 Management

Treatment of the syndrome is focused on control of complications; meanwhile dietary habits and possible drug therapy for various symptoms could be recommended.

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Syndromic Immunodeficiencies 10

Jeffrey E. Ming and E. Richard Stiehm

10.1 Introduction

In most primary immunodeficiencies, frequent infections and complications arising from defective immune function are the predominant clinical manifestations. Most individuals will have no phenotypic abnormalities except for those related to the immunodeficiency. In contrast, in syndromic immunodeficiencies, abnormalities in other organ systems in addition to the immune defects are significant manifestations. Many of these conditions are recognizable genetic syndromes [152].

In syndromic immunodeficiencies, the immunodeficiency may not present as the major clinical problem, and the immune abnormality may be characterized only after the underlying syndrome has been diagnosed. In addition, in some of these conditions, the immune defect may be present in only a subset of the patients. A number of genetic disorders, such as Wiskott-Aldrich syndrome and ataxia-telangiectasia, have been categorized as primary immunodeficiencies [3], but may also be considered as syndromic immunodeficiencies since such conditions have both characteristic organ dysfunction and/or dysmorphology unrelated to the immune system as well as a consistent, well-defined immunodeficiency (Table 10.1).

Syndromic immunodeficiencies may arise from several diverse processes, including single-gene mutations, defective embryogenesis, metabolic derangements, chromosomal abnormalities, or teratogenic disorders. Recognition of the extra-immune and immune defects will facilitate accurate diagnosis of the underlying syndrome as well as clinical management. In this chapter, we delineate syndromic immunodeficiencies that are associated with recognizable genetic syndromes. We will provide an overview of the clinical manifestations and genetic aspects of each syndrome and delineate the specific associated immune defects. While the primary immunodeficiencies will be briefly discussed, the focus of this report

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Table 10.1 Syndromic primary immunodeficiency diseases

Name	Gene	Extra-immune features
1. ADA deficiency	*ADA*	Costochondral junction cupping/flaring
2. Omenn syndrome	*RAG1/RAG2/ARTEMIS*	Erythematous dermatitis, hemophagocytosis
3. DNA ligase IV deficiency	*LIG4*	Growth failure, developmental delay
4. NHEJ1 deficiency	*NHEJ1*	Microcephaly, growth failure
5. PNP deficiency	*PNP*	Neurologic findings, hemolytic anemia
6. WHN deficiency	*WHN*	Congenital alopecia, nail dystrophy
7. Wiskott-Aldrich syndrome	*WASP*	Severe eczematous dermatitis, thrombocytopenia, bloody diarrhea
8. Ataxia-telangiectasia	*ATM*	Progressive cerebellar ataxia, telangiectasias
9. Ataxia-like syndrome	*MRE11*	Ataxia, chromosomal radiosensitivity
10. Nijmegen breakage syndrome	*NBS1*	Microcephaly, mental retardation, prenatal onset short stature, bird-like facies
11. Bloom syndomre	*RECQL3*	Short stature, sensitivity to sunlight
12. DiGeorge syndrome	*Chr 22q11/10p*	Aortic arch anomalies, hypocalcemia, thymic hypoplasia, cleft palate
13. Chediak-Higashi syndrome	*LYST*	Partial albinism, giant cytoplasmic granules in leukocytes
14. Griscelli syndrome type 2	*RAB27A*	Partial albinism, lymphohistiocytosis, episodic thrombocytopenia
15. Leukocyte adhesion deficiency type 2	*FUCT1*	Severe mental retardation, seizures, growth failure, congenital disorder of glycosylation
16. Papillon-Lefèvre syndrome	*CTSC*	Palmar/plantar hyperkeratosis; precocious periodontal disease, furunculosis, pyoderma
17. Shwachman-Diamond syndrome	*SBDS*	Metaphyseal dysplasia, exocrine pancreatic insufficiency
18. Anhidrotic ectodermal dysplasia with immunodeficiency (X-linked)	*NEMO*	Alopecia, hypo/anhydrosis, tooth anomalies
19. Anhidrotic ectodermal dysplasia with	*NFKBIA*	Alopecia, hypo/anhydrosis, tooth anomalies immunodeficiency (autosomal)
20. WHIM syndrome	*CXCR4*	Warts, hypogammaglobulinemia, infection, myelokathexis
21. Cartilage-hair hypoplasia	*RMRP*	Metaphyseal dysplasia, mild leg bowing, fine/sparse hair; severe varicella infection
22. Schimke immunoosseous dysplasia	*SMARCAL1*	Spondyloepiphyseal dysplasia, progressive nephropathy, pigmentary skin changes
23. p14 deficiency	*MAPBPIP*	Hypopigmented skin, short stature, coarse facial features
24. ICF syndrome	*DNMT3B*	Immunodeficiency, centromere instability, facial abnormalities
25. Netherton syndrome	*SPINK5*	Trichorrhexis invaginata (bamboo hair), dermatitis

will be on syndromic immunodeficiencies that are not classified as primary immunodeficiencies and for which there has been recent progress in characterization of the genetic, immune, or phenotypic features. Syndromic immunodeficiencies associated with growth deficiency (disproportionate or proportionate), gastrointestinal dysfunction, cutaneous abnormalities, neurologic dysfunction, inborn errors of metabolism, chromosome instability and/or defective DNA repair, and chromosomal abnormalities of number or structure will be discussed.

Thus, a number of genetic conditions feature immunodeficiency in conjunction with other organ system involvement. This co-occurrence could arise from several different underlying mechanisms. First, the mutated gene could be directly involved in the function, regulation, or development of both the immune and non-immune systems, resulting in abnormalities of both organ systems. Second, a contiguous gene deletion could affect different genes that are located close to each other on the same chromosome. In this case, one gene critical in the function of the immune system and a second gene important for the function of the other organ system would both be altered. Third, insults during a critical window in embryological development could affect more than one organ system if both were developing at that time. Fourth, abnormalities in bone or thymic development could affect development of immune cells by providing an inhospitable environment. Last, exposure to toxic metabolites could disrupt the immune response and activity.

Recognition of an underlying syndrome is critical for optimal clinical care so that both the immune system and the other involved organ systems can be properly treated or even diagnosed before clinical symptoms arise. For a child with a recognizable genetic syndrome that is associated with immunodeficiency, it is important to establish if the immune defect is present so appropriate treatment can be undertaken. Monitoring for laboratory or clinical evidence of immunodeficiency would also be beneficial even if the patient does not currently show symptoms of the immunodeficiency since it could develop later. Alternatively, for a child with an immune defect and other anomalies, it is vital to determine if the other malformations fit into a recognizable pattern. This will aid in giving accurate prognosis for the immunodeficiency and other involved organ systems, including cognitive development. In addition, ascertainment of the underlying diagnosis may have implications for the medical care and genetic counseling for other family members.

There are additional conditions that feature both immunodeficiency and other organ system involvement that are not presented in this chapter. We have chosen to focus on those conditions which are relatively more common and in which both the immune defect and the extra-immune manifestations are present in a substantial proportion of patients. The inheritance pattern of each condition and the chromosomal location of the disease-related genes, when known, are indicated in the tables. Online Mendelian Inheritance in Man (OMIM) [171] numbers are indicated within parentheses in the text.

10.2 Syndromes Associated with Growth Deficiency

Several immunodeficiency states are associated with growth deficiency (Table 10.2). The growth deficiency may be due to a skeletal dysplasia, in which there is an abnormality of bone formation. Many skeletal dysplasias are associated with disproportionate short stature (the limbs and trunk are not proportional to each other). Forms of short stature that are not associated with skeletal abnormalities usually show proportionate growth failure. In this case, the overall height is small, but the various body parts are commensurate with one another. Short-limb skeletal dysplasia is a form of disproportionate short stature that affects the limbs more than the trunk.

Primary Immunodeficiencies Associated with Disproportionate Short Stature

Table 10.2 Syndromic immunodeficiencies associated with growth deficiency

Name	Inheritance (Chromosome)	Associated features	Immune defect	Frequency of ID
Disproportionate short stature				
1. Cartilage-hair hypoplasia	AR (9p13)	McKusick type metaphyseal dysplasia, mild leg bowing, fine/sparse hair; varicella and other infections, increased risk for lymphoma/basal cell carcinoma	T, B	++++
2. Schimke immunoosseous dysplasia	AR 2q34-q36	Spondyloepiphyseal dysplasia, progressive nephropathy, episodic lymphopenia, pigmentary skin changes	T	++++
3. Short-limb skeletal dysplasia with immunodeficiency	AR	Short-limb skeletal dysplasia, metaphyseal dysplasia, may be associated with adenosine deaminase deficiency or Omenn syndrome; heterogeneous	T, B	++++
4. Roifman syndrome	?XL	Spondyloepiphyseal dysplasia, retinal dystrophy	B	++++
5. SPENCD1 syndrome	AR (19p13)	Radiolucencies in vertebral bodies and long bone metaphyses	T	++++
Proportionate short stature				
6. Growth hormone pathway defects (including STAT5b)	Various	Defects in growth hormone synthesis or sensitivity deficiency; sinopulmonary infections	B, T, NK	+
7. Kabuki syndrome	?AD	Long palpebral fissures, prominent eyelashes, skeletal anomalies, congenital heart disease; increased risk of autoimmune diseases	B	+++
8. CHARGE association	?	Coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness	T	+
9. Rubinstein-Taybi syndrome	AD (16p13)	Broad thumbs and halluces, prominent nasal septum below ala nasi, cryptorchidism, mental retardation	T	+
10. Mulvihill-Smith syndrome	?AD	Prenatal growth deficiency, microcephaly, small face, premature aging, multiple nevi, mental retardation	T, B	++++
11. Cornelia de Lange syndrome	AD (various)	Growth and psychomotor retardation, synophrys, limb anomalies, congenital heart disease	T, B	+++
12. Smith-Magenis syndrome	AD (17p11.2)	Growth and psychomotor retardation, sleep disturbances, characteristic facial appearance	B	++
13. Bernard syndrome	AR (8q11)	Growth failure, microcephaly, glucocorticoid deficiency	NK	++++ (1 kindred)

ID Immunodeficiency, *T* T cell defect, *B* B cell defect, *Ph* Phagocyte defect, *NK* NK cell defect. Frequency of ID: += less than 5 % of reported cases with documented ID; ++= 5–30 %; +++= 30–65 %; ++++ = >65 %. *AR* Autosomal recessive, *AD* Autosomal dominant, *XL* X-linked

10.2.1 Cartilage-Hair Hypoplasia

Cartilage-Hair Hypoplasia (CHH, OMIM#250250), a recognized primary immunodeficiency, is characterized by short-limb dwarfism, fine sparse hair, and a cellular immune defect. Varicella infections can be severe. Metaphyseal dysplasia (flared, scalloped, and sclerotic metaphyseal ends) most frequently affects the lower extremities. There is significant variability in the phenotype, and some individuals have normal hair and some may have normal immune function. The condition is caused by mutations in the *RMRP* gene, which encodes a mitochondrial RNA-processing endoribonuclease [186]. Please see Sect. 2.11 for more details.

10.2.2 Schimke Immunoosseous Dysplasia

This condition (OMIM#242900) is associated with short stature with exaggerated lumbar lordosis, spondyloepiphyseal dysplasia, defective cellular immunity, and progressive renal failure [16, 194]. Patients develop proteinuria and may progress to end-stage renal disease, and an arteriopathy with cerebral infarcts and/or ischemia may be seen. Mutations in the gene encoding the chromatin remodeling protein SMARCAL1 have been detected in affected patients [17]. Patients are prone to viral and bacterial infections and demonstrate decreases in CD4 T cell number, mitogen-induced proliferation, and delayed cutaneous hypersensitivity responses, and immunoglobulin levels are often abnormal [16]. Please see Sect. 2.11 for more details.

Other Immunodeficiencies Associated with Disproportionate Short Stature

10.2.3 Short-Limb Skeletal Dysplasia with Combined Immunodeficiency

The conditions (OMIM#200900) in which short-limb skeletal dysplasia is associated with combined immunodeficiency are etiologically heterogeneous [221]. While some of these patients have adenosine deaminase deficiency, other patients have more severe metaphyseal changes than are typically found in adenosine deaminase deficiency. Short-limb skeletal dysplasia may also be seen in association with Omenn syndrome, a fatal disorder characterized by eosinophilia, skin eruptions, and reticuloendotheliosis. Please see Sect. 2.4 for more details on Omenn syndrome. Both adenosine deaminase deficiency and Omenn syndrome are classified as primary immunodeficiencies.

10.2.4 Roifman Syndrome

This condition (OMIM#300258) is characterized by microcephaly, growth retardation, spondyloepiphyseal dysplasia, developmental delay, and retinal dystrophy [46, 190]. They had low/absent antibody titers in response to infection, decreased isohemagglutinins, and decreased mitogenic response to *Staphylococcus aureus* Cowan A. T cell number and function were normal. There was epiphyseal dysplasia of the hips and long bones and vertebral anomalies. Because all reported patients have been male, X-linked recessive inheritance has been suggested.

10.2.5 SPENCDI Syndrome

Spondyloenchondrodysplasia (SPENCD, vertebral dysplasia with enchondroma-like lesions in the long bones) with immune dysregulation (SPENCDI) has been associated with autoimmune conditions, neurologic deficits, combined immunodeficiency (low specific antibody titers, T-cell mitogenic response, and CD4 T cell count), and recurrent infections (OMIM#607944) [183, 191]. This syndrome is due to mutations in the *ACP5* gene, encoding an acid phosphatase [20, 129].

Syndromic Immunodeficiencies Associated with Proportionate Short Stature

10.2.6 Growth Hormone Pathway Defects (Including STAT5b)

Patients with defects in the growth hormone pathway as well as immunodeficiency have been described. In patients with growth hormone deficiency (GHD) with X-linked agammaglobulinemia (XLA) (OMIM#307200), individuals have recurrent sinopulmonary infections, short stature, and decreased growth hormone levels without other endocrinologic abnormalities [68]. Both B cell number and immunoglobulin levels are greatly decreased or absent, consistent with XLA. T cell number and function are normal. Mutations in the gene *BTK*, the gene associated with isolated XLA, have been detected in some but not all patients with GHD and XLA [1, 57, 207]. Please see Sect. 3.2 for more details.

Additional immune defects reported in association with isolated GHD include combined immunodeficiency [139, 213], decreased NK activity [111], and hypogammaglobulinemia [166]. However, the vast majority of children with GHD do not display an increased susceptibility to infection [31, 206].

Some patients with growth hormone insensitivity were found to have a mutation in the *STAT5B* gene, which is involved in both the growth hormone and IL-2 signaling pathways. Immune defects have included decreased regulatory T cells, T cell lymphopenia, low NK and γδT cells, and decreased proliferation to mitogen [11, 118]. These patients may have recurrent skin and respiratory infections, and T cell lymphopenia, decreased regulatory T cells, low NK and CD4 T cell numbers, and decreased proliferation to mitogens have been noted [11, 118].

10.2.7 Kabuki Syndrome

This syndrome (OMIM#147920) features short stature, congenital heart disease, developmental delay, skeletal anomalies, and cleft palate [163]. The distinctive facial features include long palpebral fissures with eversion of the lower lateral eyelid, prominent eyelashes, and abnormal ears. Frequent infections occur in approximately 60% of patients [30]. Hypogammaglobulinemia, including decreased IgG and very low IgA, is a common manifestation [95]. Autoimmune conditions, including autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and hypothyroidism, have also been reported [108, 151] and may reflect the underlying immune dysfunction. Most patients have a mutation in *MLL2* [88, 162], and a few patients have a *KDM6A* mutation [130, 153]. Both genes encode proteins involved in histone modification.

10.2.8 CHARGE Association

The abnormalities that comprise the CHARGE association (OMIM#214800) include coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital hypoplasia, and ear anomalies and/or deafness [172, 214]. Some patients with CHARGE syndrome have mutations in *CHD7*, which encodes the chromodomain helicase DNA-binding protein-7 [104, 230] or in *SEMA3E*, encoding sempahorin-3E [126] Some patients with CHARGE association also have DiGeorge sequence. T cell defects can range from severe to mild, and isolated low Ig levels have also been reported [239].

10.2.9 Rubinstein-Taybi Syndrome

Rubinstein-Taybi syndrome (OMIM#180849) is characterized by broad thumbs and great toes, characteristic facial features, short stature, mental retardation, and cardiac abnormalities. There is an increased susceptibility to infection. Decreased T cell number, impaired delayed cutaneous hypersensitivity response [187], lymphopenia, thymic hypoplasia [112], poor response to pneumococcal vaccine [227], and a deficit in polysaccharide antibody response [160] have been reported. Microdeletions and truncating mutations in the gene encoding CREB-binding protein (*CBP*), a histone acetyltransferase, are associated [176, 196]. Mutations in the gene *EP300*, which also encodes a transcriptional coactivator, have also been detected [189].

10.2.10 Mulvihill-Smith Syndrome

This disorder (OMIM#176690) is characterized by pre- and postnatal growth retardation, multiple pigmented nevi, microcephaly, reduced facial fat, genitourinary anomalies, and a high-pitched voice [45, 157]. Infectious complications are common, and the immunodeficiency is often progressive. Impaired T cell response to mitogen, decreased CD4 count, and/or low Ig levels have been described [9, 45, 66, 165].

10.2.11 Cornelia de Lange Syndrome

This autosomal dominant condition (OMIM#122470) is characterized by pre- and post-natal growth failure, mental retardation, upper limb defects, congenital heart disease, and characteristic facial features (including synophrys, long eyelashes, ptosis). Chronic respiratory infections, pneumonia, and sinusitis commonly occur, and infections and sepsis may account for 13 % of deaths [197]. Hypogammaglobulinemia was detected in 9 of 27 patients, and there was a significantly decreased percentage of regulatory T cells and T follicular helper cells [106]. Five different genes have been reported in association with Cornelia de Lange syndrome, with mutations in the gene encoding NIPBL being the most common [47, 122, 216]. All of the identified genes (*NIPBL*, *SMC1A*, *SMC3*, *RAD21*, *HDAC8*) play a role in the cohesin complex, which is important for chromosome segregation in mitosis. In immune cells, cohesin may also play a role in transcriptional regulation and V(D)J recombination [198].

10.2.12 Smith-Magenis Syndrome

This autosomal dominant condition (OMIM#182290) is associated with mental retardation, sleep abnormalities, and cardiac and renal abnormalities, and a characteristic facial appearance (including midface hypoplasia, prognathism). Low serum immunoglobulin levels have been reported in 23 % [82], and chronic ear infections are reported in the majority of patients [13]. Approximately 90 % of patients have an interstitial deletion in chromosome region 17p11.2, and a few patients have mutations in the *RAI1* gene (retinoic acid–inducible 1), which lies within the associated 17p11.2 region [13, 200]. The gene encoding TACI (transmembrane activator and CAML interactor) is in the commonly deleted region, and TACI is important for B cell differentiation and maturation. Patients with Smith-Magenis syndrome with a *TACI* deletion had reduced TACI expression, and patients with the lowest TACI expression had significantly decreased antibody response to pneumococcal vaccine [29]. Thus, it is likely that deletion of one copy of *TACI* contributes to the humoral immunity abnormalities. Of note, mutations in *TACI* have also been found in 8–10 % of patients with common variable immunodeficiency (CVID) [25, 192].

10.2.13 Bernard Syndrome

This condition is associated with pre- and postnatal growth failure, microcephaly, glucocorticoid deficiency, and hypoglycemia (OMIM#609981) [10]. DNA repair defects have also been noted [24]. Patients have less than 5 % of normal NK cell number and have recurrent respiratory infections. Mutations in *MCM4*, encoding a protein involved in DNA replication, were reported [77, 99].

10.3 Syndromes Associated with Gastrointestinal Dysfunction

Gastrointestinal abnormalities may lead to malnutrition and secondarily result in an immunodeficient state. However, in the syndromes described herein, the immunodeficiency precedes nutritional deprivation and thus is likely to be intrinsic to each condition (Table 10.3).

Primary Immunodeficiencies Associated with Gastrointestinal Dysfunction

Table 10.3 Syndromic immunodeficiencies associated with specific organ dysfunction

Name	Inheritance (Chromosome)	Associated features	Immune defect	Frequency of ID
Gastrointestinal				
1. Shwachman-Diamond syndrome	AR (7q11)	Metaphyseal dysplasia, exocrine pancreatic insufficiency, cyclic neutropenia; hematologic malignancy	B, Ph	++++
2. Familial intestinal polyatresia	AR (2p21)	Multiple atresias from pylorus to rectum	T, B	++
3. Trichohepatoenteric syndrome	AR (5q15, 6p21)	Severe infantile diarrhea, hepatic cirrhosis, Trichorrhexis nodosa, characteristic facies	B, Ph	++++
Dermatologic – primary immunodeficiencies				
1. Wiskott-Aldrich syndrome	XL (Xp11)	Severe eczematous dermatitis, thrombocytopenia, bloody diarrhea, recurrent infection; lymphoreticular malignancy; autoimmune disease	T, B	++++
2. Chediak-Higashi syndrome	AR (1q42)	Partial abinism, leukopenia, neuropathy, giant cytoplasmic granules in leukocytes; bacterial infections (especially *Staphylococcus*, *Streptococcus*)	Ph, NK	++++
3. Griscelli syndrome, type 2	AR (15q21)	Partial albinism, frequent pyogenic infections, lympho-histiocytosis, episodic thrombocytopenia	T, B, NK, Ph	++++
4. Hermansky Pudlak syndrome, type 2	AR (5q14)	Oculocutaneous albinism, platelet defects, congenital neutropenia	T, NK, Ph	++++
5. p14 deficiency	AR (1q22)	Hypopigmented skin, short stature, coarse facies	T, B, Ph	++++
6. Vici syndrome	AR (18q)	Agenesis corpus callosum, cataracts, seizures, cutaneous hypopigmentation, cleft lip/palate, cerebellar hypoplasia	T, B, Ph	++++
7. Omenn syndrome	AR (11p13)	Erythematous dermatitis, eosinophilia, lymphadenopathy, hemophagocytosis; severe combined immune deficiency	T, B	++++
8. WHN deficiency	AR (17q11-q12)	Congenital alopecia, nail dystrophy	T	++++ (2 sibs)
9. Papillon-Lefèvre syndrome	AR (11q14)	Palmar/plantar hyperkeratosis; precocious periodontal disease, furunculosis, pyoderma	Ph	+
10. WHIM syndrome	AD	Warts, hypogammaglobulinemia, infection, myelokathexis	T, B, Ph	++++
11. Hypohidrotic/anhidrotic ectodermal dysplasia	XL, AD (Xq28, 14q13)	Alopecia, hypo/anhidrosis, tooth anomalies; with immunodeficiency, hypogammaglobulinemia	T, B	++++
12. Poikiloderma with neutropenia	AR (16q21)	Poikiloderma, progressive erythematous rash, telangiectasias	Ph	++++

Table 10.3 (continued)

Name	Inheritance (Chromosome)	Associated features	Immune defect	Frequency of ID
13. Dyskeratosis congenita	XL, AR, AD (Xq28)	Atrophy and pigmentation of skin, nail dystrophy, leukoplakia of oral mucosa; risk of cancer of the mouth, anus, skin	T, B, Ph	++
14. Netherton syndrome	AR (5q32)	Trichorrhexis invaginata (bamboo hair), ichthyosiform dermatitis, atopic diathesis; skin infections	T, B, Ph	++
Dermatologic – other syndromic immunodeficiencies				
15. Incontinentia pigmenti	XL (Xq28)	Erythematous vesiculobullous eruptions, CNS involvement, swirling macules of hyperpigmentation	T, B, Ph	+
16. OLEDAID syndrome	XL (Xq28)	Anhidrotic ectodermal dysplasia, osteopetrosis, lymphedema	B	++++ (2 cases)
17. Acrodermatitis enteropathica	AR (8q24)	Vesiculobullous dermatitis, alopecia, diarrhea; due to zinc deficiency, may be associated with opportunistic infections	T, B, Ph	++
18. Keratitis-Ichthyosis-Deafness (KID) syndrome	AD (13q12)	Hypervascular keratitis, ichthyosis, sensorineural hearing loss, corneal defects	T, B, Ph	++
19. PLAID and APLAID syndromes		Cutaneous abnormalities; other organ involvment and autoimmunity in APLAID	B, NK	++++
20. Epidermodysplasia verruciformis	AR (various), AD, XL	Warts, increased skin cancer risk, papillomavirus infection	T	++++
Neurologic				
1. Høyeraal-Hreidarsson syndrome	XL, AR (Xq28, 20q13)	Cerebellar hypoplasia, absent corpus callosum, microcephaly, growth failure, pancytopenia; fungal sepsis	T, B, Ph	++++
2. Cohen syndrome	AR (8q22-q23)	Prominent central incisors, hypotonia, obesity; gingivitis, periodontitis, skin infections	Ph	++
3. Myotonic dystrophy	AD (19q13, 3q)	Myotonia, muscle wasting, cataract, hypogonadism, cardiac arrhythmia; due to triplet repeat expansion	B	++

ID immunodeficiency, *T* T cell defect, *B* B cell defect, *Ph* Phagocyte defect, *NK* NK cell defect. Frequency of ID: + = less than 5 % of reported cases with documented ID; ++ = 5–30 %; +++ = 30–65 %; ++++ = >65 %. *AR* autosomal recessive, *AD* autosomal dominant, *XL* X-linked

10.3.1 Shwachman-Diamond Syndrome

This autosomal recessive syndrome (OMIM#260400) presents with pancreatic insufficiency, neutropenia, and metaphyseal dysostosis resulting in short stature. Neutropenia (which may be intermittent or cyclic) occurs in 88 %, and leukopenia and/or pancytopenia may arise [138, 203]. The condition is caused by mutations in *SBDS*, which is involved in ribosomal function [19]. Please see Sect. 4.14 for more details.

Other Syndromic Immunodeficiencies Associated with Gastrointestinal Dysfunction

10.3.2 Familial Intestinal Polyatresia

Multiple atretic lesions are found throughout the gastrointestinal tract in this condition (OMIM#243150). Severe combined immunodeficiency and other immune defects (e.g., hypogammaglobulinemia, T cell lymphopenia, and marked lymphoid depletion in the thymus and peripheral lymphoid tissues) have been described in some affected patients [5, 35, 204], as well as in some cases of duodenal atresia [155]. Adenosine deaminase activity is normal. The recurrent infections were not due to the intestinal problems since they occurred while the patients still had good nutritional status. Mutations in the tetratricopeptide repeat (TPR) domain 7A gene *TTC7A* were detected in children with autosomal recessive multiple intestinal atresia [28, 193].

10.3.3 Trichohepatoenteric Syndrome

This condition (OMIM#222470) is characterized by severe infantile diarrhea, dysmorphic features (hypertelorism, prominent forehead, flat/broad nose), hepatic cirrhosis, and the hair abnormality of trichorrhexis nodosa. Immune defects may include poor response to vaccination with negative skin tests [78], pancytopenia [127], and hypogammaglobulinemia [63]. Severe infection, including sepsis, pneumonia, and CMV hepatitis, often occurs. Cardiac defects, developmental delay, and large platelets with thrombocytosis may be present [91]. Mutations in *TTC37*, which encodes an uncharacterized tetratricopeptide repeat protein, thespin, have been detected [220].

Another trichohepatoenteric syndome also associated with severe diarrhea in infancy, trichorrhexis nodosa of the hair, and immunodeficiency (low immunoglobulin levels and poor response to vaccines) is caused by mutations in *SKIV2L*, which encodes a cytoplasmic exosome cofactor [64].

10.4 Syndromes Associated with Cutaneous Abnormalities

While dermatitis or skin infection often occur in immune deficient patients, some immunodeficiency syndromes present with primarily cutaneous manifestations (Table 10.3). Some of these conditions present with alterations in pigmentation.

Primary Immunodeficiencies Associated with Cutaneous Abnormalities

10.4.1 Wiskott-Aldrich Syndrome

This well-defined X-linked primary immunodeficiency (OMIM#301000) is characterized by chronic eczema, thrombocytopenia (with small, defective platelets), and bloody diarrhea. Recurrent and life-threatening infections are a leading cause of death [210]. Abnormal humoral immune responses are typical. The disease phenotype is very variable. Mutations in the *WAS* gene, encoding WAS protein (WASP), have been detected [49]. A patient with features of Wiskott-Aldrich syndrome had mutations in *WIPF1*, which encodes WASP interacting protein (WIP) [128]. Please see Sect. 9.14 for more details.

10.4.2 Chediak-Higashi Syndrome

Chediak-Higashi syndrome (OMIM214500) presents with recurrent bacterial infections (especially with *S. aureus* and streptococci), partial oculocutaneous albinism, prolonged bleeding time, nystagmus, and neuropathy. Most patients eventually develop a distinctive lymphoproliferative disorder characterized by generalized lymphohistiocytic infiltrates, which are difficult to treat. The defective gene, *LYST*, encodes a regulator of lysosomal trafficking [159]. Please see Sect. 5.4 for more details.

10.4.3 Griscelli Syndrome, Type 2

This is an autosomal recessive syndrome of partial albinism, neutropenia and thrombocytopenia, and lymphohistiocytosis (OMIM#214450) [56, 84, 141]. Melanosomes accumulate in melanocytes, resulting in large clumps of pigment in hair shafts. Most patients suffer from recurrent and severe fungal, viral, and bacterial infections. T cell dysfunction, hypogammaglobulinemia, and neutropenia have been reported [56]. Mutations in the *RAB27A* gene, which encodes a GTP-binding protein of the Ras family, were detected in affected individuals [149]. A genetically distinct form of Griscelli syndrome that is not associated with immune deficits has also been described (type 1) [149, 175]. Please see Sect. 5.5 for more details.

10.4.4 Hermansky-Pudlak Syndrome, Type 2

This autosomal recessive condition (OMIM#608233) is characterized by platelet defects leading to a hemorrhagic diathesis and oculocutaneous albinism. Microcephaly, abnormal hair, nystagmus, and mild mental retardation may also occur [121]. Congenital neutropenia is a distinguishing feature of Type 2 compared to other forms of Hermansky-Pudlak syndrome. Recurrent bacterial infections often occur. Defective cytotoxic T cell activity [33], decreases in NK cell number and activity [69, 105], and lymphohistiocytosis have also been described [61]. Mutations in the gene encoding the beta-3A subunit of the AP3 complex (AP3B1) have been described [48]. Please see Sect. 5.6 for more details.

10.4.5 p14 Deficiency

A syndrome of hypopigmented skin, short stature, coarse facial features, and recurrent respiratory infections was described in four members of a kindred who had consistently low neutrophil counts (OMIM#610798) [18]. Decreased CD8 cytotoxic T cell activity and abnormal B cell differentiation were also present. Deficiency of the endosomal adaptor protein p14 (the *MAPBPIP* gene) was identified, and functional reconstitution of granule activity was achieved with p14 gene transfer [18]. Please see Sect. 5.7 for more details.

10.4.6 Vici Syndrome

This autosomal recessive syndrome features agenesis of the corpus callosum, bilateral cataracts, seizures, cleft lip/palate, cerebellar hypoplasia, and cutaneous hypopigmentation (OMIM#242840). Patients often suffer from recurrent respiratory and other infections and chronic mucocutaneous candidiasis. The immune deficiency is variable, and defects may include decreases in T cell number, response to mitogen, and delayed type hypersensitivity; hypogammaglobulinemia; or leukopenia [67]. The condition is due to mutations in the *EPG5* gene, which plays a role in regulation of autophagy [43]. Please see Sect. 5.7 for more details.

10.4.7 Omenn Syndrome

This autosomal recessive form of familial histiocytic reticulocytosis (OMIM#267700) presents

with an erythematous skin rash, eosinophilia, reticulosis, hepatosplenomegaly, protracted diarrhea, alopecia, and lymphadenopathy. A characteristic severe combined immunodeficiency leads to failure-to-thrive, recurrent infection, and premature death. Mutations in genes encoding either of three proteins that play a role in V(D)J recombination, RAG1, RAG2, or Artemis (DCLRE1C) cause Omenn syndrome with SCID [58, 226]. Additional genes are associated with familial hemophagocytic lymphohistiocytosis (*PRF1*, *UNC13D*, *STX11*, *STXBP2*) [143]. Please see Sect. 2.4 for more details.

10.4.8 WHN Deficiency

Siblings with congenital alopecia, nail dystrophy, and T cell dysfunction (OMIM#601705) [178] were found to have a mutation in the gene *WHN* (*FOXN1*), or winged-helix nude [70]. Mutations in the mouse ortholog cause the "nude" phenotype of abnormal hair growth and abnormal thymus development [161]. Please see Sect. 2.10 for more details.

10.4.9 Papillon-Lefèvre Syndrome

This is an autosomal recessive disorder associated with palmar-plantar hyperkeratosis and severe periodontal disease leading to loss of both primary and permanent teeth (OMIM#245000). Approximately 17 % of cases are associated with infections other than periodontal disease, most frequently furunculosis and pyoderma [222]. Neutrophil chemotaxis and random movement are both decreased. Mutations in the gene encoding cathepsin C (*CTSC*) have been demonstrated [89, 90]. Please see Sect. 4.11 for more details.

10.4.10 WHIM Syndrome

WHIM syndrome (OMIM#193670) is associated with multiple warts, hypogammaglobulinemia, infection, and myelokathexis (bone marrow retention of neutrophils) [80, 235]. Neutrophil count is reduced, B cell number and IgG and IgA levels are mildly decreased, and depressed T cell number and diminished response to mitogens and skin tests have been noted. Mutations in the gene encoding the chemokine receptor CXCR4 were detected [93]. Please see Sect. 6.8 for more details.

10.4.11 Hypohidrotic/Anhidrotic Ectodermal Dysplasia

A subset of patients with the form of ectodermal dysplasia associated with diminished or absent sweat glands, thin and sparse hair, and hypodontia also has immune defects (HED-ID, OMIM#300291). The subset with immune defects is genetically distinct from those forms without immune defects. The most common immune defect is hypogammaglobulinemia [53, 246]. The X-linked recessive form is due to mutations in the *NEMO* gene, which is involved in NF-κB regulation [53, 246]. Mutations in this gene have also been described in incontinenia pigmenti and OLEDAID syndrome (see below) An autosomal form of HED-ID with T cell defects and abnormal immunoglobulin levels has been described [148]. The condition is due to mutations in the *NFKBIA* gene, which encodes an inhibitor of NF-κB [38].

HED can also occur with X-linked hyper-IgM immune deficiency (XHM) that is genetically distinct from isolated XHM. Patients with ectodermal dysplasia (ED) and XHM have normal CD40L expression on T cells. Two patients with XHM-ED and decreased IgG levels had a mutation in the *NEMO* gene [100]. Please see Sect. 6.2 for more details.

10.4.12 Poikiloderma with Neutropenia

This disorder (OMIM#604173) is characterized by a progressive erythematous rash which begins in infancy and the development of telangiectasias [34]. Neutropenia and neutrophil dysfunction are variably present, and recurrent pneumonias often occur. The condition is caused by mutations in the *USB1* (*C16ORF57*) gene, encoding U6 snRNA biogenesis 1 [231].

10.4.13 Dyskeratosis Congenita

Dyskeratosis congenita (OMIM#305000) is an X-linked disorder marked by reticulate skin pigmentation, nail dystrophy, leukoplakia of the oral mucosa, aplastic anemia, and an increased risk of malignancy. Progressive bone marrow failure develops in most patients and is the major cause of early mortality. Neutropenia occurs in the majority of the patients, and both humoral and cellular immune responses may be defective [54, 205]. Thymic aplasia was reported in two patients [218]. The gene causing dyskeratosis congenita (*DKC1*) codes for a protein that is predicted to function in ribosome formation [92]. Mutations in this gene also cause Høyeraal-Hreidarsson syndrome (see below). Please see Sect. 9.17 for more details.

10.4.14 Netherton Syndrome

The triad of trichorrhexis (brittle "bamboo" hair), ichthyosiform erythroderma, and atopic diathesis make up the Netherton syndrome (OMIM#256500), an autosomal recessive disorder. Recurrent infections occur in 28 %, most commonly involving the skin [83, 209]. IgG abnormalities (both hypo- and hyper-IgG) are present in 12–14 %. Impairment of delayed cutaneous hypersensitivity response, mitogen response, and neutrophil phagocytosis can occur. Immunoglobulin supplementation can result in clinical improvement [184]. Mutations in the gene *SPINK5*, which encodes a serine protease inhibitor, have been detected in affected patients [27]. Please see Sect. 9.16 for more details.

Other Syndromic Immunodeficiencies Associated with Cutaneous Abnormalities

10.4.15 Incontinentia Pigmenti

Linear erythematous vesiculobullous lesions that evolve into hyperpigmented swirling macules on the trunk and proximal extremities are typical findings for this X-linked dominant neurocutaneous disorder with fetal lethality in most affected males (OMIM#308300). Other findings include mental retardation, seizures, alopecia, ocular abnormalities, nail dystrophy, and malformed teeth. In a review of 77 cases, 13 % had significant infection, and 4 died of infectious causes [50]. No consistent immunologic abnormality has been detected, but decreased neutrophil chemotaxis and impaired proliferative response to phytohemagglutinin have been described [101, 150]. Another girl had transient immunodeficiency that resolved, likely due to progressive selection against cells carrying an active mutated X chromosome [144]. Mutations in the gene encoding IKKγ, also termed *NEMO*, cause incontinentia pigmenti [201]. The protein is involved in the regulation of the transcriptional regulator nuclear factor-κB (NF-κB). Interestingly, mutations in this gene cause other forms of ectodermal dysplasia associated with immune defects: hypohidrotic ectodermal dysplasia and immunodeficiency (HED-ID), a primary immunodeficiency, and OLEDAID syndrome (see below).

10.4.16 OLEDAID Syndrome

Two male patients with osteopetrosis, lymphedema, ectodermal dysplasia, anhidrotic type, and immune deficiency (OLEDAID, OMIM#300301), were born from mothers with mild incontinentia pigmenti [53]. Both had multiple infections and died from infectious causes. The inflammatory response was poor, and isohemagglutinin titers and titers to Pneumococcus (despite documented infection) were decreased. Both patients had a mutation in *NEMO* [53]. Overall, four X-linked clinical syndromes are associated with mutations in *NEMO* (incontinentia pigmenti (IP), HED-ID, OLEDAID, XHM-ED).

10.4.17 Acrodermatitis Enteropathica

Acrodermatitis enteropathica (OMIM#201100) is an autosomal recessive disorder characterized by diarrhea, dermatitis, and alopecia is due to

inadequate zinc metabolism. Severe infection with opportunistic pathogens occurs frequently and recurrent infection occurs in 30% [224]. Decreased response to phytohemagglutinin and abnormal delayed cutaneous hypersensitivity skin response is typical [168]. Hypogammaglobulinemia and defective chemotaxis of neutrophils and monocytes are variably present [224, 234]. Both the clinical and immunological abnormalities resolve after normalization of serum zinc levels. Mutations in the gene encoding the intestinal zinc transporter SLC39A4 have been detected [125].

10.4.18 Keratitis Ichthyosis Deafness (KID) Syndrome

This autosomal dominant ectodermal dysplasia is characterized by hypervascular keratitis, ichthyosis, severe sensorineural hearing loss, and corneal defects (OMIM#148210). Susceptibility to bacterial, viral and fungal infections has been reported, including death in infancy from infectious complications. No consistent immune defect has been identified, although impaired delayed type hypersensitivity response to Candida, increased IgE levels, and neutrophil chemotactic defects have been reported [76]. KID syndrome is caused by heterozygous mutation in the gene encoding the gap junction protein connexin-26, *GJB2* [185, 223].

10.4.19 PLAID and APLAID Syndromes

PLAID is associated with PLCG2-associated antibody deficiency, and immune dysregulation, and APLAID has the additional feature of autoinflammation. Cutaneous manifestations are present in both (PLAID, cold-induced urticaria; APLAID, recurrent blisters), and APLAID may have involvement of the joints, lung, intestines, and eye. In both conditions, there may be B cell and NK abnormalities. These syndromes are caused by mutations in *PLCG2*, encoding phospholipase Cγ2, which plays a role in immune function [170, 243].

10.4.20 Epidermodysplasia Verruciformis

This condition (OMIM#226400) is characterized by disseminated and persistent warts and pityriasis versicolor–like macules. The skin lesions are due to papillomavirus infection, though affected individuals do not display increased susceptibility to bacterial, other viral, or fungal infections or to genital papillomavirus infections. There is an increased risk for non-melanoma skin cancer, which is associated with HPV5 infection. Decreased T cell number and abnormal delayed-type hypersensitivity and mitogen response have been reported, as well as a significant increase of memory CD4+ and effector memory CD8+ T cells and an increase of skin-homing CD4+ T-cell subsets, though the findings are not consistent [40]. In most individuals, the condition is caused by mutations in either of 2 adjacent genes: *TMC6* or *TMC8* [182], which encode transmembrane proteins that play a role in maintaining cellular zinc homeostasis. A small number of patients have been identified with a mutation in the *RHOH* (ras homolog gene family member H) or serine-threonine kinase 4 (*STK4*, or *MST1*) gene [39, 41]. These genes are associated with autosomal recessive transmission. Potential X-linked [6] and autosomal dominant [147] forms have also been reported.

10.5 Syndromes Associated with Neurologic Dysfunction

Neurological abnormalities ranging from structural abnormalities to epilepsy or ataxia have been reported in association with immunodeficiency (Table 10.3).

10.5.1 Høyeraal-Hreidarsson Syndrome

A syndrome of X-linked cerebellar hypoplasia, psychomotor retardation, microcephaly, growth failure, and progressive pancytopenia has been reported in several affected males (OMIM#300240). Decreased IgG [96] and death from fungal sepsis [12, 97] have been described.

Progressive combined deficiency has been noted in other patients [116, 212]. This condition is caused by mutations in the *DKC1* gene, the same gene that is mutated in dyskeratosis congenita [116]. Other patients have a mutation in *RTEL1*, which encodes a DNA helicase that is involved in telomere regulation [233]. *RTEL1* mutations may be more specific for Høyeraal-Hreidarsson syndrome as they have been identified in patients with this diagnosis but not in patients with only standard features of dyskeratosis congenital [233]. Please see Sect. 9.9 for more details.

10.5.2 Cohen Syndrome

Cohen syndrome (OMIM#216550) is an autosomal recessive condition featuring hypotonia, microcephaly, mental retardation, short stature, obesity, and characteristic facies with short philtrum, prominent upper central incisors, and prominent nasal root. Neutropenia is mild to moderate, intermittent, and not generally associated with severe infection, although gingivitis, periodontitis, and cutaneous infections are common [4, 113, 114, 169]. Mutations in the *COH1* (*VPS13B*) gene have been identified [119].

10.5.3 Myotonic Dystrophy

This autosomal dominant condition (OMIM#160900) is a multisystem disorder, characterized by difficulty in relaxing a contracted muscle. Muscle weakness and wasting, cataracts, hypogonadism, and cardiac conduction defects are also frequent manifestations. Cognitive function may deteriorate in adults. In the congenital form, there is severe hypotonia and respiratory insufficiency.

Most cases of myotonic dystrophy are due to a trinucleotide repeat expansion in the 3′ untranslated region of the *DMPK* gene (type 1), which encodes the dystrophia myotonica protein kinase [21, 72, 140]. In general, the size of the expansion correlates with the severity of the disease and the age of onset. Myotonic dystrophy, type 2, is associated with an expansion in a CCTG repeat in intron one of the *ZNF9* gene [132].

The most common immunologic abnormality in type 1 patients is a reduction in IgG, especially IgG1, level [107, 173, 236], although decreased IgA and IgM levels have occasionally been noted. There is generally no increased susceptibility to infection [211].

10.6 Inborn Errors of Metabolism Associated with Immunodeficiency

For most of these syndromes, it is unknown if the immunological deficit is due to block of a metabolic process important for immune function or if the buildup of toxic metabolites adversely affects immune cells (Table 10.4). Most of the immunological abnormalities appear to be secondary to the metabolic derangement since correction of the metabolic defect usually restores immune function.

Primary Immunodeficiencies Associated with Inborn Errors of Metabolism

10.6.1 Adenosine Deaminase Deficiency

Adenosine deaminase (ADA) deficiency (OMIM#102700) is a well-characterized metabolic defect and is the most common single genetic cause of autosomal recessive severe combined immunodeficiency disease [94]. The enzyme converts adenosine and deoxyadenosine to inosine and deoxyinosine, and their accumulation may lead to lymphocyte toxicity. The skeletal system is affected in a majority of patients, and manifestations include cupping and flaring of the costochondral junctions, platyspondylysis, thick growth arrest lines, and an abnormal bony pelvis. Please see Sect. 2.5 for more details.

10.6.2 Purine Nucleoside Phosphorylase Deficiency

Purine nucleoside phosphorylase (PNP) deficiency (OMIM#164050) is due to a defect in an enzyme required for normal catabolism of

Table 10.4 Inborn errors of metabolism associated with immunodeficiency

Name	Inheritance (Chromosome)	Associated features	Immune defect	Frequency of ID
Primary immunodeficiencies				
1. Adenosine deaminase deficiency	AR (20q13)	Severe combined immunodeficiency, cupping and flaring of costochondral junctions	T, B	++++
2. Purine nucleoside phosphorylase deficiency	AR (14q13)	Severe immunodeficiency, neurological findings, hemolytic anemia; viral/fungal infections	T	++++
3. Leukocyte adhesion deficiency, type 2	AR (11p11)	Severe mental retardation, seizures, growth failure, abnormal facies, congenital disorder of glycosylation IIc	Ph	++++
4. Glycogen storage disease Ib/Ic	AR (11q23)	Hypoglycemia, glucose-6-phosphate transport defect; perianal abscesses; inflammatory bowel disease	Ph	+++
5. Barth syndrome	XL (Xq28)	Endocardial fibroelastosis, myopathy, abnormal mitochondria, 3-methylglutaconicaciduria	Ph	++++
Other syndromic immunodeficiencies				
6. Congenital disorders of glycosylation	Various Types Ia, Ig, Ik	Decreased glycosylation, hypotonia, poor growth, other organ systems may be involved depending on the type	B, Ph	++
7. Galactosemia	AR (9p13, 17q24)	Hepatomegaly, hypoglycemia, jaundice, feeding difficulties; risk for E. coli sepsis	Ph	+
8. Brached chain amino acidemias	AR (various)	Methylmalonic, propionic, and isovaleric acidemias; acidosis, vomiting, ketosis	T, B, Ph	+++
9. Lysinuric protein intolerance	AR (14q11)	Dibasic aminoaciduria, hepatomegaly, failure to thrive; severe varicella infection	T, B, Ph, NK	+++

ID immunodeficiency, *T* T cell defect, *B* B cell defect, *Ph* Phagocyte defect, *NK* NK cell defect. Frequency of ID: + = less than 5 % of reported cases with documented ID; ++ = 5–30 %; +++ = 30–65 %; ++++ = >65 %. *AR* autosomal recessive, *AD* autosomal dominant, *XL* X-linked

purines. Abnormal motor development, including ataxia and spasticity, may occur. Viral and fungal infections frequently arise, and T cell number and function are greatly decreased. Please see Sect. 2.5 for more details.

10.6.3 Leukocyte Adhesion Deficiency, Type 2

Leukocyte adhesion deficiency, type 2 (LAD 2, OMIM#266265) is an autosomal recessive disorder characterized by recurrent infections, persistent leukocytosis, microcephaly, cortical atrophy, short stature, and severe mental retardation. This condition is also termed congenital disorder of glycosylation IIc (CDG-IIc). There is defective neutrophil motility and recruitment to sites of inflammation [177], although phagocytic activity is normal [62, 71]. The patient's cells lack fucosylated molecules due to mutations in the gene *SLC35C1* encoding the GDP-fucose transporter (FucT1) [135]. Although the immunodeficiency can be severe in infancy, children that have survived seem to have fewer serious infections and they may only have chronic periodonti-

tis in later childhood. Please see Sect. 4.6 for more details.

10.6.4 Glycogen Storage Disease Ib/ Ic

Glycogen storage disease (GSD) Ib and Ic (OMIM#232220, #232240) are marked by hypoglycemia. Severe neutropenia occurs in 87 % of patients with GSD Ib [229] and is also frequently found in GSD Ic [228]. Neutrophil function may be diminished [79]. Inflammatory bowel disease, oral lesions, and perianal abscesses occur with increased frequency and are most likely due to defective neutrophil function.

10.6.5 Barth Syndrome

This X-linked condition (OMIM#302060) is characterized by short stature, cardiac and skeletal myopathy, endocardial fibroelastosis, and structural mitochondrial anomalies [8]. Urinary 3-methylglutaconate and 3-methylglutarate are increased [110]. Neutropenia is often persistent and can lead to serious infections. The defective gene, *TAZ*, codes for a protein involved in cardiolipin metabolism [14].

Other Syndromic Immunodeficiencies Associated with Inborn Errors of Metabolism

10.6.6 Congenital Disorders of Glycosylation, Type I

Congenital disorders of glycosylation (CDG), also known as carbohydrate-deficient glycoprotein syndromes (CDGS), are autosomal recessive disorders characterized by decreased glycosylation of glycoproteins. In type I CDG, there is a defect in the production of lipid-linked oligosaccharides or their transfer to nascent proteins. Hypotonia and poor growth are present, and other organ system involvement is often present, depending on the type of CDG. Type Ia CDG (OMIM#212065) is due to a defect in phosphomannomutase 2 and abnormal fat distribution is characteristic. Severe infections often occur, and decreased IgA or IgG levels, defective response to vaccines, and diminished neutrophil chemotaxis have been observed [15]. Type Ig CDG (OMIM#607143) is due to a defect in the gene encoding a mannosyltransferase (ALG12). Microcephaly and male genital hypoplasia are characteristic. Recurrent infections and decreased IgG levels often occur [26]. A short-limb skeletal dysplasia was noted in two affected siblings [123]. Type Ik CDG (OMIM#608540) is due to a defect in mannosyltransferase I, and refractory seizures, microcephaly, and early death are characteristic. An affected patient was noted to have very decreased B cell number and absence of IgG [124].

10.6.7 Galactosemia

A defect in galactose-1-phosphate uridyl transferase results in galactosemia (OMIM#230400), which presents with jaundice, hepatomegaly, cataracts, developmental delay, and feeding difficulties. These patients are at increased risk for fatal sepsis from *E. coli* in the neonatal period [131]. Granulocyte chemotaxis is impaired, while bactericidal activity is usually normal. *In vitro* exposure of neutrophils to galactose also results in impaired function, especially in neonates [117].

10.6.8 Branched-Chain Amino Acidurias

Three diseases affecting branched-chain amino acid metabolism are associated with leukopenia: methylmalonic acidemia (OMIM#251000), propionic acidemia (OMIM#232000), and isovaleric acidemia (OMIM#243500) [109, 145, 156]. The conditions present with metabolic acidosis, lethargy, failure to thrive, and recurrent vomiting. These individuals are at increased risk for infection, which may precipitate episodes of acidosis. Decreases in B cell number and immunoglobulin levels have also been reported [32, 180, 237].

10.6.9 Lysinuric Protein Intolerance

This condition (OMIM#222700) is marked by defective transport of the dibasic amino acids lysine, arginine, and ornithine in the intestine and renal tubules, leading to decreased levels of these substances in the blood, hyperammonemia, protein intolerance, and failure to thrive. Decreases in CD4 T cell number [52], lymphopenia [158], IgG subclass deficiency and poor humoral response to vaccination [137], and leukopenia with decreased leukocyte phagocytic activity [241] have been reported. Varicella infection may be severe [136]. Treatment with supplemental immunoglobulin led to improved CD4 T cell number and resolution of associated anemia and cutaneous lesions [52]. The disease is due to mutations in the gene encoding the amino acid transporter *SLC7A7* [217].

10.7 Syndromes with Chromosome Instability and/or Defective DNA Repair Associated with Immunodeficiency

Syndromes associated with chromosome instability often have immune abnormalities and such patients are often at increased risk for malignancy (Table 10.5).

Primary Immunodeficiencies Associated with Chromosome Instability and/or Defective DNA Repair

10.7.1 Nijmegen Breakage Syndrome

Patients with Nijmegen Breakage syndrome (NBS, OMIM#251260) have short stature,

Table 10.5 Syndromes associated with chromosomal instability and/or defective DNA repair

Name	Inheritance (Chromosome)	Associated features	Immune defect	Frequency of ID
Primary immunodeficiencies				
1. Nijmegen breakage syndrome	AR (8q21)	Microcephaly, mental retardation, prenatal onset short stature, bird-like facies; malignancy (lymphoma); sinopulmonary and urinary tract infections	T, B	++++
2. Bloom syndrome	AR (15q26)	Short stature, telangiectatic erythema of face, sensitivity to sunlight; pneumonia, otitis media; risk for leukemia/lymphoma	T, B, NK	+++
3. Ataxia-telangiectasia	AR (11q22)	Progressive cerebellar ataxia, telangiectasias (conjunctival), choreoathetosis; risk for leukemia/lymphoma	T, B	++++
4. DNA ligase IV deficiency	?AR (13q22-q34)	Microcephaly, growth failure, developmental delay; pancytopenia, radiosensitivity	Ph	++++
5. ICF syndrome (immunodeficiency-centromeric instability-facial anomalies)	AR (20q11)	Mental retardation, chromosomal instability, facial dysmorphism; sinopulmonary, gastrointestinal, cutaneous infections	T, B	++++
6. NHEJ1 deficiency	AR (2q35)	Microcephaly, growth failure, radiosensitivity	T, B	++++
Other immunodeficiencies				
7. Fanconi pancytopenia	AR (various)	Radial hypoplasia, hyperpigmentation, pancytopenia, short stature	Ph, NK	++++

ID immunodeficiency, *T* T cell defect, *B* B cell defect, *Ph* phagocyte defect, *NK* NK cell defect. Frequency of ID: + = less than 5 % of reported cases with documented ID; ++ = 5–30 %; +++ = 30–65 %; ++++ = >65 %. *AR* autosomal recessive, *AD* autosomal dominant, *XL* X-linked

microcephaly, and bird-like facies [85]. Characteristic facial features include a receding forehead, prominent midface with a long nose, large ears, and micrognathia. Mental retardation may occur. There is an increased risk of malignancy, especially lymphoma. Cells from NBS patients are sensitive to ionizing irradiation. Bronchopneumonia and urinary tract infections commonly occur, and there is an increased risk of otitis media, mastoiditis, and sinusitis. Patients generally have abnormal immunoglobulin levels, most commonly including IgG (especially IgG2 and IgG4), and may have agammaglobulinemia [85]. Reduced CD3+ and CD4+ cell number with a decreased CD4/CD8 ratio have been noted. A markedly decreased proliferative response to T-cell mitogens was noted in 94 % of patients. Mutations in the *NBS1* gene (encoding Nibrin, or p95), which encodes a subunit of the Rad50/Mre11 protein complex involved in double-stranded break repair were detected in patients with NBS [146, 225]. Please see Sect. 9.3 for more details.

10.7.2 Bloom Syndrome

This autosomal recessive condition (OMIM#210900) is characterized by growth failure, hypersensitivity to sunlight, and characteristic facial features (malar hypoplasia, micrognathia, and prominent ears). Neoplasia, especially leukemia and lymphoma, is greatly increased and is the most frequent cause of death [75]. The diagnosis may be established by the finding of an increased number of sister chromatid exchanges in cells grown in medium with bromo-deoxyuridine (BrdU). There is an increased susceptibility to infection, especially pneumonia and otitis media. Immunological defects may involve both the humoral and cellular responses [120]. The product of the *BLM* gene encodes a RecQ DNA helicase that is involved in DNA duplex unwinding and may interact with topoisomerases or other proteins involved in DNA repair [59]. Please see Sect. 9.4 for more details.

10.7.3 Ataxia-Telangiectasia

Ataxia-telangiectasia (AT, OMIM#208900) is an autosomal recessive condition marked by progressive cerebellar ataxia, oculocutaneous telangiectasias, and chromosome instability. Patients with AT are at increased risk for malignancy, especially leukemia and lymphoma. Elevated alpha-fetoprotein is a consistent finding. There is an increased sensitivity to ionizing radiation. The severity and type of immune dysfunction is very variable. A variety of immunological defects have been reported, including hypogammaglobulinemia (low IgG, IgA, and/or IgE) [74] and decreased T-cell response to antigen and mitogen. Defects in the gene *ATM*, which is involved in DNA damage response and interacts with *NBS1*, have been identified [36, 73, 195, 242]. Patients with progressive cerebellar degeneration similar to that seen in ataxia-telangiectasia but who did not have telangiectasias were diagnosed with the ataxia-like syndrome and were found to have mutations in *MRE11* [208]. Please see Sect. 9.2 for more details.

10.7.4 DNA Ligase IV Deficiency

Deficiency of DNA ligase IV (OMIM#601837) is associated with microcephaly, growth failure, and developmental delay, and the phenotype has some resemblance to that of the Nijmegen Breakage syndrome [164]. Cell lines from these patients showed marked radiosensitivity, and pancytopenia has been reported. Please see Sect. 2.3 for more details.

10.7.5 ICF Syndrome

This autosomal recessive condition (OMIM#242860) is comprised of immunodeficiency, centromeric instability (involving chromosomes 1 and 16, often 9, rarely 2 and 10), and facial anomalies (ocular hypertelorism, flat nasal bridge) [142, 215]. Mental retardation is frequent. Deletions, breaks, interchanges between

homologous and nonhomologous chromosomes, and multibranched configurations involving pericentric heterochromatin have been described. The ICF syndrome differs from many other chromosome instability syndromes in that no hypersensitivity to clastogenic agents has been demonstrated, and hence it is not a chromosome breakage syndrome.

Severe chronic sinopulmonary, gastrointestinal, and cutaneous infections occur. Generally, at least two immunoglobulin classes are affected in each patient [142, 202], and immunoglobulin supplementation can improve the disease course [86]. T cell number and lymphoproliferative response to mitogen may be decreased [65, 202]. Mutations in the gene encoding the DNA methyltransferase DNMT3B have been identified [167, 240]. However, approximately 40 % of patients diagnosed with ICF do not have identified *DNMT3B* mutations [86, 102, 115]. Please see Sect. 9.5 for more details.

10.7.6 NHEJ1 Deficiency

A severe combined immune deficiency was seen in association with congenital microcephaly and growth failure (OMIM#611291) [22]. Fibroblasts were sensitive to ionizing radiation. Patients had greatly reduced B and T cells, hypogammaglobulinemia, and T cell dysfunction. Mutations were identified in NHEJ1 (non-homologous end-joining factor 1), which encodes a DNA repair factor needed for nonhomologuos end-joining to mediate repair of double strand breaks [22].

Other Syndromic Immunodeficiencies Associated with Chromosome Instability and/or Defective DNA Repair

10.7.7 Fanconi Pancytopenia

This autosomal recessive syndrome (OMIM#227650) is associated with hyperpigmentation of the skin, cafe au lait spots, radial hypoplasia, short stature, microcephaly, renal and genital anomalies, mental retardation, and a characteristic facial appearance (microphthalmia, micrognathia, broad nasal base, and epicanthal folds). Single chromatid breaks and gaps, as well as multiradials of the nonhomologous type are present. Increased sensitivity to the clastogenic agent diepoxybutane is useful for diagnosis and prenatal detection [103]. Neutropenia secondary to bone marrow failure occurs in over 95 % of patients. T- and B-cell functions are generally normal. At least 15 different genes are associated with this condition.

10.8 Syndromes Associated with Chromosomal Abnormalities of Number or Structure

Primary Immunodeficiencies Associated with Chromosomal Abnormalities of Number or Structure

10.8.1 Deletions of 22q11 and 10p13-p14

Deletions of the chromosomal regions 22q11 and 10p13-p14 are associated with the DiGeorge anomaly [60, 81]. This malformation sequence is due to defective development of the third and fourth pharyngeal pouches, resulting in thymic absence or hypoplasia, conotruncal cardiac defects, and parathyroid hypoplasia (with hypocalcemia). The DiGeorge syndrome (OMIM#188400) is considered a primary immunodeficiency. Please see Sect. 2.9 for more details.

Other Syndromic Immunodeficiencies Associated with Chromosomal Abnormalities of Number of Structure

10.8.2 Trisomy 21 (Down Syndrome)

Down syndrome (OMIM#190685) results from trisomy 21 and is associated with mental retardation, cardiac defects, gastrointestinal abnormalities, leukemia, and early-onset Alzheimer disease. Affected individuals can experience significant morbidity and mortality due to

Table 10.6 Syndromes associated with chromosomal abnormalities of number or structure

Name	Associated features	Immune defect	Frequency of ID
Primary immunodeficiencies			
1a. Deletion of long arm of chromosome 22 (22q11.2) (DiGeorge/ velo-cardio-facial syndrome)	Aortic arch anomalies, hypocalcemia, thymic hypoplasia, cleft palate, facial dysmorphism; autoimmune disease, immune cytopenia, hyperthyroidism	T, B	++
1b. Deletion of short arm of chromosome 10 (10p13-p14)	Hypoparathyroidism, DiGeorge anomaly; some with deafness, renal anomaly	T	++
Other immunodeficiencies			
2. Trisomy 21 (Down syndrome)	Hypotonia, flat facies, upslanting palpebral fissures, mental retardation; sinopulmonary infections; risk of leukemia; autoimmune thyroiditis	T, B, Ph, NK	++
3. Deletion of short arm of chromosome 4 (4p16) (Wolf-Hirschhorn syndrome)	Growth and developmental deficiency, "Greek helmet"-like facies, microcephaly, coloboma; respiratory infections	B	+++
4. Missing or abnormal X chromosome (Turner syndrome; XO, isoX, ring X)	Short stature, webbed neck, broad chest, ovarian dysgenesis, congenital lymphedema; pulmonary/ear infections; autoimmune disease (e.g., thyroid disease, celiac disease, arthritis); gonadoblastoma (if Y chromosome material present)	T, B	++
5. Deletion of long arm of chromosome (11q23) (Jacobsen syndrome)	Growth failure, mental retardation, trigonocephaly, thrombocytopenia, pancytopenia	T, B, Ph	++

ID immunodeficiency, *T* T cell defect, *B* B cell defect, *Ph* phagocyte defect, *NK* NK cell defect. Frequency of ID: + = less than 5 % of reported cases with documented ID; ++ = 5–30 %; +++ = 30–65 %; ++++ = >65 %. *AR* autosomal recessive, *AD* autosomal dominant, *XL* X-linked

infections, especially respiratory infections [181, 219] (Table 10.6). Although most individuals do not have clear immune dysfunction, a number of immunologic abnormalities have been noted. B lymphocyte counts are often low throughout childhood, and the T lymphocyte count may also be low in the first 15 months of life, though these normalized with time [44]. No relationship between the lymphocyte subpopulation sizes and the frequency of infections were detected. Decreased B-cell number and low specific antibody response have been reported [133, 219]. Proliferation in response to phytohemagglutinin and alloantigens, delayed cutaneous hypersensitivity response, and T cell-mediated killing are variably reduced [154, 219]. Total NK cell number is increased but the activity is decreased [37, 154]. Phagocyte number is normal, but chemotaxis and oxidative metabolism, and hence killing, is impaired [7]. There is an increased incidence of autoimmune conditions [42]. Proliferation and IL-2 production in response to phytohemagglutinin were decreased in adult men with Down syndrome [174].

10.8.3 Partial Deletions of Chromosome 4p (Wolf-Hirschhorn Syndrome)

Patients with partial deletions of chromosome 4p or Wolf-Hirschhorn syndrome (OMIM#194190) have prenatal-onset growth

Table 10.7 Other syndromic immunodeficiency

Name	Inheritance (Chromosome)	Associated features	Immune defect	Frequency of ID
1. MonoMAC syndrome	AD (3q21)	Nontuberculous mycobacterial and other infections, pulmonary alveolar proteinosis	T, B, Ph, DC	++++

ID immunodeficiency, *T* T cell defect, *B* B cell defect, *Ph* phagocyte defect, *NK* NK cell defect, *DC* Dendritic cell defect. Frequency of ID: + = less than 5 % of reported cases with documented ID; ++ = 5–30 %; +++ = 30–65 %; ++++ = >65 %. *AR* autosomal recessive, *AD* autosomal dominant, *XL* X-linked

deficiency, mental retardation, microcephaly, ocular hypertelorism, coloboma of the iris, and seizures [244]. The critical region has been narrowed to 165 kb on 4p16.3 [238], and a second critical region has been proposed [245]. Patients have frequent episodes of respiratory infections, due in part to recurrent aspiration, but antibody deficiencies are also common. Immune defects include common variable immunodeficiency, IgA and IgG2 subclass deficiency, IgA deficiency, and impaired polysaccharide responsiveness [87]. T-cell immunity is normal. Immunodeficiency does not appear to correlate with deletion size, and all of these patients were deleted for the 4p16.3 critical region. This region likely contains a gene or genes critical for B cell function.

10.8.4 Turner Syndrome (Missing or Abnormal X Chromosome)

Patients with a missing or structurally abnormal X chromosome often present with short stature, shield chest, congenital lymphedema, and ovarian dysgenesis. The syndrome is associated with an increased risk for upper respiratory and ear infections, autoimmunity, and occasional neoplasia. IgG, IgM, and/or IgA levels may be abnormal [134]. Decreased T-cell number with poor response to phytohemagglutinin, absent delayed cutaneous hypersensitivity reactions, and common variable immunodeficiency occasionally occur [2, 23, 55, 188]. The relationship, if any, between the immune defects in Turner syndrome and the X-linked primary immunodeficiencies is unknown.

10.8.5 Jacobsen Syndrome (Partial Deletion of Chromosome 11q)

This condition is typically due to a terminal partial deletion of chromosome 11q and is associated with growth failure, mental retardation, trigonocephaly, and thrombocytopenia (OMIM#147791). Other organ systems may be involved, such as the heart, kidney, skeletal system, or gastrointestinal tract. Increased infections, especially respiratory infections, have been observed. Pancytopenia may also occur. Immune abnormalities have been variable and have included decreased lymphocyte response to mitogen and allogeneic cells, lymphopenia, impaired delayed-type hypersensitivity reactions, and hypogammaglobulinemia [179, 199, 232].

10.9 Other Syndromic Immunodeficiencies (See Table 10.7)

10.9.1 MonoMAC Syndrome

This autosomal dominant primary immunodeficiency (OMIM#614172), also known as DCML, features greatly decreased to absent dendritic cells, monocytes, B lymphocytes, and natural killer cells, with relative sparing of T cell numbers. Pulmonary alveolar proteinosis may occur. Infections are often due to nontuberculous mycobacteria, papillomavirus, and fungi. Bone marrow hypocellularity may be present. The condition is due to a mutation in *GATA2*, which encodes a zinc finger transcription factor [51, 98].

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