Other Well-Defined Immunodeficiencies

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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].

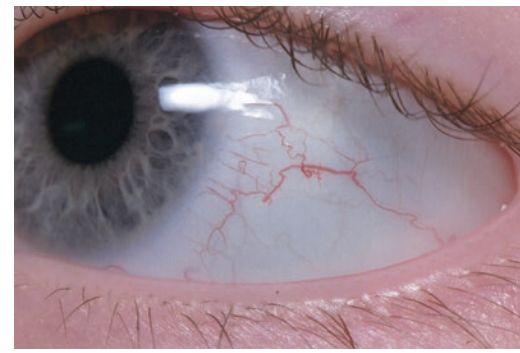

Fig. 9.1 Bulbar telangiectasia on the conjunctivae of a patient with ataxia telangiectasia (Adapted with permission from the Bubble Foundation UK)

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

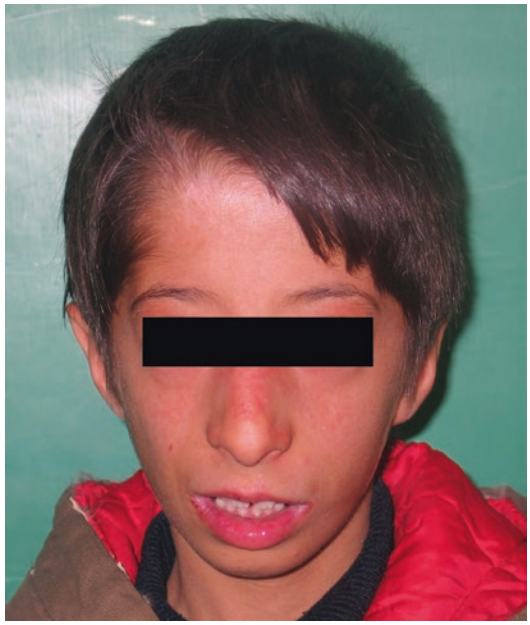

Fig. 9.2 Typical facial appearance of a patient with clinical diagnosis of Nijmegen Breakage syndrome. A similar appearance, described as bird-like facies, may be present in other DNA repair defect syndromes as in Bloom's syndrome or DNA ligase 4 deficiency

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

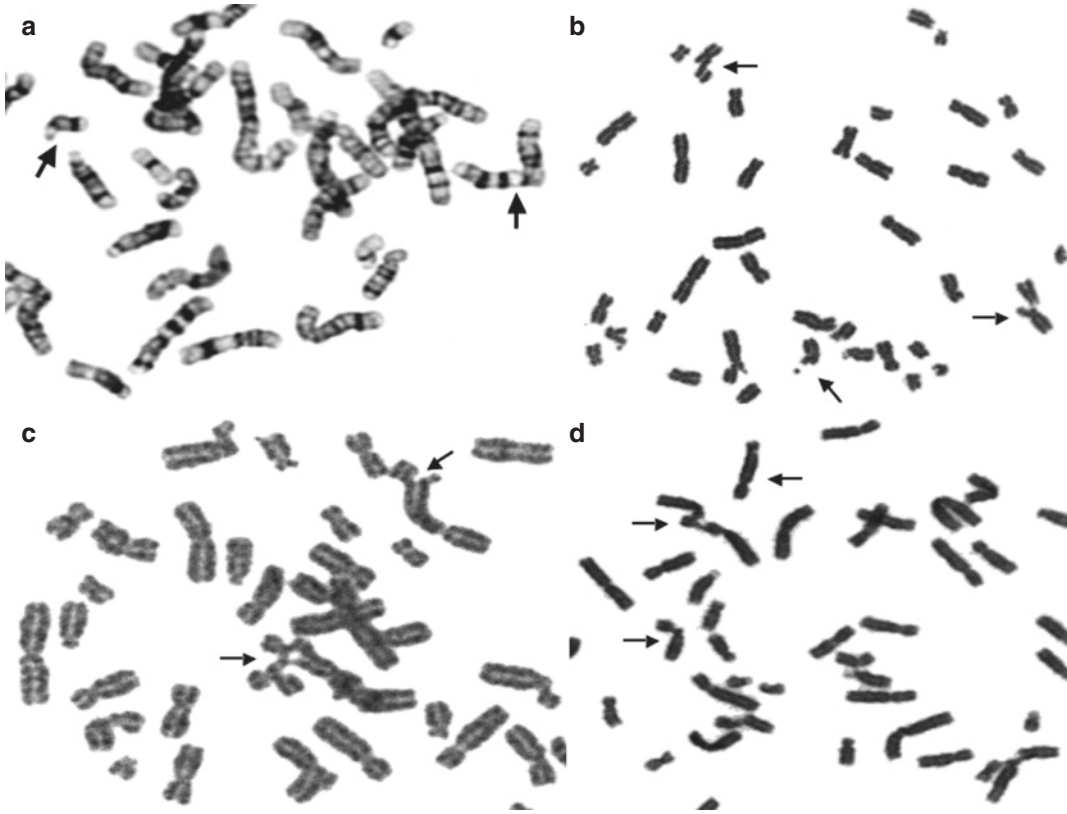

Fig. 9.3 Karyotype from a patient with Nijmegen Breakage syndrome. (**a**) Chromosome t(7;14) rearrangement (*arrows*). (**b**) chromosomal breakage following exposure to 50 centiGray ionising radiation (*arrows*). Karyotype from a patient with Fanconi anemia. (**c**) Multiradial formation (*arrows*) 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.

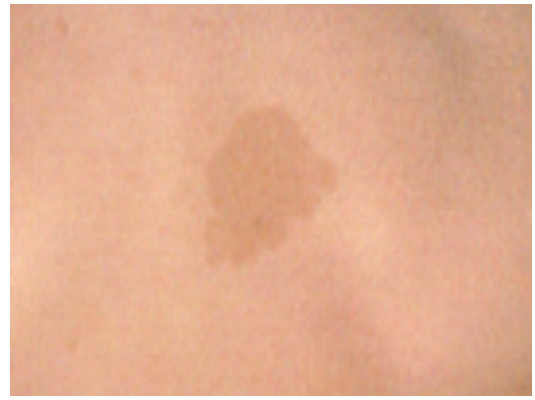

Fig. 9.4 Hyper-pigmented skin patch on the torso of a patient with Bloom syndrome (Adapted with permission from the Bubble Foundation UK)

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

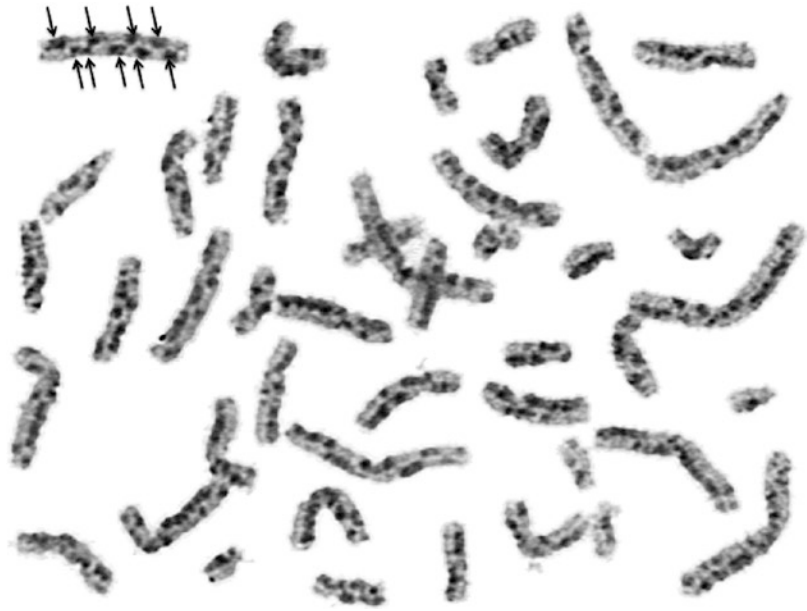

Fig. 9.5 Karyotype from a patient with Bloom syndrome. A large increase in the number of sister chromatid exchanges (*arrows*) are visible (Adapted with permission from the Bubble Foundation UK)

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.

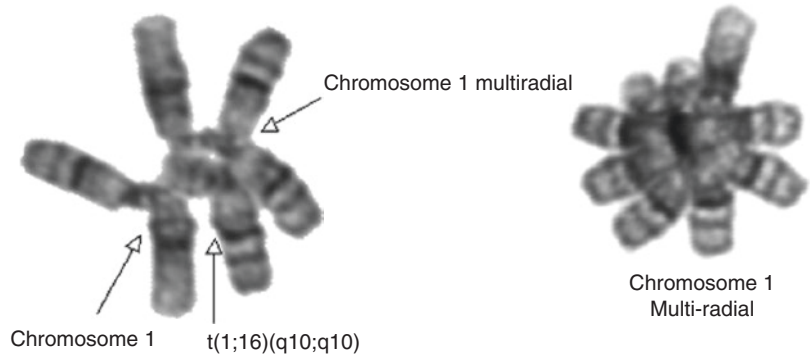

Fig. 9.6 Chromosome 1 from a patient with ICF, which shows multibranching, translocation, and decondensation of heterochromatic regions adjacent to the centromeres

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)

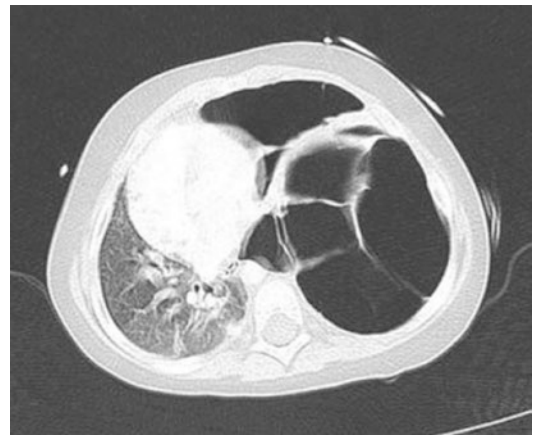

Fig. 9.7 Chest computed tomography showing enlarged pneumatoceles compressing heart and right lung

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].

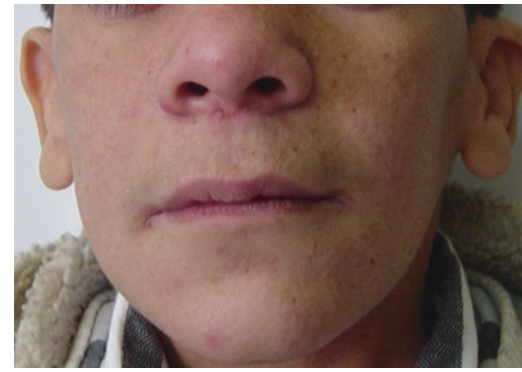

Fig. 9.8 Facial look of a patient with sporadic hyper IgE syndrome. Note the tickened skin, wide nose and perioral chilitis

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.

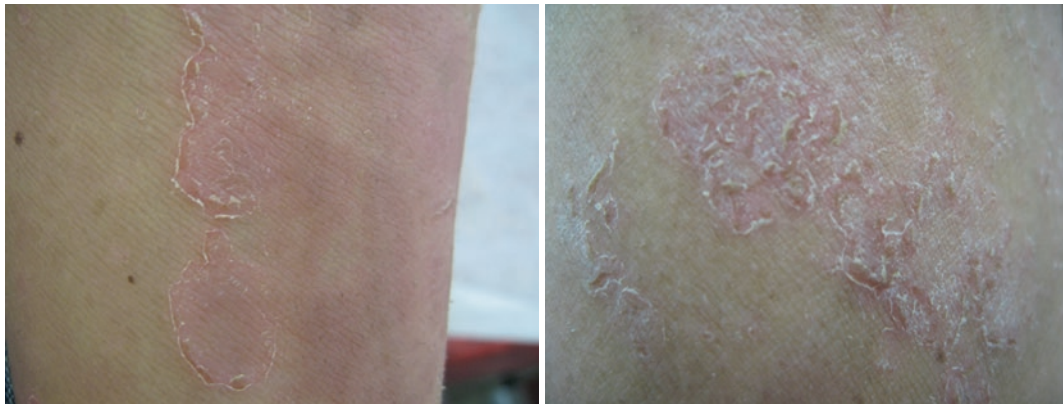

Fig. 9.9 Ichthyosis linearis circumflexa. Note the serpiginous scaling and erythematous patches surrounded by a doubled-edged scale (Courtesy of K. Balighi; Tehran, Iran)

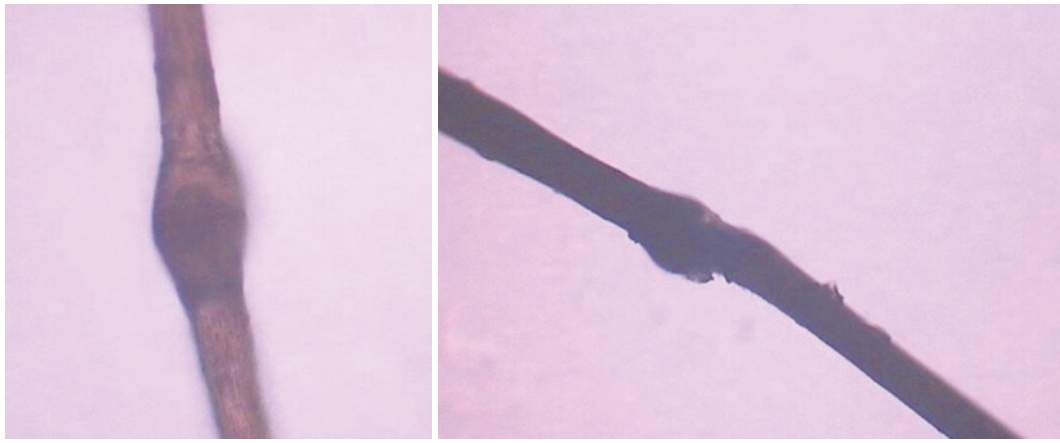

Fig. 9.10 Trichorrhexis invaginata; note the characteristic ball-and-socket appearance or Bamboo hair (Courtesy of K. Balighi; Tehran, Iran)

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

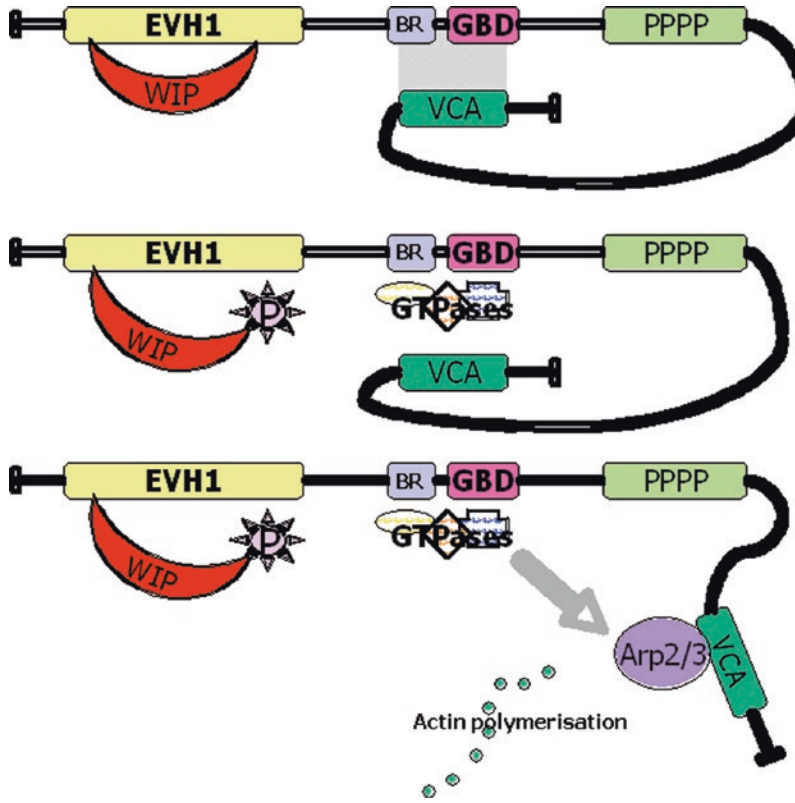

Fig. 9.11 Schematic representation of WASP and model of activation. In the inactive configuration, WASP is bound to WIP at the EVH1 domain and adopts an autoinhibited configuration in which the VCA domain interacts with the GBD and BR domains. T cell receptor (TCR)-mediated activation results in WIP 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-

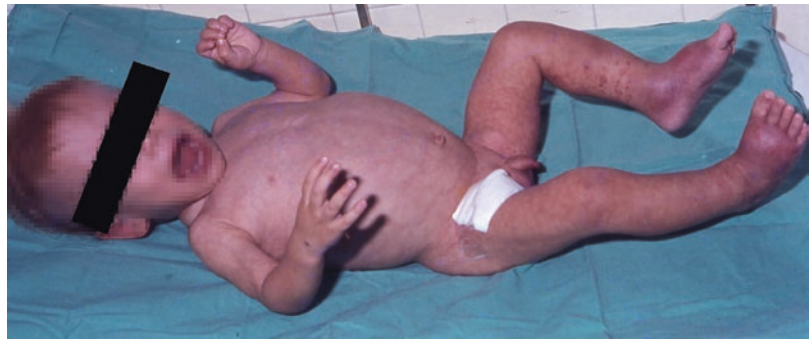

Fig. 9.12 A boy with Wiskott-Aldrich syndrome who suffered from vasculitis, intestinal bleeding and severe respiratory infections

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

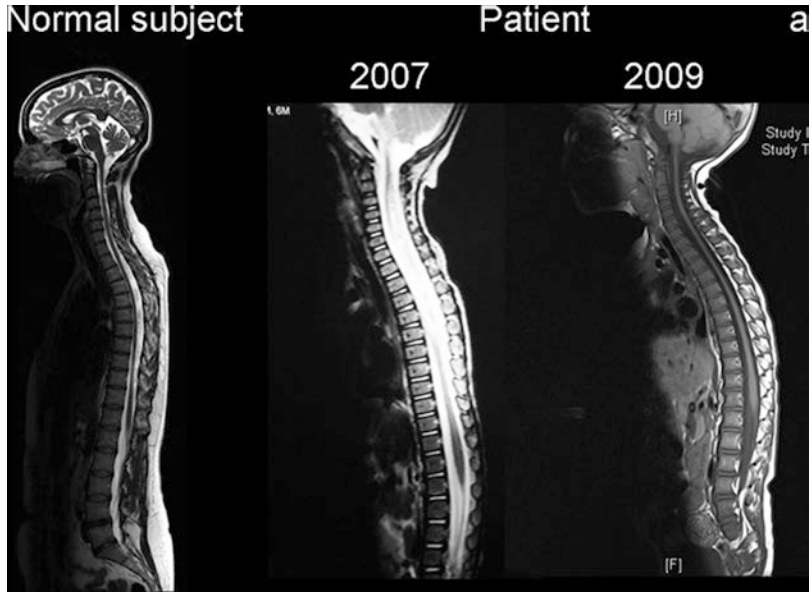

Fig. 9.13 MRI images obtained from a 2 year old boy who had an episode of spinal cord demyelination, and who represented with fitting in December, 2009. (**a**) Spinal views: the process improved over 2 years, apparently spontaneously, but functional improvement was limited; (**b**) Serial MRI images 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

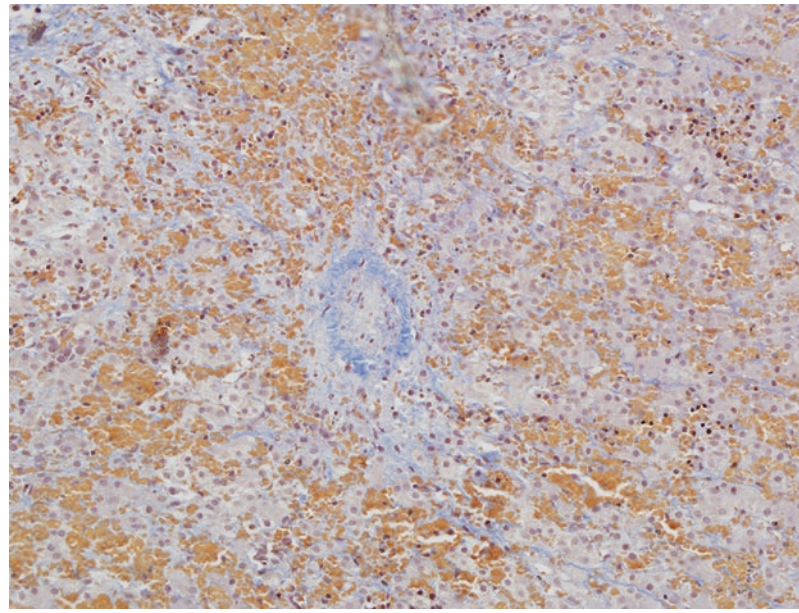

Fig. 9.14 Liver biopsy showing central vein occlusion, peri-venular fibrosis, zone 3 fibrosis and hepatocyte dropout from a girl who presented at age five months with hepatomegaly and ascites (Picro-trichrome stain, 100×)

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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