Neurocutaneous Disorders

A Clinical, Diagnostic and Therapeutic Approach

Christos P. Panteliadis
Ramsis Benjamin
Christian Hagel
Editors

Third Edition

Springer

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Preface to the Third Edition

Six years have passed since the release of the second edition of the book *Neurocutaneous Disorders—A Clinical, Diagnostic and Therapeutic Approach.* The good response from the readership on the one hand, and the quickly expanding knowledge about causative genetic alterations, pathophysiology, possibilities of early diagnosis, better diagnostic criteria, additional clinical characteristics, management and rehabilitation have driven the editors to publish a new edition.

New distinguished authors from around the world, along with many authors of the second edition, have provided sharper and more acute dimensions to the overall upgraded version of this book. All chapters have been revised and updated, evidence-based therapy has been added wherever possible and new chapters complement the multifaceted subject of the book. A number of new chapters has been included, providing an overview on genetics, sonography and neuro-imaging, and focusing on disease entities that were not included before such as Incontinentia pigmenti and Epidermal naevus syndrome.

The editors would like to thank all the expert authors for their invaluable input, cooperation and patience towards the successful realization of this project. Many thanks to the publisher Springer Medicine Books, Continental Europe and UK, for the unwavering commitment in disseminating medical knowledge. Special thanks to Dr. med. Raymund Mürbeth for his continued assistance in proofreading, literature review and administrative issues.

Thessaloniki, Greece — Christos P. Panteliadis
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Preface (Parts from First Edition)

The term "neurocutaneous" combines the Greek word "νεύρο" and the Latin word "cutaneus". The first case of neurofibromatosis, according to Murphy et al., could have existed during the Scythian period (700–200 B.C.) in a woman from the territory of Ascania (modern Azerbaijan) with peculiar skin lesions on the scalp. Another possible case of neurofibromatosis, from eighteenth to nineteenth century was noted by Knusel and Browman. In the medical literature, five other possible cases have been mentioned between the fifteenth- and the eighteenth century A.D. in rough drawings and icons (1350–1793). The first rough sketches of the disease, however, could be dated back to 1350 in the "Book of the Nature" by Conrad von Megenberg, a Bavarian naturalist and philosopher. The second description comes from the book "Des Monstres et Prodiges" in 1585 by the French anatomist and surgeon Ambroise Paré. Several detailed illustrations followed along with a reference from Ulisse Aldrovandi in the book "Monstrorum Historia", which was published posthumously in 1642. The first definitive description of neurofibromatosis was made by the physician Wilhelm G. Tilesius von Tilenau in 1793 in one of his patients, the "Wart Man".

Our purpose was to put forth in a single volume a comprehensive review of the historical perspective, the clinical features, the current understanding in the genetic, pathogenesis of each disease and the diagnostic and therapeutic strategies associated with these challenging disorders.

This edition attempts to convey that neurocutaneous syndromes and haemangiomas should fall under the same rubric of "Skin and CNS Disorders". Our philosophy is that both entities have similar clinical features, including their increased tendency towards certain types of malignancy. We thank the contributing authors and researchers who provided clinically helpful photos, their immense personal experience and ideas, not to mention their invaluable time and information. Our effort and your encouragement to learn about neurocutaneous syndromes spurred us

to improve this edition. This book is a collaboration of physicians and scientists from Greece, Germany and the USA, underscoring that knowledge has no borders.

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Templeton, CA, USA — Ramsis Benjamin
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2007

Preface to the Second Edition

Eight years have passed since the release of the first edition of the book *Neurocutaneous Disorders/Haemangiomas—A Clinical and Diagnostic Approach*, during which time the scientific knowledge concerning the management and treatment of these rare disorders has greatly expanded. Therefore, a second edition seemed inevitable in order to incorporate all the emerging data and nuances. New distinguished authors from around the world, along with the authors of the first edition, have provided sharper and more acute dimensions to the overall upgraded version of the book. All chapters have been revised, brought up-to-date, and new chapters have been added. The editors would like to thank all the expert authors for their invaluable input, the publisher Elsevier for its unwavering commitment in disseminating medical knowledge and the countless contributors for their cooperation and patience to the successful realization of this project. A special thanks is extended to Christos Livanos for his relentless administrative assistance.

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2016

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Introduction

The term "neurocutaneous" combines the Greek word "νεύρο" and the Latin word "cutaneus". The first case of neurofibromatosis, according to Murphy, was supposedly observed during the Scythian period (700–200 B.C.) in a woman from the territory of Ascania (modern Azerbaijan) with peculiar skin lesions on the scalp. In the medical literature five other possible cases have been mentioned between the fifteenth and the eighteenth century A.D. (1350–1793). The introduction describes the historical timeline of important neurocutaneous disorders, the spectrum of disorders, development of the neural crest and the book's purpose.

Historical Note

The term "*neurocutaneous*" combines the *Greek* word νεύρο and the Latin word *cutaneous*. Neurocutaneous disorders (NCD) have been long recognized because of their readily visible cutaneous signs. Neurofibromatosis skin nodules, for example, can be seen on the trunk and arms of a Roman statue at the *Museo National De Arte Romano* dating back to the first century B.C.E. [1]. Archaeological discoveries from Azerbaijan of scalp lesions on a woman point to an even earlier probable case of neurofibromatosis from the *Scythian* period [2]. The Scythians (Greek Σκύθης, Σκύθοι) were *Persian* tribal equestrians who inhabited large areas of the central Eurasian steppes between the ninth century B.C.E. and fourth century A.D. Their territories during the Iron Age were known by the ancient Greek historians as "Scythia" [3].

The first rough sketches of NCD were published in 1350 in "*Das Buch der Natur"* (*The Book of Nature*) by Konrad von Megenberg, a Bavarian theologian and philosopher. The second description appeared in *Des Monstres et Prodiges* (*On Monsters and Marvels*) in 1585 by Ambroise Pare, the French anatomist and chief surgeon to Charles IX and Henri III. Several detailed illustrations followed along with a reference from Ulisse Aldrovandi, an Italian physician, in *Monstruorum Historia cum Paralipomenis historiae omnium animalium* [4] in 1642, published

posthumously. The first definitive depiction of neurofibromatosis was made by the physician Wilhelm G Tilesius von Tilenau in 1793 on one of his patients, the "*Wart Man*", who exhibited cutaneous plexiform neurofibroma over the anterior chest wall, along with numerous skin tumours and café-au-lait spots [5–7]. In 1768, Mark Akenside published a scientifically based description of NF1, and in 1785 major reports about a patient nicknamed "*wart man*", with skin nodules and skin patches on his legs [8].

In 1846, Rudolf Virchow (1821–1902), a German pathologist, physician, and anthropologist, was the first to describe the presence of small nodules (*cartilaginous nodules*) [9]. In 1847, Virchow reported neuromas in several members of one family and in 1863 classified the tumours of peripheral nerves into true neuromas [10, 11]. Tumours associated with neurofibromatosis type 1 were first detailed by Robert William Smith in 1849 (1807–1873) [12], but Frederick von Recklinghausen coined the name of the disorder in 1882 [13]. Although the more common neurocutaneous syndromes like neurofibromatosis type 1 (NF1) were recognized centuries ago, the rarer disorders have been largely overlooked, and the severity of their clinical course was not appreciated until recently. In 1917, Cushing WC (1869–1939), an US surgeon, established multiple meningiomas and bilateral acoustic neuromas as components of NF [14] (see Chap. 26). In 1873, Michel V first reported the case of a patient with optic glioma [15].

Bielschowsky M (1869–1940) in 1919 [16], and later teaming with Rose M (1883–1937) in 1927 [17], described the characteristics of neurofibromatosis and tuberous sclerosis, referring to these clinical entities as "dysontogenetic processes". Van der Hoeve J (1878–1952), a Dutch ophthalmologist, in 1923 [18] considered skin and eye manifestations as common characteristics of NCD, and described them as "phacomatoses" (φακός, phakos, Greek for lens). In the same year (1923) Treves published the book: *The Elephant Man and Other Reminiscences*. Only recently it was shown by DNA analysis of bone from the skeleton of the elephant man that he suffered from Proteus syndrome rather than from neurofibromatosis type 1 [19].

The term "neurocutaneous syndromes" was introduced by Yakovlev and Guthrie in 1931 to describe a group of disorders that selectively affect ectodermal structures [20]. Attempts have been made to improve the diagnostic criteria of these disorders. Some authors claim genetic transmission as a necessary prerequisite for the diagnosis [21]. Some syndromes, however, occur spontaneously or independently from hereditary transmission. Lethal mutations have been noted that would only survive via chromosomal mosaicism [22]. Further, genetic transmission may be hard to prove because of the rarity of these entities (Table 1).

Description of Tuberous sclerosis is credited to Désiré-Magloire *Bourneville* (1840–1909), but Friedrich Daniel von *Recklinghausen* (1833–1910) was probably the first person to recognize the condition. A decade later and unaware of *Bourneville's* documentation, John James Pringle (1855–1922) in 1890 reported adenoma sebaceum. Between 1880 and 1900 *Bourneville* and Eduard *Brissaud* (1852–1909) summarized the clinical features. In 1885, Félix Balzer and Pierre-Eugene Ménétrier (1859–1935) described in detail the typical facial angiofibromas.

Table 1 Timeline of important neurocutaneous disorders

Neurofibromatosis (NF1, NF2)
NF1: 1350 (about) von Megenberg C; 1857 Virchow R; 1873 Michel V; 1882 von Recklinghausen F; 1886 Bergruen E; 1910 Maas O; 1896 Marie, Barnard and Chauffard; 1910 Verocay J; 1919 Bielschowsky M; 1923 Treves F; 1927 Rose M; 1977 Zanca A and Zanca A; 1980 Zanca A,
NF2: 1820 Wishart JH; 1849 Smith RW; 1877 Soyka I; 1903 Henneberg G and Koch M; 1905 Funkenstein O; Brettschneider J 1913; Cushing H 1917; 1923 Steuer O; 1930 Gardiner WT and Frazier CH; 1932 Katzenstein R; 1940 Gardner WJ and Turner O
Tuberous sclerosis (TBS)
TBS: 1861 Von Recklinghausen F; 1865 Charcot JM; 1880 Bourneville DM; 1881 Bourneville DM and Brissaud E; 1882 Brückner O; 1885 Balzer F and Menetrier P; 1890 Pringle JJ; 1899 Bourneville DM; 1901 Pellizzi GB; 1908 Vogt H; 1919 Bielschowsky M; 1920 van der Hoeve J; 1927 Rose M; 1923 van der Hoeve J; 1933 van der Hoeve J; 1935 Gunther M and Penrose LS; 1937 Lisch K
Sturge-Weber syndrome (SWS)
1860 Schirmer R; 1879 Sturge WA; 1897 Kalischer S; 1922 Weber FP; 1923 Dimitri V; 1934 Krabbe KH; Metcalfe J; 1955 Weber FP
Ataxia-Telangiectasia (Louis-Bar syndrome, ATS)
1926 Syllaba L and Henner K; 1941 Louis-Bar D; 1957 Biemond A; 1958 Boder E, Sedgwick RP and Boder E; 1960 Sedgwick RP and Boder E; 1964 Boder E and Sedgwick RP; 1964 Martin L
Angiomatosis of retina and the cerebellum (von Hippel-Lindau disease; VHL)
1882 Fuchs EF; 1895 von Hippel E; 1874 Magnus H; 1894 Collins ET; 1879 Panas F and Rémy A; 1896 von Hippel E; 1904 von Hippel E; 1906 Czermak W; 1911 von Hippel E; 1921 Brand R; 1926 Lindau A; 1927 Lindau A; 1929 Möller HU; 1928 Cushing P and Bailey P; 1936 Davison C, Brock S and Dyke S
Gorlin-Goltz syndrome
1894 Jarisch W and White; 1951 Binkley G and Johnson DR; 1959 Howel JB and Caro MR; 1995 Gorlin RJ; 1960 Gorlin R and Goltz RW; 1987 Gorlin RJ
Neurocutaneous melanosis
1861 von Rokitansky C; 1903 and 1908 Oberndorfer S; 1906 Grahl F; 1914 MacLachlan; 1939 Wilcox; Jutte H 1939; 1948 Van Bogaert LC; 1949 Touraine PA; 1955 Haferkamp O and Risopatron LS; 1972 Fox H; 1991 Kadonaga JN and Frieden IJ; 1964 Fox H, Emery JL, Goodbody, and Yates PO
Klippel-Trénaunay-Weber syndrome
1837 Geoffroy Saint-Hilaire; 1900 Klippel M and Trénaunau P; 1907 Weber FP; 1918 Weber FP; 1953 Petschelt E; 1965 Lindenauer SM
Schimmelpenning-Feuerstein-Mims syndrome
1895 Jadassohn J; 1901 Montgomery DW; 1957 Schimmelpenning GW; 1960 Berg and Crome; 1962 Feuerstein RC and Mims LC; 1968 Solomon LM, Fretzin DF and Dewald RL; 1971 Wauschkuhn J and Rohde B; 1972 Holden KR and Dekaban AD; 1973 *Lovejoy*

(contiuned)

Table 1 (continued)

FH Jr and Boyle WE Jr; 1975 Solomon LM and Sterly NB; *1976*
Besser FS; 1983 Schimmelpenning GW; 1989 Rogers, McCrossin, Commens
Bloch-Sulzberger syndrome
1901 Blaschko A; 1906 Garrod AE; 1908 Adamson HG; 1926 Bloch B; 1928 Sulzberger MB
1927 Naegeli O; 1929 Siemens HW; 1950 Doornink FJ; 1959 Pfeiffer RA

In 1901, Battista Pellizzi (1865–1950) emphasized the dysplastic nature of these lesions, and in 1905 Perusini published his studies. In 1908, Heinrich Vogt (1875–1957) defined "*adenoma sebaceum*", and later in 1923, *van der Hoeve* detailed the histology of optic nerve and retina. In 1937, Karl Lisch, an Austrian ophthalmologist, described another clinical manifestation of NF: nodules on the surface of the iris (see Chap. 27).

Sturge-Weber syndrome was first reported in 1879 by the physician *William Allan Sturge* who presented to the Medical Society of London a girl with hemiparesis, congenital glaucoma, epilepsy and facial naevus haemangioma. Several years before in 1860, *Schirmer* described a patient with a right facial telangiectasia and congenital glaucoma, and without CNS lesions. In 1897, *Kalischer* published the autopsy findings of a patient with telangiectasia and in 1922, *Frederick Parkes Weber* reported the radiological findings of the skull. In 1923, *Dimitri* described the typical "*tram-track*" sign of intracranial calcifications. *Krabbe*, in 1934, showed that this calcification was in the cortex and not the meninges. In 1955, the term encephalofacial angiomatosis was suggested by *Weber* (see Chap. 5).

Ataxia-Telangiectasia (*Louis-Bar syndrome*) was first documented in 1926 by *Syllaba* and *Henner*, and in 1941 *Louis-Bar* coined the syndrome of cerebellar ataxia and cutaneous telangiectasia in a Belgian child. In 1957, *Biemond* and later *Sedgwick* and *Boder* in 1958 and 1960 reported their pathological findings in connection with neurologic symptoms and recurrent upper respiratory tract infections. In 1964, Martin L published the manuscript "*Aspect choréoathétosique du syndrome d'ataxie-télangiectasie*" (see Chap. 6).

Angiomatosis of the Retina and the Cerebellum (*von Hippel-Lindau disease*) took the centre stage in 1985. *Eugen von Hippel,* a Heidelberg ophthalmologist, published a case of a 25-year-old patient with unusual retinal findings. Nearly a decade elapsed before *von Hippel* provided the histological description of the disease in 1904. In the meantime, between 1895 and 1906, he noted similar cases in the literature by *Collins* and *Czermac*.

The term "**neurocristopathies**" in more recent years used by Sarnat and Flores-Sarnat [22] shifts the emphasis to a particular somatic cell type; however, when the disorder results from a germ line mutation, all somatic cells are affected. There may also be additional manifestations in cells and tissues not derived from the neural crest, such as seen with dysplasia of the tibia in NF1. Hence at present it

seems a good compromise to stay with the descriptive term “neurocutaneous disorders”.

The Spectrum of Neurocutaneous Disorders

Many of the NCD are present at birth or manifest early in childhood. Cutaneous lesions possess characteristic patterns (whorled, ash leaf, streaky, often S- or V-shaped) that follow *Blaschko lines* [23]. These lines propose an embryonic origin and do not suggest a pathological mechanism. The spectrum of NCD encompasses three groups: (1) tumour suppressor defects, (2) metabolic enzyme defects, and (3) non-progressive malformations, the last of which may also be observed in the first two groups. Examples of tumour suppressor diseases include neurofibromatosis type 1, tuberous sclerosis complex, von-Hippel-Lindau syndrome and Gorlin-Goltz syndrome. Enzyme defects leading to metabolic disorders are observed in CHILD syndrome and Sjögren-Larsson syndrome, whereas Klippel-Trenaunay syndrome and PHACE syndrome exemplify primarily vascular malformations.

Development of the Neural Crest

In phylogenesis the neural crest becomes first recognizable as a separate structure in vertebrates. Neural crest cells are the origin of all melanocytes (except for neuromelanin containing neurons in the CNS), all peripheral nervous system sensory neurons, postganglionic neurons, Schwann cells, satellite cells of dorsal root and autonomic ganglia, and of endocrine cells of paraganglia including adrenergic cells of the adrenals. In addition neural crest cells at the cranial end of the neural tube differentiate into the cartilage and membranous bone of the face and calvarium, connective tissue, smooth muscle of the vasculature, and the globe (except for retina and choroid) and are involved in the formation of leptomeninges [24]. In the human embryo the neural crest develops between gestational day 22 and 26 when the lateral borders of the neural plate close to form the neural tube. Some of the cells at the lateral borders of the neural plate separate and form a flat layer between the surface ectoderm and the neural tube (Fig. 1). This process is induced by SOX E transcription factor, bone morphogenic protein (BMP), fibroblast growth factor proteins (FGF) and proto-oncogenic molecules of Wnt and the hedgehog family (Hh). Consecutively, cells delaminate under the influence of transcription factors including FoxD3, slug and snail [25]. The cells start to migrate in three different directions under the influence of Sox10 and other signalling molecules: (1) the dorsal route under the surface ectoderm gives rise to melanocytes, (2) the ventrolateral pathway leads to differentiation into sensory neurons and their satellite

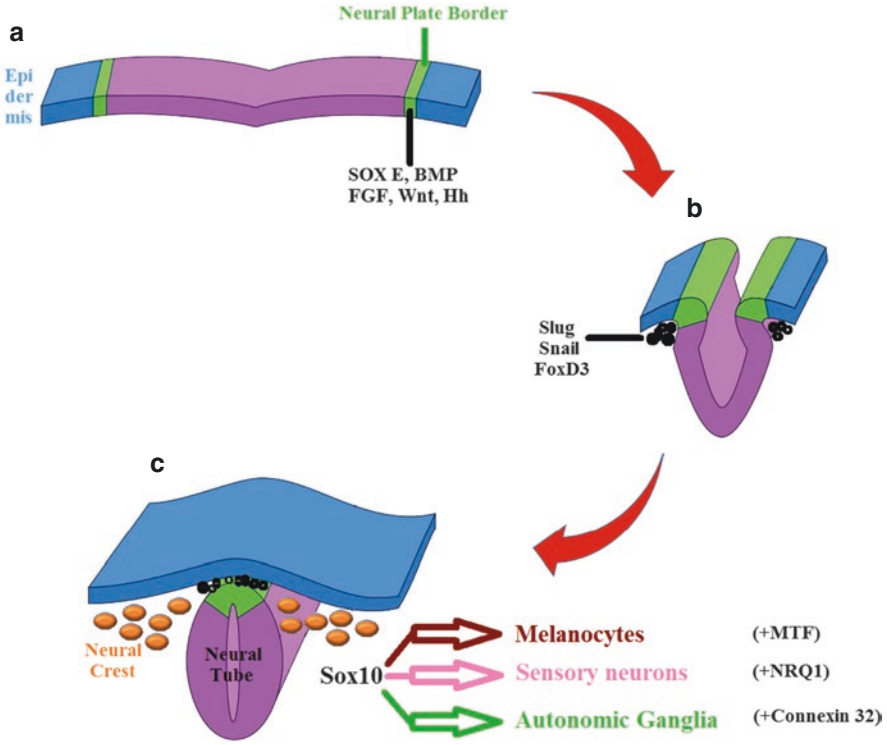

Fig. 1 Neural crest formation and cell lineage segregation: (**a**) neural crest cells are induced by bone morphogenic protein (BMP), fibroblast growth factors (FGF), SOX E, and proto-oncogenic molecules of Wnt and the hedgehog family (Hh) at the lateral border of the neural plate formation; (**b**) delamination of neural crest cells takes place under the influence of transcription factors including FoxD3, slug and snail; (**c**) under the influence of SOX10 and other signalling molecules, neural crest cells migrate in three main directions: the dorsal route under the surface ectoderm gives rise to melanocytes; the ventrolateral pathway results in formation of sensory neurons and satellite cells; and cells of the ventromedial pathway differentiate into autonomic ganglia [25, 26]

cells, and (3) cells following the ventromedial pathway differentiate into autonomic ganglia [26]. In the spinal cord, migration of neural crest cells is initiated only after the somite has formed the dorsal dermatomyotome and the ventral sclerotome. The continuous band of neural crest cells and also the axons of motor neurons can only penetrate into the rostral half of each sclerotome and are thereby segmented into sensory and motor roots [27]. Ligands that block migration are Ephrin in Eph expressing cells and semaphorin 3A and 3F in neuropilin 1 and 2 expressing cells [28].

At the cephalic level some ganglia are *not* derived from neural crest cells but rather from the ectodermal placodes, which are ectodermal thickenings induced by the neighbouring neural tube. It is still a matter of debate how the lineage specification of the neural crest cells is determined. Certainly, intrinsic factors that designate the location and time point of when the cell emerges are important, but extrinsic

factors such as gradients of signalling molecules may also play a role [28]. Schwann cell development starts at the 12th gestational week in humans [29]. In addition to Sox10, NRG1 and Notch1 are essential initiators of glial development [25]. Schwann cell precursors temporarily act as so-called boundary cap cells, which are located at the border of central and peripheral nervous system (*Redlich-Obersteiner* zone), preventing oligodendroglia to grow outside the CNS. These Schwann cell precursors later colonize nerves along the ventromedial migratory and spinal routes along or in front of the outgrowing axons [29, 30]. In addition to axon diameter, differentiation into myelinating Schwann cells is found to depend on Oct-6-EGR2/Krox-20-signalling whereas differentiation into non-myelinating Schwann cells was found to be associated with Pax-3 [30–32].

The Book's Purpose

The aim of this book is to raise awareness of both the more common and the rare neurocutaneous disorders, to provide salient features of individual condition, and to be a unique compendium and resource for all healthcare providers encountering and treating children and adults with these diseases. Historical facts as an introduction to each disease illustrate how far we have come in defining these conditions, and how much further we need to go to treat and ultimately prevent these from occurring. The numerous figures and tables are to assist in making accurate clinical diagnoses so that proper testing, counselling and treatment can be considered.
The chapters are written from the perspective of different medical disciplines. As a result, some redundancy could not be avoided, but it ensures precision and elaboration of relevant information germane to each particular disease.

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Part I
Aetiology and Diagnostics of Neurocutaneous Disorders

Chapter 1
Genetics of Neurocutaneous Syndromes

Eric Legius

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Due to the improved techniques of genetic analysis, we know the underlying genetic cause and mechanism for the majority of neurocutaneous syndromes. Genetic testing becomes more and more important to confirm a clinical diagnosis. This allows to predict and prevent potential complications and to initiate therapy in specific cases. A *genetic diagnosis* is important for the possibility of testing relatives and for reproductive choices such as prenatal and preimplantation genetic testing where relevant. The different genetic mechanisms observed in neurocutaneous syndromes will be explained in this chapter.

Mendelian Inheritance

Many neurocutaneous syndromes follow a typical Mendelian inheritance pattern. Some show an autosomal dominant inheritance pattern and others an autosomal recessive or X-linked dominant or recessive pattern (Table 1.1). Some syndromes

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are virtually always caused by variants in the same gene (Von Hippel-Lindau syndrome, ataxia-telangiectasia, Bloom syndrome, etc.), and *some syndromes* can be caused by pathogenic variants in several genes (locus heterogeneity) such as Noonan syndrome, Rendu-Osler-Weber syndrome, tuberous sclerosis complex, xeroderma pigmentosum, Cockayne syndrome, etc. (Table 1.1). Pathogenic variants in the same gene can sometimes be associated with different syndromes. Pathogenic variants in *LZTR1* are reported in autosomal dominant inherited schwannomatosis and in both autosomal dominant and autosomal recessive inherited Noonan syndrome [1, 2]. Similarly pathogenic variants in *SMARCB1* can be associated with the developmental disorder Coffin-Siris syndrome, atypical teratoid rhabdoid tumours (AT/RT) in childhood, or familial schwannomatosis [3]. Variants in *PTPN11* can be

Table 1.1 Neurocutaneous syndromes with Mendelian inheritance pattern

Autosomal dominant inheritance
Carney complex [*PRKAR1A*]
Legius syndrome [*SPRED1*] and neurofibromatosis type 1 (NF1) [*NF1*]
Neurofibromatosis type 2 (NF2) [*NF2*] and schwannomatosis [*SMARCB1, LZTR1*]
Nevoid basal cell carcinoma (NBCC, Gorlin-Goltz syndrome) [*PTCH1, SUFU*]
Noonan syndrome and Noonan syndrome with multiple lentigines (NSML) [*PTPN11, SOS1, KRAS, RAF1, RIT1, SOS2, LZTR1, MRAS, RRAS, CBL*]
PTEN hamartoma tumour syndrome (PHTS) (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome) [*PTEN*]
Tuberous sclerosis complex (TSC) [*TSC1, TSC2*]
Rendu-Osler-Weber syndrome (ROW) [*ENG, ACVRL1, GDF2, MADH4*]
Von Hippel-Lindau syndrome [*VHL*]
Autosomal recessive inheritance
Ataxia telangiectasia (Louis-Bar syndrome) [*ATM*]
Bloom syndrome [*BLM*]
Cockayne and xeroderma pigmentosum and xeroderma pigmentosum variant [*ERCC8, ERCC6, ERCC5*, *ERCC3*, *ERCC4*, *XPA*, *XPC*, *ERCC2*, *DDB2*, *POLH*]
Cerebrotendinous xanthomatosis [*CYP27A1*]
Chédiak-Higashi syndrome [*LYST*]
Dorfman-Chanarin syndrome (non-bullous ichthyosiform erythroderma) [*ABHD5*]
Ichthyosis hystrix-like deafness (HID) [*GJB2*]
Keratitis-ichthyosis-deafness autosomal recessive (KIDAR) [*AP1B1*]
Sjögren-Larsson syndrome [*ALDH3A2*]
X-linked dominant inheritance
Incontinentia pigmenti (IP, Bloch-Sulzberger syndrome) [*IKBKG = NEMO*]
Congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) [*NSDHL*]
Linear skin defects with multiple congenital anomalies (MIDAS: *mi*crophthalmia, *d*ermal *a*plasia, *s*clerocornea) [*HCCS, COX7B, NDUFB11*]
Orofaciodigital syndrome type 1 (OFD1) [*OFD1 = CXORF5*]
X-linked recessive inheritance
Angiokeratoma corporis diffusum (Fabry disease) [*GLA*]

associated with Noonan syndrome, and certain specific variants are associated with Noonan syndrome with multiple lentigines [4]. Some variants in GJB2 can be responsible for the autosomal recessive inherited ichthyosis hystrix-like deafness syndrome, and other variants are only responsible for deafness [5]. Variants in some of the genes listed in Table 1.1 are frequently observed as somatic variants in cancer cells (*NF1*, *LZTR1*, *PTPN11*, *CBL*, *KRAS*, *NRAS*, *PTEN*, *PTCH1*, *VHL*, *ATM,* etc.) [6].

Many of the syndromes listed under autosomal dominant inheritance are caused by a heterozygous pathogenic variant in a tumour suppressor gene with subsequent somatic inactivation of the normal allele in affected tissue (*PRKAR1A*, *NF1*, *SPRED1*, *NF2*, *SMARCB1*, *LZTR1*, *PTCH1*, *SUFU*, *PTEN*, *TSC1*, *TSC2*, *VHL*) (Fig. 1.1d). This is also the case for Rendu-Osler-Weber syndrome where haploinsufficiency of the implicated genes was thought to be sufficient for disease causation [7] without the need for a second hit in the normal allele of the gene. But more recently low-level second hit pathogenic variants have been reported in the vascular malformations associated with the syndrome [8]. The genes implicated in Noonan syndrome and Noonan syndrome with multiple lentigines are all part of the RAS pathway and the heterozygous pathogenic variants (Fig. 1.1b) are missense variants activating the protein resulting in a hyperactive signalling through the RAS

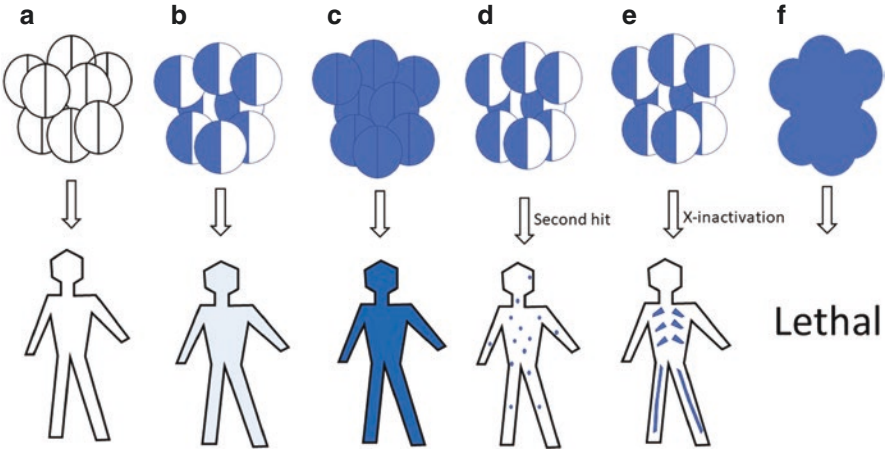

Fig. 1.1 (**a**) Shows a normal embryo with two normal alleles per gene resulting in an unaffected individual. (**b**) Shows an embryo heterozygous for a pathogenic variant resulting in an individual affected by an autosomal dominant inherited disease (e.g. Noonan syndrome). (**c**) Shows an embryo with a bi-allelic pathogenic variant resulting in an individual affected by an autosomal recessive inherited disease (e.g. Bloom syndrome). (**d**) Shows an embryo heterozygous for a dominant inherited pathogenic variant in a tumour suppressor gene causing disease after developing a "second hit" in the normal allele later in development (e.g. café au lait spots and neurofibromas in neurofibromatosis type 1). In (**e**) a female embryo is shown heterozygous for an X-linked dominant pathogenic variant resulting in a linear cutaneous phenotype in the female individual depending on the X-inactivation pattern (e.g. incontinentia pigmenti). (**f**) Shows a male embryo hemizygous for an X-linked dominant pathogenic variant lethal in males

pathway [4]. These are dominant activating variants, and there is no need for a second hit in the normal allele to cause symptoms (Fig. 1.1b). An exception to the dominant activating variants in Noonan syndrome is the *LZTR1* inactivating variants [2]. It has been shown that LZTR1-mediated ubiquitination inhibits RAS signalling by attenuating its association with the membrane. Loss of LZTR1 function results in a higher percentage of membrane-bound RAS resulting in an increased signalling through transmembrane tyrosine kinase growth factor receptors [9]. Depending on the effect size of the pathogenic variant, a heterozygous or a biallelic variant is needed to cause Noonan syndrome.

Some of the syndromes in the autosomal recessive group are caused by *pathogenic variants* in genes coding for proteins important for genome integrity (ATM, BLM, *ERCC8*, *ERCC6*, *ERCC5*, *ERCC3*, *ERCC4*, *XPA*, *XPC*, *ERCC2*, *DDB2*, *POLH*), intracellular transport (*LYST*, *AP1B1*), or cell-cell adhesion (*GJB2*) (Fig. 1.1c). The pathogenic variants in the genes involved in the X-linked dominant inherited syndromes are typically seen in females and are embryonically lethal in males (*IKBKG*, *NSDHL*, *HCCS*, *COX7B*, *NDUFB11*, *OFD1*) (Fig. 1.1e, f). Females survive because of the mosaic pattern of X-inactivation during early development with a normal activity of the gene product in a number of cells (*epigenetic mosaicism*). This mosaic pattern of involvement is frequently observed at the level of the skin in affected females [10]. Male embryos will not survive except for male embryos with Klinefelter syndrome (47,XXY), embryos with a 46,XX male karyotype, and embryos with post-zygotic mosaicism for the pathogenic variant or in case of a hypomorphic pathogenic variant associated with a minimal activity of the affected protein sufficient for the cells to survive [11]. X-linked recessive disorders are typically seen in males (*Fabry disease*) but can also be observed in females. In females the disorder is usually less severe, but this can vary depending on the X-inactivation pattern in cells of the involved tissues (see Chap. 46) [12].

Autosomal dominant inherited disorders typically show a large variability in expression, even within the same family. A large intrafamilial variability in phenotypic expression is often seen in neurofibromatosis type 1, neurofibromatosis type 2, Cowden syndrome, schwannomatosis, and some others (see Chaps. 3, 13, and 26). In these syndromes a second hit is needed for the typical symptoms to occur (Fig. 1.1d). The timing and location of second hits may vary from individual to individual, and the severity of the phenotype is difficult to predict from the genotype. In neurofibromatosis type 1, *melanocytes* from café au lait spots and Schwann cells from neurofibromas show independent second hits, specific for the individual café au lait spot or neurofibroma [13, 14]. Sometimes the genotype allows to predict the phenotype. A complete deletion of the responsible gene and some of the flanking genes might result in a more severe phenotype as is seen in microdeletions affecting the *NF1* gene [15]. Sometimes a deletion results in a milder phenotype as is observed in some deletions affecting the VHL gene including the *BRK1* gene [16]. Co-deletion of this gene together with *VHL* protects against renal cancer in VHL disease. The same *phenomenon* is also observed in 22q11 deletions responsible for velo-cardio-facial syndrome which are not associated with schwannomatosis although the *LZTR1* gene is localised in the deletion region [17]. In these syndromes

tumours result from loss of heterozygosity of the normal allele, and in case of a larger constitutional deletion affecting several genes, the total absence of these genes (*nullizygosity*) after loss of heterozygosity might be lethal for the cells and might confer protection against tumour formation.

Some genetic variants might show a specific phenotype. This has been observed in 10% of individuals with neurofibromatosis type 1 [18]. Some pathogenic missense variants in Von Hippel-Lindau syndrome are associated with a higher risk for pheochromocytoma [19] or for pancreatic neuroendocrine tumours [20] (see Chap. 28). In neurofibromatosis type 2, the location of the pathogenic variants is associated with prognosis [21]. *TSC2* variants in tuberous sclerosis are frequently associated with a more severe phenotype compared to *TSC1* variants and with a frequent occurrence of de novo mutations [22] (see Chap. 27). Some specific pathogenic missense variants in *TSC2* are associated with a milder phenotype [23].

Certain genetic diseases show a reduced penetrance with phenotypically unaffected individuals carrying the same heterozygous pathogenic variant as affected relatives. Reduced penetrance is a well-known phenomenon in *LZTR1*-associated schwannomatosis [1]. Many other autosomal dominant disorders show virtually complete penetrance but variable expressivity. In some autosomal dominantly inherited diseases, affected children do not have affected parents. This might be due to reduced penetrance in one of the parents or to a de novo pathogenic variant in the affected child. In NF1 and NF2, 50% of cases have a de novo pathogenic variant [24]. Genetic diseases with an autosomal dominant inheritance pattern and a severe phenotype frequently show a high percentage of de novo mutations due to reduced reproductive fitness in affected individuals [25] (see also *TSC2* pathogenic variants).

Mosaicism

Sometimes a de novo pathogenic variant of an autosomal dominant disorder originates after fertilisation resulting in a milder generalised or a segmental phenotype [10] (Fig. 1.2a) with less chances of transmitting the pathogenic variant to offspring. The occurrence of *mosaicism* in a de novo case might be one of the reasons to explain some of the variability in the phenotypic expression of autosomal dominantly inherited disorders, as was nicely demonstrated for TSC2 pathogenic variants [26] (see Chap. 27). A phenotypically normal parent with more than one affected child might show gonadosomatic (*gonosomal*) or only gonadal mosaicism [27]. For this reason a lower but not zero recurrence risk is given to phenotypically normal parents with a child affected by an autosomal dominant inherited disorder as a result of a de novo mutation [28]. Somatic or gonadosomatic mosaicism can be easily observed in genetic diseases with an autosomal dominant inheritance pattern and skin features (Fig. 1.2a, d). In these mosaic cases, it might not be possible to detect the responsible pathogenic variant in the DNA of the white blood cells, and analysis of the affected tissues/cells is needed to find the responsible pathogenic variant. In neurofibromatosis type 1, it is important to analyse the melanocytes from

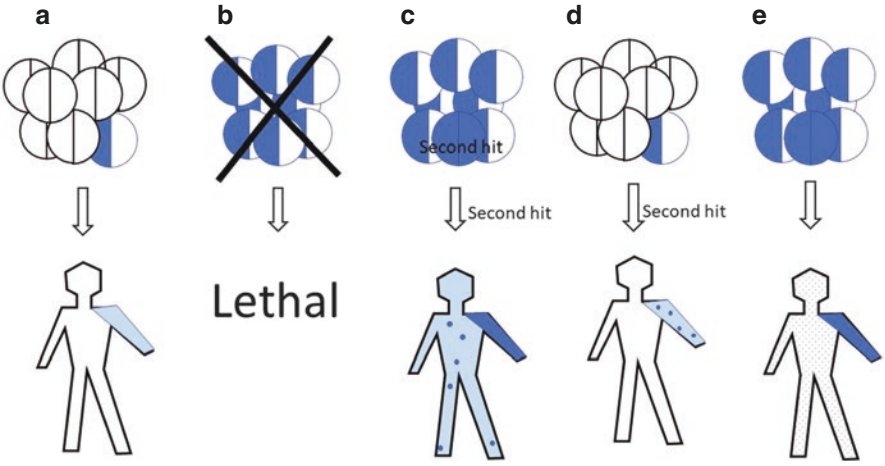

Fig. 1.2 (**a**) Shows an embryo with a heterozygous pathogenic variant in only one cell resulting in an individual with a segmental distribution (left arm) of symptoms due to somatic mosaicism as seen in PIK3CA-related segmental overgrowth syndrome. (**b**) Is a dominant pathogenic variant that is lethal for the embryo if it is present in all cells. (**c**) Is a schematic of an autosomal dominant disorder with a "second hit" in the early embryo in a tumour suppressor gene resulting in an individual with a localised more severe phenotype (left arm). The rest of the body shows the typical phenotype associated with second hits later in development. (**d**) Shows an embryo mosaic for a heterozygous pathogenic variant in a tumour suppressor gene resulting in an individual with a segmental phenotype (left arm) with symptoms in cells with a second hit in the normal allele during later development. Segmental neurofibromatosis type 1 is an example of this phenomenon. (**e**) Shows an embryo heterozygous for an autosomal recessive pathogenic variant. There is a cell in the embryo with a somatic mutation in the normal allele of the same gene resulting in a mosaic phenotype for the autosomal recessive disorder in the individual (left arm)

more than one café au lait spot to differentiate the common pathogenic variant (first hit) from the *café au lait* spot-specific individual pathogenic variant (*second hit*) (Fig. 1.2d). The same is true for neurofibroma-derived Schwann cells in NF1 individuals [29] and for schwannomas in mosaic neurofibromatosis type 2 [30] showing frequently an overlapping phenotype with schwannomatosis [31, 32]. Mosaic TSC2 genetic analysis of affected skin lesions frequently reveals the pathogenic variant [26]. A mosaic PTEN pathogenic variant has been demonstrated in a boy with several glioneuronal hamartomata and autism spectrum disorder but without macrocephaly [33]. In the future more cases of mosaicism for autosomal dominantly inherited disorders will be demonstrated due to the general use of next-generation sequencing for genetic diagnosis which allows the detection of low-level mosaicism.

Some neurocutaneous syndromes are only observed in the mosaic state (Table 1.2). It is hypothesised that pathogenic variants in the involved genes are embryonically lethal in the non-mosaic state [27] (Fig. 1.2a, b). This is similar to the functional mosaicism in X-linked dominant disorders only observed in females with lethality in hemizygous male embryos (Table 1.1) (Fig. 1.1e, f). A parent mosaic for an embryonic lethal pathogenic variant does not have an increased risk for affected

Table 1.2 Neurocutaneous disorders observed in the mosaic state

Congenital melanocytic naevus syndrome [NRAS[a], BRAF[a]]
Curry-Jones or Happle-Tinschert syndrome [SMOH]
Encephalocraniocutaneous lipomatosis (ECCL) [FGFR1[a]]
Fine and whorled Blaschko-linear hypopigmentation (hypomelanosis of Ito) [mosaic chromosomal abnormalities, RHOA, MTOR[b], etc.]
Keratinocytic epidermal nevus syndrome [FGFR3[b], KRAS[a]]
Klippel-Trenaunay-Weber syndrome [PIK3CA[a]]
Linear and whorled nevoid hypermelanosis [KITLG[b]]
McCune-Albright syndrome (MAS) [GNAS]
Phakomatosis pigmentovascularis [GNA11, GNAQ]
Phakomatosis pigmentokeratotica [HRAS[b], KRAS[a], BRAF[b]]
PIC3CA-related segmental overgrowth syndrome (PROS) [PIK3CA[a]]
Proteus syndrome [AKT1]
Sebaceous naevus syndrome (Schimmelpenning) [HRAS[a], KRAS[a]]
Sturge-Weber syndrome [GNAQ]

[a]Some variants in these genes can be germline heritable
[b]Variants causing the described mosaic phenotype could potentially be transmitted to viable offspring

offspring. Listed in Table 1.2 with an asterisk are some pathogenic variants of genes that are *embryonically* lethal and *other* variants in the same gene which are germline heritable. An example of this last phenomenon is reported in the megalencephaly syndromes associated with pathogenic variants in the PI3K-AKT-MTOR pathway [34]. Pathogenic variants in these genes are missense variants activating the protein product and the involved pathway. Variants that result in a strong activation are germline lethal, and variants resulting in a milder activation might be germline heritable. Pathogenic variants of genes in Table 1.2 with a double asterisk can be responsible for a mosaic phenotype, and the variant can be potentially transmitted to viable offspring. A current enigma is the observation that the same *HRAS* pathogenic variant can cause phenotypically different conditions even in the mosaic state. Heterozygous *HRAS* pathogenic variants are the cause of the autosomal dominantly inherited Costello syndrome. Most cases show the p.Gly12Ser variant, but in some rare cases variant p.Gly12Cys is reported [35]. The same two pathogenic variants have been detected in mosaic state in tissue from keratinocytic epidermal nevi (*syndrome*) [36, 37]. In addition some mild cases of Costello syndrome are caused by mosaicism for the same frequent *HRAS* pathogenic variant (p.Gly12Ser [38–40]), and there is one report of transmission from a mosaic parent to a child [38].

Typical autosomal dominantly inherited neurocutaneous syndromes caused by heterozygous pathogenic variants in a tumour suppressor gene are associated with a "*second hit*" pathogenic variant in the normal allele in affected tissues (Fig. 1.1d). Every tumoral lesion in neurofibromatosis type 1, type 2, Cowden syndrome, tuberous sclerosis complex, schwannomatosis, Von Hippel-Lindau disease, Carney complex, and nevoid basal cell carcinoma syndrome (*NBCC*) shows a second hit pathogenic variant inactivating the normal allele of the responsible gene in the

tumour tissue. In some rare cases, this second hit pathogenic variant might occur in early embryonic development resulting in many cells and cell types with a biallelic inactivation of the involved gene (Fig. 1.2c). This type of mosaicism originating during early development results in a much more severe superimposed phenotype with a segmental distribution. This was labelled type 2 mosaicism by Happle [10]. It has been shown for the *PTEN* gene resulting in SOLAMEN syndrome [41] or other severe congenital malformations [42]. It has also been demonstrated in Gorlin syndrome (*NBCC*) [43] (see Chap. 29). The case reported by our group as ECCL syndrome with a *NF1* pathogenic variant [44] follows the same pathogenetic mechanism (unpublished data).

Sporadic forms of mosaic autosomal recessive conditions have also been observed. These individuals inherited one pathogenic variant from a parent, and the normal allele was mutated during early embryogenesis and is only present in the affected tissues as was demonstrated in a case of ectodermal dysplasia skin fragility syndrome [45] (Fig. 1.2e).

In rare cases revertant mosaicism can be observed where the pathogenic variant reverts back to the wild-type allele in some of the cells. This *phenomenon* can be observed easily at the level of the affected skin in genodermatoses [46] and is frequently due to mitotic recombination resulting in cells homozygous for the mutant allele and cells homozygous for the wild-type allele. If the cell line homozygous for the wild-type allele shows a growth advantage, then patches of "repaired" skin can emerge. Examples are ichthyosis with confetti, dyskeratosis congenita, epidermolysis bullosa, Kindler syndrome (*form of epidermolysis bullosa*), and Wiskott-Aldrich syndrome (see Chaps. 7, 8, 10, 37, and 39). In the autosomal recessive Bloom syndrome caused by compound heterozygosity for two different pathogenic variants, it is possible to observe a small percentage of white blood cell clones revertant for the increased sister chromatid exchange phenotype at the level of the chromosomes. This phenomenon was used to identify the location of the *BLM* gene because the breakpoints of the mitotic recombination responsible for the revertant mosaicism have to be localised between the two pathogenic variants in the gene (*if compound heterozygosity is present*) [47]. In individuals with Bloom syndrome who are homozygous for a pathogenic variant, this mechanism of revertant mosaicism cannot be observed.

A very instructive summary of mosaic skin abnormalities explaining the underlying genetic mechanisms involved in mosaicism was published by a working group of the European Reference Networks for rare skin diseases [48].

Table 1.3 lists some neurocutaneous syndromes with an unknown genetic cause. The aetiology of these syndromes is still unsolved, and next-generation sequencing using exome analysis of the coding sequence of all known genes or genome sequencing was normal [49]. The genetic cause might be hidden somewhere in a non-coding part of the genome or related to low-level mosaicism in a specific cell type that is difficult to isolate. Other explanations might be digenic inheritance, epigenetic abnormalities, complex interactions between the genotype and environment, or an as yet unknown mechanism.

Table 1.3 Unresolved neurocutaneous syndromes

Cerebello-trigemino-dermal syndrome (Gómez-López-Hernández syndrome)
Oculocerebrocutaneous syndrome (Delleman-Oorthuys)
Hallermann-Streiff syndrome
PHACE (posterior fossa anomalies, haemangioma, arterial anomalies, coarctation of aorta/cardiac anomalies, and eye anomalies)
Wyburn-Mason syndrome (multiple arterio-venous malformations)

Diagnosis

For many of the neurocutaneous syndromes discussed in this book, *diagnostic criteria* have been established. In the past these diagnostic criteria were based on clinical findings only, but more recently most of the diagnostic criteria also include molecular genetic testing. Combinations of clinical findings alone or in combination with a pathogenic variant in an involved gene will allow to make a diagnosis. Diagnostic criteria can be easily found for syndromes listed in GeneReviews® (https://www.ncbi.nlm.nih.gov/books/NBK1116/). Molecular diagnosis is important in many cases due to the clinical overlap of some neurocutaneous syndromes. Examples where molecular diagnosis is crucial for diagnosis are the different segmental overgrowth syndromes caused by mosaic pathogenic variants in the PI3K/PTEN/AKT/TSC/mTORC1 signalling pathway [50, 51], mosaic neurofibromatosis type 2, and schwannomatosis [31, 32]. Molecular analysis is very helpful to make the correct diagnosis in the presence of multiple *café au lait* spots and differentiate neurofibromatosis type 1 from Legius syndrome, Noonan syndrome with multiple lentigines, McCune-Albright syndrome, constitutional mismatch repair syndrome, and others (see Chaps. 2 and 42) [52–55]. Molecular analysis is moving from single gene analysis to sequencing of panels of genes potentially responsible for a clinical phenotype [55] and to exome analysis of all known protein coding genes if the clinical phenotype is potentially associated with many genes [56]. Examples of this last situation are epilepsy, intellectual disability, and autism because they can be caused by variants in many possible genes. Next-generation sequencing allows to analyse variants in many genes at the same time. Many variants in the potentially responsible genes are detected, and it is not always simple to know if a variant is pathogenic or not and if a detected variant is responsible for the phenotype of the affected individual. For this reason standards and guidelines for variant calling [56] and the interpretation of constitutional sequence variants and copy number variants have been developed [57, 58]. Variants are classified in five different classes (*benign*, *likely benign*, *uncertain significance*, *likely pathogenic*, and *pathogenic*) using an algorithm giving specific weights to different characteristics of the variants. Initiatives to try to define the clinical relevance of genes and variants have been established such as ClinGen [59] and ClinVar [60] as well as locus-specific databases such as LOVD [61] and HGMD [62]. Nevertheless it remains sometimes very difficult to correctly classify variants, and the same variant can be put in different classes by different labs [63].

In cases of suspected mosaicism, special attention has to be paid to biopsy the correct tissue and isolate the responsible cell type if necessary and to use sequencing techniques appropriate for the detection of low-level mosaicism [26, 29, 48].

A diagnosis is important for the correct prognosis, for the start of proper surveillance and treatment [64], and to avoid potential harmful exposures such as UV exposure in xeroderma pigmentosum and irradiation in NBCC (see Chap. 31). After a correct diagnosis, the affected individual and the family can find support in the respective patient support groups leveraging patient empowerment [65]. There is an ongoing effort not only to establish diagnostic criteria but also to establish guidelines for surveillance and treatment of many rare diseases through several initiatives such as the European Reference Networks for rare diseases [48, 66, 67]. Treatment can consist of classical treatment regimens, repurposed drugs, or newer treatments such as targeted therapies [68–71], gene therapy [72], gene editing [73], or modulation of gene regulation [74]. Therapeutic options will only increase in the future as a result of a strong interest in rare diseases in the academic world as well as in the industry [64].

A molecular diagnosis is required for genetic testing of relatives and to offer reproductive choices such as *prenatal* or *preimplantation* genetic testing. Prevention of genetic disease through carrier testing, prenatal, and preimplantation genetic testing is important and will become even more important in the future.

Relevant Databases

ClinVar:

https://www.ncbi.nlm.nih.gov/clinvar/

ClinGen:

https://clinicalgenome.org/

European Reference Networks (ERN) for rare diseases

https://ec.europa.eu/health/ern/networks_en

GeneReviews:

https://www.ncbi.nlm.nih.gov/books/NBK1116/

Human Genome Mutation Database (HGMD):

http://www.hgmd.cf.ac.uk/ac/index.php

Human Genome Variation Database (HGVD):

https://www.hgvd.genome.med.kyoto-u.ac.jp/

Human Genome Variation Society (HGVS):

https://www.hgvs.org/

Leiden Open Variation Database (LOVD):

https://www.lovd.nl/

Online Mendelian Inheritance in Man (OMIM):

https://www.ncbi.nlm.nih.gov/omim

Orphanet:

https://www.orpha.net/consor/cgi-bin/index.php?lng=EN

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Chapter 2
Superimposed Mosaicism in Neurocutaneous Syndromes

Rudolf Happle

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General Considerations

Until the end of the past century, all experts in the field believed that in autosomal dominant neurocutaneous syndromes such as neurofibromatosis 1, a segmental involvement reflected the presence of a postzygotic new mutation. Today this view is no longer correct. The term "segmental neurofibromatosis" has become ambiguous since the dichotomy between simple segmental and superimposed mosaicism (Fig. 2.1) was delineated [1]. Simple segmental mosaicism originates from a postzygotic new mutation occurring in a healthy embryo. It reflects heterozygosity and becomes manifest at the age when the nonsegmental phenotype would appear. Within the involved segment, the degree of severity corresponds to that observed in the nonsegmental phenotype. By contrast, superimposed mosaicism develops in a

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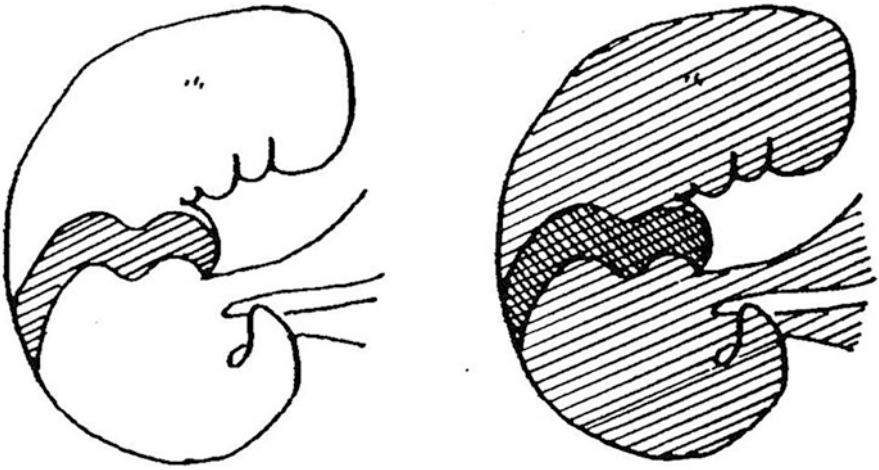

Fig. 2.1 Two different categories of segmental manifestation as noted in autosomal dominant skin disorders. Left: simple segmental mosaicism reflects heterozygosity originating from an early postzygotic mutation occurring in an otherwise healthy embryo. Right: superimposed mosaicism originating from early loss of heterozygosity occurring in a heterozygous embryo. The segmental involvement is rather pronounced and overlaid on the nonsegmental trait

heterozygous embryo. It reflects loss of heterozygosity that occurred at an early developmental stage. This form of mosaic involvement is noted in NF1 much earlier than the nonsegmental phenotype. Within the involved area, the degree of severity is far more pronounced, being superimposed on the disseminated lesions.

In the past, simple segmental mosaicism was called "type 1 segmental manifestation," whereas superimposed mosaicism was named "type 2 segmental manifestation" [1, 2]. In the synonym "superimposed mosaicism," the word segmental would be redundant because this type of mosaicism is always segmental [3].

The concept of superimposed mosaicism in autosomal dominant disorders was initially proposed as a hypothesis from *Happle.* Meanwhile, the theory has been confirmed at the molecular level in various disorders including Hailey-Hailey disease, Darier disease, neurofibromatosis type 1, Gorlin syndrome, and PTEN hamartoma syndrome [4, 5]. Hence, it can today be taken as a well-established concept.

The discrimination between simple segmental and superimposed mosaicism is of practical importance for the purpose of genetic counseling. In the simple segmental type, the risk of transmitting the mutation to the next generation is slightly increased, whereas patients showing superimposed mosaicism run a 50% risk of giving birth to a diffusely affected child. The differences between the two types will be explained in more detail in the following paragraphs.

Neurofibromatosis Type 1 (NF1)

The well-known simple segmental NF 1 has so far been documented in more than 160 cases. It is characterized by a mosaic manifestation of neurofibromas or pigmentary disturbances or Lisch nodules or by a combination of such lesions. It should be noted that the term "somatic mutation" excludes gonadal mosaicism, which is why the word "postzygotic mosaicism" is preferable. Affected individuals run an increased risk of giving birth to a diffusely affected child, because a simultaneous mosaic involvement of the gonads can never be excluded. Of note, "gonosomal mosaicism" is a misnomer that means something quite different [6].

By contrast, superimposed mosaic neurofibromatosis 1 seems to occur even more frequently than simple segmental involvement [5]. All sizable plexiform neurofibromas as noted in patients with NF1 (Fig. 2.2) can today be categorized as examples of superimposed mosaic NF1 [7]. In other patients, superimposed mosaicism may manifest in the form of a large hyperpigmented band with intralesional cutaneous or subcutaneous neurofibromas [8], or as a very large unilateral or bilateral café au lait macule (Fig. 2.3), or as a linear arrangement of large subcutaneous neurofibromas [9].

The theory of superimposed mosaic NF1 can be taken as proven at the molecular level [11, 12]. The concept offers an explanation for several reports of so-called genetic transmission of segmental NF1 [13]. Today it is clear that in such cases the parent had simple segmental NF1. Because of a simultaneous gonadal involvement, the parent can transmit the mutation to a child who may develop, by chance, superimposed mosaicism being overlaid on the nonsegmental trait that may become manifest later in life. Or, by way of exception, both parent and child may be affected by superimposed mosaic NF1 [5].

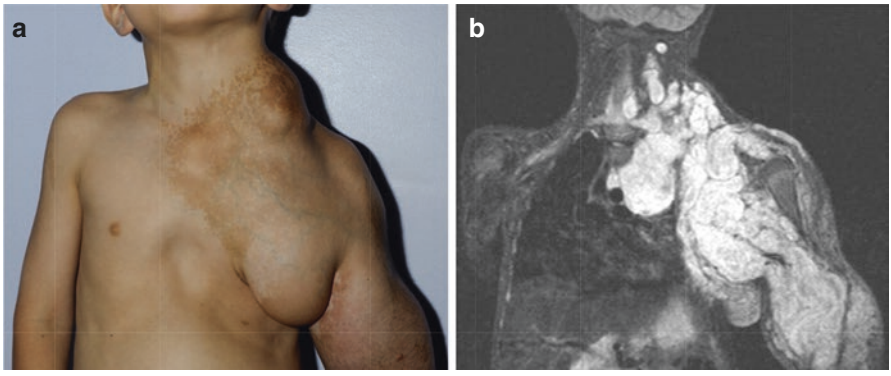

Fig. 2.2 Plexiform neurofibroma in a pediatric patient with NF1. (**a**) Clinical appearance, (**b**) MRI study [10] (Dagalakis et al. 2014; reprinted with permission from Elsevier, UK.) This case represents a typical example of superimposed mosaic NF1

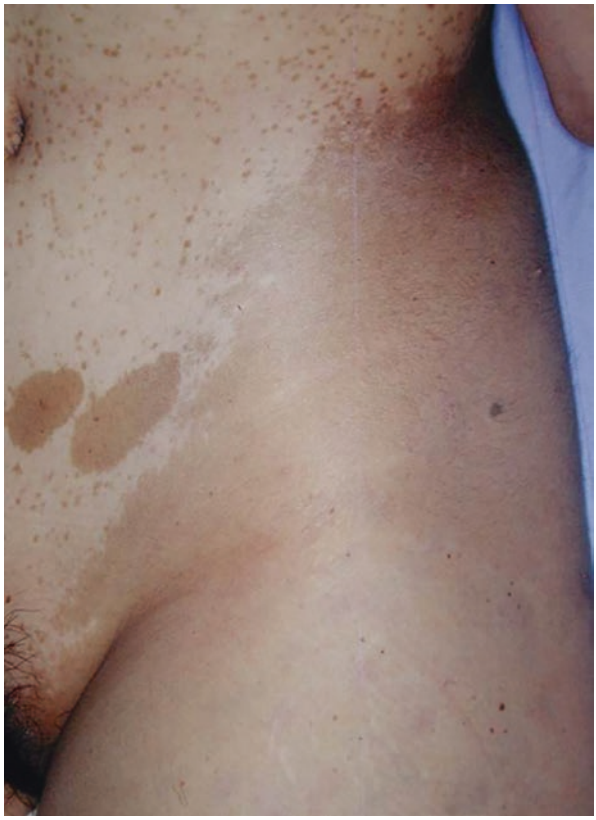

Fig. 2.3 Giant café au lait macule in a 20-year-old woman with NF1, suggesting superimposed mosaicism [11] (Yang et al. 2008; reprinted with permission from Elsevier, UK)

Moreover, the concept can explain why plexiform neurofibromas tend to manifest much earlier than the disseminated cutaneous neurofibromas of the usual type and why they are particularly prone to transform into a malignant peripheral nerve sheath tumor (see Chap. 26).

Neurofibromatosis Type 2 (NF2)

In a patient with NF2, Dr. Susan Huson from Manchester has documented a unilateral linear café au lait hyperpigmentation which can be best explained as a superimposed mosaic manifestation of the disorder (see Chap. 26) [5].

Legius Syndrome

The clinical features of this autosomal dominant disorder are reminiscent of NF1, including learning difficulties, but neurofibromas are absent and the underlying mutations involve the SPRED1 gene. The first report on Legius syndrome [14]

contains a photograph suggesting superimposed mosaicism in the form of a large, unilateral, flag-like café au lait hyperpigmentation involving the trunk (see Chap. 1). This extensive macule was apparently overlaid on multiple small disseminated café au lait spots that were clinically indistinguishable from those of NF1. The authors documented loss of the SPRED1 wild-type allele in melanocytes obtained from café au lait spots, but it is not clear whether their molecular analysis included the large segmental hyperpigmentation. The similarity between Legius syndrome and NF1 can be explained by the fact that both SPRED1 and NF1 involve the same RAS-MAPK pathway [14].

Tuberous Sclerosis Complex (TSC)

In tuberous sclerosis complex (see Chap. 27), several cases of simple segmental involvement in the form of unilateral facial angiofibromas or hypomelanotic macules have been reported (for review) [5]. Notably, however, cases suggesting superimposed mosaicism were documented even more frequently. All sizable shagreen patches (Fig. 2.4) or fibrous plaques of the forehead obviously represent a superimposed mosaic involvement, although molecular proof is so far lacking in these particular lesions [2, 5]. Other features suggesting superimposed mosaicism in TSC include folliculocystic and collagen hamartoma [16] and unilateral macrodactyly [17–19]. Notably, cases of unambiguous superimposed mosaicism have sometimes been mistaken as a "forme fruste" of tuberous sclerosis [20, 21].

Molecular corroboration of the concept of superimposed mosaic TSC has been provided by *Tessarech* et al. [22]. A 5-year-old girl had classical features of non-mosaic TSC and enlargement of her right arm with pronounced overgrowth of the first, second, and third digits. In the peripheral blood, a pathogenic *TSC2* mutation was found in exon 34. In lesional tissue of the hyperplastic arm, an additional nonsense mutation in exon 15 of *TSC2* was documented, resulting in lesional compound heterozygosity.

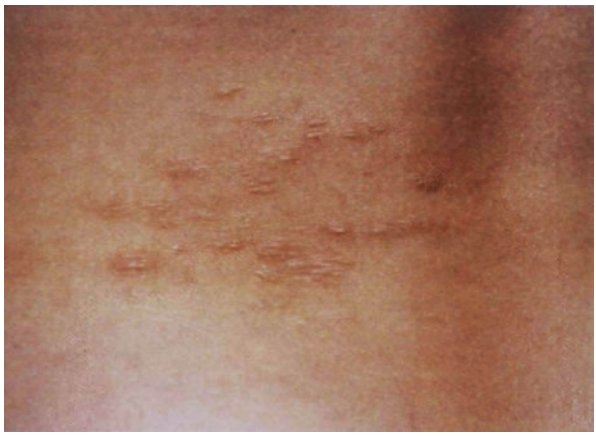

Fig. 2.4 Shagreen patch involving the left lumbar region in an 8-year-old girl with tuberous sclerosis [15], (Webb et al. 1996; reprinted with permission from Elsevier, UK). Such lesions suggest superimposed mosaicism

Extracutaneous manifestations of superimposed mosaic TSC include columnar defective structures radiating from the brain stem to cortex, cerebral "white matter migration lines," hemimegalencephaly, and linear hamartomatous lesions of the tongue [23]. Moreover, *Wiemer-Kruel* et al. [24] described multiple aortic aneurysms and congenital lymphatic malformation of the ipsilateral leg in a 7-year-old boy with TSC2.

PTEN Hamartoma Syndrome (Cowden Disease Included)

PTEN hamartoma syndrome (see Chap. 13) is also called "PTEN hamartoma tumor syndrome." This name, however, is redundant because the term hamartoma comprises the presence of tumors. The concept of superimposed mosaic PTEN hamartoma syndrome can be taken as proven [25, 26]. Many additional cases suggesting superimposed mosaicism have been documented [5]. Because the underlying genetic mechanism was not understood, numerous fanciful names such as Proteus syndrome [27], Proteus-like syndrome [28], PTEN hamartoma of soft tissue (PHOST; [29]), arteriovenous fistulas [30], or "hemimegalencephaly as part of Jadassohn nevus sebaceous syndrome" [31] were used to describe such superimposed mosaic involvement. The name *SOLAMEN* syndrome (segmental overgrowth, lipomatosis, arteriovenous malformation, epidermal nevus) as proposed by *Caux* et al. [25] has the disadvantage to suggest the existence of a distinct clinical entity, whereas the phenotype represents, in fact, merely a mosaic variant of *PTEN* hamartoma syndrome.

Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome)

In Gorlin syndrome (see Chap. 29), superimposed mosaicism was proven at the molecular level [32]. A 12-year-old girl had multiple congenital basal cell carcinomas involving exclusively the right side of her body, with an ipsilateral jaw cyst and linear arrangement of rather large plantar pits. Her father had nonsegmental Gorlin syndrome. A germline PTCH1 mutation in exon 18 was found in both father and daughter. In addition, the daughter had a postzygotic PTCH1 microdeletion in exon 3.

Another conspicuous case suggesting superimposed mosaicism was described by *Gutierrez* and *Mora* [33] (1986). A rather severe ipsilateral involvement of the brain was documented in this historical report.

Final Remark

Readers should keep in mind that, until today, many experts still ignore the genetic concept as delineated in this chapter. For example, if you read something about plexiform neurofibromas, it may happen that you know more than experienced authorities can tell you. If so, just enjoy the progress of scientific knowledge.

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Chapter 3
Neuroimaging and Sonography of Neurocutaneous Disorders

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Neuroradiology and Magnetic Resonance Imaging of Neurocutaneous Disorders

Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) is associated with an increased risk for the development of benign and malignant tumors involving neural and non-neural tissues. The most frequent tumor entity are benign neurofibromas (Fig. 3.1). MRI is the preferred imaging modality for evaluating the intracranial optic system. Intracranial signal abnormalities involving the basal ganglia, pons, cerebellar white matter, internal capsule, and splenium of the corpus callosum may be observed. These abnormalities are isointense to brain on T1WI, hyperintense on T2WI (see Chap. 26).

Brain Findings

Optic Gliomas

Optic pathway *gliomas* which are pilocytic astrocytomas (*WHO grade* I; see Chaps. 4 and 26) represent 2–5% of brain tumors in patients with NF1 and are the most common intracranial neoplasms. Fusiform enlargement of the optic nerves within the orbit can be recognized on CT or MRI. Bone windows on CT may demonstrate an enlarged optic canal. MRI is an alternative method for demonstration of intracranial abnormalities. Optic nerve gliomas usually appear isointense to the brain on short and long TR images (Fig. 3.2).

Chiasmal and postchiasmal optic gliomas are more likely to demonstrate low signal intensity on T1-weighted images and higher signal intensity on T2-weighted images. Contrast enhancement is variable [1, 2]. On MR *spectroscopy* pilocytic astrocytomas usually demonstrate low *N*-acetylaspartate, elevated choline, and increased Cho/Cr ratio and high lactate, features that are usually associated with

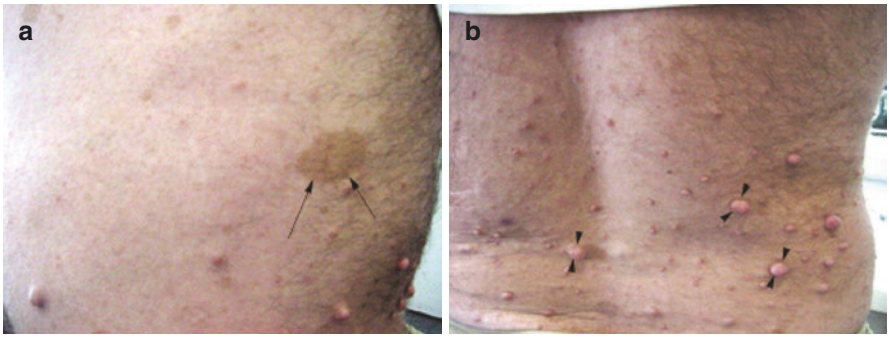

Fig. 3.1 (**a**) A 50-year-old man with characteristic café au lait spots (*arrows*); (**b**) the same man with multiple cutaneous nodules

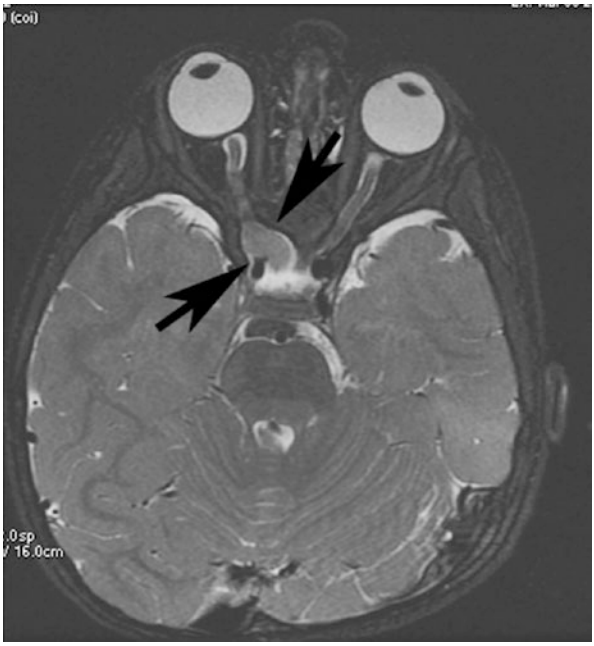

Fig. 3.2 Optic nerve glioma. Fusiform enlargement of the right optic nerve in a 4-year-old girl with NF1 (arrows)

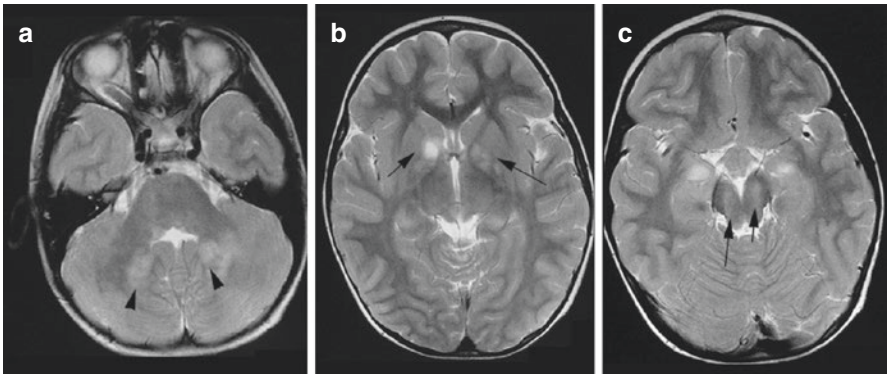

Fig. 3.3 A 5-year-old boy with NF1; (**a**) axial T2-weighted MRI demonstrates typical high signal areas in the deep white matter of the cerebellum; (**b**) bilateral high signal foci in the globus pallidus, and (**c**) in the cerebral peduncles (arrows)

high-grade tumors [3]. The most common MRI finding in the brain in NF1 consists of multiple bright areas on T2-weighted images. They are seen most often in the pons; cerebellum, especially the peduncles, midbrain, lentiform nucleus, globi pallidi, centrum semiovale and thalamus, and priventricular white matter (Fig. 3.3). These hyperintense T2-weighted image lesions are isointense on T1-weighted images and show no mass effect or contrast enhancement [4].

Basal ganglia lesions, characterized on MR by increased signal intensity on T1-weighted images, were observed in patients with documented neurofibromatosis. These lesions most often involve the globus pallidus and internal capsules in a bilateral and symmetric fashion and extend across the anterior commissure resulting in a *dumbbell* configuration. Their signal characteristics and morphology suggest that they represent heterotopias containing *Schwann cells* and/or melanin deposits.

Non-optic Glial Tumors

Fifteen to 20% of children with NF1 develop *low-grade* astrocytomas, especially pilocytic astrocytomas (see Chaps. 4 and 26). MRI is the best modality for detection and evaluation of such tumors. In NF1, two of the most common lesions are gliomas and hamartomas. *Although* most of bright signal seen on MR regress with age, development of tumors in these areas of abnormality has been published in 11% of patients. Children with a large number and volume of bright areas should be followed closely with *regular MR* examinations because of an increased risk of proliferative change. NF1-associated low-grade fibrillary astrocytoma can be difficult to distinguish from bright areas. They are usually moderately *hypointense* on T1W images and *hyperintense* on T2W and show progression on follow-up imaging.

Vascular Alterations

Vascular manifestations of NF1 include renovascular stenosis with associated hypertension, cerebrovascular occlusion, visceral *ischemia*, and aneurysms of smaller arteries. Circle of *Willis* abnormalities in children with NF1 including arterial variants occur with an estimated twofold frequency compared to controls [5].

Meningioangiomatosis is a rare, benign, focal lesion of the leptomeninges and underlying cerebral cortex. The commonest finding on CT scan is a calcified, enhancing lesion with surrounding low density. Low or mixed central signal on T1- and T2-weighted images and surrounding high signal on T2-weighted sequences is seen on MRI [6].

Scull Abnormalities

The most common location of cranial defects is in the region of sphenoid wings; lambdoid suture, facial bones, and skull base are rarely sites of involvement (Fig. 3.4). The *majority* of skull defects are associated with an adjacent structural lesion, such as a plexiform neurofibroma or dural ectasia [7].

Macrocephaly in NF1 could be a sign of abnormal brain development. Volumetric analysis suggests that macrocephalics show enlargement of white matter volume specifically, consistent with *hypertrophy* or *hyperplasia* of myelinated tracts. White

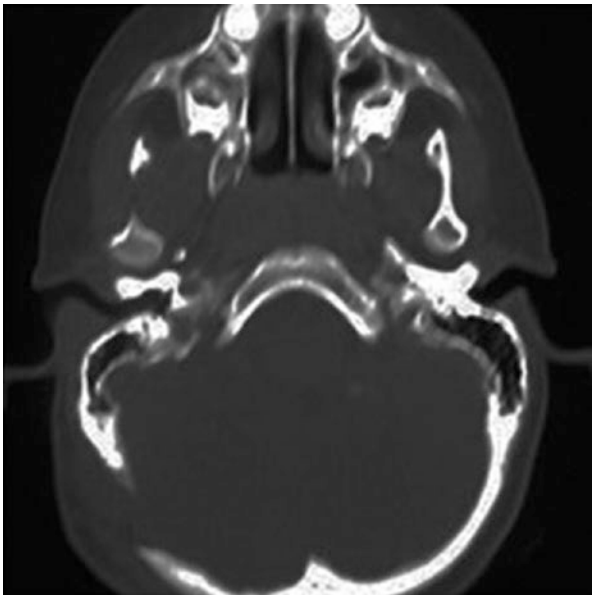

Fig. 3.4 Axial CT image (bone window) of a 6-year-old girl with NF1 shows an uncommon skull defect in the region of right lambdoid suture

matter volume in the *corpus callosum* is also increased, and the size of the brain stem is large for patient age [8].

Skeletal-Dural Abnormalities

Mesenchymal dysplasia causes numerous alterations in the skeleton and in some cases massive *scoliosis* and *kyphosis*. MRI is the modality of choice for evaluating the scoliosis. Oblique *axial* and *sagittal* and straight coronal images are best for visualizing the spinal canal and cord. Vertebral scalloping may be observed alone or in association with dural ectasia or neurofibroma [9].

Neoplasms

Spinal cord involvement in NF1 typically results from extramedullary growth of spinal nerve root tumors. On CT nerve sheath tumors usually are hypodense compared to muscle tissue. On MRI the tumors are iso- or hypointense on T1-weighted images and hyperintense compared with spinal cord on T2-weighted images. The central portion often demonstrates lower signal intensity on T2-weighted images. The *tumors* demonstrate heterogeneous enhancement on both CT and MRI [4]. Positron emission tomography with F-18 fluorodeoxyglucose is a method to assess increased glucose metabolism in malignant sarcoma [10] (see Chap. 26).

Neurofibromatosis Type 2

A hallmark in neurofibromatosis type 2 (NF2) are bilateral vestibular schwannomas which originate from Schwann cells. Schwannomas may develop in any peripheral nerve. MRI is the most sensitive imaging technique for detection of *schwannomas* even *small intracanalicular* (see Chap. 26). The signal intensity on MRI is usually similar to the brain on T1-weighted images and mild hyperintense on T2-weighted images [7]. *Heterogeneity* on T2-weighted images in large lesions is common. Intense contrast enhancement is present on T1-weighted images after intravenous gadolinium administration (Fig. 3.5) [4].

Meningiomas

The second most characteristic tumor of NF2 is meningiomas, which usually occur supratentorially in the falx and around the frontal, temporal, and parietal regions (see Chap. 4). *Typically*, they are peripheral *unilobular* masses with broad-based dural attachments and smooth, well-defined borders. On non-contrast CT the lesions appear as homogeneous high-density masses in relation with brain parenchyma. After the administration of contrast media, they show intense enhancement in approximately 80% of cases. On T1-weighted MR images, meningiomas are usually isointense or mildly hypointense to normal gray matter. On T2-weighted images, most tumors are isointense or mildly hyperintense compared with the gray matter.

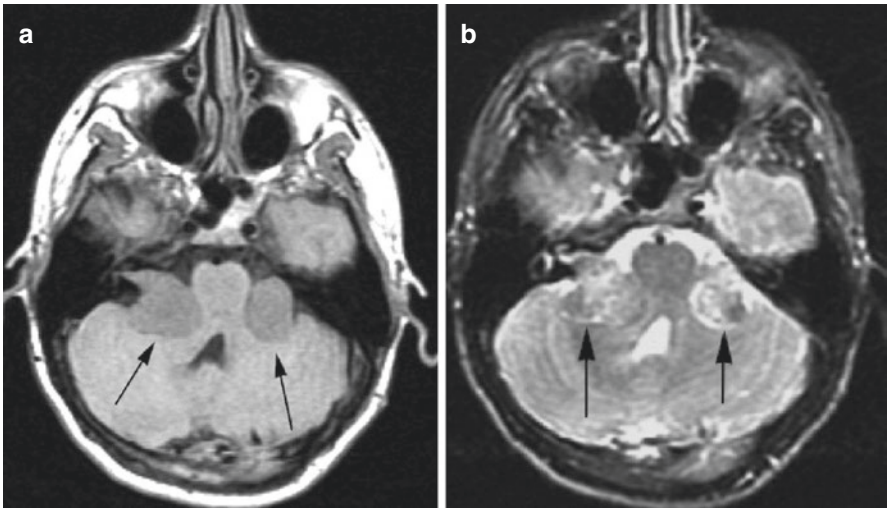

Fig. 3.5 A 19-year-old man with NF2 and bilateral neuromas; (**a**) axial T1-weighted image shows intermediate signal intensity masses in both cerebellopontine angles (arrow); (**b**) on axial T2-weighted MRI, the lesion is mild hypointense (arrows)

Ependymomas

Ependymomas may occur along the whole length of the spinal cord up to the infratentorial region [11] and enhance to varying degrees [4, 7].

Tuberous Sclerosis

CNS Manifestations

The four major intracranial manifestations of tuberous sclerosis (TBS) are *subependymal* nodules, cortical hamartomas, white matter lesions, and subependymal giant cell tumor. MRI has improved the detection of these lesions, especially cortical tubers and white matter lesions (see Chap. 27).

Hamartomas occur most commonly in the brain of TBS patients in a subependymal location (*up to 95% of patients*) protruding into the ventricle. The most common location is in the wall of the body of the lateral ventricle just posterior to the interventricular foramen. The signal intensity of *subependyma*l nodules is similar to that of white matter on TI-weighted images. Signal intensity on T2-weighted images may be heterogeneous. Densely *calcified* nodules demonstrate low signal intensity on MRI. After the administration of paramagnetic agent, hamartomas *shows* intense enhancement [12].

The *nodular* subependymal and linear parenchymal TBS lesions in infants under 3 months of age are hyperintense on T1-weighted images and hypointense on T2-weighted images as opposed to the reverse pattern of signal intensity in older persons [13]. FLAIR sequences are very sensitive for the detection of tubers in tuberous sclerosis patients [14].

Cortical tubers show a high signal intensity on T2-weighted and FLAIR sequences and can occur throughout the cerebral cortex. The frontal lobe is the most common location [15]. *Cerebellar tubers* occur in about 10% of patients and are always present in association with cerebral cortical tubers and are seen in older children. *Solitary* cortical tubers have been reported in the literature. A solitary cortical lesion in a patient without a clinical diagnosis of TBS may present a diagnostic dilemma. A “zebra-like” pattern of cerebellar tubers has been reported. The zebra-like pattern may reflect the underlying cerebellar anatomy with interposed cerebellar CSF-filled sulci between the neuronal elements [14].

Recent studies have focused on the appearance of hamartomas on diffusion-weighted images and the role of *proton spectroscopy* in diagnosing TBS. Diffusion-weighted magnetic resonance imaging may be of clinical importance for the identification of epileptogenic tubers in patients with TBS and intractable epilepsy [15]. A significant increase in the apparent diffusion coefficient is found in the epileptogenic tubers.

Proton *spectroscopy* can show differences between cortical tubers and normal-appearing white matter in patients with TSC. The reduced NA/Cr ratio is probably

due to reduced levels of NA, most likely caused by the presence of immature neurons and glia in tubers that do not express NA or by the presence of gliosis, a known histologic component of tubers [16]. Diffusion tensor imaging (DTI) is a method for modeling water diffusion in tissue and can noninvasively characterize microstructural properties of the brain. In tuberous sclerosis complex, DTI measures reflect pathological changes [17].

In addition to subependymal nodules and cortical tubers, similar regions containing disordered cells also occur in the white matter. When large enough, these regions can be identified on CT and MRI. They demonstrate as areas of low density on CT unless calcified. *Small cysts* in the cerebral hemispheric white matter and corpus callosum on the MR images are not rare.

Subependymal giant cell astrocytomas (*SEGA*) occur in 6–10% of patients with tuberous sclerosis. The peak age of occurrence is 8–18 years [15, 18]. On CT *SEGA* are hyperdense lesions with areas of calcifications. On MRI *SEGA* show mixed signal intensity on both T1- and T2-weighted images. *SEGA* become symptomatic when obstructing the foramen of *Monro* causing hydrocephalus (Fig. 3.6).

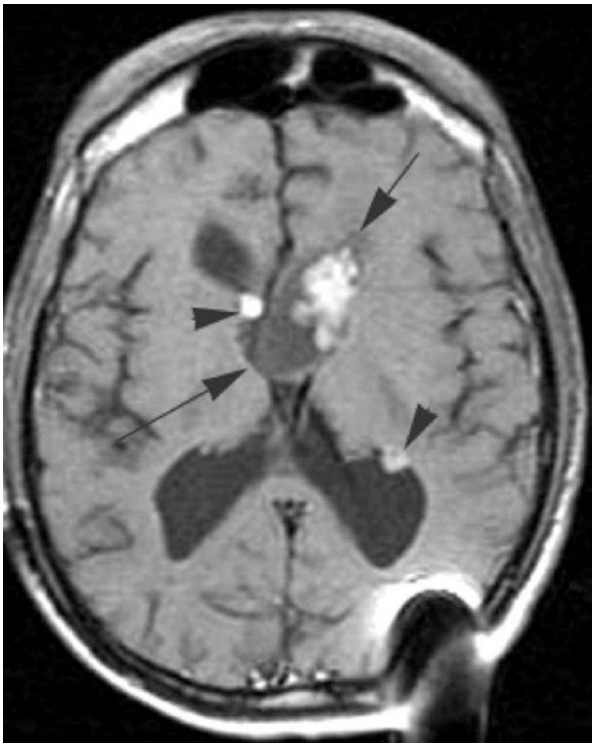

Fig. 3.6 Subependymal giant cell astrocytoma. Axial post-contrast T1-weighted MRI shows an enhanced intraventricular mass in the foramen of Monro causing obstructive hydrocephalus (arrows) and subependymal nodules (arrowheads).The artifact in the left occipital area is caused by prior craniotomy

Visceral Manifestations

Renal angiomyolipomas occur in 40–80% of patients with TBS. The detection of even a small amount of fat on CT or MRI in renal masses confirms the diagnosis (Fig. 3.7).

Cardiac *rhabdomyomas* are discovered in at least 50% of patients with TS. The majority of patients are diagnosed by obstetric ultrasound investigation or early in postnatal life. The rhabdomyomas usually appear as intracardiac tumors either protruding into the chamber or contained in the myocardium. The lesions regress in the first years of life. Lymphangioleiomyomatosis (*LAM*), a rare finding, is characterized by a proliferation of abnormal smooth muscle cells in the lungs and in the lymphatic system of the thorax and retroperitoneum. The classic triad of chest radiographic findings includes a reticular interstitial pattern, chylous pleural effusion, and recurrent pneumothoraces. The progressive disease usually ends in respiratory failure. Radiographically the disease appears as a coarse reticulonodular pattern. Bilateral thin-walled cysts with honeycomb appearance is a late manifestation. Pleural effusion and pneumothorax are common.

Sturge-Weber Syndrome

Skull radiographs show a tram-track appearance resulting from calcifications of gyri (see Chap. 5). The calcifications of the cortex can be identified early in life by CT, but rarely at birth (Fig. 3.8). CT can show some white matter calcification as well. Regional atrophy in SWS is well demonstrated by MRI. White matter below the damaged cortex may show high signal intensity on T2W images as a result of ischemia and gliosis. Gadolinium-enhanced MRI is highly sensitive to meningeal enhancement, which is a characteristic feature of SWS and is believed to represent

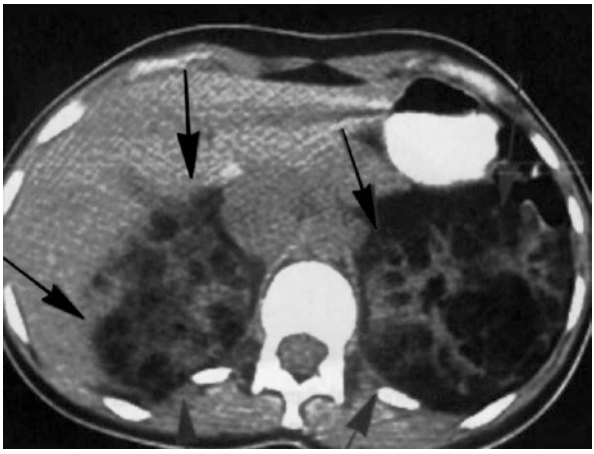

Fig. 3.7 Bilateral renal angiomyolipomas in a patient with tuberous sclerosis and large renal masses in CT scan (arrows)

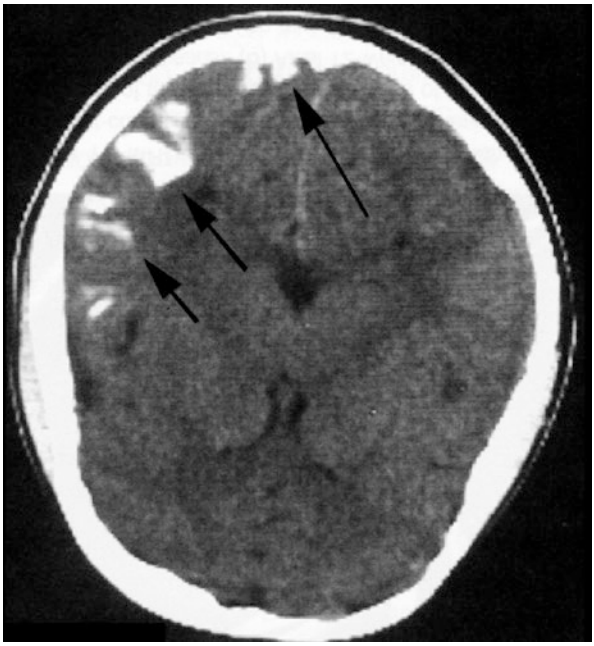

Fig. 3.8 Axial CT image of a young woman with Sturge-Weber shows coarse cortical calcifications (arrow)

leakage of contrast medium through the anomalous pial vessels that characterize the disease [19, 20].

Leptomeningeal enhancement need not be present in SWS, and the absence of this characteristic finding does not preclude the diagnosis. Areas of thickened cortex with few sulci, presumed to represent migration abnormalities, are also well visualized with MRI (Fig. 3.9). Echo-planar trace diffusion MRI reveals mildly high signal intensity changes at parieto-occipital lobes on $b = 1000$ s/mm^2 images, suggesting restricted diffusion. Proton MR spectroscopy reveals decreased N-acetyl aspartate and increased choline peaks, indicating disintegration of neural tissue associated with neuronal loss as well [21]. High-resolution *BOLD MR-venography* allows early diagnosis of venous anomalies in SWS, making early therapeutic intervention possible [19].

MRI is essential to establish diagnosis and evaluate the extent and the severity of intracranial involvement. Involvement of infratentorial structures is often subtle and should be actively sought. Although demonstration of the pial angioma is often considered crucial for the diagnosis of SWS, visualization on MRI may be delayed; the apparent absence of pial enhancement should be interpreted [22, 23]. Abnormalities of the ipsilateral eye may occur, such as buphthalmos and glaucoma (*most common*) (see Chap. 47). MRI examination of the choroidal hemangiomas *shows* thickening of the posterior wall of the globe on unenhanced T1-weighted images and abnormal signal on proton density-weighted images. After injection of contrast material, crescent enhancement is noted, thickest posteriorly, extending to the anterior portion of the globe [23, 24].

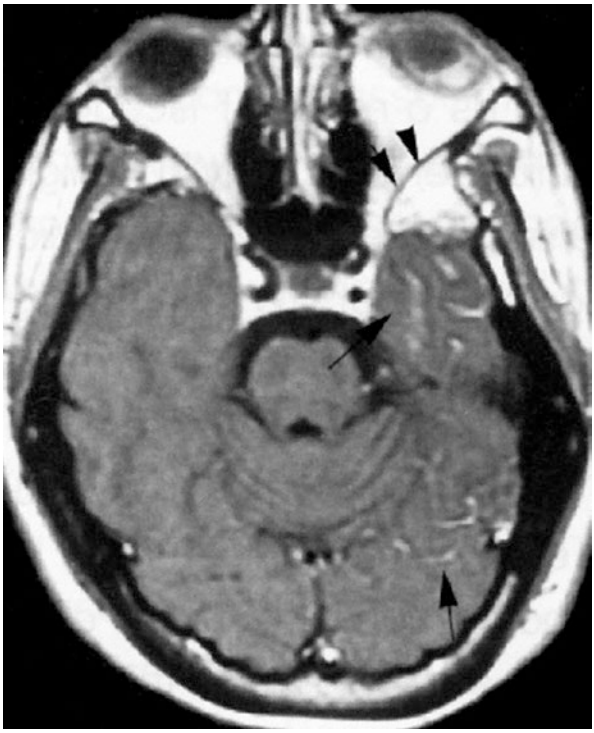

Fig. 3.9 Axial post-contrast T1W image shows leptomeningeal enhancement (arrows)

Von Hippel-Lindau Disease

Hemangioblastomas is a typical manifestation of von Hippel-Lindau disease (VHL). The tumors are benign and mostly found intra-axial in the posterior fossa (see Chap. 28). The tumor is easily detectable by CT and MRI examination. On CT scan, the cystic component is generally sharply defined, with an attenuation value equal to, or slightly higher than, the *cerebrospinal fluid*. On unenhanced scan, the mural nodule is isodense to brain tissue [25]. After intravenous contrast injection, it enhances intensely and uniformly. On MRI the cystic component of hemangioblastoma is either iso- or slightly hyperintense relative to CSF on T1-weighted images and hyperintense on T2-weighted images. This is due to the high protein content of the cysts. The solid component of the tumor is *hypo-* or *isointense* on T1-weighted images and shows marked enhancement after administration of contrast medium. The solid and contrast-enhancing portions show low signal intensities on *DWI* [25].

Renal manifestation of VHL disease includes renal cysts, renal angiomas, and renal cell carcinomas. Renal cysts are easily detected on ultrasound where they are anechoic with posterior acoustic enhancement. On CT and MRI, simple cysts are easy to identify especially with the administration of contrast medium (Fig. 3.10). CT is the most sensitive method for detecting renal tumors (particularly in the

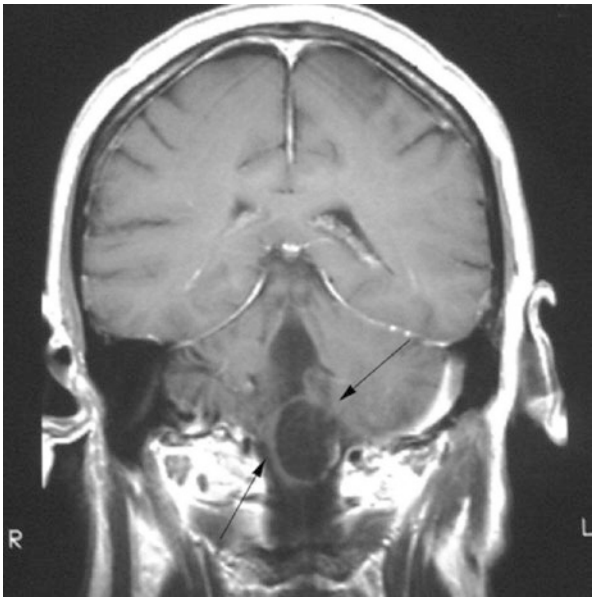

Fig. 3.10 A 50-year-old woman with VHL disease. Coronal post-contrast T1-weighted image shows a hemangioblastoma as a pure cystic lesion involving the medulla (arrows)

presence of renal cysts), and MRI or ultrasound scans are preferred for regular follow-up to avoid a large cumulative radiation load [25].

Renal *angiomas* are hypervascular like renal cell carcinomas, and diagnosis is usually not made until surgery. Post-contrast CT or MRI shows a solid mass.

Pancreatic involvement includes simple cysts, extensive cyst replacement, diffuse cytosis, cystadenoma, islet tumor, and rarely adenocarcinoma [26].

Phaeochromocytoma is another feature of VHL disease. All patients with phaeochromocytomas should be screened for VHL disease to avert further morbidity and mortality in the patients and their families [27] (see Chap. 28).

Ataxia Telangiectasia (Louis-Bar Syndrome)

Imaging findings in the brain of ataxia telangiectasia (AT) patients are best demonstrated by MRI. The cerebellum is small, especially the anterior vermis [28] (see Chap. 6). Lateral cerebellum and superior vermis show the earliest atrophic changes with progression over time to marked diffuse atrophy of vermis and cerebellar hemispheres in patients who are unable to walk [29]. *Multiple* capillary telangiectasias in the cerebral hemispheres, cerebellum, and brainstem can be seen as faint brush-like enhancement foci on post-contrast T1-weighted scans or multifocal "blooming black dots" on T2 sequences. Dineen et al. [30] in a recent publication discussed the quantitative cerebellar MRI differences between children with AT and controls. The authors provide measures of progressive cerebellar neurodegeneration and imaging markers for the neurological status of pediatric AT patients.

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Syndrome)

Hereditary hemorrhagic telangiectasia (*HHT*) is a familial disorder characterized by vascular malformations (arteriovenous malformations (AVM), telangiectases) causing nosebleeds, gastrointestinal bleeding, and hemorrhages in other organs (Curaçao criteria). Gastrointestinal bleeding is the most common symptom after epistaxis; it occurs in approximately 13–30% of HHT patients [31].

The high frequency of neurological complications justifies systematic screening for pulmonary AVMs, using chest radiography, contrast echocardiography, and/or chest CT. Cerebral MRI is currently the most sensitive noninvasive test. The *typical* MRI appearance of a complete hemosiderin rim around an AVM is not always present [32]. Brain MRI also depicts increased signal intensity on T1-weighted images involving the globus pallidus and cerebral crura bilaterally. The EASL (European Association for the Study of the Liver) guidelines recommend screening for hepatic AVMs in asymptomatic individuals with suspected or definite HHT using hepatic Doppler *ultrasound* as the first-line investigation [31]. Second-line techniques such as CT or MR scanning are indicated in the differential diagnosis in the case of nodules of the hepatic parenchyma (see Chap. 12).

Klippel-Trénaunay Syndrome

Klippel-Trénaunay syndrome is another hereditary vascular disease (see Chap. 9). Noninvasive imaging, such as plain radiographs, color duplex ultrasonography, hemodynamic assessment, magnetic resonance imaging, and lymphoscintigraphy, CT/MR subtraction angiography are used for diagnosis and follow-up [33]. By *radiography*, bone elongation contributing to leg length discrepancy, soft-tissue thickening, or calcified phleboliths may be seen. *Venography* usually demonstrates extensive dilation of superficial veins and enlarged perforating veins. Using *lymphangiography*, hypoplasia of the lymphatic system has been reported. Spin-echo MR images demonstrate a lack of enlarged high-flow arterial structures, and T2-weighted images show malformed venous and lymphatic lesions as areas of high signal intensity [34, 35].

MRI depicts deep extension of low-flow vascular malformations into muscular compartments and the pelvis and their relationship to adjacent organs as well as to bone or soft-tissue hypertrophy and shows diffuse soft-tissue hemangiomas (*venous varicosities*) unilateral. Recently, MR venography has been reported to display the significant findings in extremity venous malformations with a capability equal to that of conventional venography. Specifically, *two-dimensional* time-of-flight MR venography with an arterial flow direction pre-saturation pulse sequence can provide a global picture of the superficial varicosities, enlarged perforating veins, and absent or hypoplastic deep veins characteristic of *Klippel-Trénaunay* syndrome [36, 37].

MR Neurography: Neurofibromatosis Type 2 and Schwannomatosis

Introduction

Neurofibromatosis type 2 (NF2) and schwannomatosis are autosomal dominant tumor predisposition syndromes, with schwannomas as the most prevalent tumor entity in both syndromes. In most patients diagnosis is made according to diagnostic criteria based on anamnesis, clinical examination, electrophysiological investigations, and genetic testing. However, in cases in which pathognomonic clinical manifestations, such as the bilateral vestibular schwannoma in NF2 or mutations in investigated genes, are not detectable, differentiating between NF2 and schwannomatosis may prove difficult. MR neurography found distinct dorsal root ganglia (DRG) hypertrophy and identified primary sensory neurons as a possible vulnerable site in origination of areflexia and sensory loss in NF2 as well as a potential pathognomonic marker.

Application of High-Resolution Magnetic Resonance Neurography for Distinction of Different Subtypes of Neurofibromatosis

Especially in these patients with no clear diagnosis, recent studies highlight the importance of an additional investigation of the peripheral nervous system with magnetic resonance neurography (MRN). This examination provides high-resolution, visual information, making it possible to describe the localization and distribution pattern of nerve lesions and denervated muscle tissue [38–43]. Additionally, MRN fully depicts secondary findings such as the infiltration of adjacent tissue compartments by tumorous mass lesions. In this way valuable additional information for diagnosis, therapy, and assessment of prognosis can be obtained (see Chap. 26).

Presently, MRN is almost exclusively conducted on 3-Tesla tomographs, which enable precise diagnosis due to their high structural resolution while at the same time allowing implementation in clinical routine due to reasonably short durations of the examinations. In comparison to frequently used peripheral nerve ultrasound, MRN shows a number of marked advantages. Besides the fact that anatomic neuronal structures in deeper locations and with more complex structures, including paravertebral nerve plexus with dorsal root ganglia (DRG), can be depicted with much higher precision in detail, it also facilitates the detection of pathological findings. Lesions of peripheral nerves are precisely indicated by a circumscribed enhancement of the T2 signal of single nerve fascicles or the total cross-sectional area of the nerve in the affected region [41, 44, 45]. Furthermore, denervation of muscle tissue can be detected even in a very early stage. Among the disadvantages of this

technique is the limited availability in only few centers for neuromuscular diseases, the high costs, the weaker spatial resolution in comparison with nerve ultrasound, as well as the impairment of imaging quality by metal artifacts.

Currently, the standard sequence applied in clinical routine is a T2-weighted turbo spin echo (TSE) sequence with spectral fat saturation, which is characterized by optimum contrast for nerve imaging and a high in-plane resolution (between 100 × 100 and 300 × 300 μm). Presently the cross-sectional area of peripheral nerves or individual fascicles and the nerval T2 signal are considered the most important MRN parameters used in the detection of nerve lesions. Both an increase of the cross-sectional area and an elevated T2 signal have been shown to constitute sensitive parameters for peripheral neuropathies of diverse etiologies [44, 46].

MRN and nerve sonography allow for nerves to be examined at all individual levels in a proximal-to-distal fashion. Through an evaluation of the pattern of nerve lesion, they can be classified as either solitary, monofocal lesions, e.g., schwannoma and neurofibroma, or multifocal, polyneuropathic lesions (intrafascicular microlesions, multiple tumors). Since only monofocal nerve lesions may potentially be cured by surgical resection, this classification has profound therapeutic consequences and helps to prevent unnecessary surgical procedures [38].

Further advances in MRN are the development of new, functional MRI techniques such as diffusion tensor imaging or perfusion imaging, which provide a quantitative evaluation of nerve integrity and microstructure and blood supply of neuronal tissue [45, 47–49].

Differentiation of Sporadic vs. Tumor Predisposition Syndrome-Associated Peripheral Nerve Sheath Tumors

Peripheral nerve sheath tumors are primarily benign, slow-growing tumors resulting from neoplastic proliferation of Schwann cells, perineurial cells, or nerve sheath fibroblasts. Among benign types, neurofibromas and schwannomas constitute the most frequently described tumors. The largest proportion of peripheral nerve sheath tumors occurs sporadically as a result of somatic mutations in predisposing genes. Yet, both tumors can occur as manifestations of tumor predisposition syndromes with the occurrence of multiple neurofibromas closely linked to NF1 and schwannomas frequently described in NF2 and schwannomatosis patients. In neurofibromas and schwannomas, the risk of malignant transformation, resulting in the development of malignant peripheral nerve sheath tumors (MPNST), is generally considered low and commonly associated with syndromic, rather than sporadic, tumor manifestations.

A clear classification of a newly detected peripheral nerve tumor as either neurofibroma, schwannoma, or MPNST has profound therapeutic consequences. While surgery is the treatment of choice in all MPNST if resectable, it is only indicated in cases with pronounced growth and accompanying neurological symptoms due to a

compression of adjacent structures in benign nerve sheath tumors. MRN allows precise assessment of the microstructure of all mentioned peripheral nerve tumors [50]. Schwannomas have a distinct appearance with a T2w-hyperintense signal, a fusiform, and eccentric shape and show a diffuse uptake of contrast agent. While large neurofibromas and MPNST may have a similar appearance, several features can be identified which indicate malignancy. MPNST tend to have a larger size and are more likely to show a peripheral enhancement pattern of contrast agent, a perilesional edema-like zone and intratumoral cystic lesions [51].

MRN in Neurofibromatosis Subtypes

In NF2 and schwannomatosis, schwannomas are the predominant tumors described in the peripheral nervous system of affected individuals. While neurofibromas, as a common feature of NF1, can clearly be identified by MRN and histology, radiological diagnosis or histopathologic analyses do not allow a differentiation between sporadic schwannomas and syndromic schwannomas found in NF2 and syndromic schwannomas found in schwannomatosis. Hence, despite the marked difference in clinical symptoms and genetic background, there is a considerable overlap between diagnostic findings of these two syndromes. Peripheral neuropathy is a common clinical manifestation in neurofibromatosis, which however shows different symptoms in NF1, NF2, and schwannomatosis patients. NF1 is associated with focal sensory deficits and pain manifestation. Sensorimotor deficits and areflexia constitute major symptoms. NF2-associated neuropathy and schwannomatosis patients primarily report a severe, distally accentuated, chronic pain syndrome [52]. Initially it was hypothesized that neuropathy in all conditions can be considered as the result of the compression of peripheral nerves by massive tumor lesions. This is especially relevant for explaining symptoms in NF1 patients since in most patients neuropathic symptoms can be directly linked to the development of mass tumors in the course of affected nerves.

However, this theory is insufficient to explain complex symptoms of patients in NF2 and schwannomatosis, which are not restricted to the structures and skin areas innervated by a single peripheral nerve but rather show a diffuse, bilateral symmetric, and distally pronounced distribution. Accordingly, recent MRN imaging studies describe miniscule, intrafascicular nerve lesions in the course of peripheral nerves of NF2 patients. These microlesions correspond to histopathologically detected “tumorlets” and are, due to their diffuse and symmetric distribution, likely to constitute the pathomorphological correlate of NF2 neuropathy [38, 53]. Furthermore, the comparison of MRN findings with clinically reported and electrophysiologically evaluated symptoms revealed a strong correlation between the number of nerve microlesions and the severity of the patients’ symptoms [38]. Subsequent studies investigating neuropathy-negative children with NF2 however revealed microlesions to a similar extent compared to adults with severe NF2-PNP. Thus, the theory was established that in addition to detectable microlesions secondary processes must take place for the lesions to cause symptoms [40].

Similarly to NF2, MRN investigations of the peripheral nervous systems of Schwannomatosis patients showed intrafascicular microlesions, with neither imaging techniques nor histological analysis allowing a differentiation between microlesions of the two entities (Fig. 3.11). In patients with segmental schwannomatosis, a condition affecting only one extremity or a maximum of five directly adjacent spinal cord segments, microlesions were detected not only in the symptomatic extremity but to a similar extent in all extremities. This observation also emphasizes the necessity of secondary MR neurographically not detectable processes for lesions to become symptomatic [39].

As microlesions with the same appearance occurring in both tumor syndromes cannot explain the marked differences in the clinical presentation of neuropathy, a more proximal structure of the peripheral nervous system was subsequently investigated more closely: the DRG [41]. DRGs are an accumulation of pseudounipolar neurons, receiving impulses from the periphery and transmitting them to the central nervous system. MRN examinations of NF2 patients revealed a considerable hypertrophy of the DRGs of all investigated segments as opposed to healthy individuals, while DRG volume in schwannomatosis patients did not significantly differ from controls. Likewise, histopathological analysis of DRGs in the murine model of NF2 showed similar morphologic changes, with DRG volume increased by factor five at an age of 15 months. Histopathological analysis of mice sacrificed at different ages identified a proliferation of Schwann cells as an initial underlying mechanism of DRG hypertrophy followed by the development of manifest schwannomas with marked resemblance to human schwannoma formations [54]. Thus, an additional involvement of the DRG might be a key factor leading to sensory loss and areflexia in NF2 patients.

As an attempt to improve the understanding of the age-dependent pathogenesis of NF2, additional MRN examinations of children and adolescents as well as

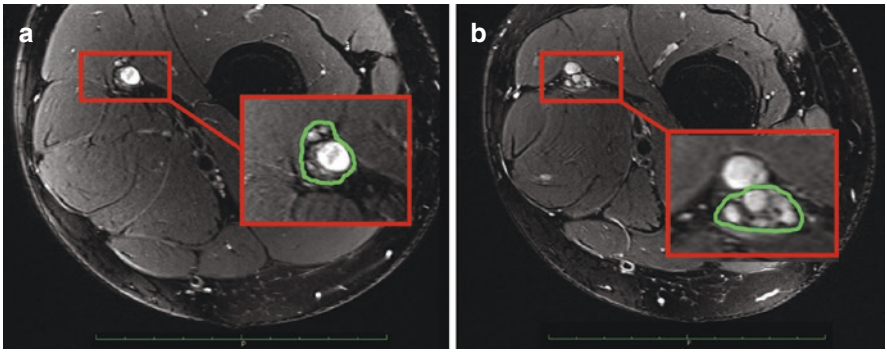

Fig. 3.11 MRN appearance of an intermediate lesion (**a**) and microlesions (**b**) in a patient with NF2 polyneuropathy Axial, T2w, fat-saturated sequence of the sciatic nerve at the thigh level, showing an intermediate lesion (**a**) and several microlesions with fascicular hypertrophy (**b**). Although peripheral nerve lesions in NF2 and schwannomatosis are not distinguishable by MRN and histology, genetic background and clinical symptoms vary greatly. Scale in (**a**) and (**b**) = 10 cm

long-term MRN and post-mortem histological analysis were conducted. Children and adolescents investigated in an early stage without symptoms or electrophysiological signs of polyneuropathy already showed marked alterations of the peripheral nervous system similar to adults. Despite the absence of symptoms, NF2 children showed DRG hypertrophy rates and counts of peripheral nerve microlesions comparable to those observed in symptomatic adults. Long-term follow-up examinations for up to 100 months revealed no further significant progression of the observed pathologies of the peripheral nervous system. Similarly to the murine model, post-mortem histopathological analysis of nervous tissue identified schwannoma tissue and onion-bulb formations as the predominant correlates of both DRG hypertrophy and peripheral nerve microlesions. Due to the infiltration of schwannomas, physiological DRG structure was no longer detectable, with only few cell bodies to be identified in the peripheral zone of the DRG. Thus, DRG hypertrophy and peripheral nerve microlesions constitute pathological findings detectable at an early stage of NF2 which show a limited rather than a linear growth as time progresses.

Apart from providing an explanation for the development of NF2 neuropathy, DRG hypertrophy also seems to be a useful parameter for differentiation between NF2 and schwannomatosis for initial diagnosis of patients. Since only NF2 patients but not schwannomatosis patients develop DRG hypertrophy, and since DRG hypertrophy is already detectable at an early age, it might prove to be a valuable diagnostic criterion. Exemplarily, this criterion may be applied in all cases, in which differentiation between NF2 and schwannomatosis at initial diagnosis is not possible as clinical diagnostic criteria are not fully met and mutations in predisposing genes are not detectable.

Future MRN imaging studies will further investigate the pathogenesis of NF2 and will in particular address the question if DRG hypertrophy occurs prior to the development of the pathognomonic vestibular schwannoma and how both DRG hypertrophy and peripheral nerve microlesions progress over time (Fig. 3.12).

Neurosonography Evaluation of Neurocutaneous Disorders

Introduction

Sonography may be transcranial or superficial or may evaluate deep body structures. We focus here on sonographic imaging of the *neuraxis*, including central and peripheral nervous system. Fetal diagnosis and the role of ocular ultrasound and ultrahigh frequency ultrasound will be briefly discussed. Many of the neurocutaneous syndromes may be associated with neoplasm, hamartoma, vascular abnormalities, or abnormal growth in the organs, but we will not focus on these indications. Neurocutaneous diseases often have variable expression, and this chapter focuses only on the sonographic findings of the conditions most commonly associated with neurocutaneous disease.

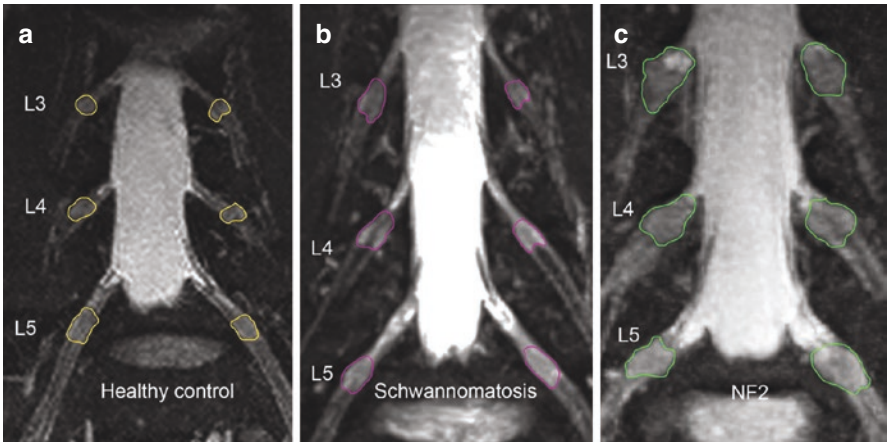

Fig. 3.12 MRN appearance of lumbar DRG morphology in a healthy control subject (**a**), in a patient with schwannomatosis (**b**), and in a patient with NF2 (**c**). Exemplary coronal 15 mm maximum intensity projection (MIP) volume rendering figure for illustration of the DRG L3 to L5. While DRG morphology in schwannomatosis patients (**b**) is not alternated compared to control subjects (**a**), NF2 patients show marked DRG hypertrophy for all levels (**c**)

Advantages to Sonography

Ultrasound is frequently used for imaging in pediatrics. It is mobile and relatively inexpensive, avoids radiation, and usually does not require sedation. There are few risks that limit the use of ultrasound. Instead, ultrasound use is limited by physical properties of tissue. The beam cannot pass through bone or air and has limited depth and spatial resolution. For *neuroimaging*, these limitations mean that intracranial structures can only be visualized in children under 6–12 months of age, before closure of the cranial sutures. *Visualization* of the central spinal canal is limited to the first month of life, before the posterior spinal elements ossify. Assessment of deep neural structures or thoracoabdominal abnormalities associated with neurocutaneous disease may be limited by depth and reflective properties of gas and bone. Many of the key features of neurocutaneous disease are described on magnetic resonance (*MR*) imaging, and evidence for ultrasound use is less robust.

However, ultrasound evaluation remains a valuable tool for assessing pediatric neurocutaneous disease. Because children are smaller than adults, ultrasound can assess much deeper structures, typically with good image quality. Ultrasound may be a primary imaging tool for the subset of patients with DNA repair deficiencies, such as ataxia telangiectasia or nevoid basal cell carcinoma (*Gorlin-Goltz* syndrome; see Chap. 29), who are at higher risk for radiation-associated malignancy. For these patients, ultrasound may be used to assess conditions normally assessed with radiography or computed tomography (*CT*), such as pulmonary disease, fractures, or abdominal pain [55, 56]. Radiation sensitivity in patients with *xeroderma pigmentosum* and *Cockayne* syndrome is associated with ultraviolet wavelengths

and is not associated with increased cancer risk, but these patients also benefit from avoiding the higher frequency X-ray wavelengths (see Chaps. 3 and 30) [56, 57]. *MR* imaging does not use radiation but frequently requires sedation for exam times lasting 30 min to 2 h. Patients with *LEOPARD* syndrome, *Klippel-Trénaunay*, and neurocutaneous conditions associated with heart failure have a higher incidence of anesthesia complications and require cardiac anesthesia services, limiting access to *MR* imaging (see Chaps. 9 and 17) [58, 59].

Fetal Ultrasound

Many of the findings associated with neurocutaneous disease in fetal ultrasound are nonspecific or subtle and only recognized in retrospect. *Tuberous sclerosis* (*TS*) may rarely be diagnosed prenatally in the presence of an intraventricular and/or cardiac mass and is associated with higher morbidity and mortality than disease diagnosed in infancy or childhood [60, 61]. Prenatal cerebellar asymmetry has been noted in cases of *PHACE* (see Chap. 21) [62, 63].

Rhomboencephalosynapsis present in *cerebello-trigemino-dermal* syndrome may also be identified (see Chap. 24) [64]. Rarely, the polymicrogyria and calcifications associated with Sturge-Weber angiomatosis may be visible prenatally [65].

Vascular malformation and limb asymmetry in *Klippel-Trénaunay* have been described on fetal ultrasound [66, 67]. Characteristic facial features have been described in cardiofaciocutaneous on 3D prenatal ultrasound [68]. However, it is more common that the features of neurocutaneous disease on fetal ultrasound are nonspecific, such as macrocephaly, ventriculomegaly, or hydrops [60, 69, 70].

Neurosonography

Transfontanellar Neurosonography

Transfontanellar neurosonography is used from approximately ages 0–6 months old, when immature ossification of the skull at the fontanelles allows insonation of the brain through the anterior, posterior, or mastoid fontanelles. The *majority* of neurocutaneous diseases do not have intracranial abnormalities detectable by sonography in the first 6 months of life. Syndromes involving early tumor formation or developmental asymmetries like those visible on fetal imaging are the exceptions. Future advances in neurosonography such as contrast-enhanced ultrasound (*CEUS*) may allow better assessment of intracranial neurocutaneous findings in their earliest stages [71].

Neoplasms

Neoplasms or hamartomas associated with neurocutaneous disease may be evident on neurosonography in the first 6 months of life. *Tuberous sclerosis* may be the neurocutaneous syndrome most frequently identified with transfontanellar neurosonography due to characteristic location of subependymal and subcortical hamartomas and subependymal giant cell astrocytoma (*SEGA*) (Fig. 3.13) [72, 73]. Additionally, a majority of TS patients are diagnosed in the first year of life, when intracranial structures are amenable to assessment by ultrasound [74]. Other relatively more common neurocutaneous syndromes associated with intracranial neoplasm, such as neurofibromatosis type 2 (*NF2*) or von *Hippel-Lindau*, present well after the first year of life and cannot be assessed with transcranial neurosonography. However, in cases of suspected neurocutaneous disease, transcranial sonography can also be a useful tool for excluding catastrophic intracranial abnormalities in the first year of life, especially in resource-limited areas [75]. *Transcranial* ultrasound evaluation of other neurocutaneous diseases may be unexplored or unpublished due to the rarity of these conditions.

Developmental Abnormalities

Developmental abnormalities associated with numerous neurocutaneous syndromes may be evident by transfontanellar neurosonography. In patients with encepaholcraniocutaneous lipomatosis, abnormalities such as porencephaly, cortical

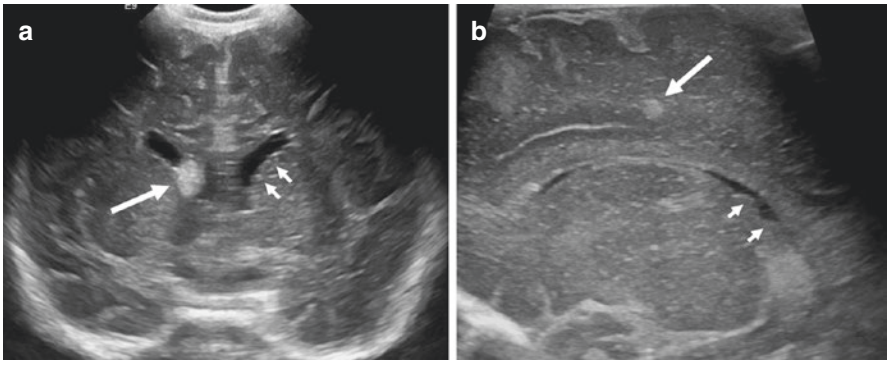

Fig. 3.13 Transfontanellar coronal plane ultrasound of a 6-day-old female (**a**) shows a circumscribed, homogenous, echogenic, intraventricular nodule at the foramen of Monro in the right lateral ventricle, compatible with a giant subependymal hamartoma (large white arrow). It does not have the cystic features classic for subependymal giant cell astrocytoma (SEGA). Irregular isoechoic contour along the inferolateral wall of the left lateral ventricle (small white arrows) suggests multiple small subependymal nodules too small to characterize. Transfontanellar sagittal plane ultrasound of a 1-day-old male (**b**) shows a circumscribed, echogenic, subcortical nodule compatible with subcortical hamartoma (large white arrow). Two circumscribed isoechoic subependymal nodules are present along the inferomedial wall of the lateral ventricle (small white arrows)

hemiatrophy, and intracranial lipoma in patients are visible in infants <2 months old and may be characterized by transcranial sonography (see Chap. 16) [70, 76]. *Agenesis* of the corpus callosum has also been described in these patients [77]. Melanotic intracranial deposits in neurocutaneous melanosis may appear as randomly distributed parenchymal echogenic foci without mass effect [78–80]. In hypomelanosis of Ito, transcranial sonography at birth may show hemimegalencephaly and pachygyria (see Chap. 7) [81]. Leptomeningeal angiomatosis ipsilateral to a facial port-wine stain in *Sturge-Weber* may be evident on ultrasound, but sensitivity is low and MR is required for complete characterization (see Chap. 5) [82]. However, in many of these cases, the cutaneous findings will be more diagnostic, and *MR* brain will be necessary for a complete evaluation of intracranial structure. But neurosonography may help quickly identify lesions and is useful when *MR* is not available.

Transcranial Doppler

Transcranial Doppler (*TCD*) neurosonography evaluates flow dynamics at the circle of Willis and its central branches by insonation through thin temporal bone at the greater wing of the sphenoid. Unlike transfontanellar ultrasound, *TCD* may be performed in patients of any age and does not require open fontanelles or sutures. Many neurocutaneous disorders include vasculopathy and stroke risk. In neurofibromatosis type 1 (*NF1*), perivascular neurofibromas may result in narrowing or occlusion in the internal carotid, middle cerebral, and/or anterior cerebral arteries (see Chap. 26). TCD may help identify NF1-related vasculopathy via abnormal pulsatility and resistive indices and mean flow velocity [83]. Asymmetry in middle cerebral artery (*MCA*) velocities may be associated seizure frequency and disease severity in children with *Sturge-Weber* angiomatosis [84, 85]. A role for TCD in neurocutaneous conditions associated with stroke and *Moya-Moya*, such as *PHACE*, incontinentia pigmenti, and Hutchinson-*Gilford* progeria syndrome, has not been characterized, despite well-established utility of TCD in assessing these risks in children with sickle cell disease (see Chaps. 21 and 40) [86].

Spinal Sonography

Spinal sonography is best performed in the first month of life, when cartilaginous physes in the posterior spinal column allow visualization of the cord and central canal contents. The majority of neurocutaneous diseases do not have spinal pathology visible by sonography in the first month of life. One exception is cutaneomeningospinal angiomatosis (*Cobb* syndrome), which in rarely published cases may have spinal hemangiomas visible by ultrasound in the neonatal period [87, 88].

Peripheral Nerve Sonography

Unlike the central nervous system, structures in the superficial peripheral nervous system are well-evaluated with ultrasound without age limitations. Plexiform neurofibromas have a variety of appearances, ranging from circumscribed, solid, predominantly hypoechoic lesions to ill-defined heterogeneous areas (Fig. 3.14). Vascularity of plexiform neurofibromas is typically hyperemic, though they may also be hypovascular [89]. They associate with bundles of nerve fascicles but do not compress or displace vessels or organs. In comparison, schwannomas associated with NF2 have a solid, circumscribed, homogeneously *hypo-echoic* appearance and are associated with a single nerve fascicle. PNS masses that show rapid growth, ill-defined borders, calcification, and central necrosis are more likely to represent a malignant peripheral nerve sheath tumor [90]. In NF1 and NF2, PNS may identify neural involvement even in asymptomatic areas, especially when combined with nerve conduction studies [43, 91]. Despite good ultrasound visualization of neurofibromas and schwannomas, the role for sonography as a screening and diagnostic tool is limited by operator-dependent variability and by the sheer number of lesions that may need to be assessed [92]. However, ultrasound offers superior spatial resolution and the option for real-time dynamic imaging compared with MR, so there remains a key role for sonography in detecting early or subtle signs of *PNS* involvement.

Ocular Sonography

Abnormalities of the globe, orbit, and optic nerve are common among neurocutaneous disease. Ocular ultrasound offers benefits beyond direct visual inspection, assessing lesions in three dimensions and displaying post-septal structures,

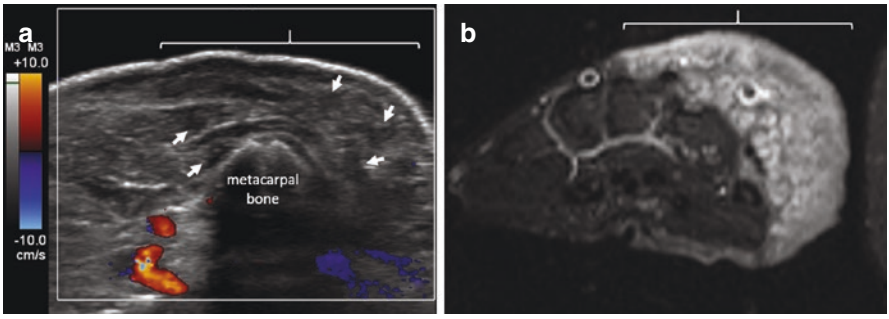

Fig. 3.14 Transverse ultrasound of the right wrist in a 12-year-old male (**a**) with neurofibromatosis type 1 shows a diffuse heterogeneous area in the subcutaneous tissues (white bracket) containing multiple small hypoechoic lesions (examples shown with small white arrows). These features represent plexiform neurofibroma, also demonstrated by T2-hyperintense signal on magnetic resonance (MR) imaging (**b**). Although MR has superior contrast (black/white) resolution, ultrasound has better spatial resolution to evaluate small details

including the intraorbital course of optic nerve. *Neoplasms* such as optic nerve gliomas and schwannoma in neurofibromatosis can be assessed [93, 94]. Early sonographic detection of retinal vasoproliferative tumors in NF1 may prevent blindness associated with hemorrhage and exudative retinopathy [95]. Anterior segment glaucoma in NF1 and other conditions can also be assessed using ultrahigh-resolution ultrasound, also called ultrasound biomicroscopy [96]. In addition, Doppler sonography can characterize abnormal vascularity in structures of the globe. Choroidal hemangioma associated with Sturge-Weber appears as thickening of the choroid and can also be followed with ocular ultrasound [97, 98]. Arteriovenous malformation of the retina may be seen in *Wyburn-Mason* syndrome (see Chap. 23) [99]. Additional neurocutaneous syndromes are associated with ocular abnormalities, but a role ultrasound in their assessment has not been explored in the literature.

Cutaneous Sonography

Ultrahigh-frequency ultrasound has been commercially available since the mid- to late 2010s and may be used in evaluating cutaneous lesions. Ultrahigh-frequency ultrasound operates up to 70 MHz with spatial resolution approaching 0.03 mm but is limited by shallow depth penetration reaching only the dermal and superficial subcutaneous tissues. This *new technology* is relatively unexplored in evaluating neurocutaneous lesions, but it may help characterize as depth and vascularity. For patients with darker skin, in whom discolor ration associated with cutaneous vascular anomalies may harder to assess visually, ultrahigh-frequency ultrasound may be a useful adjunct [100].

Body Sonography

Many neurocutaneous diseases involve organs outside the neural crest-derived tissues. Vessels and solid abdominal organs are most frequently affected, and surveillance and follow-up guidelines exist for syndromes associated with high-risk lesions such as malignant potential or large hemorrhage. *Ultrasound* is a primary tool for assessing deep venous thrombosis or atherosclerosis in patients predisposed to these conditions. Review of the vast amount of literature on ultrasound evaluation for body and musculoskeletal manifestations of neurocutaneous disease is outside the scope of this chapter.

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Chapter 4
Neuropathology of Neurocutaneous Disorders

Christian Hagel, Jakob Matschke, and Klaus Kuchelmeister

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Neurofibromatosis Type 1 (NF1)

NF1 is an autosomal dominant inherited disorder (Chap. 26). The neuropathological manifestations of NF1 are mainly related to cells derived from the neural crest (Fig. 4.1).

The most striking neuropathological feature in NF1 are benign neurofibromas (WHO grade I) [1], presenting either as (multiple) well-circumscribed dermal

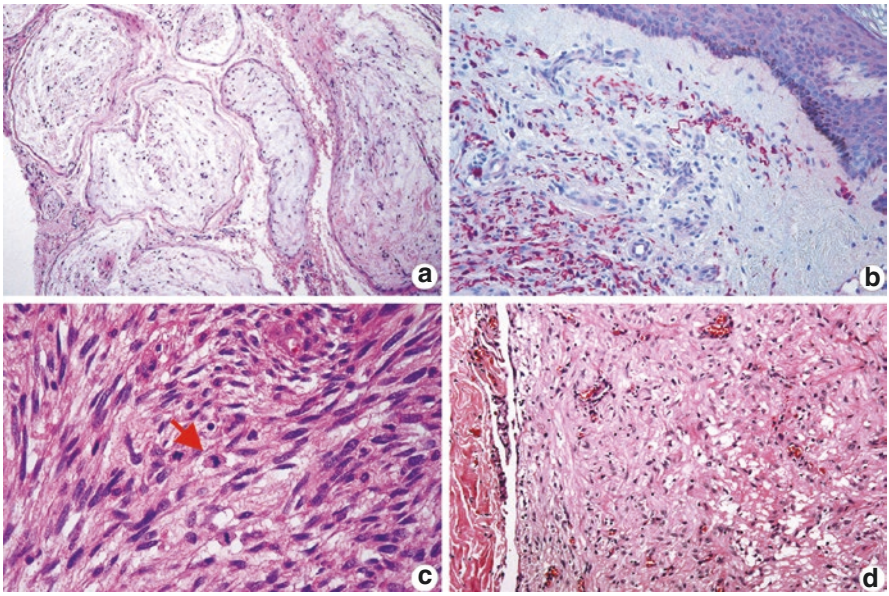

Fig. 4.1 Tumours in neurofibromatosis type I. (**a**) Plexiform neurofibroma growing within the perineurium of multiple nerve fascicles, note the low cellularity and the myxoid matrix (H&E stain); (**b**) dermal neurofibroma diffusely invading the corium, visualisation of tumour cells with S-100 protein antibodies (chromogen: fast red, APAAP method, counterstain alum haematoxylin); (**c**) malignant peripheral nerve sheath tumour (MPNST), note the increased nuclear size and pleomorphism and the mitotic activity (arrow) (H&E stain); (**d**) pilocytic astrocytoma of the optic nerve with adjacent leptomeninges (left), note the focal microcystic growth pattern (H&E stain)

lesions, as diffusely infiltrating ill-defined subcutaneous tumours, or as knotty or rope-like intraneural swellings of peripheral nerves. Accordingly, the tumours are termed dermal neurofibroma, diffuse, or plexiform neurofibroma. Frequently, there are also lesions with mixed growth pattern referred to as plexiform-diffuse neurofibroma. The plexiform neurofibroma bares a 5–10% risk of progression to a malignant peripheral nerve sheath tumour (MPNST).

Histologically, dermal and plexiform neurofibromas consist of spindle-shaped Schwann cells that show a diffuse growth or an arrangement in streams. Scattered within the tumour, few fibroblasts are found, and in plexiform neurofibromas perineurial cells may be encountered. The tissue matrix comprises mucoid substances and a varying amount of collagen fibres. Within the tumour, especially in dermal neurofibromas, mast cells and perivascular lymphocytic infiltrates may be present. In some patients focal palisading of small groups of nuclei may resemble Meissner corpuscles, and arrangement of cells in dense whorls may resemble Pacinian corpuscles. Plexiform tumours typically show a low cellularity, loose texture, and an abundant myxoid matrix. Residual nerve fibres may be encountered in these tumours. Proliferative activity is usually low or absent. Neurofibromas may display a focally increased cellularity and nuclear pleomorphism referred to as cellular and atypical neurofibroma, respectively. More recently, a combination of any two—high cellularity, nuclear pleomorphism, loss of neurofibroma architecture, and more than a single mitosis in 50 high-power fields (hpf), but less than 3 mitoses in 10 hpf—has been found suspicious of malignancy, and the term ‘atypical neurofibromatous neoplasm of uncertain biologic potential (ANNUBP)’ was suggested [2]. Immunohistochemical labelling of tumour cells with antibodies against S-100 protein is particularly helpful in tumours with extremely low cellularity like in dermal neurofibromas of the mamilla.

The typical morphology of a high-grade MPNST is that of a sarcoma. The tumour may be found in close vicinity to a plexiform neurofibroma, thus suggesting malignant transformation of a pre-existing neurofibroma [3]. In addition to the grading proposed by the WHO classification of tumours of the nervous system [1], two other grading schemes are widely used, the United States National Cancer Institute (NCI) scheme and a classification according to the *French Federation Nationale des Centres de Lutte Contre le Cancer* (FNCLCC). Both institutions distinguish three grades of malignancy which mainly reflect the risk of distant metastases [4].

Histologically, MPNST is characterised by high cellularity, spindle cells arranged in fascicles or in a loose texture, bizarre nuclear atypia, high mitotic rate, and necroses. Various subtypes have been defined according to their histomorphology: The epithelioid MPNST consists of plump eosinophilic cells with epithelial growth pattern. In MPNST with divergent mesenchymal/epithelial differentiation, cartilage, bone, or skeletal muscle formation may be encountered as well as a neuroendocrine or mucinous differentiation. The divergent differentiation occurs only focally and has no prognostic significance. In melanotic MPNST, clusters of cells or the whole tumour shows melanin production. There are no reliable immunohistochemical markers of MPNST. There may be S-100 protein expression, but only focally. Detection of nestin may be useful in combination with other markers like CD34

(about 25% of cases), transducin-like enhancer of split 1 (TLE1, 30% of cases), Sox10 (neural crest marker, nuclear expression in up to 50% of cases), and high mobility group AT-hook 2 (HMGA2) [5].

In addition to peripheral nerve sheath tumours, patients with neurofibromatosis type I have an increased risk in developing CNS tumours, the most common being the pilocytic astrocytoma of the optic nerve. Tumours which become symptomatic in early childhood (<6 years) were found to grow rapidly, whereas tumours diagnosed in late childhood (>6 years) show no progression [6]. Diffuse gliomas outside of the optic pathway may also occur in NF1, and more rarely, indeterminate low-grade gliomas, glioneuronal tumours, uncommon glial tumours (pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma), and tumours resembling tuberous sclerosis complex-associated subependymal giant cell astrocytoma (SEGA) are also reported in NF1 [7].

Neurofibromatosis Type 2 (NF2)

Similar to NF1 neurofibromatosis type 2 (NF2) is a tumour suppressor syndrome with an autosomal dominant inheritance (see Chap. 26). A diagnostic hallmark are bilateral schwannomas of the vestibular nerve (Fig. 4.2).

Schwannomas present as encapsulated globoid masses, frequently with cystic cavities and haemorrhages. In NF2, schwannomas may appear as multilobulated masses, and numerous microscopic tumourlets may develop along individual nerves. Histologically, the tumours are composed of round to elongated slender cells arranged in fibrillary (Antoni A) and reticular (Antoni B) patterns. In fibrillary areas, the nuclei may be arranged in rows (palisading). Atypical nuclei may be present at varying numbers, representing regressive pleomorphia of tumour cells; mitoses are rare. Further regressive changes are also frequently observed in form of nests of foam cells, haemorrhages, fibrosis, and cysts. The vessels are small to medium sized, and their walls commonly show extensive hyalinisation. Residual nerve fibres are usually located near the tumour capsule. Immunohistochemically, schwannomas express S-100 protein like neurofibromas, and in addition protein kinase C potentiated inhibitor (CPI-17) which may be helpful in the differential diagnostic distinction of neurofibroma [8]. Upon labelling with the proliferation marker Ki-67, more than 10% of nuclei may be stained in these benign lesions (WHO grade I) [1], due to frequent extensive inflammatory infiltrates.

Multiple meningiomas (mainly WHO grade I) [1] are another common finding in neurofibromatosis type 2. All major subtypes of these tumours are observed. There is no increased risk of developing atypical or malignant meningioma [9].

In addition to circumscribed nodular tumours, both lesions derived from Schwann cells and from meningeal cells may present as diffuse proliferations, termed schwannosis and meningioangiomatosis. Schwannosis is commonly found in the spinal root entry zones. Meningioangiomatosis is located intracranially and may resemble

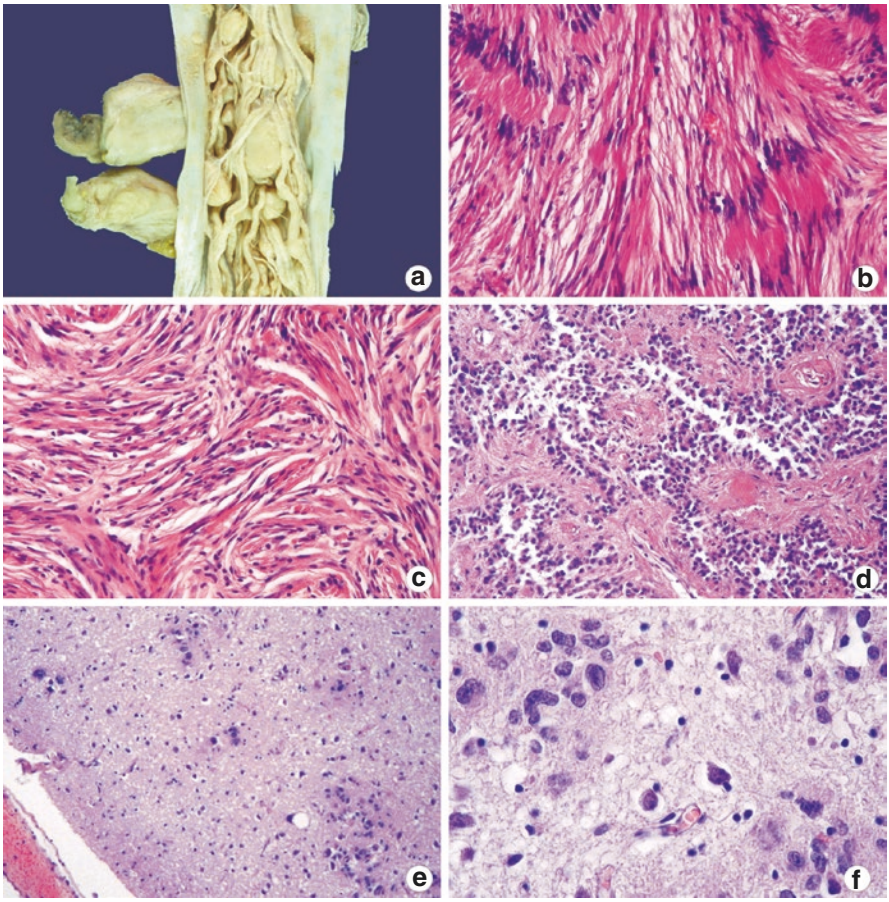

Fig. 4.2 Lesions in neurofibromatosis type II—autopsy findings in a 32-year-old female patient. (**a**) Cauda equina with multiple schwannomas presenting as globoid masses within spinal nerves; (**b**) histological presentation of a schwannoma WHO grade I with fibrillary growth pattern and typical palisading of nuclei; (**c**) fibrillary meningioma WHO grade I composed of elongated tumour cells and a high content of collagen fibres; (**d**) ependymoma WHO grade II consisting of small round cells in a fibrillary matrix with characteristic fibrillary areas devoid of nuclei around vessels, the patient died of central dysregulation due to this tumour which was located in the brain stem (H&E stain); (**e**, **f**) cortical hamartias consisting of clusters of glial cells with medium to large atypical nuclei (all histological preparations H&E stain)

meningioma en plaque if the meningeal cells predominate or as vascular malformation when there is a high vascular density. While NF2-associated meningioangiomatosis is often clinically asymptomatic and may be multifocal, sporadic meningioangiomatosis without NF2 is usually a single lesion which may cause seizures or persistent headaches [10].

NF2 is also associated with development of spinal ependymomas which are most frequently located in the cauda equina or in the medulla oblongata [11].

Glial hamartias or microhamartomas are another typical finding. The lesions are located in the cerebral cortex and consist of clusters of glial cells with medium to large atypical nuclei. Similar lesions may also be found in the basal ganglia, thalamus, cerebellum, and dorsal horns of the spinal cord. The cells are positive for S-100 protein and mostly GFAP-negative. Cerebral calcifications are preferentially observed in the cerebral and cerebellar cortex, periventricular areas, and the choroid plexus.

Some patients with neurofibromatosis type 2 suffer from a peripheral neuropathy which cannot be explained sufficiently by the tumour burden alone. In these patients a severe axonopathy was found [12] which may in part result from a defective signalling between axon and Schwann cells [13].

Schwannomatosis

Schwannomatosis has been identified as a separate tumour suppressor disorder among the neurofibromatoses around 2005. As in neurofibromatosis type 2, the patients develop schwannomas. Histologically, the tumours may differ from NF2-associated or sporadic schwannomas in that the patients may have a mutation in the SMARCB1 gene resulting in a rhabdoid morphology and loss of nuclear Ini-1 expression in the tumour [14]. Furthermore, the lesions may display a mixed morphology of schwannoma and neurofibroma (schwannoma in neurofibroma [15, 16], or hybrid neurofibroma/schwannoma [17]). Hybrid neurofibroma/schwannoma does not express CPI-17, indicating a pathogenesis different from schwannoma in these tumours [8] (Fig. 4.3) (see Chap. 3).

Tuberous Sclerosis Complex

This autosomal dominant inherited disorder is caused by mutations in the TSC1 or TSC2 gene (Chap. 27). Manifestations in the CNS comprise cortical tubers (in >80% of cases), subependymal nodules (SEN, in about 50% of cases), subependymal giant cell astrocytomas (SEGA, in about 10% of cases), and cortical radial migration lines, white matter abnormalities seen on MRI. In addition, more subtle changes have been found in post-mortem studies including isolated giant cells, areas of hypomyelination, cortical dysplasias, and heterotopias [18, 19] (Fig. 4.4).

Cortical tubers, which are clinically strongly associated with epilepsy, consist of astrocytes, giant glioneuronal cells, and dysmorphic neurons. Tubers are found in the cortex and subcortical white matter and may be confined to one gyrus but rarely may involve a complete lobe or even both cerebral hemispheres; less commonly the cerebellum is also affected [19]. The cortical lamination is disrupted in tuber formations, and there is gliosis and vascular calcification. Immunohistochemically, tubers show an antigen expression pattern similar to that of SEGA. The giant cells express

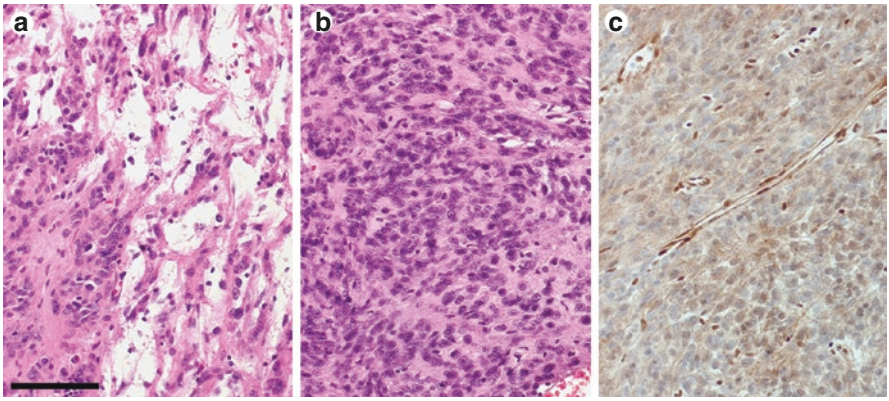

Fig. 4.3 Schwannomatosis—schwannoma with rhabdoid features. Schwannoma with rhabdoid features in a patient with co-occurrence of schwannomatosis and rhabdoid tumour predisposition syndrome; (**a**) in addition to typical schwannoma features like reticular and fibrillary growth pattern (H&E); (**b**) areas of high cellularity were noted with round clearly demarcated cells with eccentric nuclei and large nucleoli (H&E); (**c**) immunohistochemistry revealed loss of Ini-1 expression in tumour cells but not in endothelial and blood cells, scale 100 μm

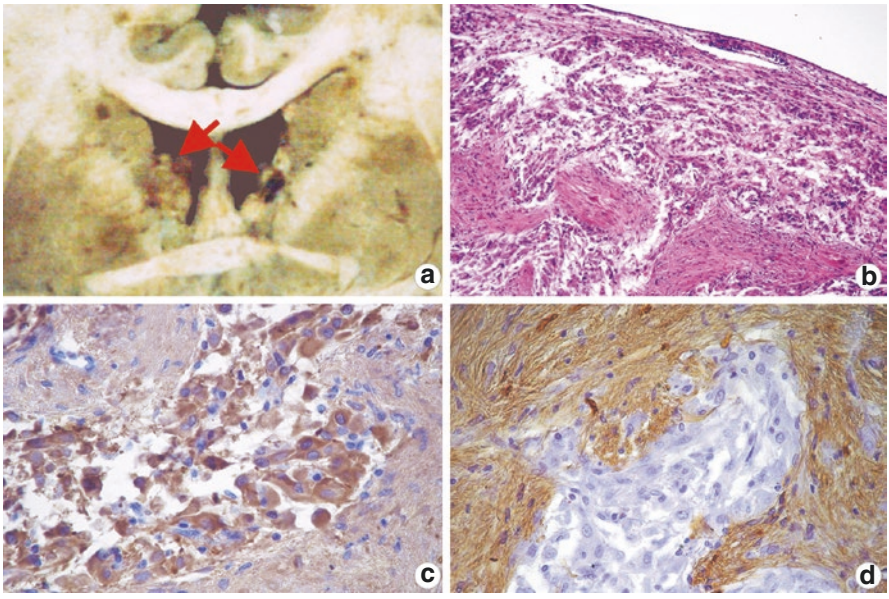

Fig. 4.4 Subependymal hamartoma and giant cell astrocytoma in tuberous sclerosis complex. (**a**) Macroscopic presentation of bilateral subependymal giant cell astrocytomas in the walls of the lateral ventricles, coronary section at the level of the commissura anterior; (**b**) at the microscopic level the tumours show clusters of large, plump cells and a fibrillary component (H&E stain); (**c**) the large cells are faintly positive for neuron-specific enolase, indicating a neuronal differentiation (chromogen: diaminobenzidine, HRP method, counterstain alum haematoxylin); (**d**) the fibrillary component of the tumours is strongly positive for glial fibrillary acidic protein (chromogen: diaminobenzidine, HRP method, counterstain alum haematoxylin)

neuronal (neurofilament, synaptophysin, class IIIb tubulin, microtubule-associated protein 2, calbindin D-28k, neuron-specific enolase, chromogranin A, somatostatin, etc.), and glial antigens (GFAP, S-100 protein, β-Crystallin) at random. In addition, intermediate filament proteins expressed in immature CNS like nestin and vimentin may be detected [20]. SEGAs also show nuclear expression of thyroid transcription factor-1 (TTF-1) which is helpful in histological differential diagnosis and may indicate an origin from cells of the TTF-1-positive foetal medial ganglionic eminence [21]. SEGAs are generally Olig2-negative [19], a finding which may also help in histological diagnosis.

Subependymal nodules (SEN) comprise astrocytes and giant glioneuronal cells, may be richly vascularised, are located in the walls of the lateral ventricles and the third ventricle, and typically present with a diameter of less than 1 cm. The lesions are separated from the ventricles by ependymal cells.

SEN are thought to be precursors of subependymal giant cell astrocytoma (SEGA, WHO grade I) which are usually larger than 1 cm in diameter and may obstruct the flow of CSF. SEGA consist of the same cell types as SEN. Although astrocytes in SEGA show a considerable pleomorphism with gemistocytic to fibrillary appearance and oval to bizarre atypical nuclei with increased mitotic activity, there are no signs of malignancy. Occasionally, even necrosis and endothelial proliferation may be observed. Immunohistochemically, a low proliferation is demonstrated by labelling of the Ki-67 antigen [22]. By electron microscopy microtubules, occasional dense-core granules and rarely synapse formation are found [23].

Sturge-Weber Syndrome

Incomplete involution of the embryonal vasculature is supposed to be the cause of this rare disorder (synonym: encephalofacial angiomatosis; Chap. 5) (Fig. 4.5).

Neuropathological manifestations include leptomeningeal angiomatosis which appears as dark purple discoloration of the meninges and in exceptional cases may present bilaterally. Microscopic investigation reveals an excessive vascularity of the meninges comprising small dilated tortuous veins. The deep collecting venous system may also show dilated vessels. Later in the course of the disease, calcifications of the vessels and free calcified granular deposits may appear in the tissue which are only exceptionally seen in newborns. Advanced cases may also present with unilateral cerebral atrophy which histologically appears as hypoxic-ischaemic damage including cortical laminar necroses, diffuse neuronal loss, and gliosis which are thought to develop consecutively to venous stasis and/or thrombotic obstruction of the overlying aberrant vasculature. Additionally, polymicrogyria and neuronal heterotopias may be found in the cerebrum and cerebellum. In a case series, Pinto et al. [24] reported a mild to moderate cortical atrophy, severe subpial gliosis, and moderate to severe white matter gliosis in 11 patients. Seven patients also suffered from focal

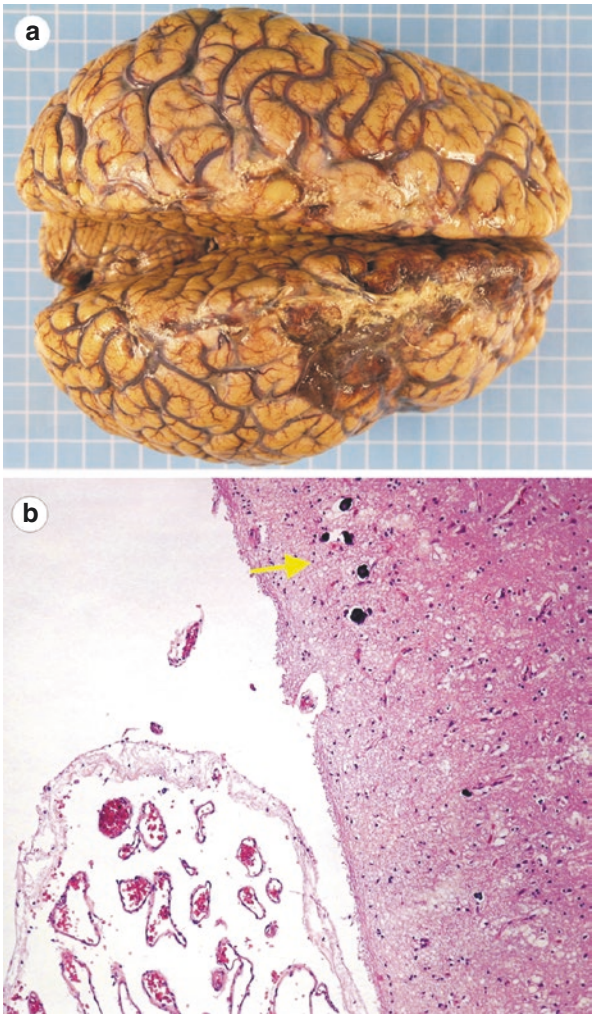

Fig. 4.5 Macroscopic and histopathological findings in Sturge-Weber syndrome. Brain of a 29-year-old patient who died in status epilepticus. The patient had a 1.5 × 5 cm large port-wine stain on his right forehead and was treated for grand mal seizures originating from the right frontal lobe; (**a**) macroscopic aspect showing a leptomeningeal venous malformation over the right frontal lobe and ipsilateral brain atrophy; (**b**) histologically the subarachnoidal veins present as convolute of dilated thin walled vessels, the underlying cortex contains free calcified granular deposits (yellow arrow) and shows a mild gliosis and diffuse loss of neurons presenting as focal sponginess of the parenchyma, and calcification of intra-parenchymal vessels was not found in this case

cortical dysplasia (FCD): two patients presented with a FCD type Ia according to the classification of the International League Against Epilepsy (ILAE) [25] with cortical microcolumnar organization and ectopic neurons in the white matter, and four cases showed abnormally orientated dysmorphic neurons with cytoplasmic accumulation of neurofilaments (FCD IIa). In one patient, a focal microgyria with a four-layered cortex associated with an abnormal tangential cortical lamination (FCD Ib) was found. Another publication records six patients with intractable epilepsy in Sturge-Weber syndrome with FCD IIIc in brain resections. Histology showed dysmorphic-like neurons with hypertrophic cell bodies resembling FCD IIa but without gross architectural abnormalities of neocortical layering of FCD IIa [26].

Ataxia-Telangiectasia (Louis-Bar Syndrome)

This progressive autosomal recessive multisystem disease results from mutations in the ataxia-telangiectasia mutated (ATM) gene (Chap. 6). Neuropathologically, the cerebellum and its efferent and afferent pathways are affected. There is gross cerebellar atrophy at autopsy which presents as marked loss of Purkinje cells and of the granular cell layer, reactive gliosis, and activation of microglia. The few residual Purkinje cells exhibit small cytoplasm and swellings of axons representing typical 'torpedo' formations; the cells further show abnormal arborisation with loss of secondary and tertiary dendrites. Ectopic neurons are found in the molecular and the granular cell layer of the cerebellum indicating migration defects during the last trimester of gestation. Directly interconnected with the cerebellum are the inferior olives and the pontine nuclei which also show neuronal degeneration. In addition, demyelination and gliosis are observed in the dorsal columns of the spinal cord, and degeneration of anterior horn cells is found pronounced at the lumbar level. There is a neurogenic muscular atrophy. In the variant form of ataxia-telangiectasia which is associated with a slightly milder clinical course, the neuropathological alterations were found to be somewhat less severe in the brain stem [27].

Von Hippel-Lindau Disease

The syndrome is caused by mutations in the tumour suppressor gene VHL on chromosome 3p25 (Chap. 28). The typical neuropathological finding in the CNS and retina consists of capillary haemangioblastomas (WHO grade I) [28] (Fig. 4.6).

Macroscopically, haemangioblastomas commonly present as soft solid nodules with associated pseudocysts. They usually show meningeal involvement. Histologically, the tumours are well demarcated, may contain large pseudocysts, and consist of two main components, large vacuolated neoplastic stromal cells and a rich non-neoplastic capillary network. The cytoplasm of the stromal cells is filled with glycogen or lipid vacuoles that give a typical 'clear cell' impression (differential diagnosis: renal cell carcinoma positive for cytokeratin, PAX2 and PAX8 in immunohistochemistry). Small lesions often present as highly vascularised tumours (reticular or mesenchymal growth pattern), whereas in large haemangioblastomas the stromal cells prevail (stromal or epithelioid growth pattern). Stromal cells are labelled with antibodies against podoplanin (D2-40), aquaporin-1 and inhibin A [28], and vimentin and S-100 protein. Hasselblatt et al. [29] differentiate between cellular and reticular variant of haemangioblastomas. The latter is much more common, while the first more often shows some GFAP-positive tumour cells and its median proliferation indices Ki67 (MIB1) are significantly higher. The brain tissue adjacent to the tumour especially near cysts may be gliotic and may contain Rosenthal fibres. Ultrastructurally, the stromal cells contain electron dense bodies resembling Weibel-Palade bodies and small granules.

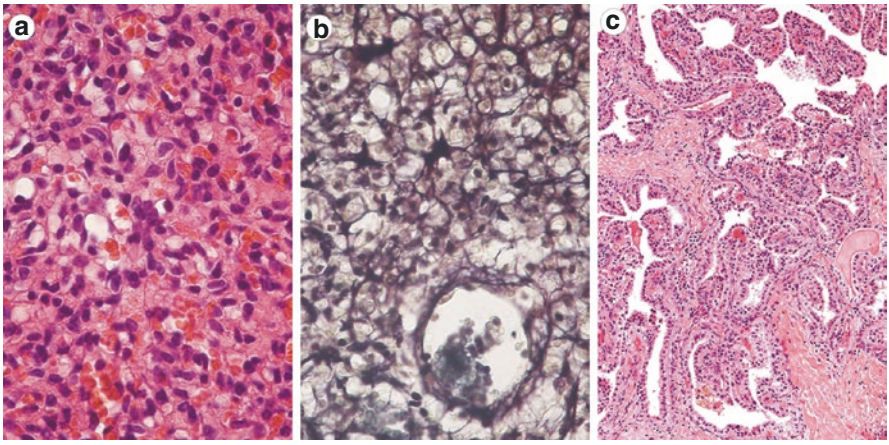

Fig. 4.6 Von Hippel Lindau disease—haemangioblastoma and endolymphatic sac tumour. (**a**) Haemangioblastoma composed of stromal cells with intracytoplasmic lipid vacuoles ('clear cells') or foamy cytoplasm, note the rich non-neoplastic capillary network which presents as small spaces between the stromal cells filled with erythrocytes (H&E stain); (**b**) same case as in a Gomori stain demonstrating the dense reticulin fibre meshwork surrounding small groups of tumour cells and single cells; (**c**) endolymphatic sac tumour with papillary adenoid structures lined by a single row of epithelial cells. There is a single structure below the middle of the right border of the figure resembling thyroid follicle (H&E stain)

Rarely, von Hippel-Lindau is associated with an endolymphatic sac tumour (ELST). Histologically, the tumours are characterized by papillary and/or follicle-like adenoid structures lined by a single row of cuboidal to low columnar or often flattened epithelial cells. Expression of cytokeratin and epithelial membrane antigen are a regular feature [30].

Nevoid Basal Cell Carcinoma (Gorlin-Goltz Syndrome)

This autosomal dominant disorder is characterised by multiple basal cell carcinomas, jaw keratocysts, skeletal anomalies, and—to a variable extent—neurological, ophthalmic, endocrine, and genital alterations [31] (Chap. 29).

The mutation in the tumour suppressor gene PTCH may lead to development of neuroepithelial tumours in some cases. In a series of 105 persons with nevoid basal cell carcinoma [32], 4 children suffered from medulloblastomas. Interestingly PTCH mutation associated medulloblastomas was found to be of the desmoplastic subtype [33]. Other CNS tumour manifestations include oligodendroglioma, meningioma, and craniopharyngioma. In addition, cysts (arachnoid, parenchymal, septum pellucidum, choroid plexus, colloid cyst of the third ventricle), calcifications (falx, tentorium cerebelli, sella turcica, petrosphenoidal ligament), focal neuronal heterotopia, and agenesis of the corpus callosum have been reported [34, 35].

Epidermal Nevus Syndrome

This condition comprises epidermal nevi which may occur in association with nervous system, skeletal, cardiovascular, and urogenital abnormalities (Chap. 10). The CNS abnormalities are manifold and include ocular defects, agyria, polymicrogyria, cerebellar and brain stem malformations, vascular malformations, hemimegalencephaly, agenesis of the corpus callosum, Dandy-Walker malformation, cortical atrophy, hydrocephalus, intracranial calcifications, and rarely malignancies like congenital medulloblastoma [36].

Linear Nevus Sebaceous Syndrome

Patients suffering from this phakomatosis (synonyms: Schimmelpenning-Feuerstein-Mims syndrome, organoid nevus syndrome, Solomon's syndrome, Jadassohn's syndrome; Chap. 10) may present with deformities of the skull like megacranium and shortened anterior fossa. Alterations of the brain comprise agenesis of the corpus callosum, enlarged ventricles, hemimegalencephaly, dysplastic hemispheres (thickened cortex with abnormal gyration: lissencephaly, pachygyria, polymicrogyria; architectural disorganization with loss of cortical lamination and convolutions, gyral fusion, neuronal heterotopia, dysmorphic neurons and balloon cells, etc.), cerebral atrophy, porencephaly, and gliomas among others. However, the brain may also show a normal appearance, both macroscopically and upon histopathological investigation [37, 38].

Encephalocraniocutaneous Lipomatosis

In encephalocraniocutaneous lipomatosis (Chap. 16), CNS tumours may be encountered. Mosaic activating mutations in the gene coding for fibroblast growth factor receptor1 (FGFR1) were found as underlying cause, like in a pilocytic astrocytoma of a 5-year-old boy with encephalocraniocutaneous lipomatosis [39].

Neuroradiologically, large cystic formations have been described which were interpreted as porencephaly or subarachnoidal cysts. Furthermore, dilatation of the lateral ventricle of the affected side, pontocerebellar atrophy, endocranial hypertension, cerebral lipomas located predominantly in the cerebellopontine angle and over the full length of the spinal cord, partial agenesis of the corpus callosum, cortical calcifications, areas of cortical dysplasia, and leptomeningeal angiomatosis have been demonstrated. The extent of intracranial lesions does not correlate with neurological symptoms or other manifestations of the disorder [40].

Neuropathological examination of the first case described by Haberland and Perou [41] revealed a defective lamination of the cerebral cortex, polymicrogyria,

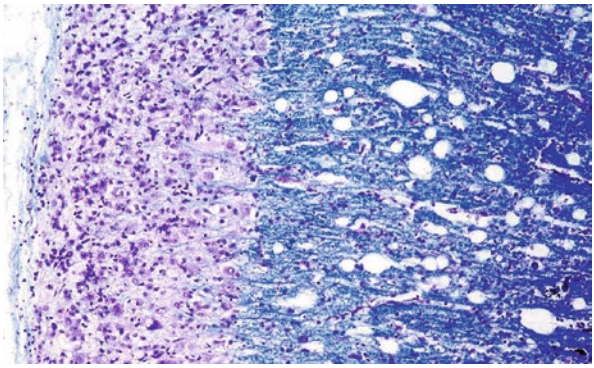

Fig. 4.7 Cortical alterations in the cerebellum in Lhermitte-Duclos. Klüver-Barrera stain demonstrating the layer of the dysplastic nerve cells (left) and the thickened and myelinated stratum moleculare (middle and right)

and calcifications of the cortex overlying a porencephalic cyst. The CNS alterations were located unilaterally to multiple lipomas of the cranium, face, and neck.

Lhermitte-Duclos Disease and Cowden Disease

Cowden disease and Lhermitte-Duclos disease are autosomal dominant inherited syndromes (synonym: dysplastic gangliocytoma of the cerebellum; Chap. 13) (Fig. 4.7).

Lhermitte-Duclos disease may be observed as isolated condition or in association with Cowden disease where it is regarded a major diagnostic criterion. Additional CNS manifestations found in Cowden disease are cortical dysplasias, megalencephaly, venous and cavernous angiomas, and meningiomas.

The major macroscopic neuropathological finding of Lhermitte-Duclos disease consists of a diffuse hypertrophy in one cerebellar hemisphere which shows a coarse gyral pattern; however, cases with multiple foci involving both cerebellar hemispheres have been observed as well. Histologically, the molecular layer appears thickened with hypertrophic hypermyelinated and non-myelinated axons which originate from two populations of underlying abnormal neuronal elements. The majority of neuronal cells morphologically and immunohistochemically resembles granule cell neurons, whereas the second smaller population comprises large neurons that show features of Purkinje cells (subpopulations of these cells are labelled with antibodies against Leu-4, L7, PEP19, and calbindin). Further, abnormal granule cells may also be observed in the molecular layer, suggesting aberrant migration during development. The white matter has a spongy and atrophic appearance, together with the hypermyelinated molecular layer leading to the typical ‘inverted cortex’ appearance of Lhermitte-Duclos disease in MRI. In the leptomeninges and subpial molecular layer, calcified small vessels may be noted. At the borders of the lesion, normal and abnormal cells coexist with gradual transition from normal to pathological anatomy. The ganglion cells in Lhermitte-Duclos disease, though dysplastic and disorganised, usually show no atypia, pleomorphism, or proliferation,

and no other neoplastic cell population is included between them. Thus, it has been proposed that the lesion may be a dysplasia or of hamartomatous origin. However, recurrent growth is not uncommon [42].

Menkes Disease

The pathological alterations in this X-linked recessive disease (synonym: kinky hair disease) result from a mutation in the gene coding for copper-transporting ATPase ATP7A [43, 44].

In the brain, microcephaly and brachycephaly were described. On the histological level, vascular lesions and mitochondrial dysfunction both result in atrophic tissue changes with focal neuronal loss and consecutive axonal degeneration in the white matter and basal ganglia. The small interneurons in the thalamus are spared from degeneration. A reactive gliosis is present in the affected areas. In the cerebellum reduction of granule cells and Purkinje cells is marked. The remaining Purkinje cells may show axonal swellings (torpedoes) and abnormal arborisation. Numerous eosinophilic spheroid bodies are seen in the molecular layer which upon electron microscopic investigation are shown to be proliferated endoplasmic reticulum. Mitochondria in the brain, retina, and muscle were found to be increased in number and may contain electron dense bodies. In skeletal muscle an accumulation of glycogen is found predominantly in type II fibres (see Chap. 43).

Refsum Disease

Neuropathological findings in Refsum disease (Chap. 44) include pigmentary retinal degeneration, cerebellar atrophy, dysplasia of the inferior medullary olives, and a hypertrophic demyelinating peripheral neuropathy in the classical form of the disorder [45]. In infantile Refsum disease, post-mortem examination revealed diffuse demyelination of the corpus callosum, periventricular white matter, corticospinal tracts, and optic nerves with additional axonal degeneration. Lipid-laden macrophages were demonstrated perivascularly. In the cerebellum ectopic Purkinje cells were seen, and the granular cell layer was found to be hypoplastic. Electron microscopic investigation disclosed intracytoplasmic accumulation of bilamellar profiles in astrocytes and macrophages. Electron microscopic evaluation of biopsies taken from non-neuronal tissues showed intracytoplasmic lipid droplets, dark bodies, and trilaminar needle-like inclusions. The needle-like deposits were found within the cytoplasm or in the dark bodies [46]. Nerve biopsy shows hypertrophic changes with onion bulb formation in light microscopy and paracrystalline inclusions upon electron microscopic investigation in the classical form, whereas in infantile Refsum disease a complete degeneration of all retinal layers is encountered [47].

Marinesco-Sjögren Syndrome

This rare autosomal recessive disorder is characterised by dry skin, hypergonadotropic hypogonadism, short stature, mental retardation, cerebellar ataxia, congenital cataracts, and a progressive vacuolar myopathy leading to muscle weakness. Mutations in SIL1, a gene coding for the endoplasmic reticulum resident protein SIL1, were reported to be causative for the disease. However, a SIL1 mutation was only detected in 24 out of 27 patients investigated suggesting a genetic heterogeneity [48]. MRI studies in 19 patients revealed marked atrophy of the cerebellum, affecting particularly the vermis [48] (see Chap. 45).

Histopathologically, alterations in the skeletal muscle comprise increased variation of fibre diameters, endomysial fibrosis, fatty degeneration, increased numbers of central nuclei, rimmed vacuoles, and nuclear changes which consist of condensed chromatin granules or nuclear vacuolation with amorphous inclusions. In early stages of the disease, fibre necroses and regeneration may be observed.

Electron microscopical changes consistent with an autophagic process are found in the muscle and, in addition, membranes which are mainly observed as enveloping structures around degenerating nuclei. At later stages the nuclei are filled with myelin bodies and amorphous inclusions resulting in fragmentation of the nuclei. Investigations by the TUNEL method showed fragmentation of DNA in scattered nuclei indicating an apoptotic process [49].

Neuropathological post-mortem examination of the brain disclosed no macroscopic alterations of the cortex, basal ganglia, mid-brain, and optic nerves, but the brain stem was small and the fourth ventricle dilated. The most remarkable finding comprised a severe atrophy of the cerebellum, the vermis being more affected than the lateral lobes. The inferior olives were small and sclerotic. There were normal findings upon histological examination of the cerebral cortex, basal ganglia, and mid-brain, whereas the cerebellum and pons showed subtotal neuronal loss and consecutive reactive gliosis with prominent Bergmann gliosis in Purkinje cell layer, mild astrogliosis in the pons, and severe gliotic changes in the inferior olives [50]. The histological alterations in the cerebellum were confirmed in a more recent report. In addition, cortical dyslamination, neuronal clustering, and giant neurons were found in the cerebral cortex [51]. In the retina, a severe loss of ganglion cells was observed.

Incontinentia Pigmenti

The nervous system is involved in about one third of cases of this multisystem X-linked dominant genodermatosis (synonym: Bloch-Sulzberger syndrome; Chap. 8). The alterations in the CNS and the retina are consistent with a vascular hypoxic-ischaemic aetiology presenting as periventricular leukomalacia, hypoplasia of the corpus callosum, enlargement of the lateral ventricles, infarctions, vascular abnormalities, neuronal heterotopias, etc. on MRI scans [52] and as neuronal dysplasia and neuronal loss upon histological investigation [53].

Lipoid Proteinosis

This very rare autosomal recessive disease (synonyms: hyalinosis cutis et mucosae, Urbach-Wiethe disease) is caused by mutations in the gene coding for extracellular matrix protein 1 [54] (Chap. 41).

Upon neuropathological investigation of an autoptic case, an angiofibrosis was noted macroscopically, and histological examination revealed an intense hyalinosis and fibrosis of the vasculature, and an accumulation of homogeneous material around small vessels [55]. The hyaline material is stained with periodic acid-Schiff (PAS).

Cerebrotendinous Xanthomatosis

This autosomal recessive lipid storage disease is caused by a defect in mitochondrial sterol 27-hydroxylase (Chap. 32). In an autoptic case reported by Soffer et al. [56], the total brain weight was 900 g. The choroid plexus of the lateral ventricles contained multinodular masses of yellow mushy tissue (Figs. 4.8 and 4.9).

Upon histological investigation lipid-laden perivascular macrophages were observed around cortical vessels, in the central grey matter, and the white matter; and a gliosis in the deep cortical layers and the subcortical white matter was disclosed by immunohistochemical labelling of glial fibrillary acidic protein (GFAP). The optic tracts showed extensive nerve fibre loss, and the white matter appeared rarefied. The tissue alterations were more pronounced towards the brain stem and the cerebellum. In the pontine nuclei, the inferior olive, the dentate nucleus, and the cerebellar cortex, a neuronal loss was found, and within the rarefied white matter of the cerebellum, closely packed crystalline clefts embedded in a fibrous tissue and surrounded by multinucleated foreign body cells and macrophages were seen. The cervical part of the spinal cord showed discrete loss of myelinated fibres in the posterior columns, and the corticospinal tracts were accompanied by gliosis, foam cells, and crystalline clefts.

Upon electron microscopic investigation, there was no sign of demyelination in the residual myelinated fibres. Ultrastructurally, the macrophages contained whorled membrane structures (so-called myelin figures).

The findings by Soffer et al. [56] were principally confirmed in a further case of undiagnosed cerebrotendinous xanthomatosis in a 52-year-old man who first presented at hospital with cognitive deficits and gait disturbances 10 years before he died [57]. In his last decade, the patient developed progressive dysarthria and ataxia. He died of acute severe central hyperthermia. The post-mortem neuropathological findings comprised xanthogranulomas in the plexus choroideus, central white matter of the cerebrum, the basal ganglia including the thalamus, the white matter of the cerebellum, and the spinal cord. DNA sequencing revealed a point mutation in exon

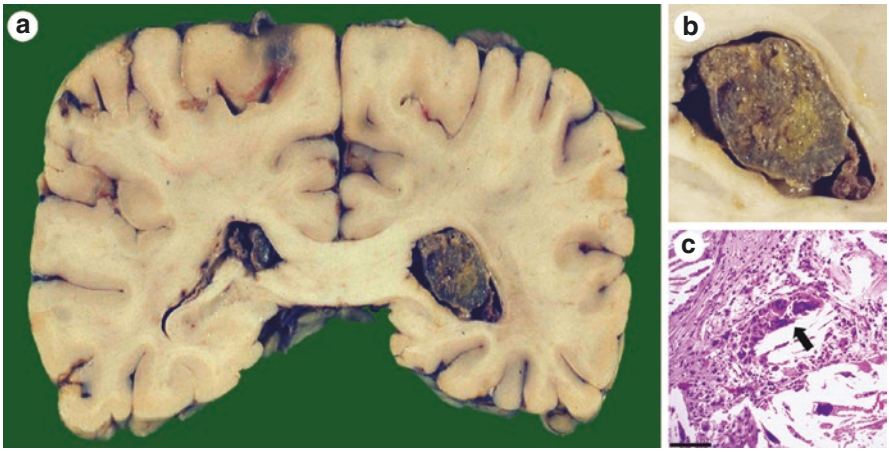

Fig. 4.8 Xanthogranuloma of the choroid plexus in cerebrotendinous xanthomatosis. (**a**) Coronal section of the brain at the level of the splenium corporis callosi demonstrating a large xanthogranuloma in the right lateral ventricle originating from the choroid plexus; (**b**) close-up view of the xanthogranuloma; (**c**) microscopic appearance of the lesion comprising granulation tissue with cholesterol clefts, giant foreign body cells (arrow), and diffuse leukocytic infiltration (H&E stain), scale 100 μm

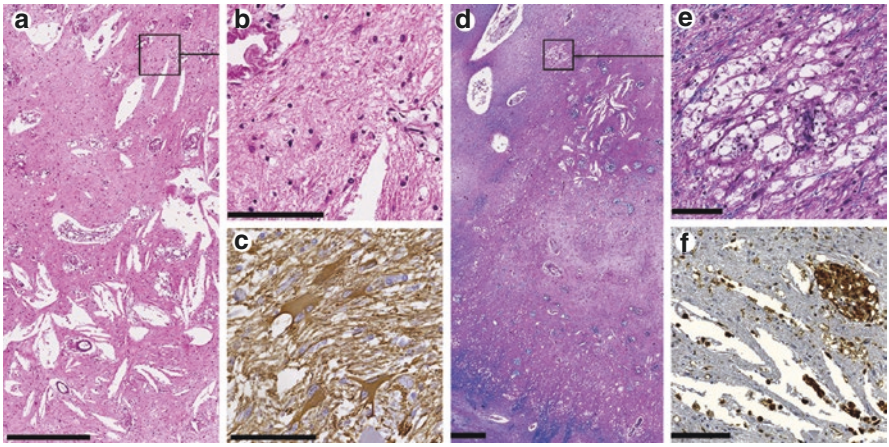

Fig. 4.9 Thalamic xanthomas, severe demyelination, and gliosis in cerebrotendinous xanthomatosis. (**a**) Overview demonstrating a xanthoma in the thalamus with large cholesterol clefts (H&E stain); (**b**) close up of the parenchyma depicting the gliosis (H&E stain); (**c**) immunohistochemical labelling of large reactive astrocytes in the lesion with antibodies against glial fibrillary acid protein (GFAP, brown stain); (**d**) overview demonstrating a xanthoma in the thalamus and loss of myelinated fibres (blue) in the thalamus (Luxol stain); (**e**) close up of a large cluster of foam cells in the demyelinated parenchyma (Luxol stain); (**f**) immunohistochemical labelling of macrophages with CD68 antibodies (brown), scales in (**a**) and (**d**) are 500 μm, scales in (**b**), (**c**), (**e**), and (**f**) are 100 μm

4 (R237X) of the sterol 27-hydroxylase (CYP27) gene and a second mutation in the intron of exon 6, expected to severely affect RNA splicing (IVS6 + 1G → A).

Neurocutaneous Melanosis

Neurocutaneous melanosis results from a primary defect in the neural crest, and an association with other neurocristopathies has been described in a number of cases (Chap. 11) (Fig. 4.10).

Neuropathologically, the meninges are mainly affected at the base of the brain, the ventral part of the brain stem, the cerebellum, and the spinal cord. In the affected areas, increased numbers of melanophores are found in the arachnoidea from which benign and malignant melanocytic tumours may develop. In malignant dedifferentiation, the melanocytes invade the parenchyma or vascular walls. In contrast, benign lesions are characterised by lack of necrosis, cellular atypia, and excessive mitotic/proliferative activity [58]. The main features of the Dandy-Walker malformation are cystic enlargement of the fourth ventricle, cerebellar dysgenesis, and an enlarged posterior fossa due to maldevelopment of the rostral embryonic roof of the rhombencephalon.

Chediak-Higashi Syndrome

This rare autosomal recessive disorder is caused by mutations in the lysosomal trafficking regulator gene LYST, located on chromosome 1q42-44 resulting in formation of enlarged intracytoplasmic vesicular structures like lysosomes, melanosomes, secretory granules, platelet dense bodies, etc. The vesicles are not secreted by the cells and

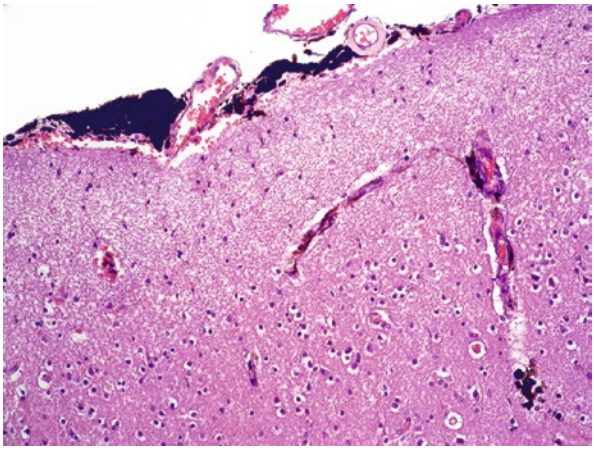

Fig. 4.10 Neurocutaneous melanosis. Photomicrograph showing the leptomeninges with increased numbers of melanophores (brown) which extend along the Virchow-Robin spaces into the upper layer of the cortex

accumulate over time [59] (Chap. 33). Histologically, the giant vesicular structures are readily identified in many cell types and present as large peroxidase-positive granules in white blood cells of the peripheral blood. In the nervous system, peripheral nerves demonstrate diffuse fusiform swelling and histologically show leukocyte infiltration and giant vesicles in Schwann cells. In the CNS there is lympho-monocytic infiltration in the meninges, around vessels and in the choroid plexus. Further, small granulomatous lesions comprising monocytes, lymphocytes, and microglial cells are observed. There are vesicular accumulations in anterior horn cells and neurons of the substantia nigra. The cytological alterations increase with age [60].

Cerebello-Trigeminal-Dermal Dysplasia

This very rare condition (synonym: Gómez-López-Hernandez syndrome) has been described in 35 sporadic cases of unrelated families (Chap. 24). The cerebellar findings were described as rhombencephalosynapsis, consisting of a cerebellum without separation of hemispheres and with a single superior cerebellar peduncle, a deficient vermis, and a horseshoe-shaped single dentate nucleus. In the case described by López-Hernandez [61], a fusion of the cerebellum with the brain stem was noted.

Ichthyosis Follicularis, Alopecia, and Photophobia Syndrome

This is an uncommon X-linked disorder in which mutations in the MBTPS2 gene at Xp22.11.3 are found. The gene codes for a protein involved in sterol control. Clinically, the disorder is characterised by retardation of growth and psychomotor development, seizures, and a range of skin alterations [62].

Neuropathological examination of one case [63] disclosed peculiar deformed temporal lobes that were tapered to basal. Further, the ventricles were slightly enlarged, the corpus callosum and optical tracts were narrowed, and the cerebellum was small and of tough consistency with shrunken folia and widened interfolial sulci. Upon histological examination there was an almost total loss of Purkinje cells in the cerebellum, a marked atrophy of the granular cell layer, and prominent Bergmann glia. Single dystopic Purkinje cells were noted, and a gliosis of the cerebellar white matter was present. The inferior olives also showed a marked neuronal depletion. A normal architecture was found in the cerebral cortex.

Fucosidosis

This lysosomal storage disorder presents in early childhood and manifests with progressive neurological deterioration, telangiectasias of the skin and conjunctivae, and angiokeratoma corporis diffusum. Furthermore, abundant sweating, thickened skin,

recurrent infections, emaciation, and cardiomegaly with myocarditis may be found [64].

Neuropathologically, there is widespread loss of neurons and deficient myelination of the white matter. Residual nerve cells show ballooning of their cytoplasm that may contain fine granular material. Upon electron microscopic investigation, the cytoplasm of neurons is packed with small clear vacuoles or less often with electron dense vacuoles [65]. Cytoplasmic inclusions of dark and light lamellae arranged in an alternating fashion may be observed. The lamellae may be flat or concentric or may resemble fingerprints. The progressive neuropathology of the disease was studied in a canine animal model by Kondagari et al. [66] demonstrating that widespread mild vacuolation in the brain can be observed already at 2 months of age and is paralleled by neuronal death and glial activation. Preclinical and early clinical animals at 8–12 months of age already showed extensive storage damage and significant loss of myelin in the cerebrum and cerebellum compared to normal adult controls. In the late clinical course, there was an additional significant decrease in myelinated areas and an increase in vacuolation.

Xeroderma Pigmentosum/Cockayne Syndrome Complex

These autosomal recessive disorders are characterised by defects in DNA repair resulting in cellular hypersensitivity to ultraviolet light (Chaps. 30 and 31).

Neuropathological findings in Cockayne syndrome comprise severe loss of peripheral and central myelin, cerebellar atrophy, and calcifications primarily in the basal ganglia. Myelination is typically relatively spared around intact blood vessels which led to the term ‘tigroid leukodystrophy’. However, frequently small vessels are obliterated (so-called string vessels) which may contribute to the leukodystrophy [67, 68]. Autoptic findings of a 6-year-old boy with xeroderma pigmentosum genotype and Cockayne syndrome phenotype were reported by Lindenbaum et al. [69]. The brain weighed only 350 g but showed normal proportions of sulci and gyri. Coronary sections disclosed a thinned corpus callosum and an enlarged ventricular system. The white matter appeared softened and showed ill-defined patchy areas of grey discoloration. The cerebellum was reduced in volume and the upper cerebellar peduncles were atrophic. Histologically, a normal lamination of the cerebral cortex was found, but a neuronal depletion was noted, and some nerve cells showed dystrophic calcification. In addition, scattered calcospherites were found in the parenchyma and vascular calcification in the basal ganglia. An astrogliosis was observed in the molecular layer and at the border between cortex and subcortical white matter. Marked atrophy and gliosis were found also in the limbic system and basal ganglia as well as in the thalamus and hypothalamus. There was gliosis throughout the white matter of the cerebrum. In the cerebellum, prominent Bergmann glia was noted, and a neuronal loss in the Purkinje cell layer and in the internal granular cell layer was observed. Many of the residual Purkinje cells demonstrated swollen proximal axons (axonal torpedoes). The dentate nuclei and the inferior olives were severely depleted of neurons.

Electron microscopically, there were no specific inclusions. The sural nerve disclosed endoneurial fibrosis, reduced numbers of large myelinated axons, and frequent re- and demyelination. Electron microscopy revealed normal lamellar appearance of the myelin sheaths.

The skeletal muscle fibres showed myopathic signs with fibre necroses, fibre calcifications, occasional bizarre hyperchromatic nuclei, and endomysial fibrosis. In addition, a neurogenic pattern of damage with fibre-type grouping was noted. Upon electron microscopic examination myofilaments were disorganised, and glycogen content was increased.

Fabry Disease

In this X-linked sphingolipidosis, deficiency of alpha-galactosidase A leads to the development of angiokeratomas of the skin and progressive deposits of neutral glycolipids in endothelia, vascular smooth muscle cells, Schwann cells, dorsal root ganglia, and CNS neurons (Chap. 46) (Fig. 4.11).

In a demented Fabry disease patient who died at the age of 47 of myocardial infarction, post-mortem examination of the brain disclosed diffuse thickening of the arachnoidal membrane, atherosclerosis of the circle of Willis, white discoloration of the subarachnoid arteries, and multiple small lacunae in the cerebral cortex, the pallidum, and the cerebellum [70]. Histologically, various organs including the

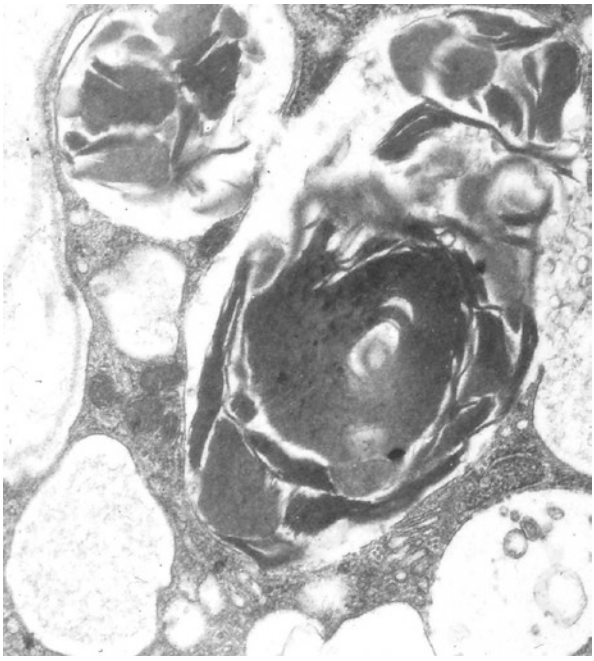

Fig. 4.11 Deposits of glycosphingolipids in a skin biopsy in Fabry disease. Electron micrograph showing concentric and irregularly shaped, partly lamellated structures

peripheral nervous system and the CNS show widespread deposition of glycosphingolipids as demonstrated by Sudan and PAS staining methods. In polarizing light, the deposits show a birefringence in the form of 'Maltese crosses'. In the CNS, neurons of the limbic system and of the brain stem as well as astrocytes are affected, presenting with swollen cytoplasm filled with storage material. In the case reported by Okeda and Nisihara [70], subarachnoidal arteries with a calibre between 0.1 and 1 mm showed degeneration of medial smooth muscle cells and prominent fibrosis and stenosis of the vascular wall. The vascular changes were hypothesized to be the cause of chronic or repeated cerebral ischemia and a prerequisite for dementia. Electron microscopic investigation of the CNS in Fabry disease reveals myelin-like lamellated structures with a periodicity of 5 nm forming parallel arrays and concentric layers. The deposits may also take the form of solid non-lamellated dense osmiophilic aggregates. In the peripheral nervous system, loss of myelinated and unmyelinated nerve fibres has been reported [71].

Dyskeratosis Congenita

This disorder (synonym: Zinsser-Cole-Engmann syndrome) may result from mutations in many different genes and may show an X-linked, autosomal dominant or autosomal recessive inheritance. Genes involved in the pathogenesis of dyskeratosis congenita include DKC1, TERC, TERT, NOP10, NHP2, and TINF2, the first five of which encode components of the telomerase holoenzyme [72]. Clinical features are skin anomalies comprising telangiectatic hyperpigmentation with scattered areas of skin atrophy, nail dystrophy and leucoplakia, combined immune deficiency, aplastic anaemia, and in a small percentage of cases cerebellar ataxia and microcephaly [73, 74] (Fig. 4.12).

The severe form of the disorder which presents with neurological alterations is termed Hoyeraal-Hreidarsson syndrome. Besides a microcephaly and hypoplasia of the cerebellum, hypoplasia of the corpus callosum and delayed myelination may be observed in these cases [75]. Histopathologically, the cerebellum shows a hypoplastic granular cell layer but no loss of Purkinje cells, a finding that differentiates dyskeratosis congenita from the myelocerebellar disorder and ataxia telangiectasia.

In a patient who died at the age of 24 years of gastrointestinal bleeding due to aplastic anaemia, we measured a markedly reduced cerebellar weight of 85 g (total brain weight 1335 g). In contrast to Hoyeraal-Hreidarsson syndrome, the cerebrum showed a normal configuration and myelination.

Oculocerebrocutaneous Syndrome (Delleman Syndrome)

This is a rare disorder, first described in 1981 [76] in its minimal form consisting of cyst formation in the CNS or hydrocephalus, orbital cysts or microphthalmia, and focal skin defects [77] (Chap. 19). On the morphological level, microphthalmia/anophthalmia,

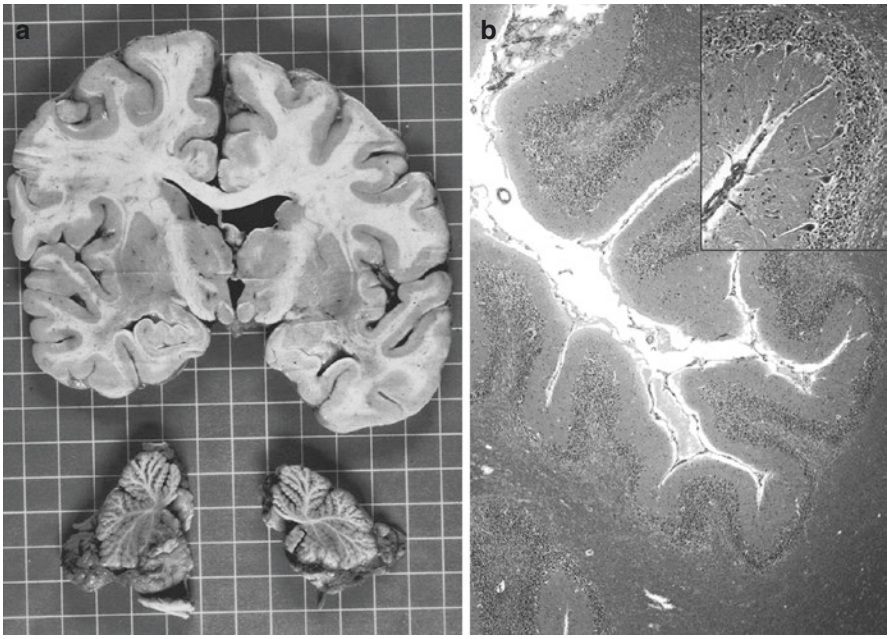

Fig. 4.12 Hypoplastic cerebellum in dyskeratosis congenita. (**a**) Hypoplasia of the cerebellum accentuated on the right side without further alterations in the cerebrum upon macroscopic inspection; (**b**) hypoplastic granular layer of the cerebellum without reduction of Purkinje cell density (insert)

orbital cysts, optic atrophy, intracranial cysts/meningoceles/hydrocephalus, agenesis of corpus callosum, cortical malformations like polymicrogyria and lissencephaly, nodular heterotopia, cerebellar malformations usually presenting as Dandy-Walker malformation, and various tumours (teratoma, haemangioma, neurofibroma) may be observed. The alterations may present bilaterally or unilaterally [78].

PHACE Syndrome

The acronym PHACE was proposed by Frieden et al. [79] for a syndrome featuring posterior fossa malformations, haemangiomas, arterial anomalies, coarctation of the aorta, cardiac defects, and eye abnormalities (Chap. 21). The commonest abnormality of the central nervous system consists of a Dandy-Walker malformation which is found in 32–75% of patients and which is characterized by a hypoplastic or absent cerebellar vermis and a posterior fossa cyst in continuity with the fourth ventricle. Furthermore, cortical dysplasia, subcortical and subependymal grey matter heterotopias, and hypoplasia or agenesis of the cerebellum, cerebellar vermis, corpus callosum, cerebrum, and septum pellucidum may be detected. Frontal lobe calcifications, microcephaly, absence of the foramen lacerum, and sinus thrombosis have been reported in individual cases.

Anomalies of the intracranial arteries are present in 80–90% of patients and comprise hypoplastic or absent carotid or vertebral arteries, aneurysmal dilatation of the carotid artery, and dilated cerebral vessels [80].

Proteus Syndrome

About 200 cases of this congenital overgrowth disorder have been described [81] (Chap. 22). Morphologically, hemimegalencephaly and dilatation of the ventricles, cortical dysplasia, and schizencephaly may be observed. Involvement of the white matter includes calcifications and hypoplasia of the corpus callosum and of the crus cerebri [82, 83].

Klippel-Trenaunay Syndrome

Similar to Proteus syndrome, vascular anomalies are the key feature in Klippel-Trenaunay syndrome (Chap. 9). The capillary and venous alterations usually occur unilateral and may result in enlargement of the affected limb. Spinal cord and cerebral cavernomas and venous and arteriovenous malformations are further recognised features. Cranial bone involvement or intracranial anomalies are rare; intracranial aneurysms, multiple meningiomas, hemihypertrophy of the skull and brain, hydrocephalus, cerebral calcifications, and cerebral atrophy and infarction have also been reported [84–86].

Hypomelanosis of Ito

This ‘melanophacomatosis’ is associated with a broad spectrum of neurological manifestations (Chap. 7). The cerebral changes include macro- and microcephaly, hemimegalencephaly, pachygyria, lissencephaly, polymicrogyria, megalencephaly with leptomeningeal neuroglial heterotopias, focal cortical dysplasia with ballooned cells, hamartomas, hypoplastic corpus callosum, hydrocephalus, periventricular cysts, degeneration of white matter, etc. [52, 87]. In some patients, tumours of the central nervous system and its coverings have been described such as medulloblastoma [88] or primary meningeal rhabdomyosarcoma [89].

Sjögren-Larsson Syndrome

This autosomal recessively inherited deficiency of fatty aldehyde dehydrogenase (FALDH) results in myelination arrest of the central white matter, of the corticospinal tracts, and of the vestibulospinal tracts, whereas the U-fibres seem to be

unaffected in MRI studies [90] (Chap. 45). Furthermore, loss of neurons in the cortex, substantia nigra, and putamen was demonstrated as well as a mild ventricular enlargement.

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Part II
Developmental Malformations

Chapter 5
Sturge-Weber Syndrome

Anne M. Comi

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Introduction

Sturge-Weber syndrome occurs in an estimated 1 in every 20,000–50,000 live births, while facial capillary malformations (*PWB*) occur in 3 in 1000 lives births [1]. It occurs in all ethnic and racial backgrounds and in both males and females. Familial inheritance of *SWS* has never been documented. Identical twins have been reported in which one twin was affected and the other twin was not [2, 3].

As predicted [4], the cause of SWS was determined to be a somatic mosaic mutation (see Chap. 1). An activating R183Q somatic mosaic mutation in *GNAQ* was originally reported [5] and accounts for about 90–95% of cases so far studied. Since then other less common GNAQ somatic mutations have been described, and mutations in the paralogue GNA11 have been reported to cause phakomatosis pigmentovascularis and extensive dermal melanocytosis [6] and to much less commonly underlie SWS [7, 8] (see Chap. 1).

GNAQ codes for the protein Gαq [5]. Gαq is an alpha subunit of a heterotrimeric GTP-binding protein that interacts with a subset of seven transmembrane-spanning

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G protein-coupled receptors. It is known to couple with several GCPRs (including certain serotonin and glutamate receptors, and endothelin-1, angiotensin 2 receptor type I, alpha-1 adrenergic receptors, vasopressin types 1A and 1B) important to vascular development and function. The R183Q SWS mutation is predicted to impair the ability of the guanine nucleotide protein to return to the deactivated state and complex with its GPCR [9]; the mutation therefore likely results in constitutive overactivation of downstream pathways, although any cellular compensatory responses to this hyperactivation are not understood. When mutant constructs were transfected into HEK 293T cells, increased phosphorylated ERK was noted compared to cells transfected with wild-type construct [5]. The downstream effectors of Gαq include p38, ERK, JNK, and Trio [10, 11] which regulate gene expression important in many cell functions, including cell proliferation and differentiation. Studies to date point to the endothelial cells being enriched in the GNAQ mutation [12, 13]; however these results are from cell sorting experiments and depend upon the mutant cells expressing typical cell markers. There is evidence of expression in multiple other cell types as well [14].

Clinical Characteristics

Skin Involvement

Port-wine birthmarks are the most common early identifier of *Sturge-Weber* syndrome [15, 16]. When a baby is born and has a port-wine birthmark that is on the forehead, temple region, and/or on the upper or lower eyelids [17–19] (Fig. 5.1), it is recommended that the infant be checked for Sturge-Weber brain and eye involvement. Depending on whether the birthmark is on one side or both, and how large the birthmark is (*larger, segmental birthmark has higher risk*), the chance that a child

Fig. 5.1 *Panel A.* Male infant with a port-wine birthmark on the left forehead. He began having seizures at 7 months of age and was found to have left-sided brain involvement. *Panel B.* A 13-year-old female with bilateral Sturge-Weber brain involvement and bilateral facial port-wine birthmark. *Panel C.* Same female child soon after receiving laser treatment for her birthmark

has SWS with a port-wine birthmark varies from 10% to about 50% [1, 20]. At birth the birthmark is flat and red [21] and can be mistaken for a bruise related to birth. Over the next few months, it can fade somewhat to a pink color. A port-wine birthmark grows commensurate with the child and does not spread; it also does not usually resolve without treatment. Soft and bony hypertrophy can develop later in adolescence and adulthood to varying degrees and is associated with larger birthmarks, particularly those affecting the lips and central face [22, 23].

Eye Involvement

Glaucoma, the most common ophthalmologic issue, occurs in 30–70% of SWS patients [15, 21]. The dilation of abnormal venous vessels in the eye contributes to the impaired venous drainage and glaucoma which can cause blindness and pain. Dilation of the venous vessels can cause increased intraocular pressure and, combined with the anterior chamber irregularities, may interfere with the proper draining of the eye [24, 25]. Eye pressure should be monitored in patients with *Sturge-Weber* syndrome beginning at birth, for glaucoma can begin any time, and early treatment may prevent vision loss (see Chap. 47). Treatments include various eye drops to decrease fluid and pressure in the eye, and if this is unsuccessful, then surgical interventions are carried out to improve eye drainage and reduce eye pressure [26]. In addition to glaucoma, patients with choroidal involvement are at risk for retinal detachment, either associated with surgery or as a spontaneous consequence of their eye involvement [27].

Brain Involvement

Patients with *Sturge-Weber* syndrome often have seizures; they occur in 72–97% of SWS patients [28–30]. Most seizures are focal motor seizures and begin in infancy [30] (see Chap. 50). These seizures may be hard for parents to spot, for they don't generally present as generalized convulsions or fulfill the usual perception of what a seizure is; anticipatory education is therefore helpful. These seizures present as focal rhythmic twitching or tapping, eyes deviated or jerking to a side, or other subtle signs such as staring and twitching of one side of the mouth. Other types of seizures *SWS* patients tend to have are partial seizures with impaired consciousness or more rarely infantile spasms or drop seizures [31]. Seizures are thought to exacerbate neurological deficits, so aggressive treatment is highly recommended [32]. Seizures can be triggered by everyday factors such as sleep deprivation, illness, or stress but also by migraines or stroke-like episodes. During prolonged or repetitive seizures, there is a significant decrease of blood flow to the side of the brain that's seizing; this seems to be correlated to worsening of brain function in patients with

SWS and probably harms the brain by contributing to strokes and brain atrophy and calcification [32] (see Chap. 4).

The neurological symptoms in *Sturge-Weber* syndrome such as seizures or migraines can evolve as the patient ages [28, 33, 34]. There is a relationship between seizures and migraines, with seizures triggering migraines and migraines triggering seizures. Another severe neurological symptom is stroke-like episodes [35], which, unlike a Todd's paralysis after a seizure, lasts days to weeks after an event. Afterward the patient's weakness may be temporary or permanent; if the hemiparesis is permanent, then the patient is said to have had a stroke, rather than a stroke-like episode. Stroke-like episodes are more common in young children and infants with Sturge-Weber syndrome [36]. Other less obvious impairments can include a visual gaze preference or early handedness.

Chronic functional disability can develop over time. Patients with hemiparesis are of a higher likelihood to have cognitive deficits [37]. Referral for a medical rehabilitation evaluation of the young infant or child is important so that physical, occupational, and speech/language therapy services can be provided if warranted [38, 39]. Around 67% of patients have psychomotor deficits, while 30–50% suffer from mental disability. Common behavioral signs are aggression, depression, and attention deficit disorders [40]. Neuropsychological testing is suggested at the ages of 3–4 years, particularly if they have some degree of hemiparesis, for this evaluation will help bring to light any other impairments not found previously [37]. A recent study in England noted autism spectrum disorder and social impairments to be very common in SWS [41]; it is not clear that this is the case in every population.

Endocrine Involvement

There are hormonal imbalances associated with SW syndrome including growth hormone deficiency [42] and central hypothyroidism [43, 44]. The rate of growth hormone deficiency in patients with *SWS*, while still low, is 18 times greater than in the general population [42]. While the cause of the deficiency is unknown, nevertheless it is important to make the diagnosis where present as it is treatable. Treatment should be pursued with caution as in some patients it has resulted in seizure relapse [45]. Untreated growth hormone deficiency in adults may result in depression and organ dysfunction; therefore even in adult patients it is important to make the diagnosis of growth hormone deficiency and offer treatment where present. Central hypothyroidism is also more prevalent in patients with *SWS* than in the average population: we noted a 2.4% prevalence at our *SWS* Center, compared to a 0.0002–0.0005% of the general population [43]. While anticonvulsant medications may contribute to the risk of central hypothyroidism, *Sturge-Weber* patients are also at additional risk of central hypothyroidism because of the disruptions in their central nervous system, which could cause hypothalamic-pituitary issues. Testing for central hypothyroidism is extremely important and must be done by testing free T4 by equilibrium dialysis method [44], and if patients have low thyroxine hormones,

they should be started on levothyroxine. Partial hypopituitarism has also been described; therefore cortisol and estrogen/testosterone levels should also be evaluated where concerns exist [46].

Pathology (See Chap. 4)

Brain involvement in SW syndrome consists of abnormal leptomeningeal vessels (Fig. 5.2) and dilated deep venous vessels, resulting in impaired venous drainage of the brain [47–49]. This impaired drainage creates compromised arterial perfusion. Injury to various brain cells can cause the calcification seen in *Sturge-Weber* patients; this is particularly seen around blood vessels on the cortex [50, 51]. The cortex can be atrophied and numbers of cortical draining vessels are decreased; calcification becomes apparent as the hemisphere atrophies. Therefore, calcification, neuronal loss, and gliosis are also probably secondary to brain injury due to impaired brain perfusion. Cortical dysgenesis has been noted in surgical brain samples [52], including focal cortical dysplasia (FCD) type IIa near the region of leptomeningeal angiomatosis, *cortical dysplasia*, and *polymicrogyria* [53]. Modestly increased proliferative index within the leptomeningeal blood vessels suggests ongoing vascular remodeling [54]. Increased VEGF expression in cortical neurons and glia underlying the abnormal leptomeningeal vessels and increased VEGFR-1, VEGFR-2, HIF-1α, and HIF-2α expression in endothelial cells of the abnormal leptomeningeal vessels suggest that chronic tissue hypoxia and VEGF may drive ongoing vascular remodeling [54]. The Ra-Raf-MEK-ERK pathway can increase both VEGF [55] and HIF activity [54]; therefore the *SWS* somatic mutation in *GNAQ* may contribute to the vascular remodeling. Indeed, increased p-ERK expression has been noted in abnormal leptomeningeal vessels of surgical brain samples from patients with SWS [56].

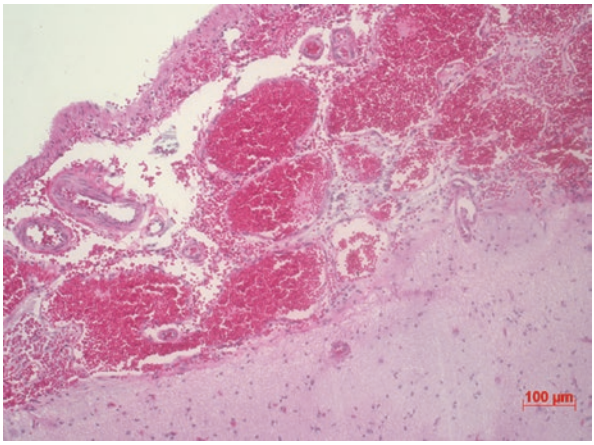

Fig. 5.2 Hematoxylin and eosin-stained, formalin-fixed brain section from a patient with Sturge-Weber syndrome removed at surgery for epilepsy. Note increased number of leptomeningeal blood vessels in the thickened leptomeninges

Diagnosis

Sturge-Weber syndrome is a spectrum disorder ranging from brain involvement alone to skin involvement only; the full presentation consists of typical brain, skin, and eye involvement; however individuals on the spectrum can include those who have only brain and skin involvement or those who have only skin and eye involvement. The precise manifestation of the spectrum likely depends on when in fetal development the somatic mutation occurs. Diagnosis of a *SWS* port-wine birthmark is usually straightforward; it is present at birth, unlike a hemangioma, and is usually off midline, unlike a nevus flammeus nuchae (angel's kiss, stork bite) birthmark. On occasion the port-wine birthmark is located midline forehead, and this has been associated with more severe neurologic prognosis [57]; it is differentiated in this case from the nevus flammeus nuchae by not being associated with symmetric upper eyelid involvement typically seen with the other benign birthmark. Occasionally the diagnosis is unclear and requires the input of a dermatologist or expert.

Diagnosis of *Sturge-Weber* syndrome brain involvement is made by MRI with and without contrast (Fig. 5.3); post-contrast flair [58] and susceptibility-weighted imaging (SWI) [59] and quantitative ADC analysis [60] can help increase the sensitivity of the imaging, yet MRI can have low sensitivity in early infancy or under the age of 1 [17]. Contrast is required to reveal the leptomeningeal angiomatosis, atrophy may be seen if injury has occurred, and susceptibility-weighted imaging (SWI) may demonstrate an increase in abnormal deep draining vessels. Calcification is best demonstrated on CT [61] (Fig. 5.4) but may also be seen on MRI if extensive (see Chap. 3). A scan that is negative for SWS brain involvement in an infant under the age of 1 does not rule out the possibility that the child has Sturge-Weber; a study

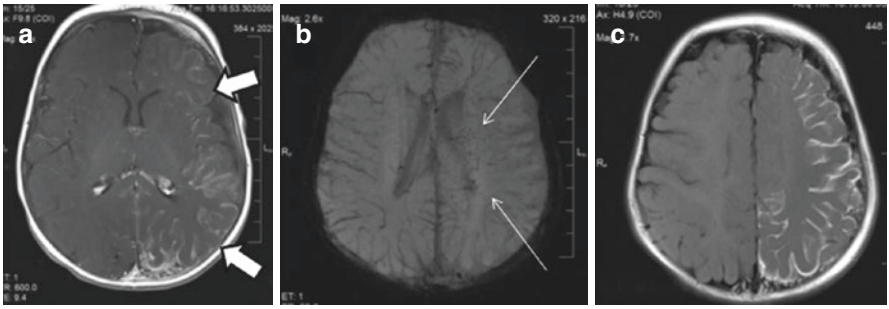

Fig. 5.3 Neuroimaging demonstrating typical features of Sturge-Weber syndrome brain involvement. A 4-month-old female with left-sided brain, skin, and eye Sturge-Weber syndrome involvement and recent onset of seizures. *Panel A:* T1-weighted contrast-enhanced MRI showing extensive leptomeningeal enhancement and mild brain atrophy involving the left hemisphere (bold arrows). *Panel B:* Susceptibility-weighted imaging showing increased number of small deep draining vessels within the left hemisphere. *Panel C:* Post-contrast flair imaging: leptomeningeal enhancement is even more prominent

demonstrated that early MRI only has a sensitivity of about 25% [17]. Imaging should be repeated after a year of age both to exclude brain involvement and, if the brain is involved, to determine the full extent of brain involvement. Other evaluations which can be helpful in the first year of life include a careful history, repeated exams, EEG looking for slowing, decreased amplitude, frequent sharps or spikes [62], and quantitative EEG evaluating [16] for a decrease in power on the affected side (see Chap. 50). Examinations should be performed as soon as possible after birth to evaluate for eye involvement and glaucoma risk and should be repeated every few months for the first few years of life and then at least yearly thereafter.

Indications for DNA testing are evolving. The most common genotype in published cases is R183Q GNAQ [63]; however the phenotype spectrum has been reported with other mutations in GNAQ [6, 63] and with GNA11 mutations [7, 8]. Capillary malformation and glaucoma can also be seen with PIK3CA mutations [64]. These other mutations can have implications for tumor risk, tissue overgrowth, and other vascular anomalies. Genetic testing can begin with blood particularly in patients with multiple birthmarks; however frequently skin or other abnormal tissue is required for testing; this situation does not lend itself to prenatal testing. Since the same mutation is found in both, DNA testing of skin tissue from the port-wine birthmark will not distinguish an infant with an isolated birthmark from one who has SWS brain and/or eye involvement (see Chap. 1).

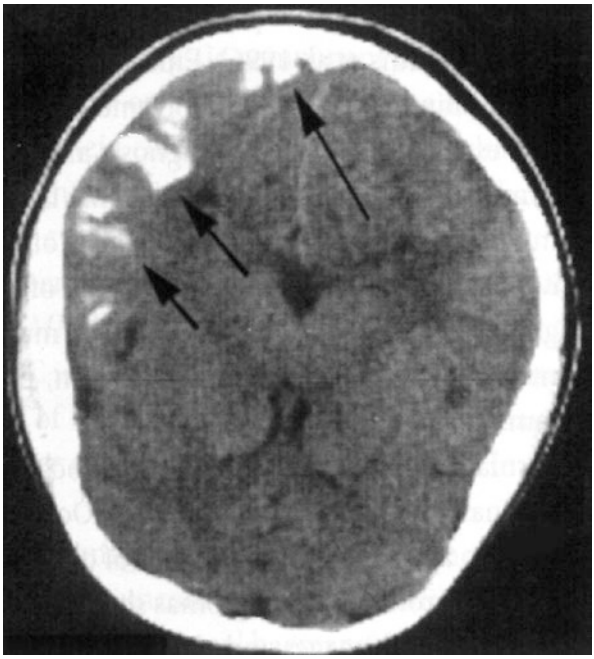

Fig. 5.4 Axial CT image of a young woman with Sturge-Weber shows coarse cortical calcifications (arrows)

Therapy

The gold standard treatment for port-wine birthmarks is *flashlamp-pumped* pulse dye laser treatment, often in combination with other older laser technologies. This will often lighten the birthmark and may also reduce the effects of physical impairments from the birthmark, as well as the risk of hypertrophy. It is recommended that treatments begin in infancy as the birthmark responds best to treatment while still flat and pink and small infants tolerate the treatments well without the need for general anesthesia [65, 66]. Six to 12 treatments are generally required to maximally lighten the port-wine birthmark, periodic maintenance treatments are usually required, and some birthmarks are resistant to laser treatment. Most birthmarks are not fully cleared with current treatment. Treatments, although brief, are painful, and the question of how best to manage this aspect ranges from topical anesthetics to oral sedation and to treatments done under anesthesia; the ethics of this are controversial. As a result, new treatment approaches are being researched and developed including topical and oral anti-angiogenesis treatments currently being studied in combination with laser treatment [67], and current practice emphasizes early, frequent treatment which usually obtains good results [65, 66] (see Chap. 50).

The *goal of glaucoma treatment* is control of intraocular pressure (IOP) to prevent optic nerve injury. This can sometimes be achieved with the following agents: beta-antagonist eye drops and carbonic anhydrase inhibitors which are both used to decrease the production of aqueous fluid and adrenergic eye drops and miotic eye drops which are used to promote drainage of aqueous fluid from the eye and thereby reduce eye pressure. However, for some patients surgery may be needed to reduce the eye pressure. There are many different types of surgeries which can be applied including goniotomy, trabeculotomy, trabeculectomy, and argon laser trabeculoplasty [68–70] (see Chap. 47). Choroidal involvement can lead to retinal detachment, which if symptomatic may be treated with photodynamic therapy or external beam radiotherapy [71].

The primary treatment for seizures in *Sturge-Weber* syndrome comprises the use of anticonvulsants [72] (see Chap. 50). These medications provide seizure control in about 50% of patients [73, 74]. However, if treatment with different anticonvulsants has been found unsuccessful, a patient may require surgery. First-line anticonvulsants, typically oxcarbazepine and levetiracetam [72], should be given aggressively at the first focal seizure. Other commonly used anticonvulsants include topiramate, phenobarbital, and carbamazepine [72]. These may be added if a single treatment has been unsuccessful. After a patient with *Sturge-Weber* has passed 3 months of age, parents are instructed to give rectal diazepam to abort seizures lasting longer than 3–5 min or clusters of seizures [45] (see Chap. 50).

Low-dose aspirin is becoming more accepted and used in the treatment of *SWS* but remains controversial, and further studies are needed. In a recent investigation of 58 patients with brain involvement, 49 children (84%) had no significant side effects to the aspirin. Six of the nine patients who reported side effects had minor complications [75]. Also, according to an online survey, low-dose aspirin significantly decreased the frequency of stroke-like episodes and seizures [76]. This

corresponds with *Udani's* results of fewer seizures and stroke-like episodes of six *SWS* patients after starting low-dose aspirin [77] and Maria's data of 14 patients, 65% of which had reduced stroke-like episodes on low-dose aspirin [61]. The modified Atkins diet and the ketogenic diet are also prescribed to patients with *SWS* to help prevent seizures. This diet consists of low daily carbohydrates but calls for high-protein and high (*unsaturated*)-fat foods. The modified Atkins diet is much less restrictive than the ketogenic diet, which also regulates calories and fluids. These diets are successful in around 50% of subjects with SWS [78] but are very difficult to maintain except in infants.

Hemispherectomies and focal brain resections are surgical options for many patients with unilateral *Sturge-Weber* syndrome. Candidates for surgery are the patients who have tried multiple anticonvulsants (and often low-dose aspirin), been on treatment for 6 months prior to surgery, don't have bilateral brain involvement, and have frequent seizures and classical SWS symptoms. It may yield more successful results to perform the hemispherectomy earlier on in childhood, but this is controversial and not all studies bear out this hypothesis [79–82]; surgery under a year of age increases the risk of inappropriately attempting surgery in a patient thought to be unilaterally involved, but who in fact is bilaterally involved and may have a higher risk of morbidity (see Chap. 48). Hemispherectomies are riskier, but more patients have fewer seizures after this type of surgery than with focal resection surgery. One study of 32 hemispherectomies performed worldwide found that 81% of subjects didn't have a decline in their motor function and were without seizures [81]. For unilaterally involved patients, surgery should be considered for those who have failed two or more anticonvulsants combined with low-dose aspirin [80, 81]. The decision to proceed with surgery is easier in those patients who also have hemiparesis and a significant visual field deficit in addition to impairing, medically refractory seizures. Surgery should also be seriously considered in patients whose cognitive development is progressively falling behind normal. The extensively bilaterally affected child with *Sturge-Weber* syndrome and severe brain involvement has the highest risk of very poor neurologic and cognitive outcome. For these infants, very aggressive treatment with anticonvulsants and low-dose aspirin is warranted. Hemispherectomy has only been recommended in bilaterally affected children with very severe disabling seizures primarily coming from one hemisphere, and the surgery is considered palliative rather than potentially curative [83] (see Chap. 48).

Headaches frequently start at an early age in patients with SWS and can be very severe. Headaches frequently happen along with seizures; other triggers include minor blows to the head [84]. Medications such as topiramate, gabapentin, and valproate may provide both seizure and migraine prevention. Migraine treatment can be an essential part of seizure management since migraines can trigger seizures [33]. Over-the-counter anti-inflammatory medications and triptans are common abortive migraine medications helpful to these patients [33]. The greater cognitive impairment a child has, the higher likelihood of behavioral problems. Stimulants may be used to treat attention deficit disorders with high success in patients with *Sturge-Weber* syndrome [85]. Individualized or special educational classes or programs can also be beneficial, along with behavioral psychology therapy.

Prognosis

There is an extremely wide range of outcomes in patients with *Sturge-Weber* syndrome. Predictive variables include their age of onset and controllability of seizures and unilateral vs. bilateral brain involvement. Genetic predisposition to seizures, strokes, and migraines likely plays an important, though undefined, role as well; a family history of epilepsy is associated with early onset of seizures in *SWS* [86], which in turn is associated with worse neurologic outcome. Therefore, each patient is unique and prognosis is difficult to predict. *Sturge-Weber* syndrome is progressive, in the usual sense, in some, but not in all, patients. Some patients can attend regular mainstream schooling, and some receive extra assistance in school; many of these patients are able to move on to higher education and can complete college and beyond. Other patients require special education services, while a subset are trainable or require full care. Many patients with *SWS* receive some sort of school accommodation. Some patients live with their parents and families of origin into adulthood, while others can live independently and start families of their own. Need for assistance with transportation is common because of epilepsy and vision issues.

Recent Treatment Trials and Future Prospects

It is to be hoped that with the discovery of the underlying somatic mosaic mutation and a new understanding of the *pathogenesis* of *Sturge-Weber* syndrome in the not too distant future, target treatment options will become available which will effectively treat the vascular basis of *SWS* and effectively alleviate its neurologic, ophthalmologic, dermatologic, and endocrine manifestations. Early progress has been made recently in the publication of the first prospective treatment trials of Sturge-Weber syndrome which have pioneered the application of several outcome measures and suggested the usefulness of cannabidiol (Epidiolex) [87] and rapamycin (mTOR inhibitor/sirolimus) [88] for the neurologic treatment of Sturge-Weber syndrome. Furthermore, because seizures exacerbate blood flow impairments in SW syndrome and increase the risk of venous hypertension, stroke, and brain injury particularly in infants and young children, presymptomatic treatment (prior to the onset of seizures) is gradually being evaluated [89–91].

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Chapter 6
Ataxia-Telangiectasia (Louis-Bar Syndrome)

Christos P. Panteliadis and Ramsis Benjamin

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Introduction

Ladislav Syllaba and Kamil Henner in 1926 first documented ocular telangiectasia and athetosis in three family members [1]. Their observation remained obscure until 1941 when *Denise Louis-Bar* identified cerebellar ataxia and cutaneous telangiectasia in a Belgian child [2]. The disorder did not bear *Louis-Bar's* name as a clinical entity until 1957 when pathological findings were correlated with neurologic symptoms, immunodeficiency, and recurrent upper respiratory tract infections.

The worldwide incidence of A-T is about 1 in 40,000–100,000 live births. The prevalence and phenotypes vary based on the degree of consanguinity and whether there is homozygous or compound heterozygous mutations in the *ATM* gene. The mutated gene *ATM* is located on chromosome 11q22-23 [3].

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Ataxia-telangiectasia (A-T), or Louis-Bar syndrome, is an autosomal recessive neurodegenerative disorder that presents in the first decade of life with cerebellar ataxia (progressive cerebellar degeneration), oculomotor apraxia, hand incoordination, choreoathetosis, cognitive dysfunction, and telangiectasias of the conjunctivae. Hyperkinetic movements (dystonia, chorea, myoclonus, and tremor) could be the presenting symptoms, making it challenging to diagnose A-T in children [4, 5]. Other symptoms include immunodeficiency or chronic inflammatory diseases, manifested as recurrent sinopulmonary infections, endocrinopathy, radiosensitivity, and an increased predisposition toward lymphoid-type cancers.

Pathogenesis

The chief microscopic feature of A-T is the degeneration of *Purkinje,* Körner, and granule cells seen as cerebellar atrophy on imaging studies (Fig. 6.1).

Degeneration of corticospinal tracts and anterior horn cells often manifest in later years. The *ATM* (ataxia-telangiectasia mutated) gene has been mapped to band 11q22-23 and is composed of 66 exons (4 non-coding and 62 coding) DNA that span across 150 kb of genomic DNA [3, 6]. The normal gene is a member of phosphatidylinositol-3-kinase genes involved in cell survival, intracellular protein transport, and genomic stability. *ATM* plays a crucial role in neurodevelopment and stem cell differentiation, but the level of its protein product does not parallel the clinical characteristics [7]. Although mutations in the kinase ATM, a regulator of the DNA double-strand break response [8], produce the clinical features of A-T, no clear mechanism short from telomere loss accounts for the cutaneous telangiectasia.

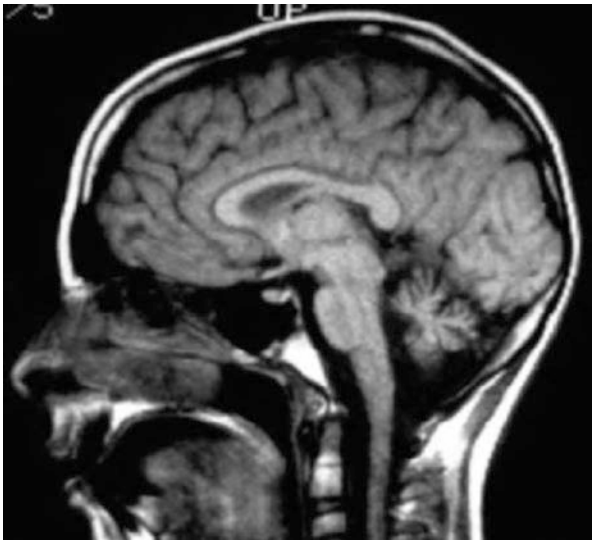

Fig. 6.1 MRI of an 18-year-old boy with cerebellar atrophy

That said, lack of ATM kinase leads to diminished integrity and function of the mitochondrial DNA (mtDNA), secondary to reduced levels of DNA ligase III (Lig3).

Pharmacological inhibition of Lig3 in wild-type cells phenocopies the mtDNA repair defects observed in A-T patient cells. As targeted deletion of *LIG3* in the central nervous system causes debilitating ataxia in mice, reduced Lig3 protein levels and the consequent mtDNA repair defect may contribute to A-T neurodegeneration. A-T is thus the first disease characterized by diminished Lig3 [9]. More than 500 unique mutations are known, most of which yield no protein product, and as a result only 1% or less share a common mutation. Certain probands have greater phenotypic predilections, such as the heterozygous mutations c.6259delG and c.6658C > T or the p.A2067D missense mutation in the *ATM* gene, which have been seen in early-onset generalized dystonia and late-onset ataxia [5, 10].

Mutations in the *ATM* gene have been reported in various forms of leukemia and lymphoma, specifically chronic lymphocytic leukemia, acute lymphoblastic leukemia, T-cell prolymphocytic leukemia, and mantle zone lymphoma. There is limited evidence implicating *ATM* polymorphisms with breast cancer [11]. The relative risk of malignancy in heterozygous individuals reaches four times that of the general population [12]. This risk depends in part on the type of mutation, such as missense versus truncating, and on the type of tumor.

Clinical Characteristics

The incidence of A-T is about 1 in 40,000–100,000 live births. Prevalence varies with the degree of consanguinity. A-T is observed around the world and affects all races and gender equally and is the most common cause of progressive cerebellar ataxia in childhood; however, ataxia with oculomotor apraxia may be more prevalent in Portugal and Japan [3, 13, 14]. Only one-third harbor ataxia, and 20% suffer from pure extrapyramidal symptoms. Individuals with extrapyramidal presentations have a milder neurological disease [15].

Infants generally display no characteristic features of the disease. Progressive cerebellar ataxia (in 30–90% of the patients) is first noticed shortly after the child attempts to stand or walk, followed by telangiectasia, oculomotor apraxia (inability to track an object across visual fields), hypersensitivity to ionizing radiation, and immunodeficiency that leads to frequent upper respiratory infections (48–81%) and malignancies (20–40%), particularly acute lymphocytic leukemia and lymphoma (85% of all tumors) [16–18]. B-cell non-Hodgkin lymphoma, Hodgkin lymphoma, and acute lymphoblastic leukemia occur at a high rate and earlier age than carcinomas [18]. A significant correlation exists between the frequency of infections and the magnitude of immunodeficiency.

The *first hallmark* of the disease is gait ataxia that becomes increasingly apparent beyond the age of 5. It ultimately necessitates the use of a wheelchair by the age of 10. Almost all ataxia-telangiectasia subjects are inflicted with abnormal involuntary movements, such as rhythmic oscillations (tremor), slow drifts (dystonia or

athetosis), and isolated rapid movements (dystonic jerks or myoclonus) [19]. The first two abnormalities occur at rest, but the jerks are typically stimulus-sensitive and partially relieved by levodopa treatment [20]. All patients with involuntary movements have both kinetic and postural tremor, while two-thirds of those also suffer from resting tremor, which suggests not only dysfunctional Purkinje neurons but also impairment within the lattice of cerebello-thalamic-cortical connections as regulated by the basal ganglia.

Walking in some individuals may improve from 2 to 4 years of age, only to deteriorate again; the perceived brief recovery relates to the rapid learning rate of young children. The combination of preserved sensation and a negative Romberg sign helps differentiate A-T from *Friedreich ataxia.*

Ocular telangiectasia represents the *second hallmark* of A-T, which occurs in approximately 97% of the patients. Difficulties with smooth pursuit and saccadic eye movements usually precede ocular telangiectasia [21]. Cutaneous telangiectasia is less frequent and rarely bleeds. The aberrant venous vessel appears between the ages of 3 and 6 (Fig. 6.2). It involves the lateral conjunctivae and extends horizontally toward the ears and cheeks. The cubital and popliteal fossa are infrequently affected.

Choreoathetosis (30–90% of patients) and dystonic posturing of the fingers are the most prominent extrapyramidal features in A-T and affect older children. Hypotonic dull and "sad" facial features, a slow-spreading smile, and seemingly inattentiveness usually accompany the movement disorder.

Other clinical findings may comprise of insulin-resistant hyperglycemia, dysphagia, dysarthria, myoclonus in the trunk and extremities (~25%), and delayed physical and sexual development, although progeric changes of hair and skin are normal occurrences. Senile keratoses, seborrheic dermatitis, hyperpigmented macules resembling large freckles, hypopigmented macules, café au lait macules, melanocytic nevi, and basal cell carcinomas have been reported in older A-T patients. Normal or above normal intelligence has been observed in most children [22, 23].

Diagnosis

Diagnosis can be made early in families with the disease. Imaging studies such as high-resolution MRI provide insight into impaired neuronal network as a result of abnormal development or progressive degenerative processes. Information can be

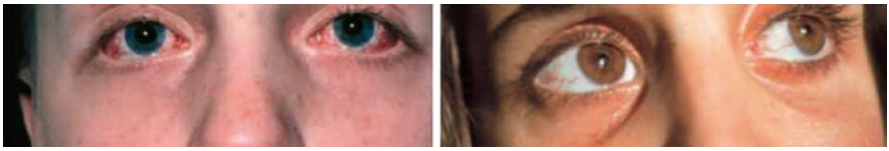

Fig. 6.2 Telangiectasia of conjunctiva in a 16-year-old boy (left image) and in a 14-year-old girl

deduced regarding the relationship between gene mutation of ataxia-telangiectasia and the integrity of motor circuitry [3, 24].

Paraclinical testing to support the diagnosis of A-T includes serum α-fetoprotein concentration (10 ng/mL or more in 95% of cases), the presence of *humoral* or *cellular* immunodeficiency (50–80%), identification of 7;14 translocation on routine karyotype of peripheral blood (in 5–15% of cells), and *in vitro* radiosensitivity assay (the test takes approximately 3 months to complete) or a serine/threonine kinase assay in conjunction with immunoblotting to quantify ATM protein in cells. Deficiencies of IgA and IgG2 are most common, and elevated IgM in approximately 60% of the patients can be used as part of the diagnostic criteria [25]. The presence of ATM protein on immunoblotting and normal radiosensitivity testing excludes the diagnosis of A-T. On the other hand, normal ATM protein level and abnormal radiosensitivity testing necessitate validation by kinase activity of ATM protein [26–28].

The *differential diagnosis* includes other rare disorders that mimic A-T, such as Friedreich's ataxia (prevalence 1–3/100,000, a multisystem disorder, affecting the central and peripheral nervous and musculoskeletal system, myocardium, and endocrine pancreas), Cogan's oculomotor apraxia (keratitis, conjunctivitis, scleritis, uveitis, retinal vasculitis, hearing loss, vertigo, tinnitus), Nijmegen breakage syndrome (rare autosomal recessive disease presenting at birth with microcephaly), cerebral palsy, ataxia oculomotor apraxia types 1 and 2 (AOA1 and 2) (a heterogeneous group of neurodegenerations due to aprataxin mutations) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5933354/-noi170108r1), and ataxia with vitamin E deficiency. Other conditions include Fragile-X tremor ataxia syndrome that typically causes a late-onset ataxia-plus syndrome; autosomal recessive spastic ataxia of Charlevoix-Saguenay (*ARSACS*); various mutations in the mitochondrial polymerase gene (POLG syndromes); ataxia with vitamin D deficiency (*AVED*) that is potentially treatable and should not be overlooked; and the autosomal dominant episodic ataxias, most importantly EA1 and EA2 [29].

Beaudin et al. [30] provide a clinical and pathophysiological classification of primary autosomal recessive cerebellar ataxias, based on consensus among a panel of 12 international experts. The top three causes include *Friedreich's ataxia*, A-T, and ataxia with oculomotor apraxia type 1. The exact clinical history and neurologic examination are invaluable toward the first step of ensuring a correct diagnosis.

Therapy

Ataxia-telangiectasia mutated (ATM) protein plays a central role in eliciting coordinated signal-transduction network called DNA damage response. ATM phosphorylates itself once activated by DNA damage, and downstream effectors arrest cell cycle for DNA repair or induce apoptosis. Preclinical studies have demonstrated that targeted inhibitors against ATM kinase may improve therapeutic outcomes [31, 32]. Regulators of the *DNA damage response* apparatus have become attractive targets [33].

At present, no cure exists for A-T. Therapeutic agents to halt the progression of the disease, especially motor dysfunction, have been disappointing. Multidisciplinary care centers experienced in treating A-T patients that combine the fields of neurology, immunology, infectious disease, pulmonology, oncology, and nutrition should be requested early, if available [34].

Supportive and symptom-based therapies take precedence. Gait stability could be prolonged with the aid of physical and occupational therapy, as the development of future contractures can be minimized. Speech therapy may assist the dysarthric individual. In a few cases, beta-adrenergic blockers may enhance motor coordination and action tremors. To augment the already compromised immune response, infusion of intravenous gamma-globulin appears to curb the frequency of serious infections [16]. Approximately 12–15% of patients require regular immunoglobulin therapy [35]. The use of prophylactic antibiotics with macrolides in patients with chronic lung problems is recommended. People with A-T often have a suboptimal response to the 23-valent pneumococcal polysaccharide vaccine [36]. Gene and stem cell-based therapies have been unsatisfying thus far.

Vitamin E, folic acid, or alpha-lipoic acid supplementation is generally recommended as it seems to reduce chromosomal breaks and prevents cancer-causing translocations [37]. Other antioxidant agents and iron chelators such as epigallocatechin-3-gallate and deferoxamine have demonstrated genomic stability in vitro, but the application and crossover to the human genome remains unfounded [38–40]. Encapsulation of dexamethasone sodium phosphate (DSP) into autologous erythrocytes (EryDex) allowing slow release of dexamethasone for up to 1 month after dosing has shown significant improvement in neurological symptoms [41].

Tactful genetic counseling should be provided to all patients with A-T and their family members. Because of the autosomal recessive pattern, asymptomatic parents of an affected child must be carriers of the gene. Each subsequent child born by this couple will have a 25% chance of bearing the diagnosis, a 50% chance of becoming a carrier like the parents, and a 25% chance of being free from disease. Data extrapolated from a meta-analysis of nine publications show a low risk between polymorphisms of *ATM* genes and breast cancer [42].

Finally, radiotherapy and ionizing radiation pose a significant risk to patients with A-T and thus should be given careful consideration before their use. Standard radiation dosimetry could be potentially lethal.

Prognosis

A-T is an extremely complex disease. The prognosis and quality of life for individuals with A-T remain overall poor, despite advances in treating underlying infections, which have extended the life span beyond 25 years. The majority of cases, however, usually die within the median age of 20. Lung disease is a significant source of morbidity and mortality among patients with A-T [36]. Those who are carriers of the gene (i.e., A-T heterozygotes) face also a greater risk of death from ischemic

heart disease or cancer [17]. Survivors beyond 30 years of age acquire severe tetraparesis and contractures, making them immobile and prone to frequent hospitalization for pulmonary, endocrine, cardiovascular, and gastrointestinal conditions [43].

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Chapter 7
Hypomelanosis of Ito (Incontinentia Pigmenti Achromians)

Christos P. Panteliadis

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Introduction

In 1952, the Japanese dermatologist Dr. Minor Ito from Tohoku University described in his studies on melanin a woman with a distinctive pattern of linear hypopigmented skin lesions over the trunk and extremities [1]. Initially Ito designated his findings as *incontinentia pigmenti achromians* to differentiate it from incontinentia pigmenti in which the lines of *Blaschko* [2] are hyperpigmented (see Chap. 8). Hypomelanosis of Ito (HI) is a rare neurocutaneous disorder, affecting both sexes with an approximate female to male ratio of 2:1. It has a frequency of 1 in every 3000–10,000 children [3, 4]. Patients usually present with hypopigmented lesions following the lines of *Blaschko*. Multiple organ systems may be involved including the brain, musculoskeletal and cardiovascular system, eyes, kidneys, and teeth. In 1992, Ruiz-Maldonado et al. described for the first time the diagnostic criteria [3].

By analyzing fibroblast cultures, a variety of chromosomal abnormalities have been observed [5]. For example, *Steichen-Gersdorf* et al. [6] have reported a girl with hypomelanosis of Ito, choroid plexus papilloma, and chromosomal

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translocation (X;17). Cytogenic analysis often reveals chromosomal mosaicism of 46, XX/47, XX and 46, XX/47, XX, + 14 [7–9]. Usually, HI is considered a sporadic disorder, but dominant and recessive (including X-linked) inheritance have also been reported. An association exists between hypomelanosis of Ito and ring chromosome 20, trisomy of chromosome 13, and other cytogenetic abnormalities [10, 11]. The different pigmented skin areas correspond to the distribution of two distinct cell lines in a single individual.

Clinical Characteristics

Skin alterations in HI typically encompass hypopigmented whorls and streaks (Fig. 7.1) that follow *Blaschko's* lines, with frequent concurrent neurologic deficits and abnormalities in other organs [12]. The streaks can be isolated or diffuse, unilateral or bilateral, and appear within the first year of life in 75% of the patients. Palms, soles, and the mucous membrane are spared. The clinical manifestations vary from small hypopigmented areas to hemisomatic large hypopigmented whorls. The achromatic areas of reduced melanin may become visible at birth or during infancy as strips along the dermatomes. Helicoids with abnormal edges are believed

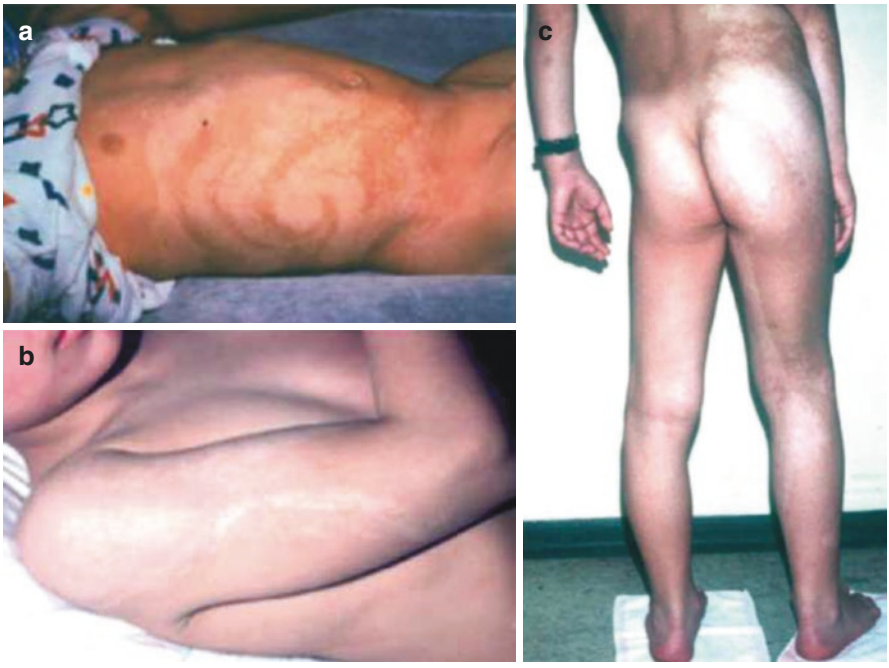

Fig. 7.1 (**a**) Large areas of hypopigmented whorls in a 2-year-old male; (**b**) hypomelanosis of Ito in a 9-year-old boy; (**c**) asymmetric abnormalities in the gluteal region in the same boy as in (**a**)

to represent undifferentiated clones formed from early ectodermal progenitor cells [13].

The *associated abnormalities* affect the central and peripheral nervous system, the eyes, and the connective tissue [14]. Central nervous system (CNS) involvement occurs with great regularity (70%) and manifests as severe cognitive dysfunction, learning difficulties, dysphasia, autism, seizures, choroid plexus papilloma, hypoplasia of the corpus callosum, micro- or macrocephaly, hemimegalencephaly, cortical malformation (neural heterotopia), encephalomalacia, scoliosis, hypotonia with pes valgus and genu valgus, and spasticity [2, 15] (see also section "Hypomelanosis of Ito"). Seizures are frequently generalized tonic-clonic or myoclonic and afflict 30% of the cases, often resistant to therapy [16].

Rarely, infantile spasms may be seen. Electroencephalography (EEG) presents multifocal asymmetric paroxysmal potentials or nonspecific abnormalities. *Esquivel* et al. [17] correlated the EEG findings of 15 HI cases with computer tomography (CT) scan data and found a weak association between the presence of abnormal rhythmic activity and radiological defects such as pachygyria, cortical dysplasia, and gray matter heterotopias. CT scan may also reveal hemispheric atrophy in one or both sides or porencephaly with widening of lateral ventricles. *Ocular* characteristics of the disease include strabismus, nystagmus, epicanthus, and retinal changes such as hypopigmentation of the fundus, optic nerve hypoplasia or atrophy, and myopia [12]. Rarely, asymmetry of the cornea, hypertelorism, keratitis, atrophic iris, macular degeneration, cataracts, retinal detachment, and frank visual loss are observed [2].

Teeth, hair, and nail abnormalities exist, such as hypodontia, enamel defects and caries, clinodactyly, syndactyly, and focal hypertrichosis of the face, the external parts of the arms, and genitalia without signs of precocious puberty. Other features may include congenital cardiopathy, renal and genital anomalies, and bone malformation such as scoliosis, craniofacial malformations, and vertebral anomalies [18, 19]. Associated gynecomastia has been rarely reported. Several benign tumors have been reported in conjunction with hypomelanosis of Ito, predominantly cystic teratoma, diploic epidermoid cyst, mature sacrococcygeal dysembryonal tumor, choroid plexus papilloma, and dental hamartomas. Malignant tumors such as medulloblastoma are rare [20, 21]. On *skin biopsy* there are dyskeratosis, mastocytosis, and sebaceous gland defects. On electron microscopy decreased numbers of melanocytes are observed. The extent of hypopigmented cutaneous lesions does not correlate with the severity of neurological disease or with neuroradiological or histological findings.

Diagnosis

The diagnosis can be made on the basis of clinical findings and genetic mosaicism. Occasional autosomal dominant and recessive inheritance have been detected. Diagnostic criteria have been proposed [3]. Major criteria include cutaneous

hypopigmented linear streaks or patches involving more than two body segments, appearing at birth or in the first months of life, with one or more neurological or musculoskeletal deformities. Minor criteria include chromosomal anomalies and two or more congenital malformations, excluding nervous and musculoskeletal systems. The diagnosis is retained with one major or minor criterion or two minor standards.

Therapy

The management is symptom-orientated, and no specific therapy exists for HI. Antiepileptic drugs are administered in the event of seizures. Intractable epilepsy may require resection of the epileptogenic cortex [22]. Orthopedic consultation for bone defects is generally required, along with physiotherapy for psychomotor impairment. Patients who only possess cutaneous symptoms and have no apparent involvement of other organs require longitudinal assessment of the eyes, hearing, and mental status [23]. In cases with neurological symptoms, brain MRI should invariably be performed and EEG repeated annually.

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Chapter 8
Incontinentia Pigmenti

Lukas Kieswetter and Elena Pope

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Abbreviations

CBCT	Cone beam computed tomography
CNS	Central nervous system
DWI	Diffusion-weighted imaging
EEG	Electroencephalography
IKBKG	Inhibitor of κB kinase gamma
IP	Incontinentia pigmenti
IV	Intravenous
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
NEMO	Nuclear factor-κB essential modulator
NF-κB	Nuclear factor-κB

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OCT	Optical coherence tomography
OT	Occupational therapy
PCR	Polymerase chain reaction
PT	Physiotherapy
RPE	Retinal pigment epithelium
SLT	Speech and language therapy
STIPs	Subungual tumors of IP
SWI	Susceptibility-weighted imaging
TNF	Tumor necrosis factor
VGEF	Vascular endothelial growth factor
XR	X-ray

Introduction

Incontinentia pigmenti (IP, OMIM # 308300), or Bloch-Sulzberger syndrome, is an X-linked dominant genodermatosis with multisystem involvement and highly variable phenotypic expressivity. It is caused by loss-of-function mutations in the *IKBKG* gene (*inhibitor of κB kinase gamma*) located on chromosome Xq28. In 80% of known cases, the molecular changes consist of a deletion at exons 4–10 [1, 2]. *IKBKG* gene encodes the NEMO (nuclear factor-κB essential modulator) regulatory protein, which in turn activates the NF-κB signaling pathway involved in a variety of cellular processes including inflammatory reactions, immune function, stress response, and suppression of apoptosis [3]. While NF-κB is present in all cell types, this transcription factor plays an essential role in the development and homeostasis of ectodermal tissues [4–8]. As a result, *IKBKG* mutations which disrupt the NEMO/NF-kB interaction can result in severe disorders of the skin and other ectodermal tissues.

The estimated birth prevalence of IP is ~0.7–1.2 in 100,000, with new de novo mutations accounting for approximately 65% of affected individuals [9–11]. The disorder is seen primarily in females as the moderating effects of X-chromosome mosaicism (*lyonization*) allow for survival. Male fetuses with pathogenic *IKBKG* null mutations miscarry in utero due to absence of the gene product. However, IP may occasionally occur in males with somatic mosaicism or XXY karyotype (Klinefelter syndrome) [12]. Affected males with both somatic and germline mosaicism may transmit the *IKBKG* pathogenic variant to their daughters [13].

Less deleterious (hypomorphic) *IKBKG* mutations that impair but do not abolish function can also give rise to surviving males with genetically related (allelic) disorders to IP. Clinical features vary in severity based on the residual function of the mutated protein. Male patients may present with ectodermal dysplasia and immunodeficiency (OMIM #300291) or X-linked recessive immunodeficiency (OMIM #300636) [14–17]. Female carriers of these mutations may be asymptomatic or have mild clinical signs of IP [18].

Clinical Characteristics

IP is typically identified by characteristic skin findings, accompanied by a spectrum of neuroectodermal manifestations affecting the eyes, nails, hair, teeth, and central nervous system (CNS). These clinical features are highly variable with no clear genotype-phenotype correlation. Cutaneous and extracutaneous manifestations have been found to occur with similar frequency in both male and female patients [19–21]. However, individuals clinically diagnosed with IP but lacking an identifiable mutation are more likely to be male and have a milder clinical phenotype (lower incidences of dental and hair anomalies) [21].

The heterogeneous presentation of IP is suspected to be a result of variable *IKBKG* gene expression between cell lines due to functional (skewed lyonization) or somatic X chromosome mosaicism, as well as the pleiotropic role of the encoded NEMO protein [2, 3, 6, 22, 23]. During gestation, cell lines expressing the mutated X chromosome (NEMO-deficient) migrate along pathways of embryonic development. Postnatally, the severity of clinical findings that begin to emerge reflects the extent of affected cell lines and the degree of expression of the mutated X chromosome.

Skin

The cutaneous manifestations of IP occur in all affected patients, although they may be subtle and not always recognized. They are the most common first presentation of the disease, with a median age of onset of 29.9 days after birth [24], although it is not uncommon for patients to be born with vesicular lesions. These skin findings are clinically diagnostic, classically evolving through four successive and overlapping stages, not all of which occurring in each affected individual.

Stage 1 (Vesicular or Inflammatory Stage) This stage is characterized by crops of superficial papules, vesicles, and/or pustules on a linear erythematous base, following the lines of Blaschko (Fig. 8.1). In the majority of cases, these lesions are diffusely distributed over both the trunk and limbs bilaterally, while the lower limbs are the most common site of involvement overall [25–28]. Lesions on the scalp/vertex, but sparing the face, are also commonly reported. An important exception to this typical pattern is the male IP phenotype which is more likely to present with focal or unilateral stage 1 skin findings [20]. This is reported to occur in 15% of affected male patients, but does not correspond to a milder overall disease as the majority eventually progress to develop bilateral skin lesions and multisystem abnormalities [20].

Stage 1 skin lesions are observed in an estimated ~80–92% of cases [20, 21, 25, 26, 28–31], presenting at birth or within the first month of life in 90% of all affected patients and before the first year in 99% [32]. Less commonly, they may occur in

utero or after 1 year of age, leading to diagnostic confusion [25, 26, 28]. The lesions tend to heal over weeks and can be replaced with new crops within the linear erythema before typically clearing by 4–6 months of age in most children. Reoccurrence of milder, self-limited vesicular eruptions can occur later in life in association with acute febrile illnesses [33–35].

Stage 2 (Verrucous Stage) The lesions in this stage are hyperkeratotic, warty papules and plaques arranged linearly along the lines of Blaschko (Fig. 8.1), but not necessarily in the same location as the stage 1 lesion. They are most commonly seen on the distal extremities, especially the digits and ankles. Scalp and neck involvement can occasionally be seen, but the trunk and face are seldomly affected [25, 26, 28, 36].

The frequency of occurrence varies within the published literature, with most studies reporting rates between ~70–85% [20, 25, 26, 29, 30] and ~15–30% [21, 27, 28, 36, 37]. It has been suggested that this large discrepancy is due to underrecognition/reporting, as stage 2 lesions are typically short lived, more localized, and diminished in appearance compared to the stage 1 vesicular eruption. Their appearance within the first 2 months often overlaps with stage 1 lesions, with ~40–50% presenting within the first month and 95–100% within the first year of life [26, 32]. Early onset as the first sign of IP has also been reported [26, 27, 37], both with and without coinciding vesicular lesions suggestive of intrauterine stage 1 lesions. While their duration varies and can last for years, an estimated 80% clear by 6 months when present [33].

Stage 3 (Hyperpigmented Stage) Stage 3 is defined by the development of linear or whorled streaks of brown-gray macular hyperpigmentation along *Blaschko's lines* (Fig. 8.1). While the extent of involvement is variable, these lesions are most commonly distributed on the trunk and limbs, frequently affecting the nipples as well as the axillae and groin [25, 26, 28].

This stage is traditionally the hallmark of IP, giving the condition its name, with characteristic lesions occurring in an estimated ~70–100% affected patients [20, 21, 25, 26, 28–31]. However, the published literature recognizes that the reported prevalence of this stage is highly influenced by the variable extent of involvement, age of assessment, and duration of follow-up. Most cases present around 6 months of age as stage 2 lesions are resolving, with 83–89% presenting before 1 year [26, 32]. Occasionally it precedes all other stages and presents at birth [20, 26, 27, 34], while approximately one third will occur within the first month [26, 32]. These lesions usually persist throughout childhood and gradually fade during early adolescence, with ~25% of cases faded by 10 years of age and almost complete disappearance by 16 years [26, 33, 38]. However, areas of residual localized hyperpigmentation may persist into adulthood for some patients, particularly on the legs, axillae, and groin [9, 31, 35, 39].

Stage 4 (Atrophic or Hypopigmented Stage) This stage is characterized by linear atrophic, hairless, and hypopigmented lesions following *Blaschko's lines* (Fig. 8.1).

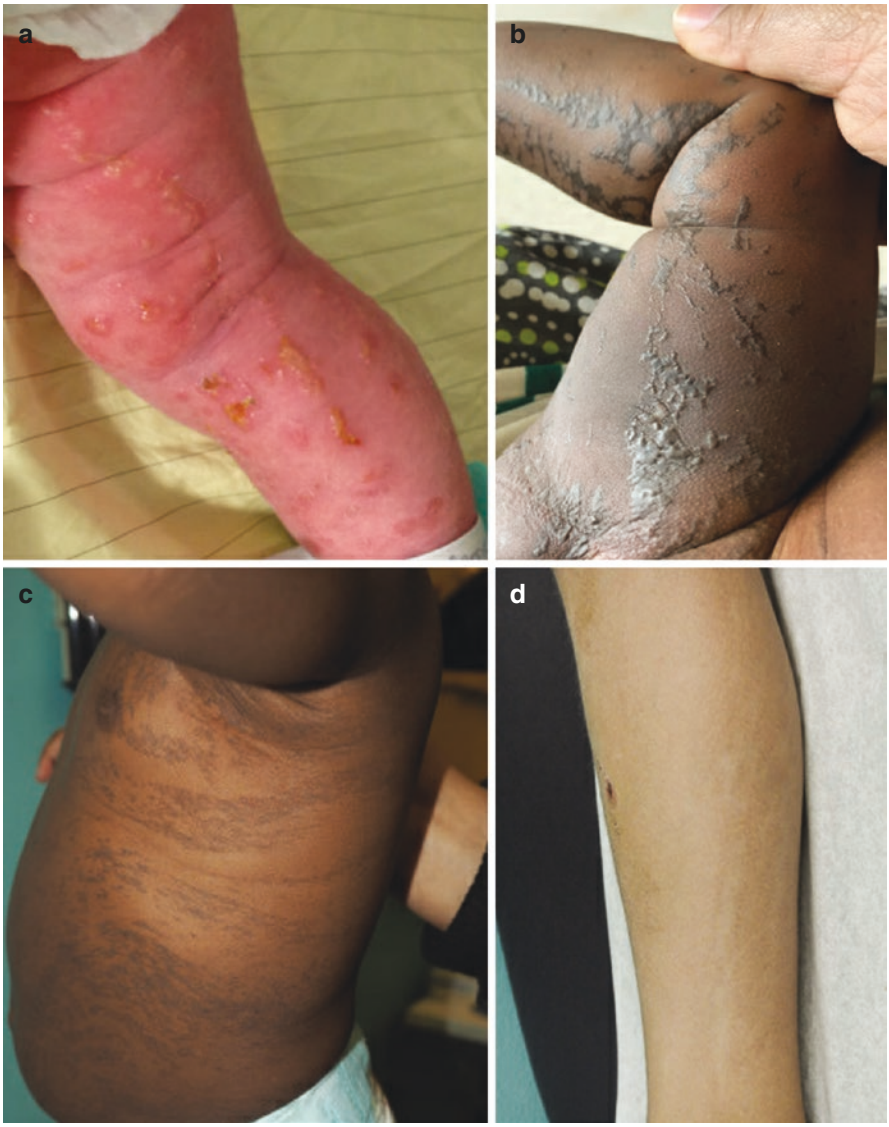

Fig. 8.1 Cutaneous lesions of incontinentia pigmenti along Blaschko lines. (**a**) Stage 1 vesicular lesions. (**b**) Stage 2 verrucous lesions. (**c**) Stage 3 linear hyperpigmentation. (**d**) Stage 4 linear hypopigmentation and atrophy

While the lower limbs are almost always involved, lesions are most frequently observed on both the upper and lower extremities [25, 26, 28, 35, 36, 39]. Stage 4 lesions characteristically demonstrate histologically an absence of pilosebaceous units and eccrine glands on biopsy, corresponding clinically to absence of hair or sweating within the affected areas. While lesions have been shown to have decreased

melanocytes/melanin in the epidermal basal layer [35], there remains inconsistency within the published literature regarding whether or not they are truly hypopigmented [9, 33]. It has been proposed that the difference in pigmentation is a minor factor and that the observed contrast with normal skin is instead due to loss of hair follicles and eccrine glands and reduced vascularity secondary to underlying ectatic vessels [9, 33, 35, 36, 40].

Stage 4 lesions are seldomly seen within the pediatric IP phenotype, with occurrence ranging from 0 to 42% [20, 21, 25–28, 30, 37]. In contrast, reported rates in the adult population are much higher at 80–100% [29, 31]. A proposed explanation for this variation is that stage 4 lesions are often subtle and may be unnoticed or overshadowed during childhood/adolescence when they overlap with the cutaneous manifestations from earlier stages of IP [28, 35]. Traditionally believed to develop during adolescence as stage 3 lesions were fading, a more precise assessment of age of onset has yet to be determined. When present, these lesions are permanent and are a subtle, but essential clinical diagnostic finding, alongside extracutaneous anomalies, in identifying undiagnosed adult IP patients [31, 35].

The pathophysiologic mechanisms underlying the IP skin phenotype are thought to be due to the mosaic pattern of NEMO-deficient and wild-type skin cells and a complex signaling cascade between the two which leads to the destruction of the deficient cells. Affected females exhibit skewed X chromosome inactivation (lyonization) which varies between cell lines, preferentially selecting to silence the mutated NEMO locus. For unknown reasons, this process appears to be less complete in the skin, resulting in a greater number of keratinocytes expressing the mutated gene (NEMO-deficient) [6].

The elimination of these cells appears to start around the time of birth when they begin to release pro-inflammatory interleukins in response to an unidentified trigger. In reply, the neighboring wild-type cells produce the cytokine tumor necrosis factor (TNF), which then induces apoptosis in susceptible NEMO-deficient cells. It also propagates inflammatory and hyperproliferative signaling among wild-type cells creating a positive feedback loop, amplifying the cellular reaction [6]. In addition, the combination of interleukin and TNF signaling at this time appears to result in a large increase in eotaxin expression from keratinocytes and endothelial cells [23]. This chemokine initiates eosinophilic recruitment leading to characteristic stage 1 dermal-epidermal infiltration, as well as peripheral blood eosinophilia (as high as 65%) which occurs in ~50–88% of patients [25–28]. Pathologically, this translates into local eosinophil degranulation resulting in spongiosis and epidermal vesicle/blister formation.

The entire inflammatory reaction is transient and continues until the initiating triggers, NEMO-deficient cells, are eradicated, at which time the stage 1 lesions disappear. However, if some survive, they can trigger reoccurrence of the inflammatory vesicular reaction later in life during periods of elevated circulating inflammatory cytokines, such as in febrile illness [6].

The keratinocyte hyperproliferation seen in stage 2 of IP has not yet been fully explained. The proliferation of wild-type cells has been proposed as the most likely

explanation, at least partly in response to the hyperproliferative signaling that was propagated during the preceding inflammatory stage [23].

The initial inflammatory process causes disruptions of the basal layer of the epidermis leading to the release (incontinence) of melanin into the papillary dermis. Macrophages then phagocytize the melanin or epidermal melanocytes (becoming melanophages) and settle in the dermis, thus causing dermal melanosis. Histopathological examination of stage 3 lesions mirrors these expected findings (see Chap. 4) [35, 39].

It has been proposed that stage 4 skin changes are the result of post-inflammatory dermal scarring which leads to reduced vascularity and loss of dermal appendages [23]. An alternative suggestion is that these findings may represent mosaic congenital skin dysplasia due to abnormal ectodermal tissue development and organization in IP. This implies that stage 4 changes are present since birth, only becoming visible after puberty when increased hair growth, hair density, and tanning on adjacent skin highlights the affected areas [31].

Central Nervous System

Of all the clinical features of IP, it is the neurologic involvement which is associated with the greatest degree of morbidity [41]. These anomalies are typically limited to the CNS and present with significant phenotypic variability. This can range from a single seizure to neonatal/childhood encephalopathy, disseminated encephalomyelitis, or ischemic stroke with devastating motor and cognitive impairment [42]. Mortality can occur, often as a result of insurmountable damage to the antenatal nervous system or status epilepticus. It has been observed that CNS abnormalities are most severe in IP patients with extensive cutaneous involvement, especially if lesions are located on the head and neck [43, 44].

CNS anomalies occur in an estimated ~30–31.5% of IP patients [22, 32, 42, 45]. However, it has been suggested that the true incidence may be lower in acknowledgment of undiagnosed individuals who have a milder phenotype and no neurological manifestations [29]. Among IP patients with CNS anomalies, almost 60% will develop their first neurological symptom within 1 week of life, 70% within 1 month, and almost 90% within 1 year [46].

Seizures are the most common neurological manifestation of IP, accounting for 42% of all CNS anomalies and affecting ~20–42% of all IP patients [32, 42]. Severity ranges from a single event in a lifetime to chronic epilepsy and seizure (see Chap. 50) disorders such as infantile spasms [47]. They also vary in type, although focal clonic episodes are most frequently reported [42]. Onset fluctuates from 12 h postpartum to 10 years; however the majority present within the first 2 weeks of life and almost all by 1 year [42].

Cognitive impairments, including intellectual and learning disabilities, characterize ~20% of neurological manifestations and occur in 29% of all patients [32, 43]. However, published literature further investigating the neurocognitive profile of

IP patients is limited. A pair of studies involving small cohorts of female IP patients were completed by *Pizzamiglio et al.* in 2014 and 2017. The first suggested that learning disabilities, particularly in arithmetic and reading, were common in IP and represented a CNS manifestation of the disease [47]. The second demonstrated mild to severe intellectual disability in approximately one third of the cohort with no correlation to CNS anomalies. In addition, they found that of school-aged patients without intellectual disability, half had learning disabilities in arithmetic, thus emphasizing the importance of early assessment, before school age, to identify and address any such deficits [48].

Psychomotor delays encompass ~26% of all CNS anomalies and affect 16.5% of patients [32, 42]. These include cerebral palsy, hemiplegia, hemiparesis, spasticity, and cerebellar ataxia. Similar to other CNS changes in IP, the risk and severity of motor impairment corresponds to the degree of CNS vasculopathy.

Microcephaly has been reported to represent 4% of CNS anomalies and affects 11% of IP patients [32, 42]. Additional CNS structural abnormalities that have been described include corpus callosum hypoplasia/agenesis, cerebellar atrophy, and cortical malformations such as polymicrogyria or neuronal heterotopia [9, 42, 45]. Despite these numerous findings, it is suspected that primary developmental defects in IP are rare and that most of these abnormalities are indicative of insults in the antenatal period due to microvasculature changes. This is supported by the results of brain imaging in affected patients which most commonly show evidence of vascular compromise including cerebral/cerebellar ischemia, necrosis, and hemorrhage [46, 49, 50].

Overall, two main patterns of neuroimaging have been described in IP patients with CNS manifestations. The first includes periventricular white matter changes (most often leukomalacia) with or without ventricular dilatation, corpus callosum hypoplasia, and mild cortical atrophy. The second involves severe cortical anomalies suggestive of acute/chronic ischemia, including areas of restricted diffusion without vascular territory, microbleeds, and severe atrophy with secondary structural abnormalities [39]. CNS manifestations are generally considered a poor prognostic sign in IP; however, neuroimaging findings may not necessarily correspond to the severity of the observed phenotypic (see Chap. 3). White matter changes in particular have been reported in neurologically intact IP patients [51], and involvement has been shown to both progress and resolve over time [49, 51, 52]. This emphasizes the importance of early neurological evaluation and follow-up of identified anomalies.

The pathogenesis of CNS anomalies in IP is still not entirely understood. *IKBKG* is present in all cell types including neurons, astrocytes, microglia, and oligodendrocytes. Considering the shared ectodermal origin with the skin, it has been postulated that apoptosis of susceptible NEMO-deficient neurons or glial cells could lead to IP CNS lesions (see Chap. 4). However, it has been shown that NEMO deficiency does not compromise the survival of these cells but rather that impaired NF-kB signaling may protect against neuronal cell death [53, 54]. Instead, NEMO deficiency does result in apoptosis of cerebral endothelial cells and impairment of the blood-brain barrier [55]. This suggests a primary vascular etiology to CNS

anomalies, compromised small vessels, and reduced blood flow in the neovasculature resulting in various degrees of ischemia and inflammation. This etiology is consistent with the clinical course, as antenatal insults to the developing CNS present acutely in neonates/infants before resolving with variable neurological sequelae [42].

Disruption in the blood-brain barrier may also have a pro-convulsive influence, increasing IP patients' susceptibility to seizures, even in the absence of ischemia [55]. However, it has been argued that this hypothesis of primary vascular dysfunction does not account for cerebral white matter and cortex changes that are not associated with vascular territories [44]. Similar to the process which occurs in the skin, a possible explanation for this observation may be radial migration of endothelial progenitor cells along Blaschko line analogs in the CNS, as well as mosaicism in the degree of NEMO deficiency/X chromosome lyonization [55–57].

Ocular

Ophthalmologic manifestations, when present, can lead to significant functional impairment [58, 59]. Screening for these features is therefore critical in patients with suspected IP as early recognition and intervention can substantially influence patient outcomes (see Chap. 47). The prevalence of ophthalmic findings among IP patients is frequently cited as ~30–38%. This range is based on a pair of comprehensive ocular-focused meta-analyses, as well as a large cohort study of 308 IP patients published in 2014 [22, 32, 59]. Since that time, similar rates have been mirrored among smaller cohort studies [21], while others vary between 11 and 77% [28, 60, 61].

Ocular manifestations of IP are generally divided into retinal and non-retinal findings, which occur in approximately the same ratio (53% vs. 47%) respectively [22]. Overall, an estimated ~55–70% of these anomalies are potentially vision threatening, with the majority (72–75%) related to retina involvement [22, 59].

Retinal abnormalities in IP primarily present in neonates and during early infancy. They are characterized by vasculopathy of the developing vessels which can lead to both peripheral and macular changes. Peripheral avascularity is considered the classic retinal finding [62, 63].

However, persistent fetal vasculature and varying degrees of vascular occlusion can also result in a spectrum of other anomalies. These range from changes in the pigment epithelium secondary to ischemia to neovascularization and partial/total retinal detachment with end-stage complications [62]. Peng et al. have recently proposed a five-stage classification system for these IP-associated retinopathy findings [60]. Retinal detachment is the most common cause of vision loss in IP with an estimated occurrence in 22–27% of eyes among investigated IP populations [60, 61]. Identified risk factors include peripheral neovascularization or ischemic optic neuropathy on initial examination [61]. A bimodal age pattern has been observed similar to that seen in retinopathy of prematurity [61]. Tractional detachment occurs

in pediatric patients due to contraction of fibrovascular tissue, with onset as early as 1 week and most by 2.5 years. In older individuals, rhegmatogenous detachment results from the development of holes in atrophic, avascular retina [60, 61]. This lifelong risk for progression emphasizes the importance of early identification and long-term monitoring of retinal abnormalities.

Nonretinal ocular manifestations often develop later than retinal issues but typically present before 2 years of age [62]. The most common of these findings are strabismus and nystagmus, which represent ~13–18% of all ocular IP anomalies and often occur in association with refractory errors [22, 59]. Along with optic neuropathy (~1–3%), these nonretinal findings are suspected to commonly result from underlying retinal pathology. Lens anomalies (~2–5%) include congenital cataracts, which are classified as an IP feature and affect an estimated ~5–6% of patients [21, 60]. Other nonretinal findings include microphthalmos (~2–3%) and corneal anomalies (~3%). This includes corneal epithelial keratopathy, which presents as asymptomatic whorl-like patterns of superficial or subepithelial opacities that are hypothesized to represent extracutaneous Blaschko lines [55, 60, 62, 64].

Advances in medical imaging have provided tremendous insight into the possible pathogenesis of the associated retinal anomalies in IP. Recent studies utilizing optical coherence tomography (OCT) imaging and multimodal extensions have supported the theory that the neural tissue changes in the retina (often thinning) are the result of primary vascular defects [65–67]. In particular, serial imaging on a limited number of patients has demonstrated the presence of vascular abnormalities preceding the pathological structural findings which subsequently evolved over time [66]. Addressing other proposed mechanisms for the neuronal changes, these studies failed to find evidence of abnormalities in the retinal pigment epithelium (RPE) or primary defects in neural architecture from abnormal NF-kB signaling [68]. Overall, these findings correspond with an ischemic mechanism for IP ocular lesions and are consistent with the small vessel vasculopathy which also contributes to the development of CNS anomalies.

Dental and Oral

After skin lesions, dental and oral anomalies are considered the most common clinical characteristics of IP. These are seldomly life-threatening but can have significant impact on the quality of life of IP patients. The prevalence fluctuates within the published IP literature due to the wide array of findings, differences in patient cohorts, and variability in which odontological manifestations were measured/reported. An occurrence rate of ~43–55% has previously been suggested in the IP literature [32, 46]. However, with increased awareness of the potential findings, within the last 10 years the occurrence rates among additional smaller IP cohorts have fluctuated from 50 to 77% [28, 60, 69] and have been recorded as high as 86–92% in adult IP populations [31, 35].

When present, congenital tooth agenesis is one of the most frequently reported dental anomalies, with ~60–90% of IP cases experiencing the absence of at least one tooth (hypodontia) and ~44–70% missing six or more (oligodontia) [61, 70, 71]. Overall, tooth agenesis affects the maxillary more frequently than the mandibular arch, as well as permanent (~90%) more than primary/deciduous teeth (~60%) [70]. The maxillary lateral incisors are the most common missing primary teeth, while agenesis of the second molars (maxillary > mandibular) are the most frequently affected permanent dentition [70].

Aberrations in crown formation are also common. These occur in an estimated ~70–100% of IP patients, most commonly affecting the central and lateral incisors in both primary and permanent dentition [60, 69–73]. These morphological abnormalities manifest as teeth with abnormal shape (conical, pegged, tulip, or notched), accessory cusps (molars), or microdontia.

Less common odontological anomalies associated with IP include malocclusion, delayed dentition, and arched palate. In a small cohort study, varying degrees of malocclusion were observed in a total of 71% of IP patients, although the frequency within the larger affected population has not yet been described [70]. It has been proposed that this finding may be a direct result of oligodontia in IP patients considering the established link between tooth agenesis and impaired alveolar development within the dental arches [74]. Primary teeth typically start to erupt after ~6 months of age; however delayed dentition has been reported to affect ~18% of IP patients [55]. This observation suggests that identification of dental anomalies as an early (<1-year) diagnostic tool may have limited use. On the other hand, oral anomalies that have been associated with IP (high-arched palate, cleft lip/palate) may be immediately detected after birth. While these anomalies account for only ~5% of odontological anomalies in the IP population, they occur ~10× more frequently than in the general population and thus may be diagnostic especially if associated with other features of IP [46]. In addition, both dental and oral anomalies are permanent findings (if uncorrected) and therefore have unique diagnostic value, especially in individuals with mild IP phenotypes or undiagnosed older patients in whom cutaneous manifestations have improved/faded [46, 69, 71].

Hair

Hair anomalies have been one of the minor clinical diagnostic criteria for IP since they were first proposed by *Landy and Donnai* in 1993 [36]. Along with the absence of pilosebaceous units noted in stage 4 skin lesions, approximately 26–32% of pediatric [20, 21, 26] and 60–65% of adult [31, 35] IP patients have other hair anomalies. Alopecia is the most common reported finding in both populations. It occurs particularly at the vertex of the scalp and is often preceded by vesicular or verrucous lesions at the site of involvement. Abnormalities in hair texture and density have also been well described, evolving with age and affecting the scalp, eyebrows, and

eyelashes. This presents with varying frequency as thin, sparse hair in childhood and progresses to woolly hair in adulthood (~40–50%), which is described as dull, wiry, and uncombable [31, 35].

Nails

A variety of nail anomalies have been described in association with IP, though none are pathognomonic. These are reported to develop in ~10–15% of affected individuals, usually after puberty during late adolescence or early adulthood [22, 32, 75]. The changes are typically seen on fingers more than toes, although all nails may be affected. The most common finding is nail dystrophy, with the spectrum of involvement ranging from mild pitting/ridging, koilonychia, or a yellow hue to severe nail disruption resembling onychomycosis. While nail anomalies are mostly transient and completely resolve, recurrent and persistent changes have also been reported [31, 36, 76].

Painful subungual hyperkeratotic lesions have also been observed in female patients, referred to as subungual tumors of IP (STIPs) [77]. Onset of these lesions is usually slightly later then nail dystrophy, typically in the mid-20s and most frequently on the fingers. Their histology mirrors the verrucous stage of IP showing hyperkeratosis, acanthosis, papillomatosis, and focal dermal dyskeratosis [78, 79]. As such, it has been suggested that they should be considered a late recurrence of the verrucous stage [35, 80]. Recognition is important as they may erode the underlying distal phalanx via pressure necrosis. However, identification and diagnosis are often delayed as lesions are frequently misdiagnosed as squamous cell carcinomas or keratoacanthomas [78]. Defining characteristics of STIPs include their recurrence in young women with multiple lesions over the course of several years and accompanying signs of IP. They rarely resolve on their own and patients usually seek treatment because of excruciating pain and disability [77, 78].

Other

Anomalies of the breast and nipples have been reported to occur in greater frequency in patients with IP than compared to the general population. Supernumerary nipples are the most common finding, but other abnormalities involving the nipple (*hypoplasia/inversion*) or breast (hypoplasia/aplasia, asymmetry, hypogalactia) can also occur [22]. Reported occurrence rates among general IP cohorts range from 2 to 10% of patients [21, 26, 33], while increased frequencies from ~12 to 30% have been observed among adult patients [31, 35]. It has been suggested that this

discrepancy is due to a focus on neonates and pre-pubertal children in the published literature.

There have been a small number of case reports describing female IP patients with immunodeficiency who presented with recurrent infections [80, 81]. In addition, a large cohort of IP patients found that ~11% had suffered from recurrent infections, suggesting that this may be a feature of the condition in a minority of patients. Recently, *Ohnishi et al.* provided evidence that such cases of immunodeficiency in female IP patients result from hypomorphic *IKBKG* mutations and a delay in skewed lyonization within immune cells [82].

Both pulmonary hypertension and cardiovascular abnormalities have been described as rare complications of IP. A variety of skeletal anomalies have also been reported in IP including limb asymmetry, talipes, contractures, dislocations, and scoliosis. However, it has been noted that these almost always occur secondary to severe neurological deficits [33, 81].

Diagnosis

Clinical Diagnosis

The clinical diagnostic criteria for IP were first proposed by Landy and Donnai in 1993. They were refined by *Minic et al.* in 2013 to account for new genetic findings and reflect a growing recognition of the wide variety of associated extracutaneous clinical features of IP. Recently, updates to these criteria have been proposed by a multidisciplinary consensus group from Europe [39]. These suggestions modernize the criteria descriptions, adjust the major/minor categories, and overall decrease the number of criteria required in order to reach the diagnostic threshold. These changes emphasize early diagnosis so that appropriate monitoring and treatment can be initiated, particularly for extracutaneous manifestations with potentially serious long-term sequelae.

The updated criteria are outlined in Table 8.1. The major criteria remain any of the four IP skin stages, with the addition of dental anomalies (Table 8.1) and identification of the common recurrent *IKBKG* gene rearrangement (deletion of exons 4–10). Eosinophilia in association with stage 1 lesions has been nominated as a minor criterion, while CNS anomalies and a history of male miscarriages have been removed from this category. It is suggested that once IP is diagnosed, it may offer more meaningful interpretation of possible unexplained neurological, ophthalmological manifestations and/or obstetric complications (such as miscarriage). In addition, the descriptions of the clinical and histological criteria (summarized in Tables 8.1 and 8.2) have been updated to provide greater detail which reflects the most recent understandings from published literature.

Table 8.1 Updated diagnostic criteria for incontinentia pigmenti, according to *Landy and Donnai* and updated by multidisciplinary consensus recommendations [39]

Major criteria	Minor criteria
• Typical neonatal rash with erythema and vesicles (stage 1) • Verrucous papules or plaques along Blaschko's lines (stage 2) • Typical hyperpigmentation along Blaschko's lines fading in adolescence (stage 3) • Linear, atrophic, hairless lesions on limbs (stage 4) or scarring alopecia of the vertex (stages 3 or 4) • Teeth: dental agenesis (hypodontia or oligodontia), shape anomalies (peg-shaped incisors, conical teeth, molar cusp pattern alteration), and delayed eruption • Common recurrent rearrangement (deletion of exons 4–10 of *IKBKG* gene)	• Eosinophilia (stage 1) • Hair: alopecia or woolly hair (dull and dry) • Nails: punctuate depressions, onychogryphosis • Mammary gland involvement (hypoplasia, asymmetry, hypogalactia) and/or nipple involvement (inverted nipples, supernumerary, difficulty in feeding) • Characteristic skin histology • Retina: peripheral neovascularization
Conditions for establishing IP diagnosis	
If no evidence of IP in a first-degree female: • Presence of at least one major criterion is sufficient for the diagnosis of IP If a first-degree female relative is affected: • One minor criterion is sufficient for IP diagnosis	

The complete absence of minor criteria should induce some doubt about the diagnosis

Molecular Diagnosis

In most cases, the diagnosis of IP is first made clinically in neonates. A molecular analysis of DNA extracted from peripheral blood is then required to confirm the diagnosis. This facilitates identification of a pathogenic *IKBKG* mutation and allows appropriate genetic counseling. A targeted analysis (with long-range PCR) of the common deletion of exons 4–10 of *IKBKG* should be completed first as this accounts for 80% of known cases [1, 2].

In the case of a negative result (or *concurrent with targeted analysis*), *IKBKG* should be sequenced in search of a point mutation, a deletion, or a duplication of different sizes [9]. The causative mutation cannot be identified using modern genetic testing methodology in approximately 5% of cases [33]. Analyses of *IKBKG*/NEMO mutations are complicated by the presence of a nonfunctional *IKBKGP1* pseudogene (deletion of first 2 exons), which is highly homologous to *IKBKG*/NEMO [39].

In affected individuals in whom an *IKBKG* pathogenic variant is not identified by the above methods, a skin biopsy of affected skin should be considered to look for a somatic mutation [33]. This is particularly important for the detection of post-zygotic mosaic variants in affected males in whom blood leucocytes carrying the mutation undergo selective apoptosis over time [19]. Karyotyping should also be

Table 8.2 The four stages of cutaneous lesions of IP, their evolution, and histopathological findings, as described within multidisciplinary consensus recommendations [39]

Stage	Lesion morphology	Stage onset	Skin histopathological findings
Stage 1: vesiculobullous	Vesiculo-pustules and erythema	Within the first few weeks to 18 months	Eosinophilic spongiosis and intraepidermal vesicles containing eosinophils. Many dyskeratotic (apoptotic) keratinocytes in the epidermis, numerous eosinophils, and some lymphocytes in the dermis
Stage 2: verrucous	Verrucous lesions	Within the first few months; usually lasts for a few months	Papillomatosis, hyperkeratosis, and acanthosis of the epidermis. Many apoptotic cells in the epidermis, sometimes disposed in clusters. Minimal perivascular lymphocytes, no more eosinophils. Major melanin incontinence
Stage 3: hyperpigmented	Hyperpigmentation	Within the first months, gradually decreasing until complete/ incomplete disappearance May persist resulting in localized residual lesions (often axillary or inguinal folds)	Marked melanin incontinence with numerous melanophages in the dermis. No more epidermal hyperplasia. Scattered apoptotic cells in the epidermis. Slight lymphocytic inflammation in the upper dermis
Stage 4: atrophic/ hypopigmented	Hypopigmentation	Most likely present from childhood even if persistently overlooked throughout life	Slight atrophy and some scattered apoptotic cells in the epidermis, hypopigmentation of the epidermis, a reduced number of melanocytes, thickened and homogenized dermis with a complete absence of hair follicles and sweat glands. There is no melanin incontinence and no inflammatory cells, and the elastic network is normal

considered for male patients due to the possibility of IP in the setting of XXY aneuploidy (Klinefelter syndrome).

When a mutation has been identified, prenatal screening can be performed for at-risk women by analysis of DNA extracted by either amniocentesis or chorionic villus sampling. In the case of in vitro fertilization, a pre-implantation diagnosis is also possible [39].

Therapy and Prognosis

The management and follow-up of patients with IP should involve a coordinated multidisciplinary team (MDT), although involved services will vary based on each patients' clinical presentation and needs. Comprehensive care can often involve a dermatologist, ophthalmologist, pediatric neurologist, developmental pediatrician, dentist/orthodontist, genetic counselor, rehabilitation services, and more. Unfortunately, there are currently no known therapeutic interventions that address the NEMO/NF-kB pathway or prevent the various manifestations of IP. Thus, the goal of management is symptom control, which involves early identification and treatment of anomalies within the affected systems in order to minimize/prevent secondary complications [9]. The same multidisciplinary consensus group from Europe who recently provided updates to the IP clinical diagnostic criteria has also created recommendations for the surveillance and management of patients [39]. In addition, *Donnai* and *Jones* recently published a review of IP which includes recommendation for the evaluation and treatment of common findings [33]. The information from these two sources was reviewed and integrated with the existing guidelines [9] in order to provide as comprehensive an overview as possible for the current management strategies in IP (Table 8.3).

Table 8.3 Assessment, surveillance, and management recommendations for IP patients [9, 33, 39]

Assessment/surveillance	Management
Dermatology	
• Careful monitoring in first few months of life • Every 3 months until 1 year, then annually until 5 years. As needed afterward • Photo-documentation is very useful • Assessment of the hair and nails should be completed at each visit • If diagnosis is uncertain, skin biopsy and serology for peripheral eosinophilia can be considered • Adjust visit schedule as needed according to patient (i.e., infection, prolonged/profuse inflammatory lesions, or disabling verrucous lesions) • Consider annual visit in a tertiary center, with MDT assessment as needed, until adulthood	• Referral to a pediatric dermatologist is recommended for all patients • Emphasis on hygiene to prevent secondary infection, especially in neonates • No specific treatments to hasten healing of vesicular or verrucous lesions – Wound care and treatment of secondary infection as needed – Topical emollients, steroids, or calcineurin inhibitors for symptom management – Topical retinoids have been used for verrucous lesions which are symptomatic of impact function (limb/digit mobility) – Reassure families that lesions will improve with time • No interventions are generally required for hyper-/hypopigmented lesions – Laser treatment of hyperpigmented lesions should be avoided (risk of triggering recurrence of inflammatory eruptions) – Photoprotection recommended (risk of cutaneous inflammation and pigmentation) • Unless there is infection/pain, surgical treatment of nail dystrophy is not indicated

Table 8.3 (continued)

Assessment/surveillance	Management
Ophthalmology	
At diagnosis: • Urgent ophthalmology assessment of the peripheral retina (with pupillary dilatation) • If peripheral vasculopathy is present, further assessment under general anesthesia ± laser treatment (ideally with retinal photography and fluorescein angiography)	• Urgent referral to ophthalmology at time of diagnosis • Prophylactic ablation (laser photocoagulation or cryotherapy) ± adjunct therapy (anti-VGEF) to prevent retinal detachment in patients with documented progression of retinal vasculopathy (neovascularization, vitreous traction or hemorrhage) • Warn adults of the symptoms of retinal tear or detachment (bimodal occurrence)
Follow-up: • In the case of normal results of the initial examination: – Repeat evaluation at months 1, 2, 3, 6, 12, 18, and 24 of life, then annually for life • In the case of early laser treatment: – Clinical examinations on days 15, 30, 45, 60, and 90 post-treatment – Follow-up then if results are normal on the initial examination	
Neurology	
At diagnosis: Full neurological examination at diagnosis→ 2 situations: 1. If no neurological manifestation is observed at birth: – Neurocognitive examination at 9 and 24 months – Brain MRI at 2 ½ years old 2. If neurological manifestation is observed at birth: – EEG: during neonatal period, at 4 and 24 months – Brain MRI: during neonatal period (DWI and SWI) and at 30 months	• Referral to pediatric neurologist to help guide management • In the neonatal period, treatments have two objectives: 1. Anti-epileptic treatments for seizures – Treatments vary according to seizure semiology and the age of the patient – Phenobarbital often gives poor seizure control in infantile IP 2. Anti-inflammatory treatment to limit neurological consequences – Steroids have been proposed as a first line of treatment, including IV methylprednisolone followed by a weaning course of oral steroids – TNF blockers have been used in a punctual manner – Gene therapy has been proposed for mitigation of severe cerebrovascular pathology • Rehabilitation with PT, SLT, and OT should be initiated as early as possible for management of neurological sequelae • Intervention for intellectual impairment and developmental delay is the same as in the general population

(continued)

Table 8.3 (continued)

Assessment/surveillance	Management
Follow-up: • Regular neurological and epileptological follow-up, as needed: – At least every 6 months in the first 3 years • Systematic neurocognitive assessment: – At 5 years of age upon the initiation of elementary school • Renewal of cognitive assessment if evidence of developmental delay or at regular intervals if adverse neurological signs in early life – Neuropsychological assessment – Psychomotor, orthoptics, and/or speech assessment – Detailed evaluation of neurocognitive abilities (developmental pediatrician)	
Odontology	
During childhood and adolescence: • Regular biannual dental checks starting at 1 year • At 3–4 years: evaluate for prosthetic treatment if multiple agenesis or dental problems interfering with feeding and/or speech • At 6 years: first panoramic XR evaluating agenesis in a permanent set of teeth and early assessment of dentofacial orthopedics • At 7 years: evaluation for restorative treatment of the permanent conoid incisors for speech and/or aesthetic problems • At 9–12 years: monitor growth/eruption of permanent teeth with second panoramic XR when necessary • At 12 years: consider pre-prosthetic and pre-implant orthodontic treatment for malpositioned teeth and subsequent prosthetic procedures • End of growth: definitive implant-prosthetic rehabilitation	• Educate affected individuals and/or parents about oral hygiene to maintain and preserve teeth • Orthodontic treatment with braces, surgical removal, crowns, and prostheses may be necessary in affected individuals. Indications for these interventions are based on specialist assessment • Prosthetic, implant-prosthetic, and orthodontic rehabilitation in adulthood as needed • Dental CBCT imaging is required prior to dental implants ± need for bone and/or mucogingival grafts

Table 8.3 (continued)

Assessment/surveillance	Management
In adulthood: • MDT assessment involving implantologists, periodontologists, and specialists in dentofacial orthopedics and in prosthesis	
Breast	
• Assess thorax at each visit for the presence of supernumerary nipples and other breast abnormalities	• Most individuals with supernumerary nipples have no major problem • The development of a supernumerary breast at puberty may necessitate surgical removal • In women with breast aplasia or hypoplasia, surgical reconstruction may be indicated and is standard
Counseling and patient support	
At diagnosis (or anytime thereafter): • Genetic counseling and patient education • Evaluation of relatives at risk • Psychological counseling **In adulthood** • Transition coordination • Family planning • Pregnancy support	• Genetic counseling should be offered to all patients/families in order to provide information on the nature, inheritance, and implications of IP so that they can make informed medical and personal decisions • Therapeutic patient education programs help to support patients and families • At-risk relatives of an affected individual should be examined for suggestive features and offered genetic consultation (± genetic testing) • Counseling can help patients/families cope with the psychosocial impacts of IP and should be offered to all, regardless of the IP severity • Facilitated transition from pediatric to adult care helps fulfill the medical, psychosocial, and educational needs of young adult IP patients • Appropriate to revisit genetic counseling for affected patients before pregnancy to discuss potential risks to offspring, prenatal screening, and reproductive options • Fertility is not impaired for affected female patients. The risk of spontaneous abortion is higher, particularly for male fetuses. If prior retinal anomalies exist, there may be risk of progression and/or detachment during labor/delivery
To other	
• Other therapeutic managements should be guided by appropriate specialists, if/when other IP manifestations are observed (e.g., cardiovascular complications)	

MDT multidisciplinary team, *VGEF* vascular endothelial growth factor, *MRI* magnetic resonance imaging, *DWI* diffusion-weighted imaging, *SWI* susceptibility-weighted imaging, *EEG* electroencephalography, *IV* intravenous, *TNF* tumor necrosis factor, *PT* physiotherapy, *OT* occupational therapy, *SLT* speech and language therapy, *XR* X-ray, *CBCT* cone beam computed tomography

Early neonatal neurological and ophthalmological manifestations have the greatest impact on IP patients' long-term prognosis and morbidity. As with phenotype, the IP sequelae vary in form and severity between patients based on the extent to which associated systems are involved. Abnormalities of the skin, hair, or teeth can be permanent and may be a cause of distress for some patients. Patients without CNS or ophthalmologic involvement usually have normal physical and cognitive development, as well as an ordinary life expectancy.Conflict of InterestThere are no conflicts of interests relevant to this article to disclose from all identified authors.

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Chapter 9
Klippel-Trénaunay Syndrome (Klippel-Trénaunay-Weber Syndrome)

Christos P. Panteliadis

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Introduction

Maurice Klippel and *Paul Trénaunay* first published their description on a fetal impairment with congenital aplasia/dysplasia of specific parts of the vascular system in 1900 [1]. The original three findings, namely, cutaneous capillary malformation, soft tissue, and bony hypertrophy of the extremity, constituted the primary diagnostic criteria of *Klippel-Trénaunay* syndrome (KTS). In 1907 and 1918, *Frederick Parkes Weber* published reports on patients in whom both arteries and veins were enlarged [2, 3]. Patients with limb hypertrophy, cutaneous capillary malformations, and venous and arterial malformations sometimes are referred to as *Klippel-Trénaunay-Weber* syndrome (KTWS). Some authors suggest that KTWS and *Sturge-Weber* syndrome represent variants of the same disease, especially when their overlapping features involve the face. KTS is a pure low-flow vascular

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condition, while *Parkes Weber* syndrome is characterized by significant arteriovenous fistulas (congenital), red skin lesion, and lymphoedema. *Cohen* argues, however, that the two syndromes are distinct and that most of the patients with overlapping features have *Sturge-Weber* syndrome [4].

Klippel-Trénaunay-Weber syndrome occurs in 1 out of 30,000 births (overall incidence: 2–5/100,000). It has no sex predilection and the exact cause remains elusive. Inherited transmission has not been reported, much the same as for *Sturge-Weber* syndrome. KTS is a complex vascular syndrome that results from somatic gain-of-function mutations in the PIK3CA gene which is part of the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway involved in cellular growth and differentiation [5].

Clinical Characteristics

Clinically, *KTS* is characterized by the triad of cutaneous capillary malformation, soft tissue, and bony hypertrophy of the extremity. It generally affects only one extremity causing limb asymmetry and varicose veins, multiple aneurysms, or other deep venous system malformations. Varicose veins observed in patients with *KTS* may be noticed in early infancy and progress until adolescence. The *cutaneous* malformations or hemangiomas (85% of the cases), nearly all of which involve the lower extremities, usually affect one extremity (Fig. 9.1).

The condition rarely involves the upper limbs, trunk, head, or neck. The skin lesions exist from birth but may go unrecognized for many years. Sometimes the entire body is affected, or the extremities are contralateral to the angioma. The capillary or cavernous hemangiomas of the skin frequently have abnormal edges, e.g., angiokeratoma (erythematous papules and nodules). In addition, hemangiomas in the trunk, tongue, pharynx, larynx, intestine, bladder, and fingers (causing polydactyly, syndactyly, and clinodactyl) may be observed [6–8].

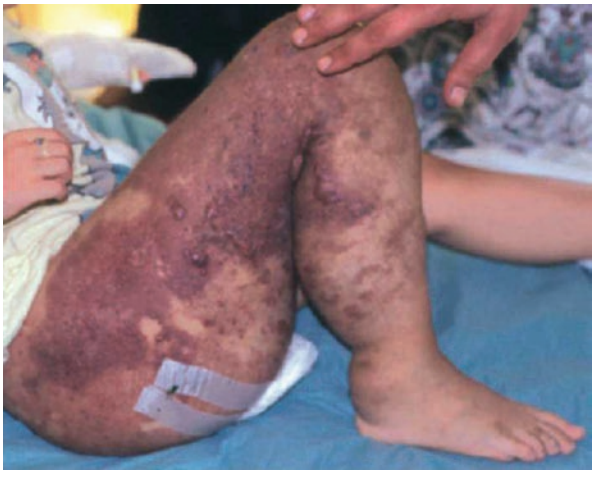

Fig. 9.1 Lateral plain hemangioma and hypertrophy of soft issue in the right lower extremities

Histologically, there are capillary spreads of the papilla dermis adjacent to the vascular lesion and within deeper layers of dermis and subcutaneous. In 1995, *Samuel* and *Spitz* reviewed the clinical features and management of 47 children with KTS, treated since 1970, and found hemangiomas and soft tissue and/or skeletal hypertrophy presented in all 47 patients; venous varicosities developed in 37 (79%); thromboembolic episodes occurred in 5 children (11%); and 25 (53%) experienced thrombophlebitis [9]. *Kasabach-Merritt* syndrome was observed in 21 (45%) [10]. Other manifestations included hematuria in five (11%), rectal or colonic hemorrhage in six (13%), and vaginal, vulval, or penile bleeding in six (13%) children with visceral and pelvic hemangiomas.

Oduber and colleagues [11] investigated 70 KTS patients for the presence of persistent embryonic veins (PEVs) by duplex ultrasonography. They discovered two types of PEVs in the legs and proposed a nomenclature based on anatomical criteria, of persistent lateral marginal vein and persistent sciatic vein.

Hemimegalencephaly most often occurs as an isolated anomaly in several neurocutaneous disorders, e.g., linear nevus sebaceous, hypomelanosis of Ito, and *Klippel-Trénaunay-Weber* syndrome [12, 13]. Brain and eye abnormalities such as epidermal nevi and venous dysplasias have also been described and could lead to seizures, mental retardation, megalencephaly, megalocornea, glaucoma, and iris heterochromia. Other features that may be seen are hyperhidrosis, scoliosis and gait abnormalities, and neuroaxial venous malformations.

Jacob et al. [14] reviewed the clinical characteristics and findings in a series of 252 patients (136 female and 116 male) with KTS. Capillary malformations (port-wine stains) were found in 246 patients (98%), varicosities or venous malformation in 182 (72%), and limb hypertrophy in 170 (67%) (Figs. 9.1, 9.2, and 9.3). All three features of *KTS* were present in 159 (63%) patients, and 93 (37%) had two of the three typical findings.

Abnormalities of the *lymphatic system,* such as decreased number of lymph trunks and lymph nodes, are present in a great number of patients. Many patients have lymphoedema, cutaneous lymphatic vesicles, and weeping of lymph. The uncontrolled enlargement of the affected extremity may lead to pelvic deviation and scoliosis without any significant impact on height. *Ulrich* et al. [15] described a case of *Klippel-Trénaunay-Weber* syndrome and pulmonary arterial hypertension not associated with chronic thromboembolic pulmonary hypertension. It is hypothesized that pulmonary arterial hypertension is due to hemodynamic changes in the abnormally small vessels. Large venous malformations are rare, and many physicians are unfamiliar with the potential complications, which include hypercoagulability, thrombosis, and pulmonary embolism [16]. *Varicosis* and *phlebectasias* are observed mainly in the lower extremities, but they can also be found in the skull, thorax, and trunk.

Rarely, congenital malformations of the heart and atresia of the rectum may be found. *Husmann* et al. [17] reviewed the clinical findings in a series of 218 patients with KTS: 30% had genitourinary involvement, including 7% with cutaneous genital abnormalities, 7% with visceral genitourinary involvement, and 16% with each type. *Sreekar* et al. [18] in a retrospective study of 19 patients with KTS documented that 2 patients have hematochezia and had to undergo bowel resection, 5

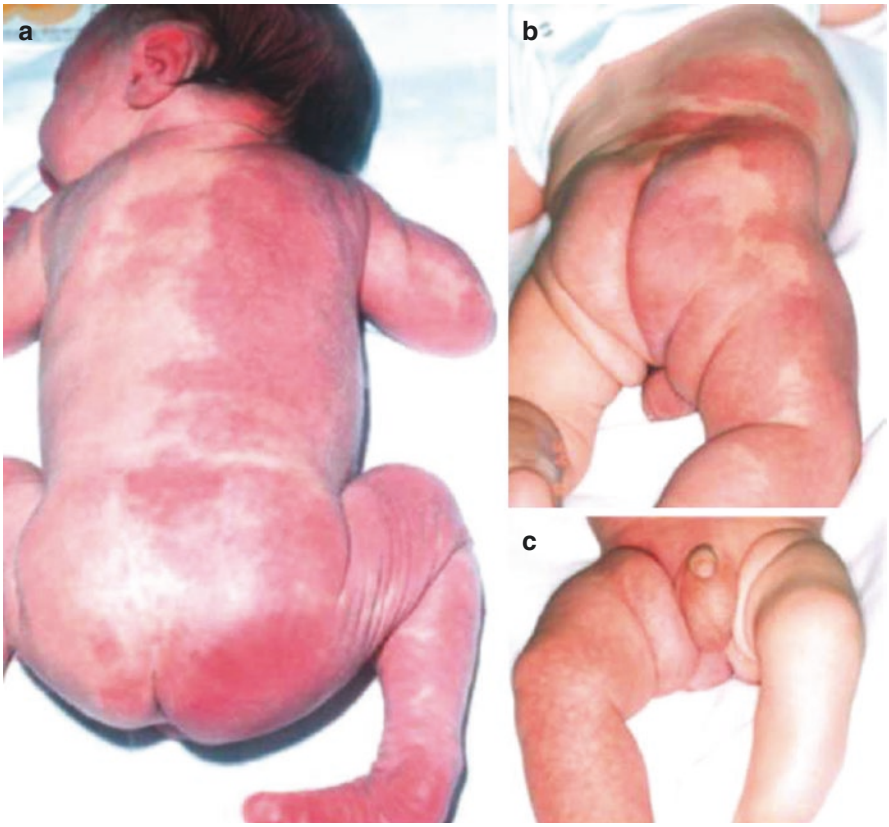

Fig. 9.2 (**a**, **b**) Port-wine stains in a 4-week-old boy; (**c**) capillary malformations in the right leg with hypertrophy of soft tissues in the same boy

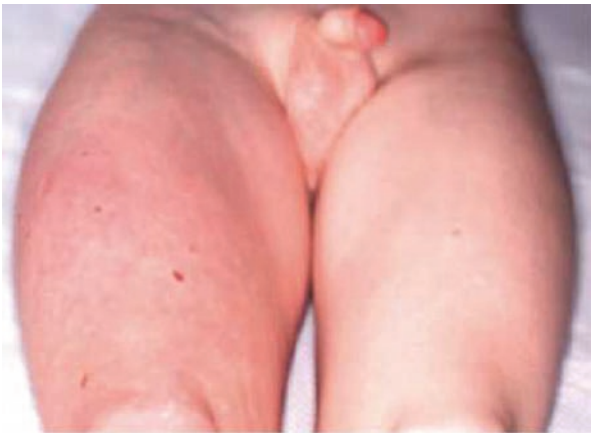

Fig. 9.3 Capillary malformations (port-wine stains in an 8-year-old boy)

patients with ulceration and bleeding from the KTS lesions, and in 2 of them the ulcers healed with conservative management.

During pregnancy the venous malformations increase with pelvic and intra-abdominal involvement. The complications, therefore, seen are venous insufficiency, cellulitis, ulcers, thrombophlebitis, thromboembolism, lymphangiectasia, consumptive coagulopathy with severe thrombocytopenia (*Kasabach-Merritt* syndrome), and increased bleeding in the intrapartum period [19].

Cavernous hemangiomas can enlarge rapidly, usually in the first year of life, producing high-output congestive heart failure or a consumptive coagulopathy *(Kasabach-Merritt syndrome*) marked by anemia, thrombocytopenia, prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), reduced fibrinogen levels, and fibrin split products.

Diagnosis

According to *Oduber* et al. [20], the diagnosis of *Klippel-Trénaunay syndrome* can be made in the presence of two main features that may manifest in different forms: (1) congenital vascular malformations (e.g., capillary, venous, arteriovenous, lymphatic malformations) and (2) disturbed growth (bone or soft tissue in length or girth). In conclusion the diagnosis is based on physical findings, sometimes with supportive imaging, of commonly a segmental anomaly with a cutaneous port-wine stain, lymphatic and venous malformations, and overgrowth [5].

Intrauterine diagnosis of KTS may aid in the decision-making process on the patients. Since KTS is the result of a somatic mutation, the risk of delivery of an ill child is low in women with *KTS* [21]. At the end of the first trimester, a sonographic investigation can exclude angiodysplastic alterations of the fetus. If the fetus shows changes compatible with *KTS,* termination can be discussed because the risk of fatal complications after delivery is high. *Rebarber* et al. [19] agree with the above recommendations and add that *KTS* was once thought to be a contraindication to pregnancy, but with careful management, successful pregnancies can be achieved.

Concerning *differential diagnosis,* atypical forms of vascular malformations must be excluded, such as the *Maffucci* syndrome, first described in 1881 [22], as a sporadic congenital disease associated with cutaneous vascular lesions (*spindle cell hemangiomas*) and multiple bony enchondromas, or the *Servelle-Martorell* syndrome with vascular malformation and hypoplasia of the bones [23, 24]. The overlap in phenotypic features between KT syndrome and PW syndrome often leads to misdiagnosis and inappropriate management. KTS should be distinguished from Parkes Weber syndrome (PWS), a fast flow-type combined vascular malformation with limb hypertrophy. MRI is very important in the diagnosis and assessment of

severity, complications, follow-up, and differentiation of KTS from other similar conditions. Different imaging modalities play complementary roles in the evaluation of KTS patients [25].

Therapy

The management of KTS is multidisciplinary and involves venous control, management of urological problems and orthopedic management of unequal limb lengths, and physical, psychological, social, and regular clinical examinations. A multiprofessional team with regular follow-up in a specialist clinic is necessary. Individualized management is needed, and it should be focused on the treatment of symptoms based on their severity. KTS patients have a very high rate of current or previous venous thromboembolisms (VTEs). About 39% of the patients would experience thromboembolic complications, including superficial thrombosis, and 8% have either a deep venous thrombosis or a pulmonary embolism [26]. Appropriate patient education on the signs and symptoms of thromboembolic complications in these patients is advised. In symptomatic cases, a low threshold for diagnostic testing for venous thromboembolism is necessary. Lifelong anticoagulation therapy should be considered in the case of a first deep venous thrombosis or pulmonary embolism, and venous thromboembolism prophylaxis should be directed to those KTS patients with hypercoagulability when they are exposed to one of the risk factors for venous thromboembolism, such as surgery, trauma, or pregnancy.

Photodocumentation of the involved extremity is recommended with each follow-up visit. Symptomatic treatment and support to the patient and family members must be undertaken. MRI and angiography are helpful in the differential diagnosis. *Prenatal* diagnosis may be achieved by sonogram [27, 28]. MRI, Doppler ultrasound, standard radiology, and magnetic resonance arteriography (*MRA*) provide information regarding the extent of the vascular lesions, particularly deep pelvic or thoracic vascular lesions. Further, dynamic magnetic resonance projection angiography (*MRPA*) is a noninvasive tool to detect the vascular malformations of the affected extremity in *Klippel-Trénaunay-Weber* syndrome [29]. Surgical therapy of symptomatic or cosmetically worrisome lesions has been controversial because of the wide spectrum of symptoms and impairments associated with KTS [30]. Specific reductive embolization or sclerozation of extensive varicoses improves the clinical picture [31, 32]. *Another* minimally invasive treatment is intracutaneous laser surgery, such as carbon dioxide laser, or electrocoagulation, cryotherapy, or excision for angiokeratomas [30]. Angiokeratoma is characterized by aggregates of hyperkeratotic erythematous papules and nodules that may coalesce to form verrucous plaques. Plastic surgery or amputation of the affected extremity is the *ultima ratio* when other measures prove futile and the quality of life deteriorates [14, 23, 33, 34]. *Finally,* the less affected the various organs and the fewer symptoms (Lyon effect), the more acceptable the prognosis. *Lee* et al. [35] report that the management of pain in patients with KTS depends on its cause.

Prognosis

Patients with KTS are best evaluated initially in a center with an experienced multidisciplinary team that includes a primary health care provider, vascular surgeons, and ancillary staff. Surgery can be undertaken in selected cases of hemangioma, for cosmetic reasons, and for chronic venous insufficiency.

According to the clinical implications, the prognosis and treatment of these two syndromes are very different [36]. The severity of the vascular malformations and the degree of overgrowth vary from patient to patient. Only a quarter of children who undergo resection of varicose veins will improve. Significant morbidity can be associated with the treatment of *Kasabach-Merritt* syndrome and high-output cardiac failure [5]. In a retrospective study, *Blatt et al.* [37] reported that the risk of embryonal cancer other than Wilms tumor in children with KTS is not higher than in the general population.

Relative to *urological complications,* the recommendation by *Husmann* et al. [17] regarding aggressive open surgical management of the genitourinary (GU) tract of KTS was based on inadequate information from isolated case reports and diverse subspecialty articles. *Patel* et al. [38] in a last retrospective review of 58 pediatric KTS patients with clinical data, such as age, age at KTS diagnosis, gender, urologic involvement, and age at urologic complication, found significant GU complications due to KTS. All patients are received in a center with an experienced multidisciplinary specialized tertiary care team. Conservative management of cutaneous bleeding from genital lesions with compressive garments and antibiotics save over half of the patients.

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Chapter 10
Epidermal Nevus Syndromes

Michael Waul, Daniel M. Klufas, and Jeffrey L. Sugarman

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Introduction

Epidermal nevi (*EN*) are benign, heterogeneous hamartomatous growths of the skin. Their clinical features are dictated largely by their cell or structure of origin, which may include keratinocytes, the pilosebaceous unit, apocrine or eccrine glands, or smooth muscle cells. Most lesions are present at birth, thus often described as birthmarks, though some may become more prominent or appear as one ages. EN appear in approximately 1–3 per 1000 live births with no predilection of sex. While generally considered benign, certain epidermal nevi do have the capacity for malignant

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transformation and may be associated with certain extracutaneous manifestations which can carry significant morbidity [1].

One of the *most striking* features of epidermal nevi is their propensity to occur in a Blaschko linear manner. This pattern refers to the whorled, streaked, or linear pattern that does not follow any known vascular, nerve, or lymphatic pathway. These patterns were first described by *Blaschko* in 1901 and believed to represent pathways of epidermal cell migration during embryogenesis. *Aside* from the unique morphologies these pathways create, a *Blaschko* linear distribution speaks directly to the pathogenesis of epidermal nevi, that is, epidermal nevi occur due to genetic mosaicism [1].

Some *authors* suggest organizing epidermal nevi into two subtypes: organoid (derived from adnexal structures such as sebaceous glands, follicular structures, apocrine glands, etc.) or non-organoid/keratinocytic (derived predominantly from the keratinocytes/epidermis) nevi. This classification was first coined by *Jadassohn* in 1895 and then later expanded by *Mehregan* and *Pinkus* 1965 and *Solomon* and *Esterly* in 1975 [2]. This framework does allow categorizing epidermal nevi by clinical morphology and histopathologic features, but advances in molecular genetics have revealed the limitations of such a dualistic categorization.

While most epidermal nevi occur as isolated cutaneous lesions, it is important to recognize that some epidermal nevi can occur in association with extracutaneous manifestations involving numerous organ systems, particularly the central nervous system, skeletal system, and ocular system. When this occurs, patients are better classified as having an epidermal nevus syndrome (*ENS*). ENS represents a broad spectrum of disorders, and advances in molecular genetics, particularly in regard to identifying specific mutations in affected tissues, have helped reveal the role of genomic mosaicism in the pathogenesis of these disorders. Better *understanding* of the molecular pathways which these mutations disrupt, as well as an improved appreciation of the importance of the impact of the timing during embryonic development at which they may occur, has helped to elucidate their unique cutaneous and extracutaneous features.

In particular, *RAS* gene mutations, both germline and somatic gain-of-function mutations, can lead to developmental disorders known as RASopathies, some of which are categorized in conjunction with ENS. Because RAS proteins (part of the RAS/MAPK pathway—an important pathway for cell proliferation, differentiation, and migration) serve as important signal relay molecules influenced by environmental stress and growth hormones, they play a critical role in the entire developmental process, but particularly the neurodevelopmental process (Fig. 10.1) (Table 10.1). Mutations leading to activation of the RAS/MAPK pathway can cause enhanced proliferation of neural stem cells, particularly those of glial lineage, leading to imbalance of neuroglial cellular subtypes, which helps to explain the neurological abnormalities seen in various forms of *ENS* as discussed later in this text [3].

In this chapter, we will describe a framework of classifying epidermal nevi based on the presence of clinical cutaneous and extracutaneous features. These categories will include well-defined epidermal nevus syndromes with central nervous system involvement, overgrowth syndromes with epidermal nevi, epidermal nevus

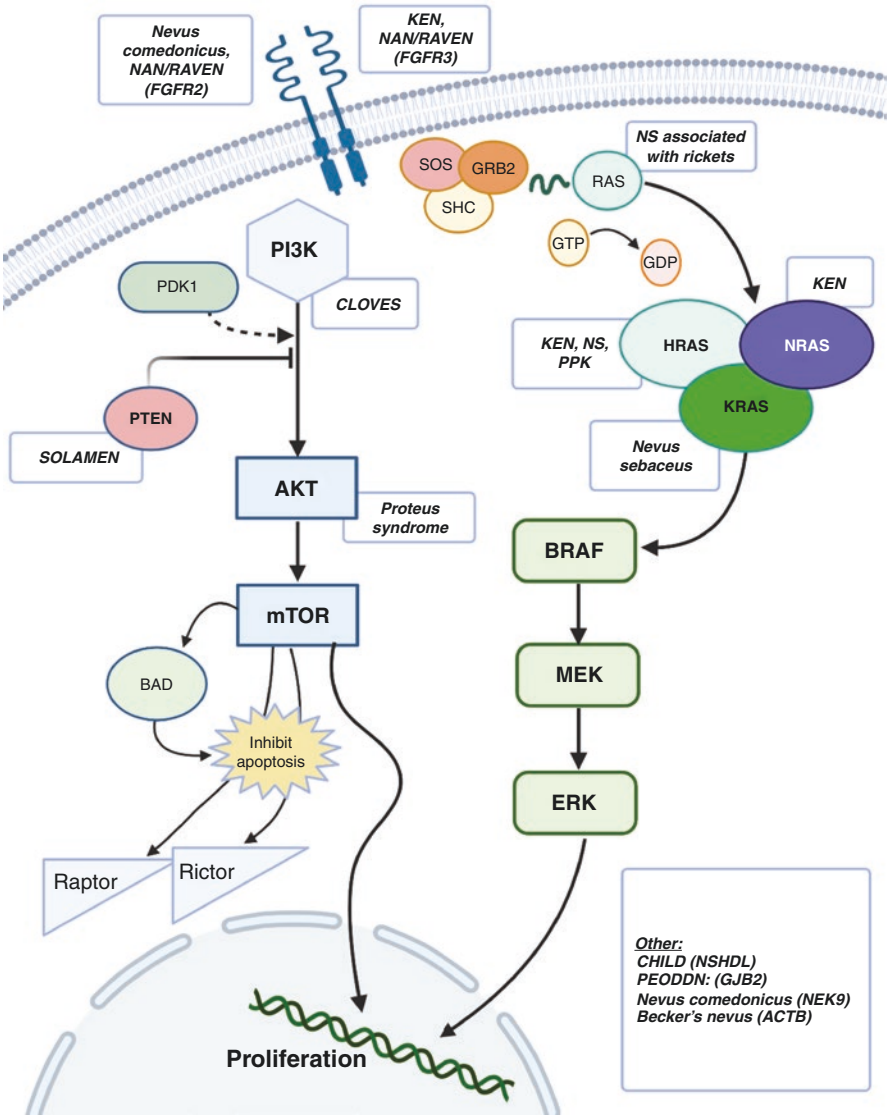

Fig. 10.1 Affected pathways in selected epidermal nevus syndromes (Abbreviations: *CHILD* congenital hemidysplasia with ichthyosiform erythroderma and limb defects, *CLOVES* congenital lipomatous overgrowth, vascular malformations, and epidermal nevus, also known as congenital lipomatous asymmetric overgrowth of the trunk, lymphatic, capillary, venous, and combined-type vascular malformations, epidermal nevi, skeletal and spinal anomalies, *KEN* keratinocytic epidermal nevus, *NS* nevus sebaceous, *PEODDN* porokeratotic eccrine ostia and dermal duct nevus, *PPK* phakomatosis pigmentokeratotica, *SOLAMEN* segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus, also known as type 2 segmental Cowden disease). Figure created using BioRender.com and modified from one originally designed by Dr. Sarah Asch

Table 10.1 Molecular and clinical aspects of epidermal nevi and epidermal nevi syndromes

	Disorder	Mutation/molecular pathogenesis	Clinical characteristics
ENS with CNS involvement	Nevus sebaceous	*HRAS* (c.37G > C), *KRAS*	– Solitary, alopecic yellow-tan plaque with velvety or verrucous texture – Seizures, intellectual disability, coloboma, choristomas
	Keratinocytic EN	*HRAS, NRAS, KRAS, FGFR3*	– Permanent linear or whorled verrucous or hyperkeratotic plaques with velvety texture – Oral and facial dysmorphisms, skeletal abnormalities, seizures, developmental delays, and intraspinal growths
	Phakomatosis pigmentokeratotica	*HRAS* (c.37G > C)	– Epidermal nevus with concurrent sebaceous differentiation along lines of Blaschko as well as speckled lentiginous nevus – Ocular involvement, scoliosis, muscular weakness, and hemiparesis, seizures, sensory or motor neuropathies, hyperhidrosis, hypophosphatemic vitamin D-resistant rickets
	Nevus comedonicus	*NEK9*, *FGFR2*, ?*ABACA12*	– Linear or segmental plaque with closely grouped dilated ostia with dark, horny plugs – Ipsilateral congenital cataracts, malformation of fingers/toes, neural abnormalities
	CHILD syndrome	*NSDHL* (encodes 3β-hydroxysteroid dehydrogenase)	– Unilateral inflammatory erythematous patches covered in dry, yellowish scales with a sharp midline demarcation in conjunction with ipsilateral skeletal abnormalities – Ipsilateral hemispheric hypoplasia and loss of white matter of the brain, cardiac anomalies, deafness, hypoplasia, or absence of ipsilateral organs

Overgrowth syndromes	CLOVES	*PIK3CA* (AKT/PI3K/mTOR pathway)	– Thoracic lipomatous hyperplasia, usually involving the back or trunk and found in conjunction with an overlying capillary malformation – Linear epidermal nevi, "sandal toe gap," scoliosis or spinal abnormalities
	Proteus syndrome	*AKT1* (AKT/PI3K/mTOR pathway)	– Rapidly progressive somatic overgrowth disorder characterized by relentless mosaic overgrowth of tissues derived from all three germ layers – High risk of thromboembolism
	SOLAMEN	*PTEN*	– Overgrowth with hemihypertrophy of limbs, macrocephaly, lipomatosis, varicosities, angiomas, hydrocephalus, seizures
ENS without CNS involvement/unclassified	NS associated with rickets	*RAS* (resulting in overproduction of FGF23)	– Nevus sebaceous, bone pain, weakness, foci of dysplastic bone, brainstem lipoma, thyroid nodules, eye, and cardiac abnormalities
	PEODDN	*GJB2* (Connexin 26)	– Verrucous, keratotic papules with keratin-filled plugs overlying eccrine ducts on palms and soles
	Becker's nevus	*ACTB* (actin gene)	– Circumscribed patch of hyperpigmentation with hypertrichosis and slight acanthosis, usually located in the shoulder or truncal regions
	ILVEN	*GJA1*	– Pruritic, unilateral linear, verrucous erythematous plaques
	Nevoid acanthosis nigricans or RAVEN (*rounded* and *velvety epidermal nevus*)	*FGFR2, FGFR3*	– Linear, hyperpigmented, polycyclic, velvety plaques on trunk or extremities

ENS epidermal nevus syndrome, *EN* epidermal nevus, *NS* nevus sebaceous, *CHILD* congenital hyperplasia with ichthyosiform nevus and limb defects, *CLOVES* congenital, lipomatous asymmetric overgrowth with lymphatics, capillary, venous, or combined-type vascular malformation, epidermal nevi, and skeletal anomalies, *SOLAMEN* segmental overgrowth, lipomatosis, arteriovenous malformation, and epidermal nevus, *PEODDN* porokeratotic eccrine ostia and dermal duct nevus, *ILVEN* inflammatory linear verrucous epidermal nevus

syndromes without associated central nervous system involvement, and less well-defined epidermal nevi. Each subsection will focus on the clinical presentation (*both cutaneous* and *extracutaneous*), histopathology, genetic basis, pathogenesis, and management. While this manuscript will classify these disorders with the above framework, it is important to understand that the research in this field is brisk, which will likely impact future classifications of these disorders.

Well-Defined Epidermal Nevus Syndromes with Central Nervous System Involvement

Nevus Sebaceous

Clinical Characteristics

Nevus sebaceous has an estimated prevalence of 0.3% in newborns and represents approximately one half of all epidermal nevi [2]. Classically, they are first noticed in the neonatal period as ovoid or linear, yellow-orange or pink, patch or thin plaque, with a smooth waxy surface (Fig. 10.2a). In some cases, a nevus sebaceous may have a cerebriform appearance with clearly defined sulci and meandering or may present with a pedunculated morphology. Diagnosis can usually be easily made based on the clinical findings; in some cases, trichoscopy and dermoscopy are useful supplementary tools [4]. The overwhelming majority of these lesions occur on the scalp and face. *Mehregan* and *Pinkus* outlined the natural history and stages of sebaceous nevi. During infancy, lesions are flat as sebaceous glands are underdeveloped. In the pubertal period, the nevus sebaceous develops a thicker and more papillomatous appearance under hormonal influences. In adulthood, various benign and malignant neoplasms may secondarily develop within the lesions. However, this paradigm does not always hold true, as there are reports of neoplastic growths even in the childhood phase (see Chap. 10).

Nevus sebaceous syndrome refers to the existence of a nevus *sebaceous* with concomitant extracutaneous manifestations (Fig. 10.2b). The central nervous, ocular, and skeletal systems are most frequently affected. Part of the difficulty with associating *extracutaneous* manifestations with specific epidermal nevi is due to historical use of the term “epidermal nevus syndrome” to encompass all types of epidermal nevi. In one review of 196 patients with nevus sebaceous, 7% exhibited neurologic abnormalities. Of these, 79% had intellectual disability and 57% had seizures. Interestingly, neuroimaging was normal in 75% of those with clinical neurologic disease. Those with abnormal findings demonstrated a poorly developed cerebral cortex. Overall, extensive nevi were four times as likely in patients with neurologic manifestations compared to those without. In *addition*, centrofacial nevi portended a tenfold increased risk of neurologic abnormalities [1, 5]. *Ocular choristomas* and colobomas are the most frequent ophthalmic findings associated with nevus sebaceous syndrome.

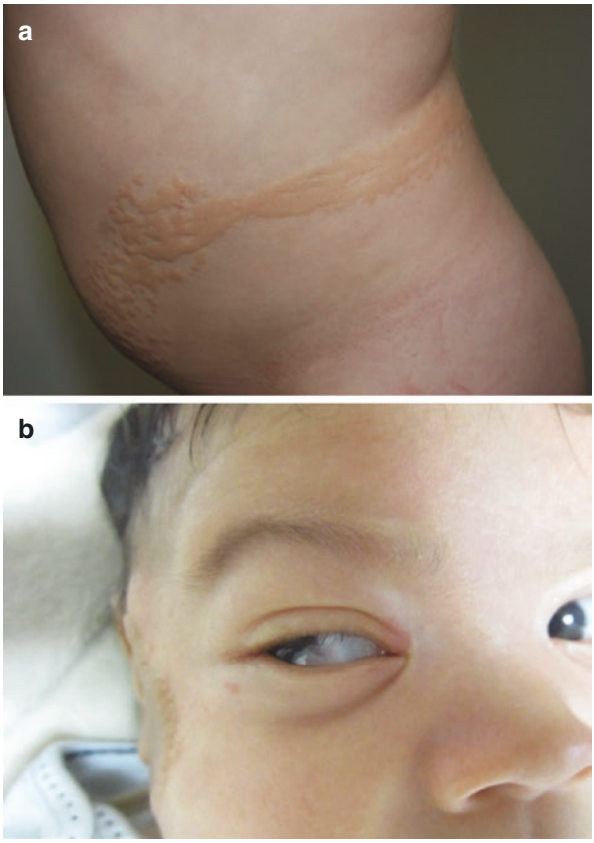

Fig. 10.2 (**a**, **b**) Nevus sebaceous—typically presents as a solitary, yellow-brown or orange plaque, sometimes with a velvety texture (*top*). In individuals with nevus sebaceous syndrome, extracutaneous findings such as corneal opacity (*bottom*) may be seen

Nevus *sebaceous* has a well-established predisposition to the development of secondary neoplasms, occurring in about 10–30% of cases [6]. However, the precise nature of these neoplasms and the frequency of malignant transformation have been the subject of robust debate and conflicting data over the past several decades [7, 8]. It is theorized that many of the "malignant" lesions arising in sebaceous nevi in the past were actually benign tumors (*mainly trichoblastomas*) misdiagnosed as basal cell carcinoma. Relatively more recent data provides a more accurate picture. Cribier and colleagues conducted a retrospective analysis of 596 cases of nevus sebaceous. *Benign* tumors were found in approximately 14% of lesions, most commonly syringocystadenoma papilliferum (5%), trichoblastoma (5%), trichilemmoma (3%), and sebaceoma (2%). Basal cell carcinoma was only found in 0.8% of cases [9]. In another study of 155 nevus sebaceous cases, not a single basal cell carcinoma was found [10].

The medical literature is replete with a myriad of uncommon secondary neoplasms and other cutaneous lesions that have arisen within a nevus sebaceous, *including* desmoplastic trichilemmoma, proliferating trichilemmal cyst, trichilemmal carcinoma, sebaceous carcinoma, eccrine poroma, hidradenoma, apocrine

hidrocystoma, primary cutaneous apocrine carcinoma, microcystic adnexal carcinoma, pilomatricoma, tumor of the follicular infundibulum, trichoblastic carcinoma, squamous cell carcinoma, malignant melanoma, and osteoma cutis. In many cases, multiple tumors may arise within a single lesion.

Histopathology

As the clinical features of a nevus sebaceous change with age, so do the histopathologic findings. In the prepubertal stage, there are small sebaceous glands, with incompletely differentiated follicular structures (see section "Neurofibromatosis type 1 (NF1)"). *After* puberty, hyperkeratosis, acanthosis, and papillomatosis are common, with large sebaceous lobules and ectopic apocrine glands. There is loss of mature hair follicles, especially for lesions on the scalp. At this stage, lesions may also develop secondary neoplastic growths of follicular, sweat gland, and sebaceous differentiation, among others [11, 12].

Molecular Genetics and Pathophysiology

Nevus sebaceous is well defined as a mosaic RASopathy, with earlier and more extensive mosaicism responsible for syndromic forms [13–15]. The most common mutation is c.37G > C (p.Gly13Arg) in *HRAS*, which is present in >90% of nevus sebaceous cases (see Chap. 1). These *mutations* result in constitutive activation of the RAF-MEK-ERK and phosphoinositide 3-kinase signaling pathways, potentiating increased cellular proliferation [16]. Activating *HRAS* and *KRAS* mutations have been identified in lesional keratinocytes, but not in the blood or non-lesional skin of affected individuals. The lack of corresponding mutations in the fibroblasts underlying sebaceous nevi confirms that the genetic alteration is limited to epidermal cells. Laser capture microdissection to isolate DNA from lesional epidermis and dermis also confirms this finding [17, 18]. *Germline* activating HRAS mutations are known to cause Costello syndrome, a rare disorder characterized by papillomatous skin lesions and increased lifetime risk of malignant neoplasms [19]. Interestingly, *Costello* syndrome is not associated with nevus sebaceous, an observation possibly explained by differences in the specific causative HRAS mutation for the two conditions. Additionally, germline mutations in KRAS have been identified in cardiofaciocutaneous*, Noonan* and Costello syndromes, but the somatic mutations which give rise to nevus sebaceous have not been observed in the germline [20]. FGFR2 mutations have also been implicated in the development of nevus sebaceous. In one report, a papillomatous pedunculated nevus sebaceous exhibited a postzygotic de novo FGFR2 c.1144T > C (p.Cys382Arg) mutation, which was thought to activate RAS signaling [21].

Treatment

There is no definitive management plan for patients with *nevus sebaceous*. Isolated lesions in locations where they are cosmetically acceptable to the patient may be serially monitored for the low risk of malignant transformation. There is ongoing debate regarding the utility and timing of surgical excision, compared to continued clinical monitoring. In a *2018* survey of dermatologists and plastic surgeons in the UK, 30% of dermatologists routinely recommended excision for malignancy prevention, while 58% of plastic surgeons commonly recommended excision in children less than 13 years [22]. It is prudent to manage each case individually, educating patients and their families on the risks and benefits of each option and taking into account their management preferences.

Keratinocytic Epidermal Nevi

Clinical Characteristics

Keratinocytic epidermal nevi (*KEN*) are the most common form of epidermal nevi [23]. They appear as linear or whorled verrucous or hyperkeratotic, pink or brown plaques sometimes with a soft, velvety texture arranged along the lines of Blaschko (Fig. 10.3). While usually present at birth, lesions may have onset early in infancy or within the first few months or years of life. These nevi may begin flat but eventually become more raised, verrucous, and darker in color.

KEN may have different morphologies depending on anatomic location. For example, *KEN* located in intertriginous areas may be softer and less verrucous as compared to those on the trunk, extremities, or acral surface, with the latter referred to as "verrucous EN." When involving the nail matrix, the primary manifestation may be nail dystrophy.

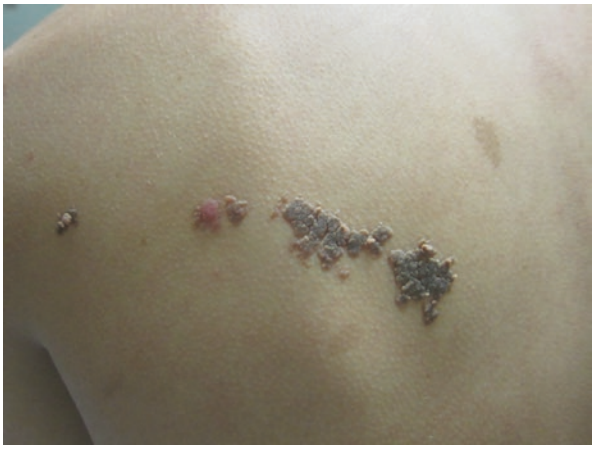

Fig. 10.3 Keratinocytic epidermal nevus (KEN)—appear as linear or whorled verrucous or hyperkeratotic, pink or brown plaques sometimes with a soft, velvety texture arranged along the lines of *Blaschko*

These nevi may be solitary or widespread and vary widely in their size. The distribution may involve any anatomic location though most commonly found on the trunk and extremities and less commonly on the head or neck. When unilateral, *KEN* have been referred to as "nevus unius lateris," but KEN may be bilateral as well though usually exhibiting a sharp demarcation at the dorsal or ventral midline. When KEN are symmetric and bilateral, the term systematized EN or *ichthyosis hystrix* has been used [24].

While KEN may be limited to the skin, there are instances where it may be associated with extracutaneous manifestation. While not fully characterized, some refer to KEN with systemic findings as keratinocytic epidermal nevi syndrome (*KENS*). These extracutaneous manifestations include oral and facial dysmorphisms, skeletal abnormalities, as well as CNS abnormalities such as seizures, developmental delays, and intraspinal growths [25, 26]. As more mutations are identified (and discussed in subsequent sections), we have begun to better understand how certain mutations lead to specific phenotypes. Within KEN, the distinct subtype epidermolytic *KEN* may be distinguished from other KEN clinically. They present with thinner, softer, and more scaly plaques and have a distinct genotype.

Histopathology

When biopsied, keratinocytic or verrucous *EN* will exhibit acanthosis, orthohyperkeratosis, papillomatosis, and an expanded papillary dermis with a clear demarcation from adjacent normal skin. In one study examining 167 specimens from 160 patients with *KEN*, 67% showed hyperkeratosis and epidermal hyperplasia, whereas 13% showed acrokeratosis verruciformis-like features with marked hyperkeratosis, hypergranulosis, and acanthosis. A *smaller subset* showed epidermolytic hyperkeratosis (5%), seborrheic keratosis-like features (5%), psoriasiform hyperplasia (3.6%), verrucous changes (2%), and features similar to Darier's disease, porokeratosis, and acanthosis nigricans (1.2%, respectively) [27]. Almost certainly, the epidermolytic changes seen in a small minority of the *KEN* sampled in this study represented the epidermolytic KEN subtype, but at the time of that publication, its distinct clinical appearance was not yet appreciated, and its specific genetic features were not yet known. Additionally, in our experience, many *KEN* exhibit seborrheic keratosis-like features, and this is also likely related to specific genotypic differences. As discussed below, many *KEN* are associated with FGFR3 mutations, which are also found in a subset of seborrheic keratoses [28].

Molecular Genetics and Pathophysiology

Non-epidermolytic *KEN* arise as a result of prenatal postzygotic mutations either in the RAS/MAPK pathway or the PI3K/AKT pathway [29]. Both of these pathways are critical for cell signaling, proliferation, and survival, thus supporting the notion that activating mutations in these pathways can lead to proliferation and overgrowth

of keratinocytes in *KEN* (see Chap. 1). In a landmark 2006 study, *Hafner* et al. [28] first identified an activating FGFR3 mutation almost exclusively at codon 248 (*R248C*) in 11 of 33 patients with non-organoid, non-epidermolytic *KEN*. In four of these cases, the mutation was not found in histologically normal skin [30]. In a later study analyzing 72 KEN with DNA mutational analysis, they found that 39% of KEN harbored RAS mutations (HRAS (29%) > NRAS(4%) > KRAS(1%)) and 27% harbored FGFR3, PIK3CA, or a combination of mutations. Some 38% of *KEN* harbored no identifiable mutations in RAS, FGFR3, or PIK3CA. Given the lack of abnormality, 10 of these were further screened for mutations in 19 other oncogenes, and no mutations were uncovered [29]. In 2016, *Toll* et al. reported the detection of FGFR2 mutations in 4 of 23 *KEN*, extrapolating that approximately 5–10% of KEN harbor embryonic FGFR2 activating mutations [31]. More recent studies have found mutations in the EGFR gene, particularly a heterozygous c.2582T > A (p.L861Q) variant specifically in the affected epidermis of a 6-year-old boy presenting with a variant of *KEN* presenting clinically as velvet-like whitish papules [32]. Because the genetic cause of 80–90% of *KEN* are activating mutations in oncogenes, some authors have proposed to extend the concept of "mosaic RASopathy" to one of "mosaic signalopathy" to this and related conditions [31].

As mentioned earlier, *KEN* can present with extracutaneous findings, and patients presenting in this fashion may be classified as having keratinocytic epidermal nevus syndrome (KENS). In a recent review of eight cases of KENS analyzed with molecular analysis, six different somatic mutations were identified in KENS with pathogenic mutations in the KRAS (c.35G > A), HRAS (c.34G > A, c.37G > C), FGFR3 (c.742C > T, c.746C > G), and PIK3CA (c.3140A > T) genes. These patients had their respective mutations also detected in other tissues such as within a rhabdomyosarcoma, urothelial carcinoma with lung metastases, thymoma, oral mucosa, and spinal tissue (*neurofibromas*). In one patient with a large intraspinal lipomatous tumor leading to progressive paraparesis, a mosaic c.35G > A (p.Gly12Asp) *KRAS* mutation was detected in the KEN, intraneural *Schwann cells*, and lipoma (see section "Neurofibromatosis type 2 (NF2)" and Chap. 26) [26]. In another study examining *KEN* associated with skeletal abnormalities, particularly hypophosphatemic rickets and dysplastic bone lesions better known as cutaneous skeletal hypophosphatemia syndrome [33], the authors presented two patients with *HRAS* mutations with a review of the literature showing similar mutations in patient with KEN and bone lesions [34].

Treatment

Treatment for *KEN* is not required. If the lesion is small and causing cosmetic or functional issues, then surgical excision may be considered. Ablative laser such as carbon dioxide or erbium:YAG laser may also be used to treat KEN though results vary. Finally, topical retinoids or keratolytics can be used to smooth textural changes.

Nevus Comedonicus

Clinical Characteristics

Nevus comedonicus (NC), a hamartoma of the pilosebaceous unit, is a rare type of epidermal nevus. It was first described by *Kofmann* in 1895 and has an estimated prevalence between 1 in 45,000 and 1 in 100,000 persons with no racial or sexual predisposition [35, 36]. About half of cases are present at birth, whereas the other half develop later in life but usually by the first decade of life with accelerated growth experienced during puberty. Nevus *comedonicus* can be found on various sites but has a predilection for the face, neck, chest, and upper arms [37].

When present at birth, nevus *comedonicus* can appear as a shiny patch though with age it will take on the more characteristic appearance of closely grouped dilated ostia (*follicular openings*) with dark, horny plugs mimicking comedones (Fig. 10.4). Similar to other cutaneous mosaic disorders, nevus comedonicus often presents in a linear or segmental honey-combed pattern along the lines of *Blaschko*, representing the dorsoventral migration of epithelial progenitors during embryonic development. While some authors split nevus comedonicus into two subtypes (*non*-pyogenic and a type associated with formation of cysts, pustules, and abscesses), the authors of this chapter take these entities to be overlapping enough to be considered collectively as nevus comedonicus with features displayed along a spectrum. The inflammation (e.g., inflammatory papules and pustules) that is sometimes seen in association with NC may be likened to inflammatory acne that arises in conjunction with comedonal acne, likely by the proliferation of *C. acnes* operating in the favorable milieu of the dilated and occluded microcomedo [38].

Nevus *comedonicus* is usually asymptomatic though can be complicated by inflammation or secondary infection. Development of benign dermatologic neoplasms such as hidradenoma papilliferum and syringocystadenoma papilliferum has been documented. Malignant transformation of nevus comedonicus is exceedingly rare [39].

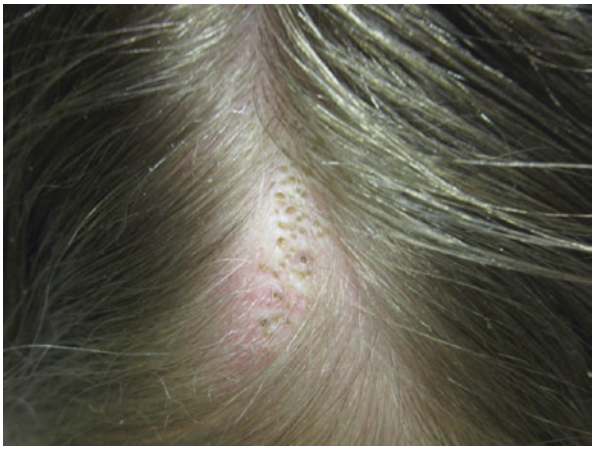

Fig. 10.4 Nevus comedonicus—this may initially appear as a shiny patch though over time it will take on the more characteristic appearance of closely grouped dilated ostia (follicular openings) with dark, horny plugs mimicking comedones

Though nevus comedonicus is usually limited to the skin, extracutaneous manifestations can occur and represent an entity known as nevus comedonicus syndrome (*NCS*), which was first described by *Engber* et al. in 1978 [40]. NCS is mainly categorized as a nevus comedonicus found in association with *ocular* (typically ipsilateral congenital cataracts), *skeletal* (malformation of fingers and toes), and *neural* abnormalities. In a recent systematic review of 43 established NCS cases, it was quantified that ocular, skeletal, and central nervous system abnormalities were detected in 53.2%, 51.1%, and 36.2% of cases, respectively [41].

Histopathology

Microscopically, nevus comedonicus will show poorly differentiated hamartomatous follicular structures, which likely represents the dysregulation of the pilosebaceous unit in this condition [42]. Biopsy will reveal wide invaginations of the epidermis resembling dilated follicular ostia filled with compact keratin. Unlike acne, closed comedones are not typically present. Since the affected follicular structure is unable to produce terminal hairs, hair follicles and arrector pili muscles are usually absent and the sebaceous glands are rudimentary. The epidermis may be acanthotic or hyperkeratotic [42].

Molecular Genetics and Pathophysiology

Mutations in fibroblast growth factor receptor 2 (FGFR2) were first postulated to play a key role in the formation of nevus comedonicus (see Chap. 1). Mutations in FGFR2 identical to those seen in Apert syndrome were detected in involved skin, but not from peripheral blood or involved skin, supporting the hypothesis of NC representing a mosaic condition involving a FGFR2 mutation, which, if present in germ line, would result in *Apert* syndrome (which is also characterized by severe acne) [43, 44]. It was rationalized that these mutations change the affinity of the receptors for ligands that are differentially expressed in the epithelium and mesenchyme, thereby disrupting the normal interactions during the development of the skin and hair follicle.

However, in a 2016 study by *Levinsohn* et al. [45], whole-exome sequencing on tissue from nevus comedonicus identified somatic *NEK9* mutations in highly conserved residues within its kinase or RCC1 domains in all three subjects of the study. The mutations were all gain of function, resulting in increased Thr210 phosphorylation, which is critical in NEK9 kinase activation. *NEK9 kinase*, which is found in the follicle, interfollicular epidermis, and cysts, is a serine/threonine kinase that plays a critical role in cell cycle regulation, possibly in the Wnt, Notch, and Sox9 signaling pathways. As such, these findings suggest NEK9 mutations may disrupt normal follicular differentiation [45]. Additionally, *NEK9* recessive germline mutations have been reported to cause skeletal disease without cutaneous features which may explain why NC syndrome can also present with skeletal and bony abnormalities, suggesting that the *NEK9* mutation may also affect bone progenitors [46, 47].

In a 2018 study, *Liu* et al. [48] reported the discovery of upregulated expression of ATP-binding cassette sub-family A member 12 (*ABCA12*) in the sebaceous glands of two patients with nevus comedonicus, who did not express an *ABCA12* mutation. While it is postulated that ABCA12 may play a role in lipid transport and accumulation of keratin, it is unclear what role it truly plays in the development of nevus comedonicus [48].

As mentioned previously some authors elect to divide NC into "pyogenic" and "non-pyogenic"; however, in recent systematic review, it was instead found that nevus comedonicus can be classified into three morphologic subtypes: (1) predominantly comedonal type (most common), (2) "Selhorst type" (giant comedones, nodules, and cysts with prominent inflammation and scarring), and (3) "atrophodermal vermiculatum" type (collection of small scarred pits resembling atrophoderma vermiculatum with interspersed comedones) [41]. *Torchia* et al. suggest there is no evidence to suggest that different genetic mutations can explain these phenotypes; rather, they propose that these phenotypes are likely attributable to a combination of patient-specific factors (i.e., molecular, anatomical, hormonal, ethnic, and age-related variables). The authors of this chapter hypothesize that these variants, however, may be due to epiphenomenon. For instance, the Selhorst type may be due to the result of androgen hormones active on comedone-rich targets, thus leading to this severe, inflammatory phenotype (analogous to those with comedonal acne developing severe inflammatory acne and scarring). Nevertheless, further investigation is needed to further elucidate the role of genetic mutations in these specific subtypes.

Treatment

Given that most lesions are asymptomatic, treatment is not necessary and, if pursued, can be challenging. Most treatment methods are aimed at controlling complications such as cyst formation, secondary infection, and development of scarring. Keratolytics such as salicylic acid or topical retinoids (alone or in combination with topical antibiotics like clindamycin), vitamin D derivatives (*like calcipotriene*), and keratoregulators such as ammonium lactate can be trialed though success is likely to be limited. Laser (CO2, erbium:YAG, diode) and surgical resection may be more definitive treatments. There is a recent report detailing success using a microneedling fractional radiofrequency device, which achieved complete resolution without long-term side effects [49].

Phacomatosis Pigmentokeratotica

Clinical Characteristics

First described in 1996, phacomatosis pigmentokeratotica (*PPK*) is characterized by concurrence of an epidermal nevus with sebaceous differentiation (multiple dark to light brown, hyperkeratotic, verrucous plaques) along the lines of *Blaschko* as

well as a speckled lentiginous nevus (SLN, also known as a nevus spilus and manifests as a large light brown patch with multiple small, dark brown macules and papules overlying it) in a checkerboard pattern (broad segmental areas respecting the midline) [50]. PPK is a rare condition with only about 35 cases reported in the literature and has a male predominance [51]. Based on clinical associations and mutational analysis, some consider PPK a variant of *Schimmelpenning-Feuerstein-Mims* syndrome (*SFMS*) (see Chap. 4).

Nearly all cases of *PPK* are associated with extracutaneous manifestations, which include most commonly neurologic, ocular, and musculoskeletal abnormalities. More specifically, neurologic involvement may manifest as hemiparesis, hyperhidrosis, mental retardation, seizures, and sensory or motor neuropathies [36, 52]; ocular involvement may manifest as strabismus, ptosis, congenital glaucoma, and esotropia [52]; and musculoskeletal abnormalities may present as scoliosis, muscular weakness, and hypophosphatemic vitamin D-resistant rickets [36, 52]. More recently, there have been reported cases of endocrine abnormalities manifesting as precocious puberty suspected to be secondary to pituitary gland involvement in patients with PPK [53]. Additionally, there is also a report of a patient with *PPK* presenting with unilateral renal hypoplasia [51].

Histopathology

The histopathologic findings of *PPK* would include those consistent with nevus sebaceous and *SLN* on skin biopsy. A nevus sebaceous will often show papillomatosis, hyperkeratosis, and elongation of rete ridges usually with an increased number of sebaceous glands (see Chap. 4). The histopathologic findings of SLN include uniform melanocytes in the superficial dermis and at the dermoepidermal junction with focal areas of nests of uniform melanocytes involving adnexal structures.

Molecular Genetics and Pathophysiology

The underlying pathogenesis of *PPK* was originally thought to be due to the "twin spot phenomenon" (*also referred to as didymosis*), which suggested that the cutaneous manifestation of the nevus sebaceous and speckled lentiginous nevus was secondary to two homozygous recessive mutations occurring in the early stages of embryogenesis (see Chap. 1). However, this theory was dismissed following the discovery of a postzygotic activating *HRAS* mutation in a single multipotent progenitor cell, which can give rise to sebaceous and melanocytic components [52]. The heterozygous postzygotic mutations in the HRAS gene are specifically c.37G > C (p.Gly13Arg) and c.182A > G (p.Gln61Arg) [52]. Since the publishing of this single activating *HRAS* mutation in heterozygosity responsible for PPK, cases have been reported showing *BRAF* [54, 55] and *KRAS* [56] mutations, meaning that perhaps PPK can be caused by several different mutations on different genes. Nevertheless, given that these aforementioned genes play critical roles in the Ras-Raf-MEK-ERK pathways, PPK can now be classified as a mosaic form of a

RASopathy. This is important because mutations in *Ras* signaling play an important role in tumorigenesis with these mutations being found in 30% of human cancers [56]. As such, patients with PPK are at greater risk of developing skin and internal malignancies. Skin malignancies may include basal cell carcinoma arising within nevus sebaceous and melanoma arising within SLN [57]. Internal malignancies usually appear to involve the renal and urologic systems with some recent reports showing embryonal rhabdomyosarcoma of the abdominal wall and vaginal botryoid rhabdomyosarcoma [56, 58, 59]. As such PPK patients should be regularly monitored and screened for cutaneous and visceral malignancies in order to improve clinical outcomes.

Treatment

There are no medical therapies currently available to treat PPK though certain procedural interventions such as carbon dioxide laser can be considered for the cutaneous manifestations. Given the significant extracutaneous features of *PPK*, a multidisciplinary approach involving dermatologists, neurologists, and ophthalmologists should be considered.

*Congenital Hemidysplasia with Ichthyosiform Nevus and Limb Defects (*CHILD*) Syndrome*

Clinical Characteristics

In 1980, *Happle* et al. described a very rare condition known as CHILD syndrome, an acronym standing for congenital hemidysplasia with ichthyosiform nevus and limb defects (OMIM #308050) [60]. The earliest reports of this condition, however, date as early as 1903 [36] with later reports referring to the condition as "congenital unilateral ichthyosiform erythroderma" [61]. As an X-linked dominant disorder, CHILD syndrome is lethal in males, thus seen almost exclusively in females (see Chaps. 4 and 34). Variations in phenotype from one patient to the next are thought to be a consequence of skewed postzygotic X-inactivation known as lyonization. The characteristic signs of CHILD syndrome are present at birth or during the first few weeks of life, which manifest typically as unilateral inflammatory erythematous patches covered in dry, yellowish scales with a sharp midline demarcation in conjunction with ipsilateral skeletal abnormalities. While the ichthyosiform morphology is most common, there are reports of the skin findings of CHILD syndrome being predominantly yellow, waxy plaques, thus having a more verruciform xanthoma-like in appearance [62]. The cutaneous findings often occur in a *Blaschko* linear array, sparing the face and accentuated in the skin folds (i.e., vulva, axilla, and gluteal fold). Though the nevi most commonly present with a striking midline demarcation, bilateral cutaneous involvement has been reported [63]. Interestingly, the cutaneous features of *CHILD* syndrome may undergo spontaneous partial regression during childhood.

The extracutaneous features of *CHILD* syndrome include central nervous system abnormalities, skeletal changes, cardiac anomalies, deafness, and absence/hypoplasia of ipsilateral organs such as the kidneys, liver, and lungs [64]. While the skeletal defects can range from slight hypoplasia of the phalanges to entire absence of a limb, it is important to note these defects are not limited to the limbs as they can also affect the axial skeleton and skull. Additionally, there are reports of *CHILD* syndrome occurring without hemidysplasia or limb defects [65]. *Neurologic* abnormalities include ipsilateral hemispheric hypoplasia with pronounced loss of white matter and electroencephalogram abnormalities. Life-threatening cardiovascular defects are also reported in the literature [60, 64]. Of note, there are reports of *CHILD* syndrome occurring without extracutaneous manifestation [66].

Histopathology

The histopathologic findings of CHILD syndrome include acanthosis and elongation of the rete ridges with marked parakeratosis and loss of the granular layer, which is better characterized as psoriasiform hyperplasia, perivascular and lymphohistiocytic dermal infiltrates, as well as foamy histiocytic cells infiltrating the dermal papilla (see Chap. 4) [64]. This latter finding of foamy and lipid-laden histiocytes in the dermal papillae makes CHILD syndrome unique from a histopathologic perspective as compared to other epidermal nevi and helps to distinguish CHILD syndrome from inflammatory linear verrucous epidermal nevus (ILVEN).

Molecular Genetics and Pathophysiology

CHILD syndrome usually results from heterozygous nonsense or missense mutations (*though large* heterozygous deletions are reported) in the *NAD[P]H steroid dehydrogenase-like protein* (or *NSDHL*) gene (see Chap. 1) [67]. While these mutations may be detected with classical Sanger sequencing, it may not be adequate to detect all mutations of *NSDHL* leading to *CHILD* syndrome; therefore newer methods such as real-time quantitative PCR and next-generation sequencing may be more effective [62]. *NSDHL* encodes a 3-beta-hydroxysteroid dehydrogenase, an enzyme critical in cholesterol biosynthesis [67]. A defect or shortage of this enzyme causes lack of available cholesterol in cell membranes and toxic metabolites to build up in critical tissues, thereby leading to growth disruption and development [68, 69].

Treatment

Better understanding of the cholesterol development pathway led to the development of a novel pathogenesis-based treatment approach with topical combination lovastatin and cholesterol. Lovastatin, an inhibitor *of HMG CoA* reductase (the rate-limiting enzyme of cholesterol synthesis), can prevent accumulation of toxic metabolites, whereas cholesterol could compensate for the defective cholesterol synthesis

pathway, thereby providing sufficient cholesterol necessary for normal stratum corneum formation. When used in combination, cholesterol and *lovastatin* virtually clear skin lesions after 3 months, accompanied by histologic and ultrastructural normalization of epidermal structure and lipid secretion [69].

Overgrowth Syndromes with Epidermal Nevi

Proteus Syndrome

Clinical Characteristics

Proteus syndrome is a rare, asymmetric, often rapidly progressive somatic overgrowth disorder characterized by relentless mosaic overgrowth of tissues derived from all three germ layers. Because of this, bone, fat, skin, and connective tissue are typically involved (see Chap. 22). It was first described by Cohen and Hayden in 1979 and subsequently named after *Proteus*, a Greek god whose name means "the Polymorphous," in 1983 [70, 71]. Most individuals have few or no findings at birth with most clinical features first appearing between 6 and 18 months of age. *Proteus syndrome* is extremely rare with actual prevalence unknown though suspected to affect approximately 1:1,000,000–1:10,000,000 persons [72]. The diagnosis is based on a set of clinical features and confirmed by molecular genetic testing confirming presence of a somatic, heterozygous pathogenic variant in the *AKT1* gene. The clinical phenotype criteria for diagnosis comprise two components: *general* (of which all three must be met) and *specific* (of which a well-delineated subset must be met). The general criteria include mosaic distribution of lesions, progressive course, and sporadic occurrence. The *specific criteria* include cerebriform connective tissue nevus (*CCTN*) (*Category A*) or two of the following: linear epidermal nevus; asymmetric, disproportionate overgrowth; and ovarian or parotid tumors (*Category B*), or three of the following—lipomas or fat hypo-/aplasia, vascular malformations, bullous pulmonary degeneration, and characteristic facies (*Category C*) [73]. Recently, a newly published integrated dual phenotype-genotype scoring system, which detects the aforementioned clinical features as well as identification of the *AKT1* mutation, has been proposed to more accurately diagnose *Proteus* syndrome [74]. While findings may be minimal at birth, a recent report suggests the possibility of prenatal testing via exome sequencing of cultured amniocytes [75].

While the presentation of *Proteus* syndrome may be variable, one of the key hallmark dermatologic findings includes the near *pathognomonic* cerebriform connective tissue nevus, usually found on the palms, soles, nasal ala, or ear, and has a distinct pattern resembling a brain with a firm texture. The CCTN is usually absent at birth but appears more readily as the child ages. The other key common dermatologic finding is a linear verrucous epidermal nevus. *These nevi* are usually subtle at birth but increase in size and darken over the first year of life. As *diagnosis* of the disease improves, several other newer features have been identified such as

abnormalities in hair length, thickness, and distribution, ranging from mosaic hypertrichosis to irregularities in scalp density and color [76].

As mentioned previously, extracutaneous manifestations are variable though the most striking feature is the severe and rapidly progressive overgrowth which may manifest as hemihypertrophy, asymmetric macrodactyly, skull and other anomalies, and tonsillar and adenoid enlargement. Lipomas and lipoatrophy and vascular malformations (*usually venous*) are also common. Tumors developing in Proteus syndrome are often benign and can include meningiomas, ovarian cystadenomas, and parotid monomorphic adenomas [72]. *Thromboembolic* events such as pulmonary emboli and deep vein thrombosis, particularly in the perioperative period, represent the most common life-threatening complication of Proteus syndrome [77].

Molecular Genetics and Pathophysiology

Proteus syndrome is caused by a somatic, activating, mosaic mutation of the *AKT1* gene (c.49G > A, p.(Glu17Lys)). The *AKT1* protein is a serine-threonine kinase that is a key regulator of the AKT/PI3K/mTOR cell signaling pathway (see Chap. 1). When this protein is constitutively active, this leads to unchecked growth and limited apoptosis, resulting in the overgrowth symptoms of Proteus syndrome. Similar to other overgrowth disorders, the mutation is mosaic, meaning detection in a patient requires sampling affected tissues via skin biopsy or surgical excision rather than peripheral blood [78].

Treatment

Management of Proteus syndrome is complex and requires a *multidisciplinary* approach including specialists such as dermatologists, pediatric surgeons, orthopedists, and radiologists. Dermatologists can play an important role in helping prevent infections and treating malodor which can arise within the cerebriform connective tissue nevi. Pediatric *surgeons* and *orthopedists* can assist with surgical correction of skeletal deformities, debulking of tissues, and managing bullous pulmonary disease. Management of extensive venous malformations may require assistance of interventional radiologists. Due to high risk of thromboembolism, some authors suggest the need for clinical surveillance of thrombosis in patients with Proteus syndrome though the establishment of a registry to collect data on these events will be necessary to fine-tune these recommendations [79]. Despite interdisciplinary management, morbidity and mortality of *Proteus* syndrome is high—in one cohort study of 64 patients, nearly a quarter of patients died before reaching their mid-20s. As such, there is great need for improved clinical studies and therapeutic trials for these patients [80].

While there is currently no cure, recent studies show promising early results for treatment of Proteus syndrome. In 2015, *Lindhurst* et al. demonstrated for the first time efficacy of *ARQ 092*, an allosteric pan-AKT inhibitor originally developed for

treatment of cancer, in suppressing AKT signaling in in vitro models derived from tissues Proteus syndrome patients [81]. In 2019, *Keppler-Noreuil* et al. performed a non-randomized, phase 0/1 pilot study of six patients with *Proteus* syndrome which demonstrated an acceptable safety profile and encouraging preliminary data for efficacy of miransertib (ARQ 092) [82]. Long-term clinical trials are required at this time to better assess clinical benefits and the full safety profile of this medication.

CLOVES Syndrome

Clinical Characteristics

CLOVES syndrome, an acronym which stands for *c*ongenital *l*ipomatous asymmetric *o*vergrowth with lymphatic, capillary, venous, or combined-type *v*ascular malformation, *epidermal* nevi, and *s*keletal anomalies/scoliosis, is a rare overgrowth syndrome first defined by *Sapp* et al. [83]. Though originally thought to be a form of Proteus syndrome, it is now better classified as an entity within the *PIK3CA*-related overgrowth spectrum (*PROS*). While most deformities may be present prenatally and therefore detected at birth, for some patients, overgrowth may not be fully appreciated until early childhood. CLOVES syndrome appears to affect males and females equally, irrespective of ethnicity, and to have an incidence of less than 1 in 1,000,000 [84]. The diagnosis is made based on clinical features though can be confirmed by genetic studies of affected tissue to identify a *PIK3CA* mutation.

One of the key hallmark signs of *CLOVES* syndrome is thoracic lipomatous hyperplasia, usually involving the back or trunk and found in conjunction with an overlying capillary malformation though other forms of irregular, sporadic deposition of fibroadipose tissue elsewhere on the body may also be seen [85]. Unlike Proteus syndrome, this growth pattern is described as "ballooning" (as opposed to destructive) and generally does not appear distorted. All patients present with capillary, venous, or lymphatics malformations. Capillary malformations may present as port-wine stains on lateral surface of the trunk or extremities, whereas lymphatic malformations can be microcystic, macrocystic, or combined and typically found adjacent to a lipomatous mass in the thoracic or abdominal cavities [86]. Most vascular malformations are venous (*low-flow*) though arteriovenous (*high-flow*) malformations have been reported. Patients often have linear epidermal nevi, which is a differentiating feature from *Proteus* syndrome, where patients present with connective tissue nevi. Musculoskeletal findings may include overgrowth of hands and feet, macrodactyly, "sandal toe gap" (increased interphalangeal space between first and second toes), or cubital deviation of the hand [87]. Finally, scoliosis or spinal anomalies may be present, resulting in neurologic findings of radicular pain, sensory dysfunction, loss of strength in extremities, gait issues, and sexual dysfunction. Recently, studies have identified other clinical findings such as pancreatic abnormalities (pancreatic steatosis/lipomatosis) and an increased incidence of Wilms tumor, suggesting CLOVES syndrome may manifest in a broader fashion than

originally thought [88]. Better understanding of these findings may implicate certain screening tests in the management of these patients.

Molecular Genetics and Pathophysiology

CLOVES syndrome is caused by a somatic, mosaic, gain-of-function mutation of the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) gene mapped to chromosome 3q26.32 [85]. The *PIK3CA* gene is an upstream regulator of the AKT-mTOR cell signaling pathway; when constitutively active this leads to uncontrolled signaling cascades resulting in unchecked cell proliferation, growth, and survival, manifesting clinically as overgrowth symptoms of *CLOVES* syndrome. Given that this mutation is mosaic, detection in a patient requires sampling affected tissues via skin biopsy or surgical excision; genetic analysis of peripheral blood will not yield useful results. Lack of detection of a *PIK3CA* mutation will classify the disease as probable but does not exclude the diagnosis if clinic features are present (see Chap. 1) [89].

Treatment

Management of *CLOVES* syndrome is complex and requires a multidisciplinary approach which includes specialists such as dermatologists, pediatric surgeons, orthopedists, neurologists, and radiologists. *Generally*, there is no cure and most interventions are aimed at improving quality of life. While capillary malformations may be electively treated with pulsed-dye laser, venous, arteriovenous, and lymphatic malformations are recommended via sclerotherapy or embolism methods for definitive treatment to prevent complications such as visceral disorders, pain, breathing difficulties, intestinal bleeding, or obstruction [90]. Disabling lipomatous overgrowth or macrocystic lymphatic malformations may be treated with surgical debulking though recurrence is likely [87]. Limb discrepancies or digital anomalies may require amputation or debulking techniques.

While procedural interventions may be necessary to improve *quality of life*, some of these procedures are associated with high morbidity and postoperative recurrence. In recent years, fortunately, there have been advances in developing target therapies to treat the underlying etiology of this growth syndrome. Recent studies of PROS and complex vascular anomalies patients treated with the mTOR inhibitor sirolimus have shown some therapeutic response and an acceptable side effect profile [91, 92]. In one study evaluating 150 patients with complex vascular anomalies, there was an 85% overall efficacy reported though only 5 patients (3.33%) achieved complete remission [93]. Most promising may be BYL719, or alpelisib, a selective inhibitor of *PIK3CA*, which resulted in improved disease symptoms (intractable vascular tumors became smaller, congestive heart failure improved, hemihypertrophy reduced, and scoliosis attenuated) in all 19 patients with PROS [94]. These early promising results have led to further investigation of *BYL719* with clinical

trials currently enrolling pediatric and adult with PROS, including CLOVES syndrome, in order to better understand its safety profile and therapeutic effect.

SOLAMEN Syndrome

Clinical Characteristics

SOLAMEN syndrome is an acronym that derives its name from the *combined* features of *s*egmental *o*vergrowth, *lipomatosis*, *a*rteriovenous malformation, and *epidermal* nevus. It is also referred to as type 2 segmental Cowden disease, and its associated epidermal nevus has been called "PTEN nevus," which not only reflects its genetic foundation but also serves as a clinical descriptor: the nevus is *p*apillomatous, *t*hick, *e*pidermal, and nonorganoid [95].

The phenotypic findings in *SOLAMEN* syndrome include limb hemihypertrophy, cutis marmorata-like lesions, macrocephaly, vascular malformations, varicosities, lipomas, angiolipomas, ballooning of the toes and feet, and fibrotic papules. Extracutaneous manifestations include hydrocephalus, seizures, thyroid adenomas, ovarian cystadenomas, and fibrocystic breast disease.

SOLAMEN syndrome shares some clinical overlap with Proteus syndrome, and further work is needed to establish diagnostic criteria that can differentiate between the two. In fact, existing reports of *Proteus* and *Proteus*-like lesions in the medical literature may, upon further review, be better characterized as *SOLAMEN* syndrome [36]. A few distinguishing features have so far been outlined. The epidermal nevus associated with *SOLAMEN* syndrome may be thicker and more papillomatous compared to Proteus syndrome. In addition, the cerebriform hyperplasia of plantar connective tissue nevi seen in Proteus syndrome may be absent in *SOLAMEN* syndrome. Lastly, the *cutis marmorata*-like lesions that have been reported in *SOLAMEN* may be absent in Proteus syndrome [96].

Histopathology

The unique histopathological features of this epidermal nevus have not yet been elucidated.

Molecular Genetics and Pathophysiology

SOLAMEN is thought to arise from loss of heterozygosity in an embryo with a germline *PTEN* mutation. The segmental pattern of the disease may be due to mosaic *PTEN* nullizygosity. Interestingly, it has been postulated that biallelic inactivation of *PTEN* has different consequences depending on the cell type affected. Caux et al. found allelic loss in the dermis, adipose, and vascular tissue, but not

from the epidermis of biopsies from lesional skin. It may be that epithelial cells are more prone to develop malignant transformation when subject to genetic instability, as compared to cells of mesenchymal origin. This may explain why the malignant complications of Cowden disease (which is also due to PTEN inactivation) are mainly of epithelial origin [97].

Epidermal Nevus Syndromes Without Central Nervous System Involvement

Becker's Nevus

Clinical Characteristics

Becker's nevus typically presents as a single, well-marginated, unilateral, hyperpigmented patch with overlying hypertrichosis on the trunk or upper extremities (Fig. 10.5). However, the presence of multiple, bilateral, and extensive lesions can occur. One of the hallmarks of this epidermal nevus is the *pseudo-Darier sign*: stroking or rubbing the lesion induces transient and robust piloerection, resulting in an indurated appearance. This phenomenon is due to increased erector pili smooth muscle fibers within the nevus. *Becker*'s nevi were classically thought to arise in late childhood or adolescence. However, in one series, 26% were noted at birth [98]. Since these lesions exhibit increased expression of androgen receptors [99], they are more conspicuous in the pubertal period and are perhaps underdiagnosed at earlier stages. With androgenic stimulation, *Becker*'s nevi may develop coarse hairs as well as an acneiform eruption. Some patients have developed neurofibromas within Becker's nevus lesions [100], and there are reports of patients with Becker's nevi

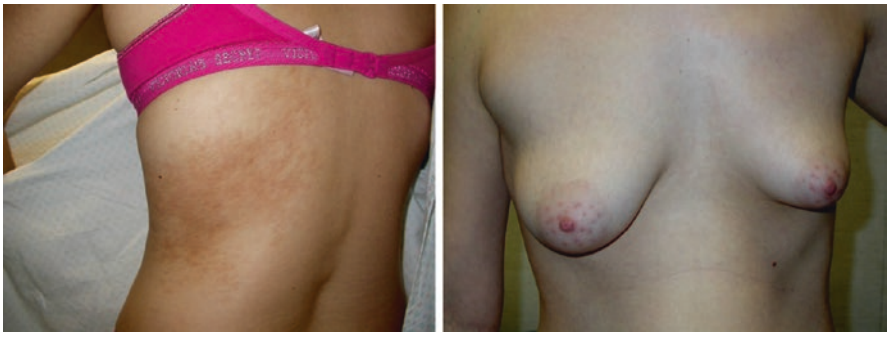

Fig. 10.5 Becker's nevus—typically presents as a single, well-marginated, unilateral, hyperpigmented patch with overlying hypertrichosis on the trunk or upper extremities though it should be noted that in female patients, hypertrichosis may be absent (*left*). Becker's nevus syndrome may present with ipsilateral breast hypoplasia (*right*)

who also meet clinical criteria for neurofibromatosis type 1 [101, 102]. One case report showed basal cell carcinoma arising within a *Becker*'s nevus at a photoprotected site in a young patient [103].

Males and *females* are likely equally affected [104]. Previous reports of male predominance are likely skewed; since female patients are less likely to exhibit hypertrichosis, *Becker*'s nevi tend to be underdiagnosed in this cohort. *Becker*'s nevi also share overlapping clinical features with smooth muscle hamartomas, and some posit that these conditions exist on the same continuum [105]. In a case report of a hypertrichotic congenital smooth muscle hamartoma without associated pigmentary changes, the authors suggested classification as a so-called amelanotic Becker nevus [106].

When associated with concomitant cutaneous, soft tissue, and skeletal defects, the term Becker's nevus syndrome is used to describe the constellation of findings. The most common associations, in order of documented frequency in the medical literature, are ipsilateral breast hypoplasia (Fig. 10.6), scoliosis, limb asymmetry, and supernumerary nipple [107]. In one case, a patient with a facial Becker's nevus also had alveolar bone hypertrophy in the anterior mandible [108]. Another report outlined fused carpal bones in a patient with an acral *Becker*'s nevus [109].

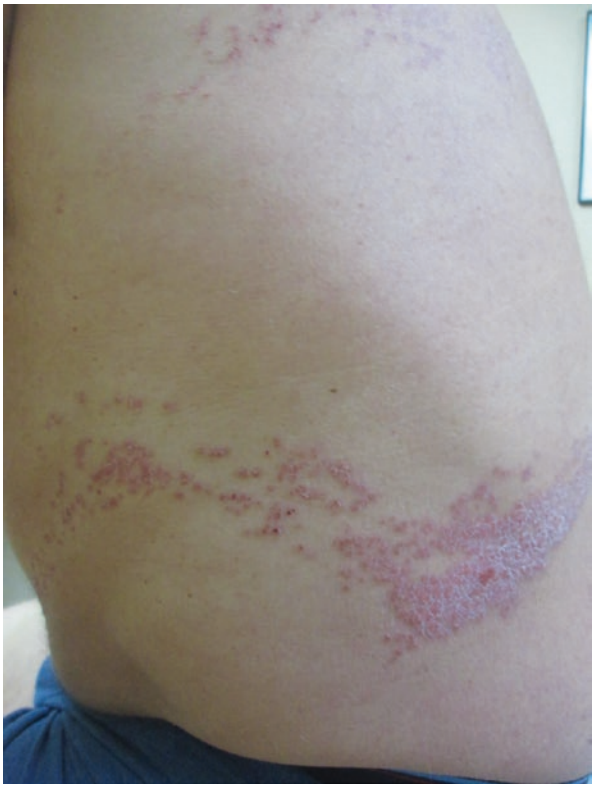

Fig. 10.6 Inflammatory linear verrucous epidermal nevus (ILVEN)—presents as a Blaschko linear, erythematous, hyperkeratotic plaques unilaterally on the lower extremities or trunk in younger children

Interestingly, there is also a case of *Becker*'s nevus syndrome and phakomatosis pigmentovascularis type II [110].

Histopathology

The histological features of *Becker*'s nevi include epidermal acanthosis with basal pigmentation, ectopic smooth muscle bundles, and increased terminal hair follicles [111]. Although pigmentation can be noted clinically, the number of melanocytes is unchanged.

Molecular Genetics and Pathophysiology

The pioneering work of *Cai* et al. [111] demonstrated that postzygotic mutations in beta-actin are associated with Becker's nevus and *Becker*'s nevus syndrome. *Exome sequence* analysis identified ACTB point mutations (*ACTB* p.*R147C* and p.*R147S*) in mesenchymal cells that appear to drive the development of *Becker's* nevi and *Becker*'s nevus syndrome. The authors further hypothesize that these mutations potentiate Hedgehog signaling, disrupting hair follicle and pilar muscle development. They postulate that *Becker*'s nevus syndrome, as compared to isolated (non-syndromic) *Becker*'s nevus, may reflect a mutation earlier in development, affecting multiple cell lineages [111].

Interestingly, the identified ACTB mutations are lethal for the developing embryo. Thus, *Becker*'s nevus syndrome is one of the growing list of sporadic cutaneous phenotypes caused by lethal autosomal mutations surviving as mosaics [104]. Other examples include Proteus syndrome from AKT mutations and CLOVES from PIK3CA mutations, which are discussed elsewhere in this chapter. Given current understanding of the genetic etiology, the reports of familial aggregation of Becker's nevi and Becker's nevus syndrome are somewhat puzzling, and some theorize whether these familial cohorts are simply coincidental [112].

Treatment

Various treatment options have been reported in the literature. Topical therapies (such as *glycolic acid*) have been used to decrease pigmentation, but results remain inconclusive [113]. Intense pulsed light [114] and laser therapy has been widely reported, including Er:YAG [115], long-pulsed 1064-nm Nd:YAG, and 755-nm alexandrite lasers [116]. Overall, laser treatment has yielded inconsistent results. In one study, Q-switched laser-resistant melanocytes accounted for repigmentation after treatment [117]. Breast hypoplasia associated with Becker's nevus syndrome has been treated with spironolactone [118] as well as lipofilling [119].

Inflammatory Linear Verrucous Epidermal Nevus (ILVEN)

Clinical Characteristics

Inflammatory linear verrucous epidermal nevus (*ILVEN*) is a relatively uncommon subtype of epidermal nevus, accounting for approximately 6% of cases in one review [23]. *Characteristic* phenotypic features include a linear, Blaschko linear, or whorled array of pruritic, erythematous, hyperkeratotic, warty papules and plaques (Fig. 10.7). Lesions are usually unilateral and present at birth or within the first 6 months to 1 year of life, although rare adult-onset cases have been described. ILVEN usually affects the lower half of the body; the legs, pelvis, and buttocks are common sites [120]. However, any body part may be affected.

ILVEN has overlapping clinical features with linear psoriasis. Onset near birth, intense pruritus, and resistance to typical psoriasis treatments are helpful distinguishing features that favor *ILVEN*. A skin biopsy is often performed to help establish the diagnosis. Interestingly, *ILVEN* and psoriasis may occur concomitantly in the same patient; some suggest that *ILVEN* may be associated with an underlying psoriatic diathesis [121]. One report has described dermoscopy as a useful clinical adjunct when differentiating ILVEN and one of its clinical mimickers, lichen striatus [122].

Unlike some other forms of epidermal nevi, *ILVEN* is rarely associated with extracutaneous manifestations. There are early reports of ipsilateral skeletal anomalies [123]; however, subsequent studies have doubted these associations. It is possible that the patients in the initial studies were misdiagnosed cases of CHILD syndrome rather than *ILVEN* [120]. *ILVEN* has also been associated with arthritis. In one case, a patient developed erosive arthritis in the distal interphalangeal joint of a finger with an overlying *ILVEN* lesion [124]. One report suggested an association between *ILVEN* and *odontodysplasia* [125]; however, the diagnosis of *ILVEN* was made based on weak clinical criteria, and it is possible the patient had a keratinocytic epidermal nevus instead.

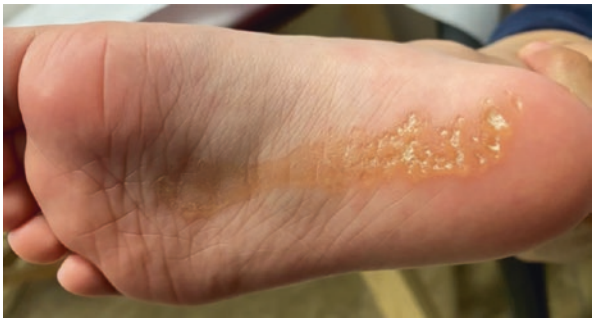

Fig. 10.7 Porokeratotic eccrine ostia and dermal duct nevus (PEODDN)—this eccrine hamartoma presents as an asymptomatic, linear, keratotic plaques, usually on the plantar surface with comedo-like openings

Histopathology

ILVEN shows a histological pattern of orthohyperkeratosis alternating with parakeratosis [126]. Differentiation from psoriasis based on the microscopic findings alone can be challenging. There are conflicting reports on the utility of distinguishing *ILVEN* from psoriasis by immunostaining for involucrin, filaggrin, Ki-67, K16, IL-17, IL-36, and other markers [127, 128].

Molecular Genetics and Pathophysiology

A recent study outlined a case of *ILVEN* in which there was a somatic mutation in *GJA1*, a gene which encodes a gap junction protein (*connexin*). The authors suggested that, in this patient, *ILVEN* may have arisen as a form of mosaicism of erythrokeratodermia variabilis et progressiva, which is known to arise from mutations in GJA1 and other related epidermal connexins [129]. Further work is needed to more comprehensively describe the genetic abnormalities that underlie the development of *ILVEN*.

Treatment

Therapeutic management of *ILVEN* is notoriously frustrating and is an open area of research. *Various* agents and techniques have been reported, including topical corticosteroids, crisaborole [130], intralesional steroids, calcipotriene, podophyllin, 5-fluorouracil, topical and oral retinoids [131], cryotherapy, photodynamic therapy, *CO2* laser ablation [132], 308 nm excimer laser [133], and surgical excision. TNF-α blockers [134] and thalidomide [135] have also been used in refractory cases. No single treatment appears most effective. In most cases of successful treatment reported in the literature, ILVEN lesions were finally responsive after multiple failed treatments with other modalities.

Porokeratotic Eccrine Ostia and Dermal Duct Nevus

Clinical Characteristics

Porokeratotic eccrine ostial and dermal duct nevus (*PEODDN*) is a rare epidermal nevus classically characterized by verrucous hyperkeratotic pink to hyperpigmented clustered papules and plaques, in a linear or Blaschko linear array. It usually affects the trunk and distal extremities, with classic involvement of the palms and soles (Fig. 10.7). PEODDN typically presents at birth or in early life, although there are several emerging reports of onset in adulthood [136]. Growing evidence suggests

that this entity has diverse phenotypic presentations, and cases of bilateral systematized forms have been reported [137].

PEODDN has an interesting history with regard to its nomenclature [12]. *Porokeratotic* eccrine nevus (PEN) was first described as *comedo nevus* of the palm [138] and later called porokeratotic eccrine ostial and dermal duct nevus (*PEODDN*) [139]. More recently, the term "porokeratotic adnexal ostial nevus" (*PAON*) was suggested, to incorporate both PEODDN and porokeratotic eccrine and hair follicle nevus (*PEHFN*), which shares clinical and histopathologic features [140].

There are reports of associated squamous cell carcinoma [140], proliferating pilar tumors [141], and ipsilateral calcinosis cutis [142] with PEODDN lesions. As such, careful clinical monitoring is recommended once the diagnosis is made.

Histopathology

PEODDN is characterized by dilated eccrine *acrosyringia* and a dilated *acrotrichia* with an overlying cornoid lamella [143]. Available histologic data suggest that this entity represents abnormally keratinizing epidermal invagination involving the acrosyringia rather than a hamartoma of the acrosyringia and dermal duct [144].

Molecular Genetics and Pathophysiology

Genetic studies have shown that somatic GJB2 mutation is sufficient to cause *PEODDN*. This gene encodes for a gap junction protein, connexin 26. Patients with somatic mosaicism are at risk of having a child with keratitis ichthyosis deafness syndrome, which arises from germline defects within the same gene [145]. PEODDN is also associated with other conditions that arise from mutations in connexin 26, including palmoplantar keratoderma with deafness, Bart-Pumphrey syndrome, and Vohwinkel syndrome.

Treatment

In rare cases, significant spontaneous regression without active intervention has been reported [146]. Various therapeutic options have been reported in the literature, but results have been mixed. A recent review of treatment options found that *PEODDN* responded to treatment with *tazarotene gel* and *topical photodynamic* therapy, but laser treatment seemed to be a more efficient option. Topical steroids and topical *tretinoin* appeared mostly ineffective [147].

Nevoid Acanthosis Nigricans or RAVEN (Rounded and Velvety Epidermal Nevus)

Clinical Characteristics

Nevoid acanthosis nigricans (*NAN*) and *RAVEN* (rounded and velvety epidermal nevus) represent two forms of extremely rare, benign acquired hamartomas that share features with epidermal nevi and acanthosis nigricans. NAN was first described by Curth in 1976, and since then less than 30 cases have been published in the literature [148]. These lesions can appear at any age, ranging from as early as birth to as late as adulthood. There is a slight male predilection.

Morphologically, both conditions present similarly to true acanthosis nigricans with hyperpigmented, velvety textured plaques. However, unlike classic acanthosis nigricans, *NAN* and *RAVEN* typically do not favor the intertriginous sites—rather, the most common locations are the trunk, extremities, head, umbilicus, and occasionally intertriginous areas such as the axilla or submammary skin [149]. NAN will typically take on a linear morphology along the lines of Blaschko, whereas *RAVEN*, as its name suggests, presents as rounded, polycyclic plaques.

Unlike acanthosis nigricans, *NAN* and *RAVEN* are not associated with any underlying endocrinopathy, obesity, internal malignancy, or specific medication use [150]. As such, the identification of these conditions should not prompt a systemic workup of a patient.

Histopathology

Histologic assessment of *NAN* and *RAVEN* will be similar to true acanthosis nigricans. Skin biopsy will show acanthosis with papillomatosis, hyperorthokeratosis, hyperpigmentation of the basal layer, and elongation of the rete ridges [151].

Molecular Genetics and Pathophysiology

Based on clinical features, *NAN* and *RAVEN* were long postulated to occur as the result of a postzygotic mosaicism, similar to other epidermal nevi. More recently, specific mutations in *FGFR2* (c.755C > G) and *FGFR3* (c.755C > G, c1921G > A), both genes that encode tyrosine kinases, have been identified in several patients as the precise molecular genetic underpinnings responsible for the peculiar pathogenesis of these conditions [151]. The mutation in *FGFR2* is thought to alter ligand affinity and specificity of the receptor allowing abnormal autocrine and paracrine activation [151]. Of note, somatic activation mutations in *FGFR2* may be associated with mosaic forms of acne, whereas those in *FGFR3* are associated with epidermal nevi and seborrheic keratoses [151].

Treatment

The expected course for *NAN* and *RAVEN* is unpredictable with some patients experiencing progression, while others regression, of their lesions. Treatment is not necessary though if distressing to the patient, CO2 laser and calcipotriene have been reported to be efficacious [149, 151].

Endocrine Manifestations of Epidermal Nevus Syndromes

Clinical Features

There have been rare reports of endocrine abnormalities associated with ENS. *Yu* et al. [152] reported a case of ENS associated with the syndrome of inappropriate antidiuretic hormone (*SIADH*). Their case involved an infant with seizures, hyponatremia, and SIADH. There have been several reported cases of central precocious puberty associated with ENS [153].

Sugarman and Reed [154] were the first to report the association of nevus sebaceous with *hypophosphatemic* rickets. Since then, there have been multiple reports of hypophosphatemic vitamin D-resistant rickets associated with NS syndrome [155]. CNS abnormalities were present in 36% of these 14 cases, and 12 out of 14 (86%) of these children had mental retardation. Rickets, muscle weakness, and bone pain developed at an early age in many of the patients. There has also been a case of phacomatosis pigmentokeratotica associated with hypophosphatemic vitamin D-resistant rickets [156].

Molecular Genetics and Pathophysiology

The *hypophosphatemic* vitamin D-resistant rickets that is associated with NS is thought to result from abnormal phosphate excretion secondary to defective renal tubular reabsorption of phosphate. These metabolic derangements are not rectified by *calcium*, *phosphate*, or *vitamin D* administration. This condition is analogous to the rare association of vitamin D-resistant hypophosphatemia and associated osteomalacia associated with mesenchyme-derived neoplasms (tumor-induced osteomalacia), in which the tumor produces a phosphaturic factor that leads to osteomalacia. The phosphaturic factor responsible for tumor-induced osteomalacia has been identified. These tumors secrete large amounts of FGF23 [157]. Similarly, patients with autosomal dominant hypophosphatemic rickets have increased levels of circulating *FGF23* due to the production of a mutant *FGF23* that makes it resistant to cleavage and degradation.

Treatment

There have been reports of at least partial reversal of the *hypophosphatemia* with removal of a portion of an EN [156, 158, 159]. Based on these findings, they speculated that EN produce a phosphaturic factor that leads to osteomalacia, suggesting that the hypophosphatemic rickets seen associated with NS is related to overproduction of *FGF23*. More recent immunohistochemical studies have revealed increased FGF23 production in the bone (where it is normally produced in response to low serum phosphate) but not in the NS, suggesting that ablation or removal of the *NS* would not be curative of the metabolic derangements seen in these cases. Activating *NRAS* and *KRAS* mutations in bone and in the nevus have been identified in cases of NS associated with hypophosphatemic rickets providing the first evidence that elevated *FGF23* levels, hypophosphatemia, and osteomalacia are associated with pathologic Ras activation and may lead to future insights into *FGF23* regulation by Ras [160]. This same report also included a case of giant melanocytic nevus associated with hypophosphatemic rickets which was also associated with *RAS* mutation. All five patients in this cohort had multiple extracutaneous findings including foci of dysplastic bone, brainstem lipoma, thyroid nodules, and eye and cardiac abnormalities. The term cutaneous-skeletal hypophosphatemia syndrome (*CSHS*) has been designated for this condition given the broad multisystem systemic findings with a shared origin from an early somatic mutation [160].

A *monoclonal antibody* against *FGF23* (*burosumab*) has been developed and recently approved for the management of X-linked hypophosphatemia which is also characterized by excess *FGF23* production. Administration of burosumab to a 13-year-old girl with CSHS dramatically improved serum phosphate levels, eliminated near constant bone pain, and led to a 10 cm increase in her height after 1 year (*personal communication* JLS). It is *likely* that biologic treatments such as burosumab will become increasingly used as targeted therapies for mosaic skin disease as more specific genetic abnormalities are characterized.

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Chapter 11
Neurocutaneous Melanosis

Christos P. Panteliadis

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Introduction

Von Rokitansky is accredited in reporting the first description of the disease in 1861 [1]. He described a 14-year-old girl with extensive cutaneous naevi and infiltration of the leptomeninges by pigmented cells. Since its first description, more than 100 cases of neurocutaneous melanosis have been reported in the literature. About 60–80% of all cases with NCM develop features, which usually appear before 5 years of age. Neurocutaneous melanosis (*NCM*) is a rare congenital, non-familial sporadic syndrome. It is characterized by the development of congenital melanocytic naevi and benign or malignant melanocytic in the letomininges of the central

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nervous system (*CNS*). Due to the CNS lesions, there is a high rate of mortality early in life [2–5]. Congenital melanocytic naevi are seen in approximately 1/20,000–50,000 live births.

Pathophysiology

During embryologic development, melanocytes are derived from the neuroectoderm. These neural crest cells normally migrate to their final position in the basal layer of the epidermis, appearing in embryonic skin by day 50 of development. In *addition* to their presence in the skin, melanocytes are normally found in hair follicles, leptomeninges, and the uvea of the eye.

Although the *pathogenesis* of neurocutaneous melanosis is not fully understood, it is thought that congenital melanocytic naevus and neurocutaneous melanosis represent a spectrum of diseases resulting from an error in embryologic development. After neural crest cell migration, proper differentiation of these cells into mature melanocytes has been proposed to be heavily influenced by the local microenvironment and key cell signalling pathways. Studies in animal models have demonstrated an association between deregulation of growth factor signalling during a critical period in embryogenesis [6, 7].

Two-thirds of patients with NCM have a giant congenital melanocytic naevus, and the remaining third have multiple small lesions that are usually present at birth but may also develop later in life [4]. Additional studies may help to fully elucidate the mechanism of the development of giant congenital melanocytic naevus, its relation to the subset of patients who are affected by neurocutaneous melanosis, and the impact that growth factor deregulation has on the propensity of these melanocytes to undergo malignant transformation [8].

Fox et al. [9] defined physiologic melanotic cells histologically as those surrounding blood vessels, but not extending into *Virchow-Robin* spaces. Conversely, in leptomeningeal involvement of neurocutaneous melanosis, melanotic cells typically infiltrate both the perivascular and Virchow-Robin spaces (Fig. 11.1). Although at times difficult, the diagnosis of malignant melanosis relies on the presence of invasive disease within the vascular basal lamina. The melanotic cells can be pleomorphic and present in various histologic forms. Asymptomatic patients with giant congenital melanocytic naevi have an incidence of neurocutaneous melanosis between 23 and 30%, and up to 25% have a positive family history of a congenital melanocytic naevus in a second-degree relative [3].

The melanophores in the arachnoidea show no increased proliferative activity or atypia as they do in leptomeningeal melanocytoma or malignant melanoma. Accurate determination of malignant status usually is not clinically imperative because the prognosis of neurocutaneous melanosis with neurologic symptoms is grave. *Kadonaga* and *Frieden* [10] reported that the predominant histological finding in neurocutaneous melanosis consists of an excess of nodular or diffuse melanocytes in the leptomeninges.

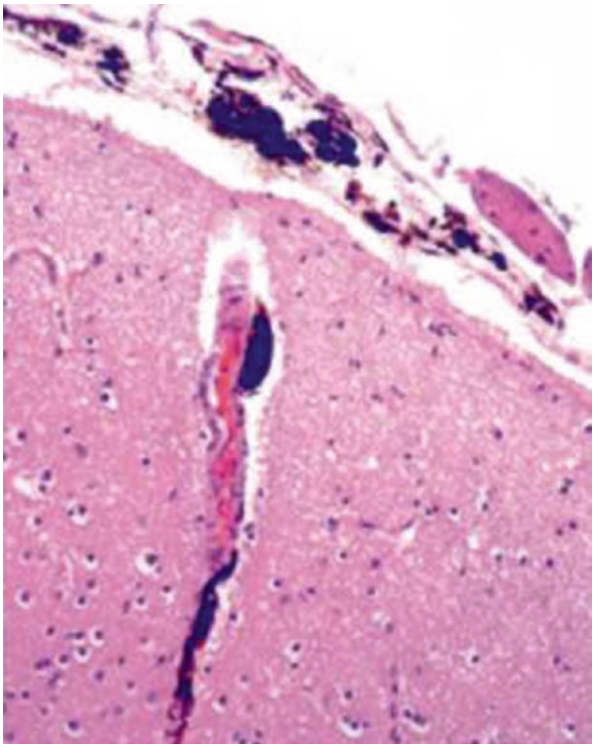

Fig. 11.1 Histological examination demonstrating melanophores packed with brown granules of varying diameter within the leptomeninges and along the Virchow-Robin spaces of penetrating small cortical vessels

Clinical Characteristics

Clinically, the disease is characterized by large or multiple congenital melanocytic naevi that frequently have a *"bathing suit"* distribution [11]. The raised brown-black plaques possess small nodules and increased hair growth [12, 13] (Figs. 11.2, 11.3, and 11.4). In most infants, the main portion of the giant pigmented naevus overlies the lumbosacral or posterior axial area.

De David et al. [14] reviewed a series of 289 patients (45% male, 50% female, 5% sex unknown) and concluded that patients with large congenital melanocytic naevi in the posterior axial location, especially when associated with *"satellite"* melanocytic naevi, appear to be at a higher risk of developing symptomatic NCM than patients with melanocytic naevus in the extremities or without associated satellite naevi. *CNS* involvement was identified in 33/289 patients with NCM, and melanomas occurred in 21 of the 33 patients. Ten patients died before the age of 5 years. The median age of death was 3 years (range 1 month to 50 years; average, 12.3 years). In some cases, the melanocytic naevi are found in the arachnoid mater in the posterior cranial fossa and the spinal cord [15]. Once apparent, the symptoms are progressive and usually rapidly fatal, often with development of ataxia and loss of bowel and bladder control [16]. Death occurs within 3 years of the initial symptoms

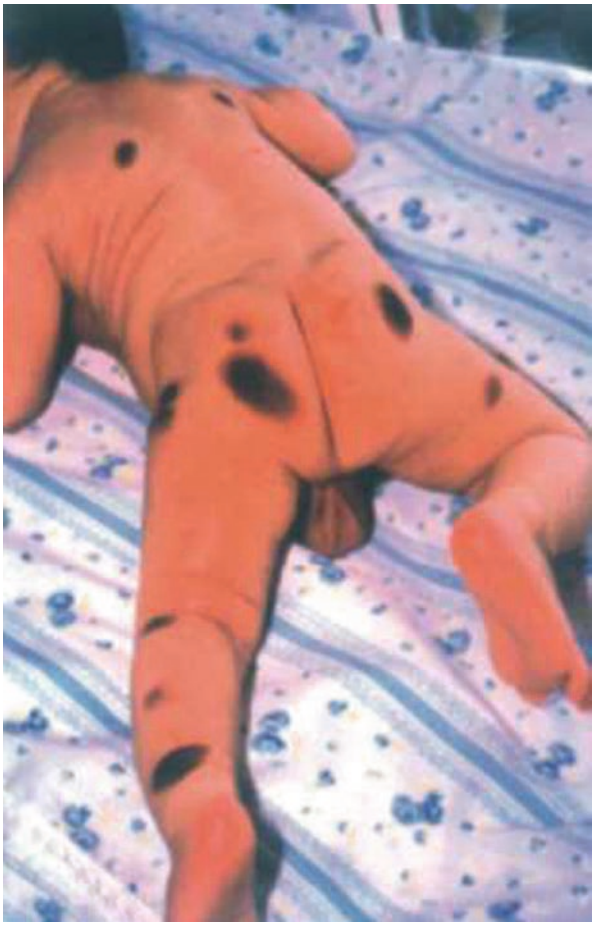

Fig. 11.2 Several large melanocytic naevi in a 6-month-old child

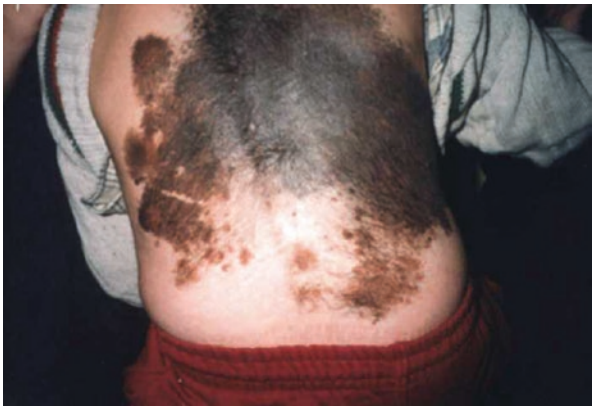

Fig. 11.3 Diverse melanocytic naevi in an 8-year-old child

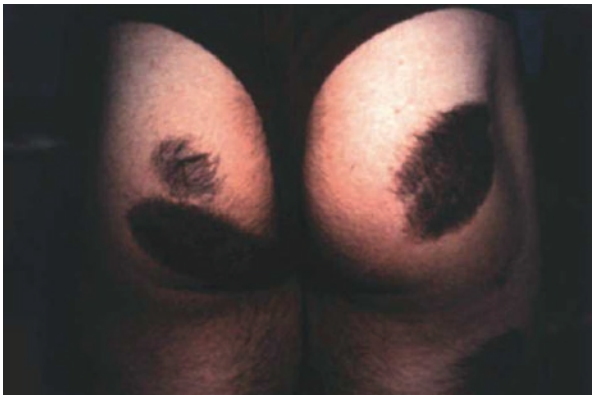

Fig. 11.4 Typical melanocytic naevi in a 14-year-old boy in the gluteal region

in more than half of the patients. Three features of naevi are associated with an increased risk of neurocutaneous melanosis: (1) the location of the naevi in the posterior axis, (2) a greater number of satellite lesions, and (3) large naevus size [3].

Neurologic Involvement

The most common neurological complications are hydrocephalus, seizures, cranial nerve dysfunction, and signs of spinal cord and root involvement. Leptomeningeal melanosis is the commonest cause of neurological symptoms, especially in children with NCM. Infiltration of the brainstem, the cerebral aqueducts of the foramina *Luschka* (*lateral aperture*) and *Magendie* (*median aperture*), typically causes hydrocephalus [4, 10, 13, 17, 18]. Most neurologic manifestations of increased intracranial pressure, mass lesion, and spinal cord compression appear in the first 2 years of life, with a second smaller peak in the second and third decades [19–21]. A prenatal diagnosis of malformations, such as macrocephaly, hydrocephalus, enlargement of the fourth ventricle and posterior fossa, cortical dysplasia, cerebellar hypoplasia, etc., is possible by sonography in the second trimester of pregnancy between gestational weeks 16–20.

Other findings are intractable seizures (most common), psychomotor retardation, cranial nerve paralysis, and myelopathy. Myelopathy in children is due to spinal cord invasion with proliferating malignant cells of the leptomeninges [22]. An infrequent association of NCM with diabetes mellitus has been reported in the literature [23]. Fundus features, such as multiple uveal coloboma-like lesions of various sizes, and irregular areas of retinal pigmentation and epithelial alteration have been reported [20].

Until recently, the diagnosis of leptomeningeal involvement was impossible to establish in vivo. Earlier reports used cranial CT, and in some cases myelography or angiography, for diagnosis. Hyperdensity of sulci on CT scans may mimic subarachnoid haemorrhage. MRI demonstrates unenhanced T1-weighted

hyperintensity within the hippocampi, medulla, and cerebellum and marked leptomeningeal enhancement in 20% of the cases attributed to the malignant form of *NCM*. Rarely, certain neuroanatomic abnormalities can also be seen, including *Dandy-Walker* syndrome, tethered spinal cord, and occipital meningohydroencephalocele [18, 24–26]. Cranial MRI with gadolinium contrast medium is now the best method for diagnosing leptomeningeal melanosis, because intraparenchymal melanin deposits usually lead to severe shortening of T1 relaxation time due to paramagnetic effects [11, 19, 27, 28].

The *differential diagnosis* includes (1) metastatic melanoma of the skin to the brain; (2) hereditary familial melanosis [29], which is a benign autosomal dominant disorder; (3) primary malignant leptomeningeal melanoma; (4) progonoma, which is a benign melanotic neuroectodermal tumour; and (5) melanotic naevus (*Scheidentumour*) in subcutaneous tissue, which is sometimes associated with meningeal and spinal melanomatosis [9, 10]. Congenital melanocytic naevi of the skin and the central nervous system (*leptomeninges*) are usually benign and more rarely may progress to melanoma or non-malignant melanosis of the brain.

Diagnosis

In 1964, *Fox* et al. [9] established the following criteria to assist with diagnosing NCM: (1) extensive pigmented naevus of the skin larger than 20 cm in diameter, and/or multiple congenital naevi, (2) no malignant transformation of the cutaneous naevus, (3) no primary malignant melanoma, and (4) proven histological central nervous system lesion.

The criteria were further refined in 1991 by *Kadonaga* and *Frieden* [10] to include the following:

1. One large (>20 cm in adults) or multiple (3 or more) congenital naevi in association with meningeal melanosis or melanoma. The diameter of the skin lesions in an infant is acceptable at 9 cm on the head and 6 cm on the body, allowing for the projected growth into adulthood,
2. No evidence of cutaneous melanoma except when the meningeal lesions are histologically benign.
3. No evidence of meningeal melanoma except when cutaneous lesions are histologically benign.

Although the pathogenesis has not been elucidated, the syndrome is thought to represent a congenital error in differentiation of neural crest cells. Patients with both cutaneous and central nervous system melanomas are excluded due to the possible metastatic origin of the central nervous system lesions. Physical examination, EEG, brain/spinal cord MRI, MR angiography, and positron emission tomography are priority and are necessary.

Management

In many reported cases, a rapid neurologic deterioration has been observed due to malignant transformation of *NCM* [24, 25]. Neurological sequela of neurocutaneous melanosis portends a poor outcome, even in the absence of malignancy. The association of *Dandy-Walker* syndrome with *NCM* appears to have an extremely bleak prognosis (Fig. 11.5) [18]. In 80% of the cases, there is malignant transformation that leads to death before the 25th year of life. It is difficult to recognize malignant transformation in *NCM* by MRI. An important caveat is the degree of contrast enhancement.

Chemotherapy has been shown to have little effect on the rapid course of *NCM* with malignant leptomeningeal involvement. The most important palliative treatment in children with *NCM* and hydrocephalus is insertion of a shunt with a filter to prevent dissemination and seeding of melanoma throughout the peritoneal cavity [27]. Krause et al. in a recent publication [18] described all surgical interventions in obstructive hydrocephalus caused by aqueductal webs, malformations or other deformities with insertion of ventriculoperitoneal or ventriculoatrial shunts, and endoscopic septostomy with or without endoscopic third ventriculostomy.

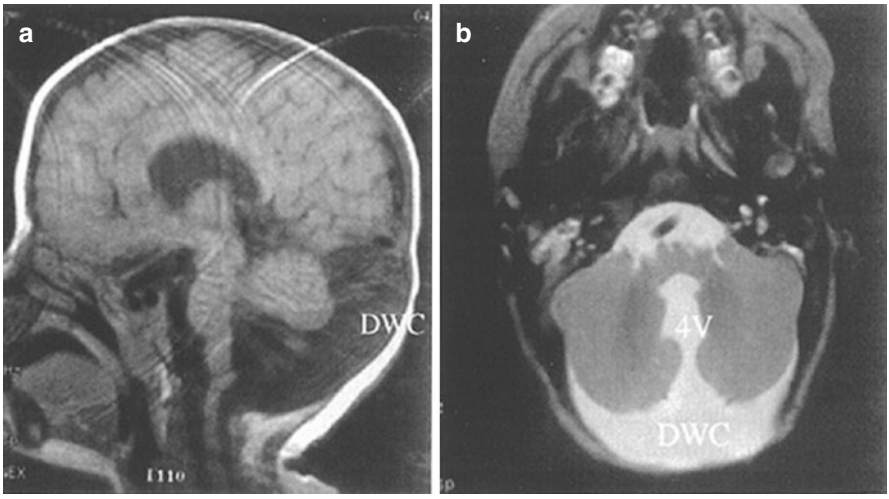

Fig. 11.5 Dandy-Walker variant. (**a**) T1-weighted midline sagittal image shows expanded posterior fossa containing cerebrospinal fluid (CSF) and small superiorly rotated vermis. The CSF collection represents a Dandy-Walker cystic malformation (DWC) of the posterior fossa. (**b**) This Tl-weighted axial image demonstrates the connection of the posterior fossa Dandy-Walker cystic (DWC) fluid collection with the fourth ventricle (4V)

Prognosis

In general, the prognosis of patients with symptomatic NCM is poor, even in the absence of malignancy, while the prognosis of patients with asymptomatic neurocutaneous melanosis detected via screening varies and is more difficult to predict [19]. The association of *Dandy-Walker* syndrome with neurocutaneous melanosis appears to have an extremely bleak prognosis [17, 30, 31]. Within 3 years after the first neurologic symptoms, more than 50% of patients die generally to increased intracranial pressure [12]. In the vast majority of patients, the clinical course shows progressive deterioration and early death [27]. The interval between the patient's age at the initial presentation with neurocutaneous melanosis and death ranges from a few days to 21 years. The prognosis of patients with neurological symptoms, such as increased intracranial pressure, myelopathy, seizures, dysarthria, or psychomotor problems within the first 2 years of life, is extremely poor. Some patients develop a drug-resistant epilepsy (for more, see Chaps. 48 and 50).

Prophylactic resection of dermal lesions is to reduce the risk of malignancy, which is estimated at 5–15% in NCM patients, and also to improve cosmetic outcome. However, the benefit of resection is still controversial in the presence of leptomeningeal disease.

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Chapter 12
Hereditary Haemorrhagic Telangiectasia (Osler-Weber-Rendu Syndrome)

Ramsis Benjamin

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Introduction

Hereditary haemorrhagic telangiectasia was recognized as a distinct entity from haemophilia in the late 1800s by William Osler, a Canadian physician and a founding father of Johns Hopkins Hospital, who observed a familial trait in patients with nonfatal bleeding tendencies. Henri Rendu, a French physician, also differentiated haemophilia from a set of patients with hypervascularity of the skin. Dr. Frederick Weber, of the Sturge-Weber and Weber-Cockayne fame, highlighted the cutaneous and mucosal vascular anomalies, at times pointed out to him by Dr Osler—"On the fingers, and notably under the finger-nails, there are several minute (pin-point) red angiomata, which I had not observed until Professor W. Osler, when he recently saw the patient, kindly drew my attention to them" [1].

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Osler-Weber-Rendu syndrome, now better known as hereditary haemorrhagic telangiectasia (HHT), has a worldwide incidence of 1:2500 to 1:40,000. A higher prevalence exists among the Afro-Caribbean residents of Curaçao Island and Bonaire, about 65 km north of the Venezuelan coast [2]. The large variance in incidence rate reflects the degree of phaenotypic penetrance and under-recognition of the bleeding diathesis [3]. The disease carries an autosomal dominant inheritance, although 20% of the patients are unaware of a positive family history. The homozygous condition is presumed to be fatal.

Clinical Characteristics

Curaçao criteria are often utilized to make the initial screening for HHT, which consists of recurrent epistaxis, telangiectasia, visceral vascular malformations (AVMs), and a first-degree relative with HHT [4] (Fig. 12.1). Vascular anomalies lie within the mucocutaneous lining of the body and rupture in response to minor trauma or exertion, including lifting or bearing minimal weight.

Recurrent epistaxis is usually the earliest and most frequent symptom (95% of individuals) that occurs in early puberty to young adulthood and typically during nighttime [5, 6]. In the second to fourth decade of life, numerous telangiectasias materialize on the face, hands, lungs, central nervous system, and gastrointestinal tract (Fig. 12.2).

Retinal arteriovenous aneurysms are uncommon. Other sites of haemorrhage may involve the kidney, spleen, bladder, and liver; however, over 90% of haemorrhages affecting the visceral organs remain asymptomatic and go unnoticed. Otherwise, chronic iron deficiency anaemia, pulmonary artery hypertension with pressures above 25 mg at rest, and high-output heart failure may arise [7, 8]. About

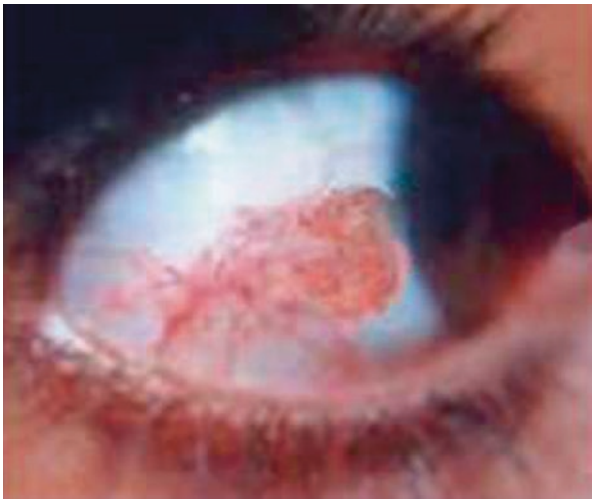

Fig. 12.1 Conjunctival telangiectasia

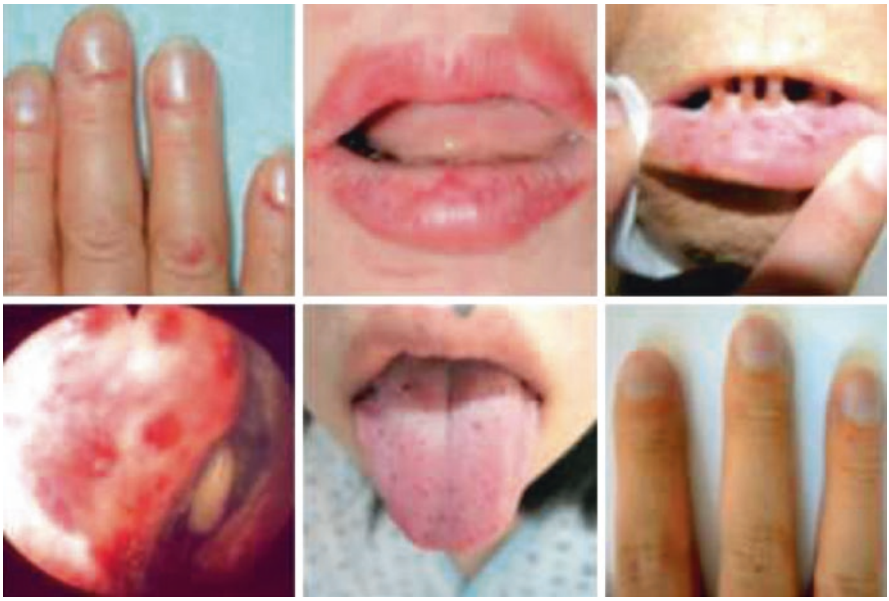

Fig. 12.2 Typical cutaneous and mucosal manifestation of hereditary haemorrhagic telangiectasia (from Lee et al. 2009, reproduced with permission, the Korean Academy of Medical Sciences)

half of the cases have pulmonary, hepatic, and cerebral arteriovenous malformations [9]. The AVMs could be half a centimetre or larger.

Pulmonary and hepatic AVMs of >3.0 mm in diameter pose a serious threat to 30–40% of individuals as malformations allow air, thrombi, and bacteria to bypass the filtering mechanism of the organs, which may lead to embolic strokes, cerebral abscesses, congestive heart failure, and portal hypertension [10]. Because pulmonary AVMs frequently enlarge with time, polycythaemia, dyspnoea on exertion, cyanosis, and clubbing of the nails arise from a protracted course of the disease in more than half of the cases [11].

Pathogenesis

Large, irregular, and fragile blood vessels within the superficial cutis, endothelial cell junction defects, and perivascular connective tissue impairment comprise some of the pathological features seen in HHT. In the dermis, the walls of dilated vessels may be thickened [12]. Pulmonary and cerebral AVMs with epistaxis and mucosal telangiectasia occur more commonly in type 1 HHT, whereas hepatic AVMs and dermal lesions exist in type 2 HHT [13, 14].

The pathogenesis regarding the heterogeneity of vascular malformations in patients with HHT remains obscure. Although over 600 missense, nonsense,

frameshift, and deletion mutations have been discovered, 4 genes have been implicated the most*:* *ENG* (*endoglin*, *chromosome* 9q34), *ACVRL1* (activin A receptor type II-like 1, ALK1, chromosome 12q), *MADH4* that codes for SMAD4 co-transcription factor downstream of the TGF-β pathway (chromosome 18q), and *BMP9* (GDF2) [15, 16]. The first three genes are respectively responsible for type 1, type 2, and juvenile polyposis/HHT syndrome [17]. The gene responsible for type 3 HHT is not known, but it is mapped to chromosome 5q31 and HHT4 to chromosome 7p14. Combined, approximately 85% of the individuals with HHT have mutations in *ENG* or *ACVRL1* [18].

Endoglin and *ACVRL1* code for two types of transforming growth factor-beta (TGF-β) receptors, exclusively expressed on endothelial cells. Endoglin catalyses the binding of TGF-β to its type II receptor, which in turn phosphorylates ACVRL1, type I TGF-β serine-threonine kinase receptor. Further signalling cascade activates downstream intracellular proteins of SMAD2/SMAD 3 and SMAD1/SMAD5/SMAD8, which ultimately regulate gene promoters for angiogenesis (Fig. 12.3).

Diagnosis

The diagnosis can be made on the basis of clinical findings and family history; however, punch biopsy of the skin is often helpful for confirmation. Ancillary tests include analysis for iron-deficiency anaemia, thrombocytopenia, elevated transaminases, haematuria, and occult or overt haematochezia. Chest radiography, angiography, multiphase computed tomography, and magnetic resonance imaging may be required for the evaluation of AVMs within the internal organs, particularly in individuals being considered for organ transplantation. Doppler ultrasound, however, may suffice as the initial screening tool for the assessment of liver AVMs; it can detect with great accuracy any flow irregularity in the hepatic artery, portal vein, and hepatic vein [19].

The differential diagnosis is broad and includes ataxia-telangiectasia, CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), Fabry syndrome, and systemic sclerosis.

Therapy

In mild cases of HHT, no treatment is necessary. Medications such as aspirin and nonsteroidal anti-inflammatory agents should be avoided to reduce the risk of haemorrhage. Frequent surveillance for AVMs is mandatory as they arise quickly and frequently at any age. Individual skin lesions may be obliterated with cauterization or laser surgery. Epistaxis and/or GI bleeding can cause mild to severe anaemia, sometimes requiring blood transfusion and/or iron replacement therapy. Laser ablation and endoscopic cryotherapy may be the most effective intervention to control

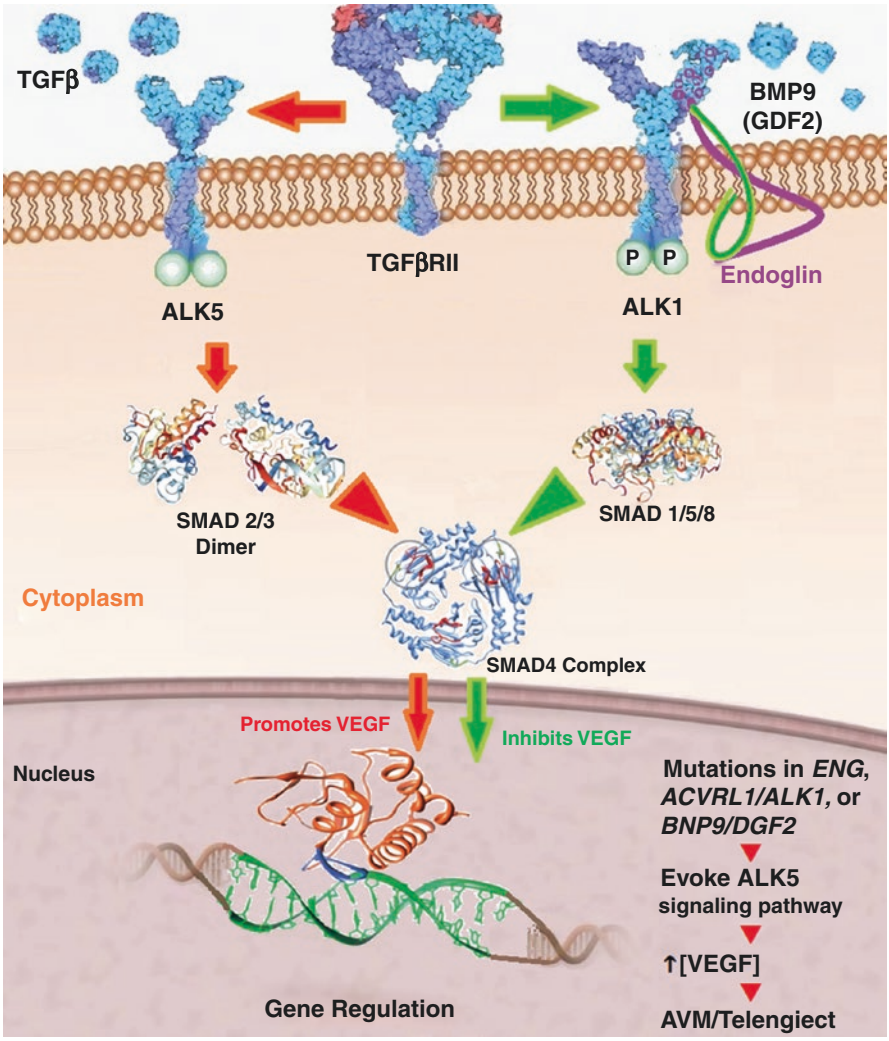

Fig. 12.3 Transforming growth factor-β (TGF-β) and its interaction with ALK1/endoglin to inhibit or with ALK5 to promote VEGF (vascular endothelial growth factor) via SMAD dimers and complexes (Illustration by ©R Benjamin, 2021)

mild-to-moderate epistaxis; otherwise, septal dermoplasty using split-thickness skin grafts from the lower trunk has been employed successfully [20].

Intranasal bevacizumab, an anti-angiogenic VEGF inhibitor, has emerged as a promising tool to reduce epistaxis and telangiectasia, but it is not curative [8, 21, 22]. For refractory cases, intravenous bevacizumab or in combination with thalidomide has also been used, especially in treating epistaxis and GI bleeds [23, 24]. Antifibrinolytics and estrogen therapy at doses used for oral contraception may be beneficial in some women with HHT [25]. Pulmonary AVM with a feeder artery

greater than 3.0 mm detected by chest CT requires transcatheter embolization to offset cardiac failure and future embolic strokes. For pulmonary hypertension, treatment includes endothelin receptor antagonists, phosphodiesterase inhibitors, prostacyclins, continuous oxygen, diuresis, and digoxin administration. Cerebral AVMs with a diameter of 1.0–3.0 cm could undergo stereotactic radiosurgery or conventional craniotomy. Hepatic AVMs generally necessitate orthotropic transplantation.

Prognosis

Most patients with HHT have a favourable prognosis, depending on the degree of pulmonary, hepatic, and central nervous systems involvement. Early diagnosis and genotyping can curtail mortality in patients with HHT. Genetic counselling should prove helpful to prospective parents with a family history of hereditary haemorrhagic telangiectasia. Systematic surveillance and screening for visceral AVMs at annual or biannual intervals may help with early intervention and avoidance of severe haemorrhagic complications. Specialized multidisciplinary centres are needed to manage patients with HHT [26].

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Chapter 13
Cowden Disease, Lhermitte-Duclos Disease, and Bannayan-Riley-Ruvalcaba Syndrome

Christos P. Panteliadis

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Introduction

CS is a sporadic genodermatosis of autosomal dominant inheritance and incomplete penetrance. As of today, less than 250 cases have been reported in the literature. *PTEN* hamartoma tumor syndrome refers to a spectrum of disorders linked to autosomal dominant mutations in the *PTEN* gene with loss of heterozygosity at 10q23, namely, *Cowden* disease (CD), *Bannayan-Riley-Ruvalcaba* syndrome (BRRS), adult *Lhermitte-Duclos* disease (LDD), and autism spectrum disorders associated with macrocephaly. The protein coded by *PTEN* comprises 403 amino acids and acts as a negative regulator of the PI3K/Akt signaling pathway by dephosphorylating PIP3 *(phosphatidylinositol-3 kinase).* The protein is almost ubiquitously expressed in the body. In the bibliography, the majority of published data affect cases with *Cowden* syndrome. To the present, there is a lack of correlation between specific *PTEN* mutations and clinical presentation [1, 2].

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Lloyd and Dennis reported the first description of Cowden's disease in 1963 [3]. Diagnostic criteria were initially proposed by *Salem* and *Steck* in 1983 [4] and revised further by consensus of an international consortium of researchers in 1996 before the identification of the gene [5]. *Cowden's* disease is rare, characterized by facial papules (trichilemmomas), gingival papillomas (frequently), keratoses of the palms and soles, and an increased risk for malignancies in the breast and thyroid.

Lhermitte-Duclos disease, first described in 1920 [6], presents with abnormal development and unilateral hemispheric expansion of the cerebellum. It is often associated with Cowden disease [1, 2, 7, 8].

Clinical Characteristics

Although the published data are limited, the estimated prevalence of CS is 1/200,000 individuals. *Cowden* disease shows cutaneous manifestations, such as mucocutaneous facial papules, gingival papillomas, and keratoses of the palms and soles. Mucocutaneous lesions are present in about 100% of affected individuals. Systemic hamartomas are common, and there is high risk of breast, thyroid, genitourinary, polydactyly, and endometrial malignancies, as well as benign hamartomatous overgrowth of tissues (skin, colon, thyroid). Benign thyroid disease is expected in 50–70% of the patients [7, 9, 10].

Lhermitte-Duclos disease, or dysplastic cerebellar gangliocytoma, is a peculiar hamartoma arising from the cerebellar cortex, often associated with cerebellar dysfunction, with diffuse hypertrophy of the stratum granulosum likely to be caused by mutations of the *PTEN* gene [7, 11, 12] (see Chap. 4). The clinical presentation is typically characterized by cerebellar dysfunction, ataxia, headaches, visual disturbances, gait disturbances, occlusive hydrocephalus, and cranial nerve dysfunction in young adults, although the age of onset ranges from birth to sixth decade [1, 12]. According to *Vinchon* et al. [13] one-third of the approximately 80 reported patients died as a direct result of mass effect from the cerebellar gangliocytoma. So far, 221 cases of this disease have been reported in the medical literature.

An association between *Lhermitte-Duclos* and *Cowden* disease was first recognized by *Padberg* et al. [14] and *Albrecht* et al. [15]. The *Cowden-Lhermitte-Duclos* complex represents a true *"neurocutaneous syndrome."* More than 70 mutations have been described in the *PTEN* gene in patients with *Cowden* syndrome [10]. The coexistence of these two rare disorders is often underrecognized and underreported.

Bannayan-Riley-Ruvalcaba syndrome is an autosomal dominant genetic disease, characterized by diverse clinical manifestations of excessive growth before and after birth (large birth weight). *Clinical characteristics* include macrocephaly, lipomas, retinal malformations, benign hamartomas of the subcutaneous tissue, within the intestines or of the pharynx and tonsils, and/or abnormally pigmented areas of skin. Macrocephaly is found in the majority of BRRS patients. Other symptoms

include developmental delay, vascular anomalies, seldom hemimegalencephaly and uveitis, and joint hyperextensibility [7, 16–18].

Macrocephaly (defined as a head circumference greater than the 97th percentile) has been found in 80–100% of patients with *PTEN* mutations. Further diagnostic workup is necessary if skull circumference increases extremely and symptoms of intracranial pressure develop [18, 19].

Diagnosis

The diagnosis is established clinically by the presence of mucocutaneous lesions, for example, six or more papules, at least three of which are trichilemmomas, which are wart-like adnexal tumors that arise near hair follicles, cutaneous facial papules, palmoplantar keratoses, and cobblestoning of the oral mucosa, or by a combination of one major criterion, e.g., breast cancer, endometrial carcinoma, thyroid cancer, macrocephaly, or macular pigmentation of the glans penis (present in almost half of the male patients), and one minor criterion, e.g., thyroid lesions, renal cell carcinoma, mental retardation, lipomas, autism, fibromas, or vascular abnormalities [5].

The diagnostic criteria proposed by *Pilarski* et al. [9] encompass wider phenotypes associated with *PTEN* mutations in about 80% of the cases. They have been tested on only a small group of patients, and further assessment and application in the clinical practice will be required to determine their utility. According to *Tan* and *Eng* [20], the criteria are unacceptable by modern diagnostic standards. *Other* related disorders caused by mutations of the *PTEN* gene include *Proteus syndrome* as well as hereditary mixed polyposis syndrome (see Chap. 22). The diagnosis is based on clinical criteria [11, 21, 22]. In Lhermitte-Duclos, the MRI (radiological findings) is an important tool for establishing the diagnosis by demonstrating typical striated, laminar/tigroid folial pattern of the cerebellum [1, 2, 8].

Therapy

The management is symptomamatic, and patients should be looked after on a regular basis by an experienced multidisciplinary team. In addition to surgical management of existing lesions, there are several clinical trials with PI3K/AKT/mTOR pathway inhibitors on the way [23, 24]. For PHTS, direct inhibition of PI3K is the most attractive therapeutic prospect. Further, sirolimus has been used. Three treatments with this mTOR inhibitor were reported. Two patients had severe forms of PHTS. Upon treatment with sirolimus, the size of lipomatous and vascular lesions improved. However, the effects reversed when the drug was discontinued, suggesting a rather preventive action and the necessity of long-term administration [23, 24].

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Chapter 14
Spinal Arteriovenous Metameric Syndrome (Cutaneomeningospinal Angiomatosis or Cobb Syndrome)

Ramsis Benjamin

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Introduction

Berenbruch first described the disorder in 1890, but it became more widely known after Cobb's report in 1915 [1]. Cobb syndrome, also known as cutaneomeningospinal angiomatosis in the past, is a rare, noninherited disorder that combines spinal osteomuscular angioma or arteriovenous malformation (AVM) with congenital, cutaneous vascular naevus within the two to three segments of the same somite, or the neural tube. This has led to recent changes in terminology, now being considered as spinal arteriovenous metameric syndrome 1–31 (SAMS 1–31) [2].

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Clinical Characteristics

Cobb syndrome is a rare entity. Less than 100 cases have been published. No racial predilection is known, although most reported cases have been Caucasians. The syndrome is based on the identification of two cardinal features: (a) subarachnoid/intramedullary haemorrhage within the spinal cord, or dural angiomas or AVMs of the nerve roots, and (b) cutaneous haemangiomas that typically present as port-wine stains (PWS), but angiokeratomas, angiolipomas, and lymphangioma circumscriptum are also present [3, 4].

The major debilities from *Cobb syndrome* are weakness, paresis, paraplegia, sensory loss, and loss of bowel and bladder control [5]. Patients generally experience a sudden onset of back or lower extremity radicular pain associated with numbness that can be localized below a specific dermatome. Less commonly, weakness or bowel/bladder dysfunction may be the presenting symptoms. These symptoms may remit or remain stable; however, they do tend to worsen over time either by discrete steps or a gradual decline. Midline back anomalies, on rare occasions, are associated with spina bifida, such as tethered cord syndrome [6].

Cutaneous lesions may be distributed anywhere in the metamere, from mid-back to abdomen. Unilateral lesions provide a clue to the location of the feeding artery in the spinal canal. It may be faint but becomes pronounced as the patient performs Valsalva manoeuver. The increased abdominal pressure causes preferential filling of the cutaneous angioma.

Diagnosis

Prior to the advent of CT and MRI, the classic finding on plain film was vertical striations of the vertebral body. Usually, though, there is nothing remarkable on plain X-rays. MRI probably is the most pertinent study (Fig. 14.1).

Imaging findings include “palisade sign” on CT and high signal intensity on T1- and T2-weighted images with enhancement on postcontrast MRI [8]. Angiomas can be demonstrated within the vertebral bodies.

The differential diagnosis includes angiokeratoma corporis diffusum (Fabry syndrome), herpes zoster, infantile haemangioma, naevus flammeus, neurocutaneous vascular hamartomas, and Klippel-Trenaunay-Weber syndrome.

Therapy

Patients require laminectomy and decompression as attempted ligation of the vascular malformation in the past resulted in haemorrhage and subsequent death. Therapeutic radiation has been attempted with moderate success. Patients

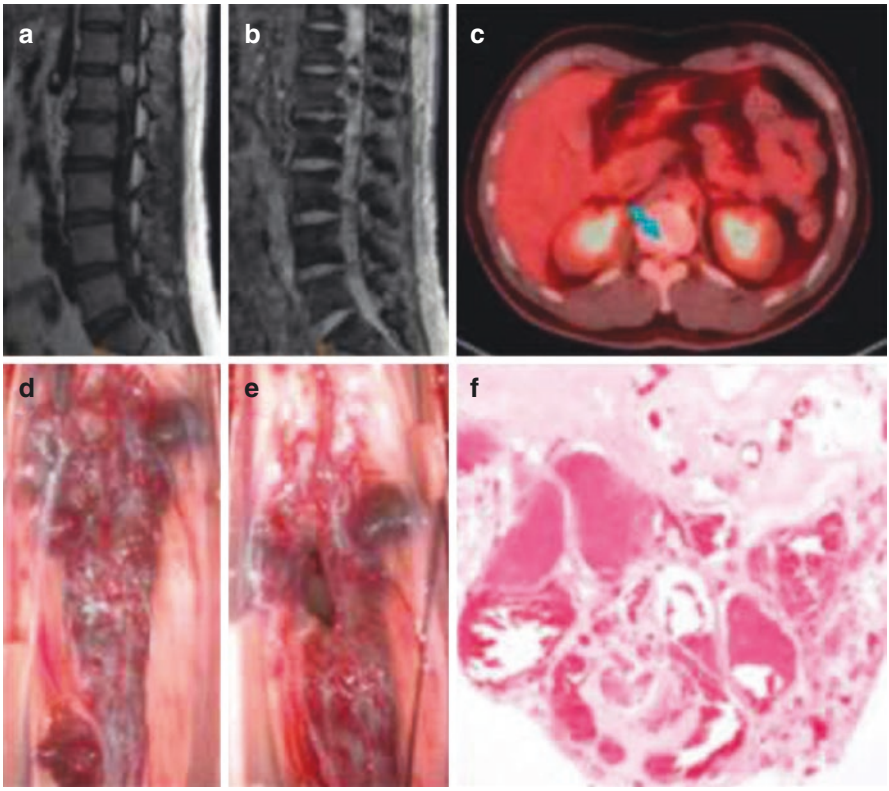

Fig. 14.1 Spinal lesions in a patient with Cobb syndrome. Sagittal contrast-enhanced T1-weighted (**a**) and noncontrast T2-weighted MR images (**b**) of the thoracolumbar spinal cord, revealing intramedullary spinal lesions at T12-S1. A PET scan (**c**) demonstrates increased uptake of FDG in the largest lesion at T12-L1 (arrow). Intraoperative view of a vascular anomaly around the conus medullaris before (**d**) and after (**e**) evacuation of the haematoma. Photomicrograph (**f**) illustrates a cavernous angioma. H&E, original magnification ×10 (from Matsui et al. 2014, with permission) [7]

should be referred to neurosurgery and interventional neuroradiology for decompression and endovascular embolization with n-butyl-2-cyanoacrylate (NBCA) [4, 5].

Prognosis

Delayed surgical ligation and decompression could lead to Foix-Alajouanine syndrome or subacute necrotic myelopathy due to thrombosis in the spinal angioma. Current interventional strategies provide some hope for minimizing permanent neurological damage. The key is early diagnosis and treatment.

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Chapter 15
Cutis Marmorata Telangiectatica Congenita (Van Lohuizen's Syndrome)

Christos P. Panteliadis

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Introduction

Cutis marmorata telangiectatica congenita (*CMTC*) is a rare, sporadic congenital disorder with local or generalized cutaneous vascular anomalies (slow-flow lesions) of unknown etiology. The disease was first described in 1922 by *van Lohuizen* [1], and in 1970, *Petrozzi* et al. reported the first case of CMTC in America [2]. CMTC has been referred in the literature under several different terms, including congenital generalized phlebectasia, nevus vascularis reticularis, congenital phlebectasia, congenital livedo reticularis, and van Lohuizen's syndrome [3]. Concerning the etiology, *Happle* suggested the concept of an autosomal lethal mutation surviving through mosaicism [4]. More recent studies identified *GNA11* mutations in skin biopsies from CMTC-affected skin areas, proposing a postzygotic mosaic condition. Further, autosomal recessive inherited homozygous mutations of the *ARL6IP6*

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gene have been described in CMTC patients [5], the impact of which, however, is not clear.

CMTC usually presents at birth with persistent cutis marmorata, vascular telangiectasia, and, occasionally, ulcers [6, 7]. Ocular lacy capillary anomalies with prominent terminal bulbs observed in CMTC have not been described in other syndromes of vascular dysgenesis [8]. The ocular manifestations present at birth or during the first year of life. Other associated alterations include musculoskeletal and vascular abnormalities, cardiac defects, neurological defects, body asymmetry (difference in leg length), and anomalies of the gastrointestinal and genitourinary system [5].

Clinical Characteristics

Cutis marmorata telangiectatica congenita (*CMTC*) is a rare malformation characterized by persistent reticulated marbled erythema and tends to be associated with cutaneous atrophy, ulcerations, and body asymmetry. The vascular malformation comprises a network of capillary and venous-sized vessels, resulting in patchy bluish marbling, livedo-like discolorations of the skin that may involve large parts of the body. The discoloration may be enhanced in cold environment or become pale on palpation [9]. A recent case reported by *Khambati* et al. [10] exemplified the phenotype in a girl born with flat purple patches over the right leg and arm and small faded markings over the buttock and leg. The presence of a reticular erythema, generalized or localized in a specific area or limb, is pathognomonic of CMTC [11].

CMTC is classified as a simple vascular malformation and subclassified as a capillary malformation (*CM*) by the International Society for the Study of Vascular Anomalies (ISSVA). *Bui* et al. [5] reviewed 485 cases of CMTC, 206 (42.5%) of whom showed associated anomalies, 146 patients (30%) had no associated anomalies, and the remaining 133 patients (27.5%) did not have this information. The most frequent anomaly was body asymmetry (37.7%), which included asymmetry of the limbs, trunk, and face as a result of either hypertrophy or hypotrophy. The second most frequent associated alterations (10.1%) related to neurological defects, followed by ophthalmological complications in 9.9% of patients, half of which were congenital glaucoma. Furthermore, 5.2% had cardiovascular defects, 4.5% had Mongolian spots, 3.3% had dysmorphic features, 2.5% had genitourinary defects, and 1.0% had endocrinological defects.

The plethora of CMTC-associated alteration results in very diverse phenotypes of CMTC. The typical vascular alterations of CMTC may occur in combination with vascular streaks of the lips and philtrum, hemangioma, or port-wine stain or even in association with other vascular syndromes, like in a patient with Sturge-Weber syndrome, facial infantile hemangioma, and cutis marmorata telangiectatica congenita [12]. The affected cutaneous areas may develop cutaneous atrophy and ulcerations. The extracutaneous findings in 20–80% of cases include ocular and

neurological abnormalities [6, 13, 14]. The latter alterations comprise mental retardation, seizures, macrocephaly, cerebral atrophy, arteriovenous malformation of the brain, hydrocephalus, corpus callosum agenesis, hemispheric vascular anomaly, hearing impairment, microcephaly, and various occlusive vascular conditions like transient ischemic attack or porencephaly [5]. Malformations and dysmorphic features of the body seen in CMTC are syndactyly, renal hypoplasia, *Kartagener's* syndrome, micrognathia, hypertelorism, frontal bossing, low-set ears, club foot, and cleft palate among others [5].

Diagnosis

Kienast and Hoeger [13] published the diagnostic criteria for CMTC, which comprise three major criteria and five minor criteria, of which at least two have to be fulfilled. The major criteria are as follows:

- Congenital reticulate (marmorated) erythema
- Absence of varicosity (*venectasia*)
- Unresponsiveness to local warming

The minor criteria include the following:

- Fading of erythema within 2 years
- Telangiectasia
- Port-wine stain outside the area affected by CMTC
- Ulceration
- Atrophy

However, these diagnostic criteria have not been validated. According to *Lunge and Mahajan* [15], these criteria are sufficient for the diagnosis of CMTC. Diagnosis is based on clinical features that frequently are obvious even at birth [3, 16, 17].

Reticular erythema presenting at birth is a common finding in all reported cases and therefore was considered a major criterion for CMTC. Further, absence of venectasia in the affected region of cutis is a very important finding in differentiating CMTC from *Klippel-Trenaunay-Weber* syndrome (see Chap. 9).

Macrocephaly-cutis marmorata telangiectatica congenita is a recently recognized syndrome described mainly in the genetics literature. It denominates an association of the dermal vascular malformation with macrocephaly, dysmorphic facies, seizures, and body asymmetry affecting the face and limbs [18].

Another extremely rare variation comprises cutis marmorata telangiectatica congenita characteristics associated with hemiatrophy. Hemiatrophy refers to wasting or loss of tissue on one side of the body, possibly resulting from an intrauterine insult. In a recent report, *Leung* et al. [19] described two cases of this condition and found eight further cases in the literature using the key terms "cutis marmorata telangiectatica congenita" and "hemiatrophy."

Therapy

Therapy is mainly geared toward treating the symptoms of glaucoma, seizures, and bony defects.

Complete ophthalmologic evaluation, including measurement of intraocular pressure, gonioscopy, dilated fundus examination, and fluorescein angiography, is recommended in infants with suspected CMTC shortly after birth [3, 8]. Psychological support and physiotherapy prove invaluable to both the child and the family members. Follow-up examination includes continued screening for associated major and minor anomalies. The prognosis in uncomplicated cases is good.

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Chapter 16
Encephalocraniocutaneous Lipomatosis (Haberland Syndrome)

Christian Hagel and Christos P. Panteliadis

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Introduction

Encephalocraniocutaneous lipomatosis (ECCL), also known as Haberland or Fishman syndrome, is a rare sporadic congenital neurocutaneous disorder caused by sporadic mosaic activating mutations in the gene coding for fibroblast growth factor receptor 1 (FGFR1, either p.N546K or p.K656E) [1] or by mosaic KRAS mutations in codon 146, which also causes oculoectodermal syndrome [2]. ECCL was first described by Haberland and Petrou in 1970 [3]. Years later, Fishman et al. [4, 5] reported more cases of this disease. In 1993, Happle and Steijlen added a further case of a 3-year-old boy with multisystem birth defects, which heralded novel clinical criteria to distinguish ECCL from other mosaic neurocutaneous

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phenotypes of Schimmelpenning (epidermal naevus), Proteus, Goldenhar, and Delleman syndrome [6]. The unique clinical features include ocular oedema or hamartoma, abnormal skin on the head and neck, and corresponding hair loss on the scalp. Since its first description, less than not more than 54 cases have been reported [7–9].

Clinical Characteristics

The primary findings of ECCL include unilateral cutaneous, ophthalmologic, and neurologic abnormalities [4, 5, 10]. Lipomatous lesions include an extensive fatty tissue nevus of the scalp, lipodermoids of the conjunctiva, and multiple intracranial lipomas, which may also occur in the cervical spine. In addition to subcutaneous lipomas, the craniofacial lesions comprise alopecia, connective tissue naevi (naevus psiloliparus), periocular skin tags, and lipomatous papules [11]. Histopathologically, these papules represent fibrolipomas [12].

Ipsilateral ocular abnormalities include choristomas, iris dysplasia, colobomas, papilloedema, lipodermoids, corneal and scleral anomalies, microphthalmia, local or diffuse hyperplasia of the ocular surface, and calcification of the globe [4, 5, 8, 13, 14]. According to Moog [14], 40% of patients showed bilateral abnormalities of the skin and/or the eyes.

Further changes comprise protuberances of the cranium, calvarial exostosis, and jaw tumours (ossifying fibroma and compound odontomas) [15, 16].

The spectrum of the central nervous system (CNS) abnormalities includes homolateral cerebral atrophy, dilated ventricles or hydrocephaly, porencephaly or porencephalic cysts, cerebral calcifications, intracranial lipomas (frequently of cerebellopontine region), spinal lipomas, and lipomas of the leptomeninges. Porencephalic cyst is a commonly encountered CNS abnormality on imaging.

As a result of the CNS abnormalities, ECCL patients may suffer from various neurological symptoms like focal seizures, which may start in infancy and may be refractory to antiepileptic drugs. Further, mild to severe mental retardation may be observed [10, 17, 18]. However, Donaire et al. [19] reported a case of a 24-year-old woman diagnosed with ECCL, who was evaluated for epilepsy surgery. The brain MRI of this patient showed extensive cortical malformation and multiple temporal-occipital cysts, while her IQ and mental status appeared within normal range.

In addition to malformations, intracranial tumours have been reported. Apart from a rare meningioma [20], astrocytic tumours have been diagnosed. Valera et al. [21] acquired five of these brain tumours from different ECCL patients and analysed the tissue by histology, methylome analysis, and whole exome sequencing, revealing that the tumours all fall into the group of midline pilocytic astrocytoma. The authors concluded that for tumourigenesis, somatic mutations in the FGFR1/RAS/MAPK pathway have to occur in addition to the initial FGFR1 mutation.

Diagnosis

Diagnostic criteria of encephalocraniocutaneous lipomatosis include (a) unilateral skull hamartoma, (b) ocular choristoma, (c) skull asymmetry due to an increase in angiolipomatous tissue in the diploic space, and (d) intracranial defects. Moog [14] divided the manifestations into major and minor changes for the skin, eye, CNS, and other systems involved (Table 16.1).

Other neurocutaneous disorders can be entertained as part of the differential diagnosis, which belong to mosaic RASopathies, resulting from postzygotic KRAS, HRAS, NRAS, or FGFR1 mutations. Differential diagnoses include Schimmelpenning-Feuerstein-Mims syndrome, epidermal naevus syndrome,

Table 16.1 Diagnostic criteria in encephalocraniocutaneous lipomatosis

Eye, major criteria	1. Choristoma, with or without associated anomalies
Eye, minor criteria	1. Corneal and other anterior chamber anomalies
	2. Ocular or eyelid coloboma
	3. Calcification of globe
Skin, major criteria	1. Proven naevus psiloliparus (NP)
	2. Possible NP and more than 1 minor criteria 2–5
	3. More than two minor criteria 2–5
Skin, minor criteria	1. Possible NP
	2. Patchy or streaky non-scarring alopecia (without fatty naevus)
	3. Subcutaneous lipoma(s) in frontotemporal region
	4. Focal skin aplasia/hypoplasia on scalp
	5. Small nodular skin tags on eyelids or between outer canthus and tragus
CNS, major criteria	1. Intracranial lipoma
	2. Intraspinal lipoma
	3. More than two minor criteria
CNS, minor criteria	1. Abnormal intracranial vessels, e.g. angioma, excessive vessels
	2. Arachnoid cyst or other abnormality of meninges
	3. Complete or partial atrophy of a hemisphere
	4. Porencephalic cyst(s)
	5. Asymmetrically dilated ventricles or hydrocephalus
	6. Calcification (not basal ganglia)
Other major criteria	1. Jaw tumour (osteoma, odontoma, or ossifying fibroma)
	2. Multiple bone cysts
	3. Aortic coarctation
Definite diagnosis	1. Three systems involved, major criteria in more than two systems
	2. Three systems involved, proven NP (naevus psiloliparus) or possible NP plus more than one of minor skin criteria 2–5
	3. Two systems involved with major criteria, one of which is a proven NP or possible NP plus more than one of minor skin criteria 2–5
Probable diagnosis	1. Two systems involved, major criteria in both
	2. Two systems involved, proven or possible NP (nevus psiloliparus)

various sporadic cutaneous manifestations, ocular lesions (see Chap. 10), and oculoectodermal syndrome (OES; OMIM 600268), characterized by epibulbar dermoids, aplasia cutis congenita, and other abnormalities [22, 23]. Further, the Proteus syndrome is characterized by postnatal overgrowth of multiple tissues, such as the skin, subcutaneous tissue, connective tissue, central nervous system, and viscera (see Chap. 22) [24], and some cases of ECCL have also been confused with Delleman syndrome or oculocerebrocutaneous syndrome characterized clinically by skin appendages, dermal hypoplasia, orbital cysts, microphthalmia, and cerebral malformations (see Chap. 19) [25].

Therapy

There is no effective causative therapy for encephalocraniocutaneous lipomatosis. The management is symptomatic and includes both administration of drugs (e.g. antiepileptic treatment) and surgical correction of ocular, intracranial (e.g. resection of lipomas), and cutaneous lesions. In pilocytic astrocytoma, chemotherapy may be considered in case of tumour progression. Cosmetic improvement (e.g. for alopecia) is desirable in order to support the patient psychologically [26]. A regular clinical follow-up to recognize complications as early as possible should be part of the basic care [27].

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Chapter 17
LEOPARD Syndrome (Multiple Lentigines; Lentiginosis Profusa)

Christian Hagel and Christos P. Panteliadis

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Introduction

LEOPARD syndrome is also known as Gorlin syndrome II or Moynahan syndrome with multiple lentigines. It is a rare, genetically predetermined multisystemic disease with autosomal dominant inheritance and variable expressivity [1]. The clinical symptoms of this syndrome comprise the presence of multiple lentigines (café au lait spots) on the face and trunk, which increase with age, and a number of other anomalies that led to the acronym, namely, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary valve stenosis, abnormalities of the genitalia, retardation of growth, and sensorineural deafness [2, 3]. The most

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common cardiac manifestation (approximately 80–85%) is myocardial hypertrophy [4–6]. The first description of the LEOPARD syndrome was probably made by Walther et al. in 1966 in a family (mother, son, and daughter) [5]. Before, in 1936, Zeisler and Becker described a syndrome in a 24-year-old woman with multiple lentigines, hypertelorism, pectus carinatum, and prognathism [7]. Sporadic descriptions were added through the years. In 1962, Moynahan revealed cardiac abnormalities and short stature were first associated with the condition [4], and in 1968, Matthews described another case of a mother with two children [2]. Gorlin et al. [8, 9] coined the acronym LEOPARD, emphasizing the concept of a generalized condition.

Pathogenesis

In 95% of patients with LS, loss-of-function mutations in the PTPN11 gene (protein tyrosine phosphatase, non-receptor type 11, located on chromosome 12q24.1) are found. The gene codes for SRC homology-2 cytoplasmatic protein tyrosine phosphatase (SHP-2) [10]. SHP-2 transduces signals between growth factor receptors at the cell surface and the Ras-Erk1/2 cascade. The protein has two SH2 domains (N-SH2 and C-SH2) arranged in a tandem and one protein tyrosine phosphatase (PTP) domain. In its inactive form, the protein has a closed conformation, which, by binding to pTyr ligands of growth factor receptors, opens up activating the protein [3, 11–13].

While inactivating germline mutations of the PTPN11 gene result in LS, activating mutations play a role in about 50% of cases of Noonan syndrome (code protein tyrosine phosphatase SHP-2) [14]. Both syndromes share several clinical features, which seems contradictory since LS is associated with loss-of-function and NS with gain-of-function of SHP-2. However, Yu et al. [14] found that LS mutant SHP-2 associates longer to the vicinity of its substrate, resulting in a low but prolonged substrate turnover and thus a net gain-of-function. A small number of cases of LS were also found to be associated with RAF1- and BRAF mutations [15, 16].

Activating the Ras pathway, both LS and NS belong to RASopathies, a group of developmental disorders with overlapping clinical features which also include neurofibromatosis type 1, Costello syndrome (CS), and the cardiofaciocutaneous syndrome. Main symptoms in CS (inherited in an autosomal dominant manner, delayed development) comprise severe postnatal feeding difficulties, short stature, intellectual retardation, coarse facial features, hypotonia, congenital heart defect, and cardiac hypertrophy [17].

Clinical Characteristics

Patients usually have a characteristic "inverted" triangular facial appearance due to frontal bossing, hypertelorism (is virtually present in all cases), and low-set ears. The facial dysmorphisms usually are less obvious at birth but become evident during childhood [2]. Small, dark-brown lentigines (on the face and upper trunk, irregularly shaped) are the classic skin alteration of this syndrome (although occasionally café-au-lait spots may appear first). Lentigines from the Latin lentigo, "small lentil" (<0.5 cm), consist of flat-pigmented macules on the skin and mucosa (Fig. 17.1). They are often the first clinical manifestation in childhood and increase in number with age [7–9, 18]. Other cutaneous abnormalities include hypo- and hyperpigmentation (Fig. 17.2) and axillary freckling [19, 20]. Approximately 85% of LS-affected patients have heart defects, including hypertrophic cardiomyopathy, heart rhythm

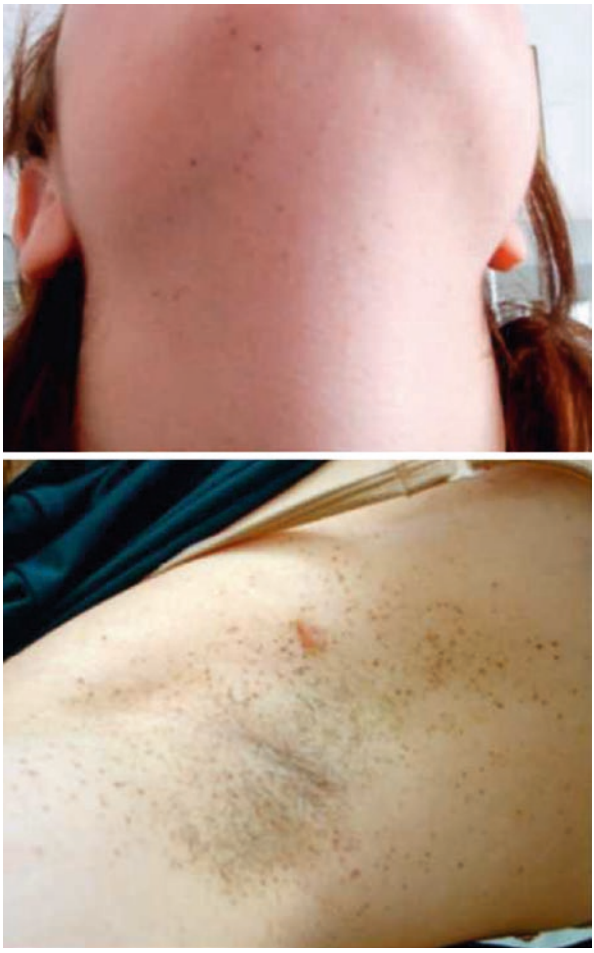

Fig. 17.1 Lentigines in the skin of the neck (upper picture) and arm (lower picture) in LEOPARD syndrome (with kind permission of Dr. Varlamis)

Fig. 17.2 Hyperpigmentation of the skin in LEOPARD syndrome (with kind permission of Dr. Varlamis)

disorders, and pulmonary valve stenosis [21]. The electrocardiogram may reveal left axis deviation representative of hypertrophic obstructive cardiomyopathy [1, 2, 22]. Hypospadia exists in about 50% of male patients. Female patients may show an absent or hypoplastic ovary. Various skeletal anomalies have been detected, such as short stature, pectus excavatum or carinatum, winging of the scapulae, scoliosis, missing of ribs, broad chest, mandibular prognathism or defects of the elbow joints, ocular hypertelorism, sensorineural deafness, and growth retardation [10, 23]. Thorax anomalies are found in up to 75% of the newborns [22]. In some patients, mild mental retardation is present, but intellectual capacity may be completely normal in this syndrome [24].

The clinical manifestations of LS overlap with NS, in that patients of both disorders may present with multiple lentigines and various developmental defects, notably cardiopathies, dysmorphism, and short stature [25, 26]. Colmant et al. in 2018 described cases with all characteristics of LEOPARD syndrome and multiple melanomas [3].

Diagnosis

The diagnosis of LS is made on clinical grounds and can in more than 90% of cases be confirmed by molecular genetic testing [27, 28]. Minimum criteria proposed for the clinical diagnosis of LS are multiple lentigines plus features of at least two other categories, e.g., skin, cardiac, genitourinary, craniofacial, endocrine, neurologic, and skeletal abnormalities.

Management

In patients suspect of suffering from LEOPARD syndrome, a complete cardiovascular, genitourinary, neurological, and auditory screening as well as a molecular genetic analysis of the PTPN11 and RAF1 gene should be performed. A regular follow-up of patients at annual intervals is recommended, and patients with hypertrophic cardiomyopathy should be carefully assessed concerning the risk of sudden death. Severe pulmonary valve stenosis and left ventricular outflow obstruction may need to be treated surgically. Other manifestations are monitored and treated as necessary, such as growth hormone therapy, hearing aid, protection against UV light, infant stimulation program/alternate teaching methods, etc. Sensorineural hearing loss may occur later, but it must be periodically monitored during childhood and adolescence. In general, the prognosis of LS is favorable, and most adult patients do not require special medical care [12]. The prognosis depends on the cardiac involvement (hypertrophic cardiomyopathy).

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Chapter 18
MIDAS Syndrome (Microphthalmia with Linear Skin Defects)

Christian Hagel and Christos P. Panteliadis

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Introduction

MIDAS syndrome (microphthalmia, dermal aplasia, and sclerocornea), also called microphthalmia with linear skin defect (MLS) syndrome, was first described in 1988 by Al-Gazali et al. [1]. The disorder is characterized by ocular defects (microphthalmia, orbital cysts, corneal opacities/sclerocornea) and linear skin dysplasia of the neck, head, and chin. Nervous system (development delay, hearing loss, etc.) and cardiac anomalies, diaphragmatic hernia, genitourinary tract abnormalities, and anal atresia may also be associated.

MIDAS is a rare neurocutaneous syndrome with an X-linked dominant transmission pattern and male lethality [2, 3]. The majority of cases arise from deletions or

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unbalanced translocations in the short arm of X chromosome (Xp22.3). Mutations in the HCCS and COX7B gene, encoding proteins of mitochondrial respiratory chain complexes III and IV, have been identified to cause MLS [2, 4]. In addition, it was shown that NDUFB11, which encodes a subunit of NADH/ubiquinone oxidoreductase (complex I), may lead to MLS [2]. Hence, MLS is a hereditary neurocutaneous disease caused by specific mutations in genes coding for enzymes of the mitochondrial respiratory chain.

MIDAS has been reported in about 50 patients worldwide. Most cases occur de novo, but familial recurrence has been described, with no clear genotype-phenotype correlations [5].

Clinical Characteristics

According to Happle [6], the microphthalmia is usually bilateral, but unilateral involvement has also been reported. The anterior-posterior diameter allows for the diagnosis of microphthalmia. Other anomalies include sclerocornea, corneal opacities, microcephaly, cognitive impairment, focal brain dysplasia, septum pellucidum defects, agenesis of corpus callosum, and cardiac defects. Dermal aplasia comprise nail dystrophy and linear skin defects mainly located in the face, scalp, neck, and upper trunk, which may appear as pink, depressed plaques and may be present at birth [7]. Anguiano et al. [8] reported twin brothers with microphthalmia, facial dermal hypoplasia, sclerocornea, and supraventricular tachycardia. Their clinical features are compatible with the MIDAS syndrome; their karyotypes, however, showed an XX-chromosome modality with a subtle Xp/Yp translocation proven by the presence of SRY gene. A case of a 33-week-old fetus reported by Herwig et al. [9] presented with anterior segment abnormalities in both eyes and with all characteristics of MIDAS syndrome. Postmortem findings included craniofacial stigmata, such as hypertelorism, a flat nose, low-set ears, and an agenesis of the corpus callosum. Array comparative genomic hybridization revealed a deletion of the short arm of the X chromosome in region Xp22.2 to p22.32. The ophthalmologic investigation of fetal eyes can be of great value for the further classification of syndromes. Durac et al. [4] presented a 5-day-old female infant with cutis linear atrophic skin defects in the facial area and divided the alterations in major diagnostic criteria (linear skin defects, dermal aplasia, microphthalmia) and minor criteria (other ocular abnormalities, developmental delay, congenital heart defects, short statue, diaphragmatic hernia, nail dystrophy, hearing loss, genitourinary malformations). Enright et al. [10] reported a case of a patient to support the similar histologic and cytogenetic findings in patients with MLS and Xp22.3 microdeletion. Molecular studies have revealed that in many cases of MLS, the genetic alterations include the HCCS gene, which encodes a mitochondrial holocytochrome c-type synthase. Deficiency of this antiapoptotic enzyme may influence the balance between apoptosis und necrosis in tissues [8].

The differential diagnosis of MIDAS includes Goltz syndrome, also known as focal dermal hypoplasia (see Chap. 29), incontinentia pigmenti (see Chap. 8), and

the oculocerebrocutaneous syndrome (see Chap. 19). Goltz syndrome is an X-linked dominant, multisystem birth defect with lethality for male embryos. Manifestations include cutis aplasia, dermal hypoplasia, papillomas, chorioretinal colobomas, absent/dysplastic teeth, and skeletal anomalies. The hypoplastic skin lesions follow Blaschko's lines and often show herniation of subcutaneous fatty tissue. Extracutaneous defects mainly involve the brain, the bones, the teeth, and the eyes [11, 12]. The dermal lesions (dermal aplasia, melanocytic) can be helpful for diagnosis [4]. In 2014, Almeida et al. [12] described a female newborn with congenital facial linear skin defects following Blaschko's lines, some of which were covered with hemorrhagic crusts, and bilateral microphthalmia; HCCS at Xp22.2 was detected in the patient but absent in the mother, and the MRI was normal (Fig. 18.1).

Therapy

After initial diagnosis, the manifestations of the syndrome need to be thoroughly evaluated by an interdisciplinary team of specialists. The investigations should comprise an ophthalmologic examination, test of hearing, MRI of the brain,

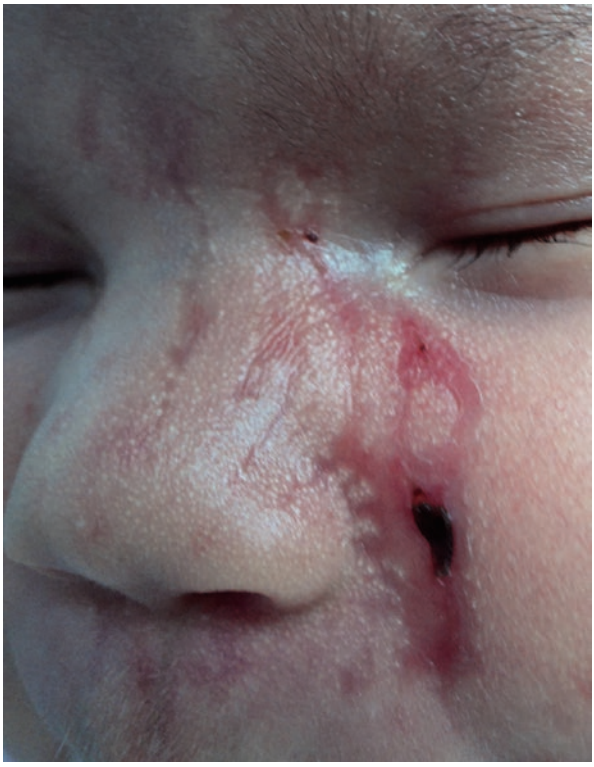

Fig. 18.1 Linear facial defects following Blaschko's lines (with kind permission of Dr. Hiram and the Annals Bras. Dermatol [13]

assessment of cognitive functions and developmental status, cardiac function, evaluation for skin lesions, and abdominal MRI for possible diaphragmatic hernia.

The therapy is symptomatic and includes prosthesis under the guidance of an oculoplastic specialist for severe microphthalmia and anophthalmia, routine dermatologic care for skin lesions, and treatment of seizures and/or other neurologic problems [14].

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Chapter 19
Oculocerebrocutaneous Syndrome (Delleman-Oorthuys Syndrome)

Christos P. Panteliadis

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Introduction

Oculocerebrocutaneous syndrome or Delleman-Oorthuys syndrome (OMIM 164180) is a sporadic disorder, characterized by orbital cysts, microphthalmia, hamartoma, and focal cutaneous hypoplasia, which occurs predominantly in males [1]. Most skin appendages are located in the face, especially around the orbit, and only rarely extend to the trunk [2, 3]. Delleman and Oorthuys first described this syndrome in 1981, who reported on two cases with this syndrome [4]. Since then, about 40 cases have been reported, and no patient with an abnormal karyotype has been described. Although the etiology of OCCS is still unknown, in a last publication, it is hypothesized to result from postzygotic mosaic variants in an X-linked gene [3].

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Clinical Characteristics

This sporadic syndrome is characterized by orbital cysts, anophthalmia, microphthalmia, eyelid coloboma (seldom), hamartoma (seldom), periorbital or postauricular appendages, and the most common focal cutaneous hypoplasia or aplasia (pink-colored or flesh-colored). Other symptoms are skull defects, rib dysplasia (seldom), intracranial cysts, corpus callosum agenesis, malformations of the ventricular system, polymicrogyria, psychomotor/developmental retardation, and seizures [1, 4–7].

Scholz et al. [8] described a full-term, 22-h-old newborn with atrophic lesions on his scalp and torso and left orbital mass and tag-like lesions on his face. Magnetic resonance imaging of the brain demonstrated absence of the left globe without an orbital cyst. The mid-hindbrain malformation appears pathognomonic for the oculocerebrocutaneous syndrome. The eye and skin features show considerable overlap with several other syndromes, such as encephalocraniocutaneous lipomatosis, oculo-auriculo-vertebral spectrum, and focal dermal hypoplasia, none of which has a comparable pattern of brain malformations [2, 9, 10]. Arora et al. [11] described a case of a 1-month-old male with an orbital cyst in the left eye since birth and skin and neurological anomalies, e.g., lateral ventricular dilatation with corpus callosum agenesis. Ortiz-Basso et al. [12] presented a case with coloboma of the lower lid. According to Hunter [13], a major criterion is microphthalmia with cyst, and a minor criterion is an arachnoid cyst. Over 85% of cases were reported to have ocular cysts, skin appendages, and focal dermal hypoplasia. Moog and Dobyns [3] in a recent review of OCCS syndrome presented 40 patients and stated ocular defects, such as orbital cyst, eyelid coloboma, and anophthalmia/microphthalmia with or without cyst to be present in all of the cases. In the same publication, the most probable pathogenesis is a neurocristopathy that interferes with craniofacial morphogenesis [3]. Jamjoom et al. [14] described a 4-day-old newborn with congenital glaucoma in the left eye and microphthalmia in the right eye.

A subtle distinction between Gorlin-Goltz syndrome and Delleman syndrome could be made based on the location of the cysts and skin appendages—in Gorlin syndrome, the skin appendages appear in the periorbital and perianal regions (see Chap. 29), whereas in Delleman syndrome, they occur in periauricular areas [15, 16]. Delleman syndrome shows overlapping clinical features with Goldenhar syndrome, which is characterized by epibulbar dermoids, preauricular appendages, micrognathia, and vertebral and other anomalies [17]. The differential diagnosis of OCCS includes brain malformation such as Aicardi syndrome (OMIM 304050; agyria, pachygyria, focal cortex dysplasia, double cortex syndrome, which occurs only in females), orbital cysts (mainly midline cysts), microphthalmia with linear skin defects (see Chap. 18), encephalocraniocutaneous lipomatosis (see Chap. 16), intracranial cysts, and cleft of lip and palate.

Diagnostic Criteria

Moog and Dobyns [3] differentiate between major and minor diagnostic criteria:

The major criteria include congenital orbital cyst or microphthalmia with cyst, crescent-shaped skin defect above or behind the ear, pedunculated skin appendage, finger-like and moving, or proven striated muscle hamartoma, novel mid-hindbrain malformation consisting of giant, dysplastic tectum rotated upward, and absent or severely malformed vermis.

The minor criteria include isolated microphthalmia/anophthalmia, any other colobomatous defect, ocular or eyelid, pedunculated skin appendage, possible SMH, subcortical or periventricular nodular heterotopia, corpus callosum agenesia, and hydrocephalus.

The diagnosis is based on the clinical, ophthalmological, and radiological (brain CT/MRI) symptoms.

Therapy

The management is symptomatic or supportive, organized by a multidisciplinary team. Anticonvulsants are used if seizures occur. Supportive options include management of the orbital cyst and cleft lip or palate, as well as insertion of a shunt in case of hydrocephalus. Long-term follow-up of neurologic status is necessary, and the prognosis depends on type, severity, and progression of these symptoms.

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Chapter 20
Oral-Facial-Digital Syndrome

Christian Hagel and Christos P. Panteliadis

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Introduction

Oro-facial-digital syndromes (OFDS) are a heterogeneous group of disorders resulting from mutations in at least 16 different genes determining the structure of primary cilia [1]. The phenotypical pattern was first described by Mohr in 1941 [2], later defined as oro-digital-facial dysostoses by Papillon-Léage and Psaume in 1954 [3] and finally named OFDS in 1967 by Rimoin and Engerton [4]. In parallel, Morton and Jordan [5] and Gorlin and Psaume [6] reported cases of children with similar malformations and indicated that the first observation of this syndrome dates back to 1883. Clinically, OFDS include various malformations of the face and oral cavity, such as cleft lip and palate, vestibular frenulum, tongue lobulation, hypoplasia of the nasal cartilages, hamartomas, and variable digital defects, such as polydactyly,

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clinodactyly, syndactyly, micromelia, and talipes equinovarus [7, 8]. In addition, the clinical phenotype often includes mental retardation (30–50%) and renal impairment (polycystic). Multiple cysts are observed mostly on the face, scalp, auricles, and dorsal hands [9]. Patchy alopecia or apparent hypotrichosis may be found in 65% of cases. Since the different OFDS differ in prognosis, an exact diagnosis is important.

According to clinical heterogeneity confirmed by various atypical signs, there existed an overlap between OFD subtypes.

Pathogenesis

OFDS result from structural changes in primary cilia (PC). PC are hair-like organelles that stand out from the cell surface and contain receptors for transduction of signals important for development and survival, including determination of asymmetry of internal organs and neural tube and limb development [10]. PC are involved in the sonic hedgehog, notch, and wingless pathways among others. The most frequently affected gene OFD1 encodes for a centrosomal protein in PC. Ciliopathies are a group of disorders caused by an abnormal formation/function of primary cilia. Presently, mutations in 16 genes have been identified as cause of OFDS, all of which encode for proteins located in different compartments of PC [1]. OFDS are typically inherited in an autosomal recessive fashion except for OFDS1, which follows a dominant X-linked trait and is lethal in males.

Clinical Characteristics

Considerable clinical overlap exists within this heterogeneous group of rare syndromes and with other entities, leading to difficulties in the classification of OFDS [11]. Further, description of new causative mutations necessitates the revision of classifications that were previously proposed. According to Bruel et al. [1], three main well-defined OFDS subtypes can be distinguished, complemented by another five subtypes based on the genotype for cases that do not fit into the main subtypes. The main three subtypes are as follows:

OFDS type I (OMIM 311200, Papillon-Leage-Psaume syndrome, affected gene, OFD1). It is inherited in a dominant X-linked manner and is lethal in males. Clinical features include tongue nodules, bifid tongue, midline lip cleft, clef palate, micrognathia, frenulum hypertrophy, polydactyly, syndactyly, facial milia, renal dysplasia, cerebral atrophy, and mental retardation. OFDS I is also a cause of polycystic kidney disease [12]. It can be present at birth or develop later [13]. Del Giudice et al. [14] reviewed a cohort of 117 molecularly diagnosed OFD type I patients and found 71 cases showing CNS involvement in neuroimaging studies and neuropsychological testing. She found CNS involvement in more than 60% of cases, brain structural anomalies in 88.7%, cognitive impairment in 68%, and associated neurological

disorders and signs in 53%. The most frequently observed brain structural anomaly was agenesis of the corpus callosum. Surgical correction of the malformations associated with this syndrome is a challenge for the pediatric surgeon [15]. Approximately 75% of affected individuals represent simplex cases. The diagnosis is established by identification of an OFD1 pathogenic variant on molecular genetic testing [14].

OFDS IV (Mohr-Majewski syndrome, affected gene, TCTN3) [MIM 258860] presents with severe tibial anomalies and club foot [16]. An overlap between More syndrome and lethal short-rib-polydactyly/Majewski syndrome is probable.

OFDS VI (Varadi syndrome, MIM 277170) is an autosomal recessive disorder distinguished from other oral-facial-digital syndromes (affected genes, TMEM216, TMEM231, TMEM138, C5orf42, TMEM107, KIAA0753), which presents with mesoaxial polydactyly, syndactyly, hypoplasia of the cerebellar vermis (molar tooth sign), and variants of the Dandy-Walker complex [17]. A prenatal diagnosis with sonography between 16 and 21 weeks of gestation is possible [18].

The complementary classification based on genotype comprises [1] the following:

Median cleft of the upper lip (DDX59, NEK1)
Cardiac defects (INTU, WDPCP)
Retinopathy (SCLT1, TBC1, D32/C7orf170)
Severe microcephaly (C2CD3)
Chondrodysplasia (IFT57)

Therapy

Most important for patient management are the registration of all symptoms and malformations and an exact and early diagnosis of the type of OFDS. Further, family history and any abnormalities during gestation should be noted. Clinical diagnosis should be confirmed by molecular genetic analysis, followed by counseling to family members. Surgical correction of malformations, like hard palate plastic, and correction of frenulum hypertrophy help to improve function and quality of life.

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Chapter 21
PHACE Syndrome

Christos P. Panteliadis

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Introduction

The first report of a patient with PHACE syndrome was in 1978, when Pascual-Castroviejo described a patient with a large facial haemangioma in association with cervicocranial arterial abnormalities and intracranial malformations [1]. The acronym PHACE syndrome (OMIM 606519) was suggested in 1996 by Frieden et al. for the constellation of posterior fossa brain malformations, large haemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities [2, 3]. The most common extracutaneous involvement is vascular anomalies in the cervical spine and brain. Thus, neurologic and cognitive impairments constitute significant morbidity in these patients. PHACE syndrome represents 2–3% of all cases of infantile haemangioma (IH) and affects females more frequently (9:1) [4]. Infantile haemangioma is the most common vascular tumour of infancy with an estimated 80,000 annual cases in the United States alone. These tumours usually do not present with systemic involvement, unlike PHACE syndrome. Approximately

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90% of the haemangiomas in PHACE syndrome are located on the cephalic segment [5–7].

Pathogenesis

The pathogenesis and aetiology of PHACE syndrome remain unclear. The female predominance may indicate an X-linked inheritance with lethality in males. Evidence points to a developmental error (during embryogenesis) in the morphoregulatory genes that determine a spectrum of anomalies in a spatially coordinated, temporally synchronous manner. This occurs between 6 and 8 weeks of gestational age. Complete deletion of SLC35B4 (solute carrier family 35 member B4) on 7q33 has been observed but unlikely to be the only cause of this syndrome [8]. The gene encodes for glycosyltransferases that transport nucleotide sugars from the cytoplasm into the Golgi apparatus [9]. It is conceivable, however, that the phaenotypic expression in this locus is an epiphenomenon that provides genetic susceptibility to secondary environmental factors.

Clinical Characteristics

PHACE syndrome represents a spectrum of anomalies. The majority of patients are girls [3, 10]. In almost 70% of the children, only one extracutaneous manifestation exists, commonly structural or arterial anomalies in the brain. The most common clinical characteristics are Dandy-Walker malformation, agenesia or hypoplasia of the vermis during embryogenesis, cystic dilatation of the fourth ventricle, and hydrocephalus (Fig. 21.1) [11].

In particular, Dandy-Walker malformation occurs in approximately one-third of reported cases. Posterior fossa malformations are found in 32–74% of patients with PHACE syndrome [12]. Cerebellar atrophy and arachnoid cyst have also been observed, and about 30% of infants with large facial haemangiomas have extracutaneous manifestations, e.g. anomalies in the craniocervical arteries (most commonly) and cardiovascular system [13–15]. Intracranial anomalies are the most common extracutaneous feature of PHACE syndrome, and the contribution of the neuroradiologist in the recognition of such anomalies is important for the diagnosis [16, 17].

Other less common defects include hypoplasia of the vermis, corpus callosum and septum pellucidum, as well as isolated cases of microcephaly, absence of foramen lacerum, transverse sinus thrombosis, frontal lobe calcification, and endocrine abnormalities, including hypopituitarism and ectopic thyroid [18]. Dental abnormalities and enamel hypoplasia have also been observed that usually coincide with haemangiomas in the oral cavity [19].

Arterial anomalies include coarctation of the aorta; agenesis or hypoplasia of the carotid or vertebral arteries; aneurysms and anomalous branches of the internal carotid artery; occlusion of the distal internal carotid artery or proximal anterior,

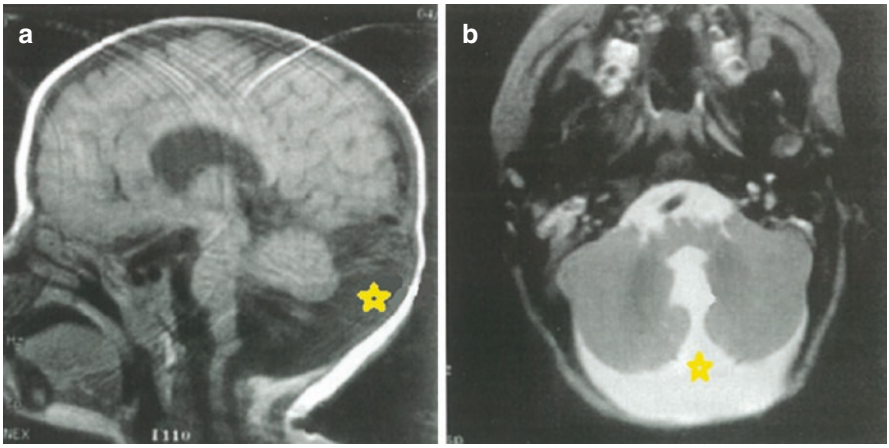

Fig. 21.1 (**a**) T1-weighted midsagittal magnetic images of Dandy-Walker malformation (yellow asterisks) in the posterior fossa, displacing the cerebellum superiorly; (**b**) T2-weighted axial views of the cystic lesion contiguous with the fourth ventricle

middle, and posterior cerebral arteries with dilated basal collaterals (Moyamoya phenomenon); dilated cerebrovascular vessels; aberrant left subclavian artery; and subclavian or innominate artery aneurysms [2, 15]. The prevalence of congenital cardiac diseases is 41–67%, with coarctation of the aorta responsible for 19–30% of these cases. Approximately 50% of patients with cardiac involvement have an aberrant origin of the subclavian artery, with or without a vascular ring. The most frequent changes affect the transverse and descending portions of the aortic arch [6, 20, 21].

Coarctation of the aorta is the single most common defect, whereas arterial anomalies of the head and neck occur in more than one-third of cases. Infants with PHACE syndrome are at an increased risk of developing arterial ischaemic strokes [22]. Other less common reported vascular anomalies include retro-orbital, parasagittal arteriovenous malformations and aortic anomalies other than coarctation, such as ascending aorta or aortic arch aneurysms and/or dilatation, anomalous left superior vena cava, congenital aortic valve stenosis and cervical aortic arch, subclavian steal syndrome, absent right aortic arch, hypoplastic descending aorta, and double aortic arches and coarctations [3]. Among patients affected with both cerebral and arterial anomalies, the majority of them develop secondary neurological sequelae, such as seizures, developmental delay, contralateral hemiparesis, hypotonia, apnoea, opisthotonus, vomiting, severe migraine headache, borderline to severe cognitive delay, and intention tremors. However, the potential for secondary neurological sequelae among patients with underlying brain involvement is not known. In addition, symptoms do not appear to be directly attributable to the cerebrovascular anomalies. Because the majority of previously reported cases did not have neuroimaging studies, it is unknown whether the vascular changes detected were present since birth or infancy or developed later in life [3]. In a retrospective study, arterial ischaemic stroke was identified by head and neck angiography in 20 out of 22 cases. The most common findings were aplasia, hypoplasia, or occlusion of a major cerebral artery (present in 19/20), which appeared to be a significant risk factor for

arterial ischaemic stroke, especially in patients when more than one vessel was involved, or in cases of coarctation of the aorta (13/22) [23].

Cardiac abnormalities, such as tricuspid and aortic atresia, patent ductus arteriosus, and ventricular septal defects, have also been reported. Other anomalies include atrial septal defects, pulmonary stenosis, cor triatriatum, tricuspid atresia and stenosis, tricuspid aortic valve, atrial enlargement, ventricular hypertrophy, patent foramen ovale, and tetralogy of Fallot [3].

Ophthalmologic abnormalities, observed in about a quarter of the patients, include microphthalmia ipsilateral to the facial haemangioma, optic atrophy, optic nerve hypoplasia, cataract, iris vessel hypertrophy, iris hypoplasia, sclerocornea, lens coloboma, exophthalmos, and increased retinal vascularity. The majority of patients had the ocular anomalies ipsilateral to the side of their facial haemangiomas. Visual complications, also ipsilateral to the haemangioma, include strabismus, monocular blindness, ocular motor apraxia, and partial Horner's syndrome (miosis, ptosis, and pseudoenophthalmos) [10]. Congenital glaucoma and esotropia are less common ocular findings contralateral to the facial haemangioma. The facial haemangiomas are usually large and plaque-like and involve more than one dermatome. The ophthalmic branch (V1) of the trigeminal nerve is the most commonly affected dermatome, which is involved singly or in combination with the trigeminal divisions V2, V3, or both [8]. Children with PHACE syndrome are at an increased risk of ocular morbidity, which can potentially lead to blindness [8].

Metry et al. [24] undertook a prospective, cohort study of 1096 children with haemangiomas, 25 of whom met the criteria for PHACE syndrome. These patients represented 20% of infants with segmental craniofacial haemangiomas. Craniofacial haemangiomas follow diverse segments that include the frontotemporal, maxillary, mandibular, and frontonasal regions (Fig. 21.2) [15, 16]. Segment 1 is the most

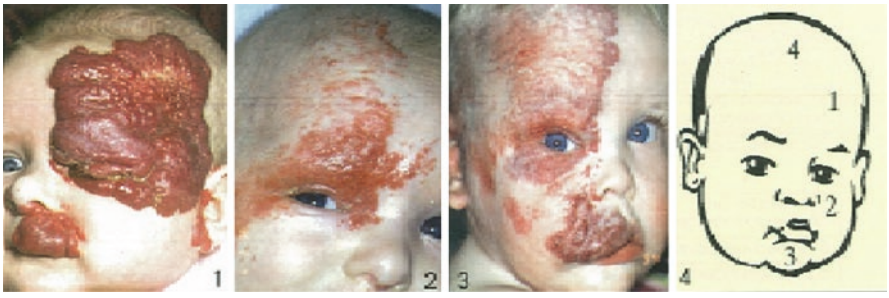

Fig. 21.2 (1) A 4-month-old infant showing large haemangiomas involving segment 1 and partially segment 2; there is complete occlusion of the left eye; (2) an 11-month-old infant with segments 1 and 2; (3) a 3-month-old child with segments 1, 2, and extension into 4; (4) segmental distribution of children with PHACE syndrome. Seg. 1, frontotemporal; Seg. 2, maxillary; Seg. 3, mandibular; Seg. 4, frontonasal. Adapted from Haggstrom et al. [16], with kind permission from Hansjörg Cremer, Haemangiomas, Anshan

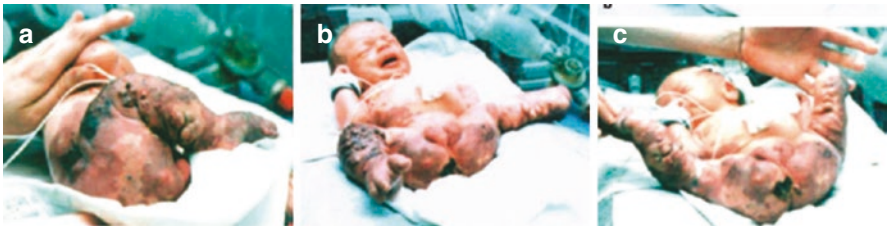

Fig. 21.3 (**a**–**c**) Typical haemangiomas involve the upper trunk, extremities, and gluteal region

common (74%), followed by segment 3 (61%), segment 2 (35%), and segment 4 (35%). About half have involvement of multiple segments. Haemangiomas are right-sided in 39%, left-sided in 30%, and bilateral in 30% [25].

Most patients seek medical attention because of the large size and/or complex nature of their facial haemangiomas. One-third of infants with large facial haemangiomas have extracutaneous manifestations, such as cerebrovascular and cardiovascular anomalies [26]. In addition, haemangiomas involve areas other than the head and neck, such as the upper trunk and extremities (Fig. 21.3).

Patients with PHACE syndrome appear to be at a greater risk of airway haemangiomas [2]. Other internal organs include the pancreas, thyroid gland, bowel, liver, and brain. Sternal cleft and/or supraumbilical raphe, congenital micrognathia, thyroid anomalies, and ear abnormalities have also been reported. PHACE syndrome could be associated with oropharyngeal maldevelopment, lip or oropharynx haemangiomas, dysphagia, or speech and language delay [27].

The use of propranolol (a-blocker) for complicated infantile haemangiomas is under review [28]. However, propranolol may increase the risk of stroke due to arterial abnormalities present in PHACE syndrome and mask or worsen heart failure [29].

Diagnosis

The diagnosis is based on recently revised clinical features and includes major and minor criteria (Table 21.1) [3, 6, 26].

The diagnosis of PHACE syndrome can be made in the presence of (1) facial haemangioma >5 cm in diametre plus one major criterion or two minor criteria or (2) facial haemangioma >5 cm in diametre plus one minor criterion. Possible PHACE syndrome is diagnosed in cases with haemangioma in the neck or upper torso plus 1 major criterion, or in cases of two minor criteria, or two major criteria in the absence of haemangioma. Foetal MRI scans may guide further in clinching the diagnosis of PHACE syndrome in utero [30].

Table 21.1 Diagnostic criteria for PHACE syndrome

Organ system	Anomaly/defect
Major diagnostic criteria	
Cardiovascular	Anomalies of the major cerebral arteries, aneurysm, persistence of trigeminal artery
Nervous	Dandy-Walker malformation, unilateral/bilateral hypoplasia/dysplasia of the cerebellum
Ocular	Optic nerve hypoplasia, coloboma, vascular anomalies of the retina
Skeletal	Ventral or midline sternal anomalies (sternal cleft)
Minor diagnostic criteria	
Cardiovascular	Persistent embryonic artery other than trigeminal artery, primitive ophthalmic artery, ventricular septal defect
Nervous	Extra-axial lesions with features consistent with intracranial haemangioma, hypopituitarism
Ocular	Sclerocornea, coloboma, cataracts, microphthalmia
Skeletal	Sternal cleft

Therapy

There is no standard or targeted therapy for PHACE syndrome. Like other neurocutaneous disorders, a multidisciplinary group would be required to manage these cases. Future complications could be averted by timely surveillance and longitudinal monitoring [31]. Children presenting with large plaque-like facial haemangiomas should receive a careful neurologic, cardiac, and ophthalmologic evaluation. Long-term outcome data from affected individuals are needed before further diagnostic and therapeutic guidelines can be established [3, 32].

The structural and vascular anomalies in the brain are potential causes of morbidity in these patients. Ventriculoperitoneal shunt and CSF diversion for hydrocephalus or endoscopic surgical intervention could be lifesaving [33]. The use of blockers should be administered with caution, particularly in children with vascular anomalies who are at a higher risk for strokes. “Go low and slow” method applies, starting at 3 mg or less per day dosing of propranolol with close blood pressure monitoring and frequent neurologic assessment [34]. About a third of the cases with aortic arch anomalies will need surgical intervention. Nonsurgical cases should be followed with an annual echocardiogram. Brain and cervical vascular anomalies are observed in most cases, but there are no long-term reports on the clinical outcomes after propranolol use. Routine follow-up visits may capture new comorbidities, such as headaches, endocrinopathies, hearing disturbances, speech problems, and dental changes [6]. Prognosis is variable and depends on the associated brain malformations, haemangiomas, and arterial and cardiac defects.

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Chapter 22
Proteus Syndrome

Christos P. Panteliadis and Reinhard E. Friedrich

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Introduction

Proteus syndrome (PS) is an extremely rare congenital disorder of cellular growth affecting ectodermal and mesodermal tissues [1–5]. Prevalence of PS (Online Mendelian Inheritance in Man No. 176920) is estimated approximately 1:1,000,000. However, some authors suspect that the disease occurs more frequently than previously assumed because oligosymptomatic patients may escape the correct diagnosis [6]. Like the god Proteus, the syndrome manifests in many forms, which often leads to its misdiagnosis [7, 8]. Male to female ratio is 1.9:1. PS is a progressive disorder that manifests as asymmetric, disproportionate overgrowth of tissues derived from any germline layer. Progressive segmental or patchy overgrowth most commonly is affecting the skeleton, skin, adipose tissues, and central nervous systems [9–12].

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Macrodactyly, vertebral anomalies, hyperostosis, and asymmetric development of vasculature, muscle, adipose, and connective tissues are some of the characteristics of the disease. Although overgrowth of body segments or organs is the most striking finding of PS, local underdevelopment of organs or body regions also occurs [13]. Because of the rarity of this disease, only few authors have contributed more than one-on-one observations to the description of the syndrome [14–17]. Therefore, the natural history has yet to be completely delineated. The diagnosis of PS is based on clinical criteria, such as mosaic/segmental distribution of lesions, sporadic occurrence, progressive course, and additional specific clinical features (Table 22.1).

Genetics

PS is a representative of the group of genetic diseases that are characterized by manifestations of lethal genes surviving by mosaicism [18]. In describing PS, Happle [13] designated the allelic mutations as "Pleioproteus alleles" (a term

Table 22.1 Diagnostic criteria to establish Proteus diagnosis according to Biesecker and Sapp (2019) (for clinical diagnosis of Proteus syndrome, the following combinations of findings are the minimum: all of the general criteria and specific criteria from categories A–C – one from category A, or two from category B, or three from category C)

General criteria (mandatory)	Category A	Category B	Category C
Mosaic distribution of lesions	Cerebriform connective tissue nevus (CCTN)	Linear epidermal nevus	Dysregulated adipose tissue (either of the following): Lipomatous overgrowth Regional lipoatrophy
Sporadic occurrence		Asymmetric, disproportionate overgrowth[a] (≥1 of the following): Limbs Hyperostosis of the skull Hyperostosis of the external auditory canal Megaspondylodysplasia (i.e. abnormal growth of vertebrae) Viscera: Spleen/thymus	Vascular malformations (one of the following): Capillary malformation Venous malformation Lymphatic malformation Bullous pulmonary degeneration
Progressive course		Specific tumours with onset before the second decade (either of the following): Bilateral ovarian cystadenoma Parotid monomorphic adenoma	Facial phenotype (all of the following): Dolichocephaly Long face Downslanting palpebral fissures and/or minor ptosis Depressed nasal bridge Wide or anteverted nares Open mouth at rest

[a]The authors of the classification emphasize that asymmetric, disproportionate overgrowth should be carefully distinguished from asymmetric, proportionate, or ballooning overgrowth.

derived from the Greek word "πλεϊον", meaning plus) or "Elattoproteus alleles" (after the Greek word "λαττον" or "λασσων", meaning minus) to distinguish findings that are characterized by local hypertrophy or hypotrophy. It is worth mentioning that Professor Rudolf Happle, to this day, uses ancient Greek terminologies to characterize various syndromes. The coexistence of Pleioproteus and Elattoproteus has tentatively been explained as a twin-spot phenomenon [13, 18].

About 90% of cases have a somatic activating mutation (c.49GV → A, p.Glu17Lys) in the oncogene AK strain transforming 1 (AKT1) (cytogenetic location, 14q32.33), encoding the AKT1 kinase (previously used synonym, RAC-alpha serine/threonine protein kinase), an enzyme known to mediate cell proliferation and apoptosis [17, 19]. Recent studies show allelic heterogeneity of PS in AKT1 mutations, so lack of evidence of the characteristic mutation should no longer be interpreted as an exclusion diagnosis of a case of PS [20]. In diagnosing PS patients, differentiations from other overgrowth syndromes are of great importance. Overlaps in the phenotype and uncertainties in the diagnosis of oligosymptomatic patients have contributed to the fact that the disease is still poorly defined [7]. Even the CCTN, which was previously known as the hallmark of the disease and highlighted as a specific finding (Category A) for PS (Table 22.1) [12], has recently been detected in another disease [21], whose genetic basis is also changes in the PI3K/PTEN/AKT/TSC/mTORC1 signalling pathway [22].

A major difference between PS and several other syndromes is the somatic mosaic status in contrast to, for example, the autosomal dominant inheritance of phosphatase and tensin homologue (PTEN) gene-associated hamartomas [7, 23]. On the other hand, certain overgrowth-associated diseases defined by somatic mutations like in PS, e.g. the so-called PIK3CA-related segmental overgrowth spectrum (PROS) [24, 25] including CLOVES syndrome, manifest prenatal asymmetric overgrowth [26] that usually is primarily [1] proportionate in nature in postnatal life [17], whereas disproportional body asymmetry is a hallmark of PS starting several month after birth [17].

Clinical Characteristics

The partial/localized overgrowth can involve the subcutaneous tissue, connective tissue (including bone) [27, 28], the central nervous system [10], and viscera [29]. The disproportionate developments of localized/segmental body regions usually only arise a few months after birth of an initially inconspicuous, normally developed child with properly proportioned body parts [17] (Fig. 22.1). It is characterized by severe deformities, such as hemihypertrophy with macrodactyly [2]; hyperostosis of the calvarium, facial bones, and mandible; vertebral anomalies; partial gigantism; hemimegalencephaly [10]; abnormally distributed adipose tissue (lipomas); vascular anomalies [8, 30]; and skin findings [12]. Less conspicuous phenotypes are diagnosed late [6] or not recorded at all [17]. It is essential to differentiate this syndrome from other congenital hamartomatous diseases like neurofibromatosis, Klippel-Trenaunay-Weber syndrome, enchondromatosis, Maffucci's syndrome, and Bannayan syndrome [18, 31].

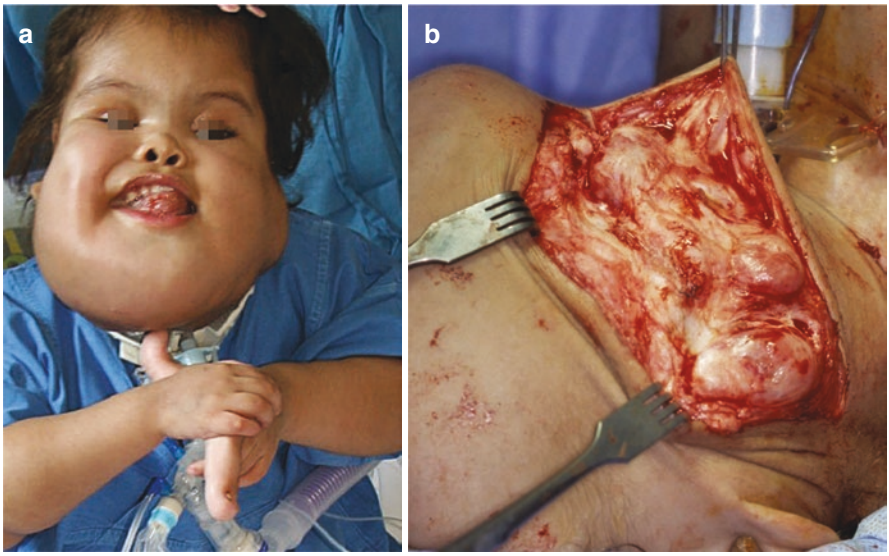

Fig. 22.1 (**a**) Young girl with Proteus syndrome: unilateral hyperplasia of two left digits, massive lipomatous tumour of submandibular region and cheek, hyperplasia of tongue (and open mouth at rest), downslanting of upper eye lids with mild ptosis, depressed nasal bridge, and long face. Patient has been tracheotomized due to rapid tumour growth, causing insufficient breathing. (**b**) Exposed right submandibular region illustrating the tumorous site prior to debulking procedure. The tumour is predominantly consisting of masses of disorganized fatty tissues

Biesecker [5] and Turner [14] have provided a working diagnostic tool that is comprised of three general and three specific criteria. Two of the specific criteria are further subtyped. The general criteria are based on the mosaic/segmental distribution of the lesions, a sporadic occurrence of the disease, and a progressive course of findings. Specific criteria are subdivided into three categories: A (cerebriform connective tissue naevus), B (linear epidermal naevus), and C (dysregulated adipose tissue; Table 22.1).

In addition to the noticeable, disproportionate increase and deformation of bones, numerous soft tissue increases are another facet of PS. Multiple cutaneous manifestations include verrucous epidermal naevi, mesodermal hamartomas such as lipomas, connective tissue hyperplasia (cerebriform), vascular malformations, fibromas, and lymphangiomas [8]. Lipomas are the most common tumour type in PS. The subcutaneous masses may affect the neck and face (Fig. 22.1). The soft tissue growths assessed as "lipomas" characterized by dominant proportion of adipocytes do not correspond to the typical characteristics of a lipoma with pseudocapsularly defined volumes [17]. The lesions are typically non-capsulated fatty and fibrous masses with vascular channels, often lymphangiomatous. The subcutaneous masses may develop unexpectedly and grow rapidly [9]. The frequently recorded uneven increase in subcutaneous soft tissue with wrinkling of the skin on the sole of the foot creates an image on the surface of the body that is reminiscent of the uncovered brain [12]. The finding is termed "cerebriform connective tissue naevus" (CCTN),

considered to be pathognomonic for PS and which occupies the only diagnostic field of category A of specific clinical findings in diagnosis (Table 22.1).

Complications of PS include progressive skeletal deformities, invasive lipomas, benign and malignant tumours, and deep venous thrombosis with pulmonary embolism [13]. The growth of muscles is excessive, without weakness. However, myopathy was noted in rare cases. It was suggested that myopathy in PS represents a new category of neurocutaneous diseases due to faulty paracrine growth factors [32]. Indeed, both hypoplasia and aplasia of tissue may be observed in PS [33]. Patchy dermal hypoplasia with prominent superficial vasculature appears to be the characteristic cutaneous feature of PS [33].

Other findings of PS include spinal stenosis, primary mental retardation, occipital dysmyelination and compression of the corpus callosum, and epilepsy [13]. Intellectual impairment and seizures are seen in 20% and 13% of cases, respectively [9]. Skeletal abnormalities, such as kyphoscoliosis (in about 60%), craniosynostosis, decalcification and thinning of the cortical layer of long bones, talipes equines, and dislocated hips, were recorded [28, 34]. Cancers of the thyroid, ovary (bilateral cystadenoma), and parotid monomorphic adenoma in the second decade of life have also been documented [4]. New cases have been described with ophthalmological features (in about 42%), such as blue sclerae, telecanthus, strabismus, epiblepharon, epibulbar cysts, and hemimegaly of the optic nerve [14].

Therapy and Prognosis

Caring for patients with PS presents enormous challenges to clinicians and caregivers because of the various medical and psychosocial consequences of the disease [35]. A multidisciplinary team is essential and must incorporate the specialties of geneticists, neuropaediatricians, haematologists, dermatologists, radiologists, and orthopaedic surgeons [4, 5]. Vascular complications are common in patients with PS, especially through late adolescence. Bullous pulmonary diseases have recently been defined more precisely as relevant for patients with PS [17]. Monitoring for and treating deep vein thrombosis and pulmonary embolism is mandatory, and perioperative anticoagulation is recommended.

Surgical reconstruction of overgrowth anomalies, such as macrodactyly and large lymphangiomas, is warranted to reduce the risk of irreparable complications and to improve the patient's quality of life [5]. However, amputations are unavoidable in individual cases if the overgrowth of the body region leads to severe functional restrictions [36, 37]. There are initial studies of the pharmacologically induced reduction in excess growth in PS [24]. Rehabilitation includes physical and occupational therapy, correction of skeletal deformities such as scoliosis, and dermatological management of the skin manifestations such as CCTN.

Long-term prognosis varies. Approximately 20% of PS patients suffer from premature death [38], most commonly due to venous thromboembolism, pulmonary embolism, cardiac arrest, pneumonia, or surgical complications [4, 14, 29].

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Chapter 23
Wyburn-Mason Syndrome (Bonnet-Dechaume-Blanc Syndrome)

Christos P. Panteliadis and Christian Hagel

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Introduction

The first case was published in 1874 by Hugo Magnus, followed by further sporadic reports over the next decades [for historical background, see Chap. 1]. In 1943, Wyburn-Mason characterized birth anomalies in the eye, brain, and face as a separate entity in a group of nine patients [1]. The main features of Wyburn-Mason syndrome (WMS) or Bonnet-Dechaume-Blanc syndrome [2] comprise congenital unilateral arteriovenous malformations (AVMs) affecting the face, eye, and midbrain. Diagnosis is based on a detailed family and patient history and identification of the key clinical morphology (especially ocular findings). Computed tomography (CT) and magnetic resonance imaging (MRI) are important tools to detect/exclude cerebrovascular malformations. WMS patients may show all features of the syndrome (including facial AVM, typical WMS) or just some of the alterations

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(incomplete WMS). Reviewing 121 cases, Schmidt et al. [3] found 27 typical manifestations of WMS, 25 without skin lesions, 57 patients with isolated retinal AVM, and 12 patients with retinal lesions and neurological symptoms, but no intracerebral AVM. Only few cases of bilateral involvement have also been reported in literature.

Clinical Characteristics

The syndrome includes a retinal AVM (unilateral dilated and tortuous retinal vessels) and one or more ipsilateral AVMs of the brain and/or the face. Retinal vascular malformations characteristically present as dilated and tortuous vessels over the optic disc extending variably to the retinal periphery [4]. The retinal malformation may be asymptomatic or produce minimal to severe visual impairment [5–7]. The ipsilateral cephalic AVMs may involve the visual pathways from the retina and optic nerve to the ipsilateral occipital cortex and may involve the chiasm, hypothalamus, basal ganglia, midbrain, and cerebellum. In a study by Lester et al. [8], a patient with an AVM extending from the orbit to the hypothalamic region along the optic nerve was described. Since AVMs are high-flow systems in which veins are exposed to arterial blood pressure, they are susceptible to turbulent blood flow and to vessel wall damage, which can lead to thrombosis and occlusion, as well as to profound bleeding such as life-threatening epistaxis or gingival haemorrhage. Over time, components of an AVM may grow, bleed, sclerose, thrombose, or involute [9].

Standard methods for visualization of cerebral AVMs are carotid angiography, CT angiography, and MR digital subtraction angiography [10]. Ocular AVMs are demonstrated by ophthalmoscopy or in smaller lesions by means of fluorescein angiography.

Bhattacharya et al. [11] suggested that Wyburn-Mason may be a metameric syndrome of the neural crest or adjacent cephalic mesoderm involving the (1) facial region (facial skin, maxillofacial region), (2) the orbital region (retina, optic nerve), and (3) the cerebral region (hypothalamus/chiasm/pituitary, thalamus, occipital lobe, midbrain, cerebellum). Hitherto, an inherited basis of the disorder has not been shown.

The differential diagnosis of WMS includes von Hippel-Lindau syndrome, (see Chap. 28), Sturge-Weber syndrome (see Chap. 5), vasoproliferative tumours (VPT) including uncommon primary retinal lesions, conditions secondary to other ocular alterations, and retinal cavernous haemangioma, a benign vascular lesion that is mostly unilateral [4]. VPT are nodular retinal lesions composed of capillaries, hyalinized blood vessels and glial cells, which are observed in retinitis pigmentosa and Coats disease among others. Retinal cavernous haemangiomas consist of convolutions of atypical enlarged veins. Coats disease is an idiopathic retinal vascular disorder with telangiectasia or intraretinal and/or subretinal exudation.

Therapy

Clinical management should comprise of regular follow-up evaluations by an interdisciplinary team, including radiologist, geneticist, ophthalmologist, and neurosurgeon. Therapeutic strategies of AVM include observation of unruptured asymptomatic lesions and endovascular, surgical, and radiation techniques [4, 12, 13]. Treatment is directed towards the specific symptoms that are apparent in each individual. Some AVM may not require treatment, especially retinal lesions which usually remain stable [4]. Bleeding of retinal AVMs is controlled by laser or cryosurgery. Surgical removal of the vitreous (vitrectomy) has been performed in some cases if bleeding persists, although this approach is controversial. Nonsurgical interventions are radiotherapy in cases with endocrine abnormalities in hypothalamic-pituitary axis. Anti-VEGF agents have been successfully used for treatment of macular oedema [13].

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Chapter 24
Cerebello-Trigemino-Dermal Dysplasia (Gomez-López-Hernández Syndrome)

Christos P. Panteliadis

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Introduction

Gomez has been credited for the first description of Gomez-López-Hernández syndrome in 1979, in a girl with focal congenital alopecia, trigeminal anaesthesia, cerebellar ataxia, brachycephaly, hypertelorism, and convergent strabismus [1]. However, the syndrome was initially featured by Kayser half a century earlier [2]. Three years after, Gomez-López-Hernández independently reported on two Mexican girls with craniosynostosis, ataxia, trigeminal anaesthesia, and parietal alopecia with pons-vermis fusion anomaly [3]. The three main diagnostic criteria—(1) focal scalp alopecia, (2) trigeminal nerve anaesthesia, and (3) rhombencephalosynapsis (partial or complete lack of the cerebellar vermis with fusion of cerebellar hemispheres and fusion of dentate nuclei)—were complemented by additional inconsistent features in the following years [4–7], including craniosynostosis, symmetrical midface hypoplasia, and temporal muscles, brachycephaly or turribrachycephaly, corneal opacities, hypertelorism, low-set ears, mental retardation, and short stature. Although some findings point to a genetic basis of the syndrome, its aetiology remains unknown [8].

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Clinical Characteristics

The most characteristic anomaly is rhombencephalosynapsis, which develops between the gestational age of 28 and 41 days [9]. Rhombencephalosynapsis (RES) was long regarded as a constant feature of Gomez-López-Hernández syndrome (GLHS); however, a literature review recently reported 1 case out of 57 without RES [10]. Hence, it was proposed that GLHS should be considered in patients presenting with at least two of the following four alterations [8]:

1. Focal scalp alopecia (often symmetrically in the parietal-occipital regions)
2. Rhombencephalosynapsis
3. Craniofacial anomalies (brachyturrycephaly, brachycephaly, or midface retrusion)
4. Trigeminal anaesthesia or anatomic abnormalities of the trigeminal nerve

Clinical manifestations not only include symptoms attributable to the cerebellar anomalies, like ataxia and muscle hypotonia, but also comprise mental retardation, seizures, behavioural/psychiatric problems like depression (in early childhood aggressive behaviour), short stature, autism spectrum disorder, and hyperactivity [4–7, 11].

The aetiology of GLHS remains unknown. Without a clear genetic marker or universally accepted clinical criteria, the diagnosis should be entertained cautiously. Genetic, teratogenic, and mixed origins have been hypothesized [10, 12]. De Matos et al. [13] presented a case with a family history of consanguinity, which reinforces the possibility of an autosomal recessive inheritance. At present, a diagnosis can only be reached on grounds of typical dysmorphic signs (rhombencephalosynapsis, brachycephaly and/or turricephaly or midface retrusion, and alopecia), which necessitate neuroimaging (MRI) [14, 15], and by clinical investigation for trigeminal anaesthesia. A prenatal three-dimensional ultrasound investigation is recommended. Some authors described an overlap with RES and VACTERL (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities). This association between VACTERL and RES is the only feature. RES shows a conjunction with more other anomalies [16].

Therapy

An exact description of all symptoms and lesions is essential. Follow-up investigations should include EEG, ophthalmological investigation, psychological follow-up, genetic counselling, and management of behavioural problems. In general, therapy is symptomatic.

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Chapter 25
Vascular Tumours (Haemangiomas)

Markus Schneider

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Introduction

Since 1982, the descriptive term "vascular anomalies" was divided into two groups: (a) vascular malformations and (b) haemangiomas. Based on growing scientific evidence, those two groups were strictly separated. In 1996, the ISSVA (International Society for the Study of Vascular Anomalies) replaced the term "haemangioma" with vascular tumour to state clearly the difference in comparison to vascular malformations.

Vascular malformations is a collective term for capillary, lymphatic, venous, arterial and arteriovenous malformations [1]. This text only focuses on vascular tumours.

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Epidemiology

Haemangiomas are the most common benign tumours in infancy with a frequency ranging from 2 to 10%. In preterm infants with low birth weight (less than 1500 g), the incidence is about 25–30%. Haemangiomas occur in girls three to four times more often than in boys.

Haemangiomas are defined as proliferating vascular tumours consisting of vascular endothelium. The cause of haemangiomas is still unknown, although there are several theories. Those theories go from localized soft tissue hypoxia to a coincidence of tocolytics like fenoterol (especially in preterm infants). During the last years, scientific evidence has been found for GLUT-1 as a specific marker for haemangiomas in infants, which can be detected reliably at any stage of their growth. This marker cannot be found in other vascular tumours or vascular malformations.

Clinical Characteristics

Usually not visible at birth, 90% of all haemangiomas become visible until the end of the second month of life, initially appearing as light red maculas. Within weeks, they start to grow rapidly (first proliferation phase), followed by a slower growth rate (second proliferation phase). After weeks to months, the haemangioma becomes complete (rest stage, usually between the ninth and 15th month of life (Fig. 25.1). In about 70% of all cases, involution of the vascular tumour follows, which can range from several years up to adolescence, depending on the size and extensiveness of the haemangioma (Fig. 25.2). Nearly 40–50% of all haemangiomas, especially the extensive ones, leave behind scar-like residua, telangiectasia, skin atrophy, hypo- or hyperpigmentation or slack wrinkles, which correlate with the size and shape of the haemangioma at the time of its maximum expansion [2, 3].

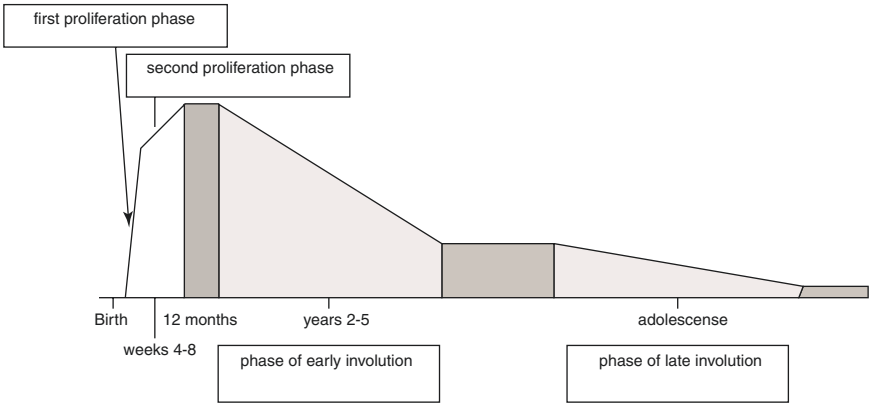

Fig. 25.1 Spontaneous involution of haemangioma

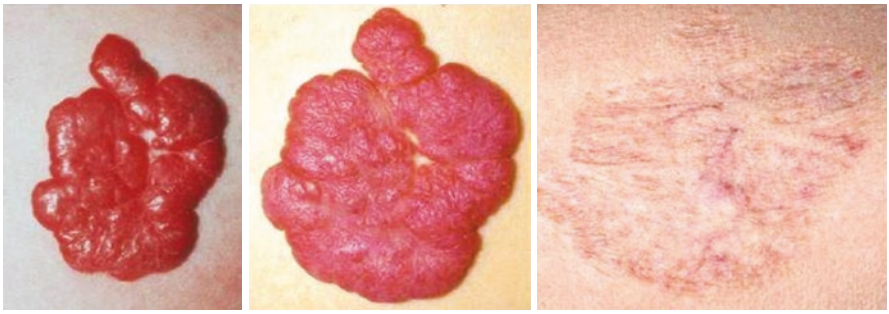

Fig. 25.2 Spontaneous involution of a haemangioma at the trunk without any treatment

The beginning involution is clinically visible by a meshed grey discoloration of the haemangioma. Superficial parts tend to involute faster than cavernous parts. Mainly cavernous haemangiomas (with or without superficial portions) usually present as growing compressible tumours. A final diagnosis is usually made with additional diagnostic methods, such as colour duplex sonography.

The vast majority of the vascular tumours are the so-called localized classic haemangiomas. To classify them from a clinical point of view, we modified a classification published in 2006 (Table 25.1).

Localized haemangiomas usually impress as sharply bounded red maculas appearing on the surface of a central focal point. Mainly superficial cutaneous haemangiomas can be distinguished from mainly cavernous and subcutaneous haemangiomas (with or without superficial portions). Cutaneous haemangiomas are either flat on the skin surface or even elevated and convex.

There are other rare vascular tumours that differ fundamentally from localized classic haemangiomas by their clinical impression, process, histology and prognosis. Those rare vascular tumours are discussed later. About 60% of all haemangiomas are localized in the head/neck area but can appear in any part of the body.

Diagnosis and Differential Diagnosis

The diagnosis of a haemangioma is mainly visual in combination with the typical history of not being visible at birth but growing after a few weeks of life. This makes the differential diagnosis between proliferating haemangiomas and vascular malformations, especially port-wine stains, easier. Short period of clinical observation (age of the infant in months = control period in weeks) is recommended. Every proliferating haemangioma should be measured and photographed.

Superficial haemangiomas may have subcutaneous parts. For this reason, colour duplex sonography should be undertaken to measure the penetration into the

Table 25.1 Classification of vascular tumours based on a clinical point of view

1. "Classic haemangiomas"
1.1 Localized haemangiomas, mainly superficial (LHs)
1.1.1 Single standing localized haemangiomas
1.1.2 White haemangiomas
1.1.3 Large surface LHs with no sharp borders
1.1.4 Group-like haemangioma papules
1.1.5 LHs with a telangiectasia character
1.2 LHs, mainly cavernous (with or without superficial parts)
1.3 Segmental haemangiomas (SHs)
1.3 Indeterminate haemangiomas
1.4 Abortive haemangiomas
2. Other vascular Tumours
2.1 Haemangiomas fully developed at birth
2.1.1 RICH = rapid involuting congenital haemangioma
2.1.2 NICH = non-involuting congenital haemangioma
2.2 Haemangiomas with distinct histological peculiarities
2.2.1 Tufted angioma
2.2.2 Kaposiform haemangioendothelioma
2.2.3 Spindle-cell haemangioendothelioma
2.3 Infantile haemangiomatosis
2.3.1 Benign haemangiomatosis
2.3.2 Disseminated haemangiomatosis
2.4 Vascular tumours acquired after birth
2.4.1 Pyogenic granuloma

subcutaneous tissue, especially in the critical regions such as the periorbital and peri-inguinal. The choice of treatment will depend on the depth of extension.

Cavernous/subcutaneous haemangiomas attract attention by a light blue colour on a growing compressible tumour. Depth extension and vascularization can be well-evaluated by colour duplex sonography. Often, the strength of the haemangioma vascularization in the course is a good tool to distinguish between haemangiomas that are in the proliferating phase and haemangiomas that are beginning to involute. Vascular trained sonographers could distinguish haemangiomas from other tumours or malformations. MRI is a good diagnostic option, particularly in unclear sonographic results or results that are not completely visible by ultrasound, especially in poorly accessible periocular region or in segmental haemangiomas.

A histological validation is not necessary if the clinical diagnosis is obvious. Immunohistochemical differentiation by GLUT-1 should be done in unclear cases.

Further diagnostic methods depend on the localization and the extensiveness of the haemangioma:

– If there is concern for impending amblyopia, an ophthalmological evaluation is necessary.
– For haemangiomas in the "beard area" and accompanying wheezing, a laryngoscopy is strongly necessary to exclude critical haemangiomas invading the trachea

Table 25.2 Differentiation between haemangiomas and other vascular tumours (selection of the most frequent differential diagnoses)

Vascular tumour	Differentiating factors
Pyogenic granuloma	Usually rapid appearance of a dark red node after infancy Very rapid growth Localization in the face High risk of bleeding
Tufted angioma	Unobtrusive small tumours Rarely more extensive No spontaneous involution Possible coincidence with Kasabach-Merritt syndrome
Kaposiform haemangioendothelioma	Visible at birth in most cases Continuous growing beyond the typical proliferation phase of haemangiomas Frequent coincidence with Kasabach-Merritt syndrome
Spindle-cell-haemangioendothelioma	Appearance mostly in adolescence, rarely in infancy Mainly hands and fingers are affected After apparent involution, the tumours show rapid proliferation again at other localizations

Table 25.3 Differentiation of haemangiomas and vascular malformations

Haemangiomas	Vascular malformations
Distribution between the sexes f/m 3–4:1	No relevant distribution
Appearance days or weeks after birth	Apparent at birth (not always clinically visible)
Rapid growth in the beginning	Growth appropriate to the body growth
High tendency of involution	No involution
No pain (except ulceration)	Frequent periods of pain
GLUT-1 positive	GLUT-1 negative

or the pharynx. -For haemangiomas in the skin area of the tailbone, a sonographic examination of the lower parts of the spine should be done to exclude a tethered cord syndrome.

– If there is a cutaneous haemangiomatosis, a visceral affection should be excluded by ultrasound of the abdomen (especially the liver).
– If there is suspicion of a syndrome (PHACE or PELVIS syndrome), accompanying anomalies should be excluded (see further text and Chap. 25).

The important differentiating factors to distinguish haemangiomas from other vascular tumours or vascular malformations are summarized in Tables 25.2 and 25.3.

Management

The vast majority of haemangiomas are not associated with complications and do not need any treatment, especially when located at an uncomplicated body region or when there is no relevant growth. In these cases, a close inspection of the

Table 25.4 Impending risks of a non-treatment of complicated haemangiomas

Body region	Impending risks
Eyes, periocular area	Line-of-sight obstruction followed by amblyopia and "functional blindness"
Tip of the nose	Development of a "Cyrano" nose Persistence of fatty tissue with cosmetic defacement
Lips and mouth	No spontaneous involution frequently Cared transformation Impending organ involvement (feeding problems)
Ears	Ulceration
Anogenital area	Ulceration
Unilateral segmental haemangioma of the face	Rapid proliferation frequently Risk for orifices of the body PHACE syndrome
"Beard area"	Breathing problems (haemangiomas inside the trachea and pharynx)
Tailbone area	Tethered cord syndrome
Hands and fingers, feet and toes	Rarely organ involvement because of loss of sensitivity
Cleavage region	Scars with cosmetic problems

haemangioma in the proliferation phase and a strict therapeutic intervention are sufficient [4].

The medical therapy on haemangioma in infancy has changed rapidly in the last few years. Today, for potentially complicated infantile haemangiomas, there are treatment options that are well tolerated with small rates of side effects [5]. These treatment options can be offered early if medically necessary and from a cosmetic point of view in selected situations. The main treatment goal is to assure growth arrest as soon as possible and, ideally, to achieve early involution of the haemangioma. Even more important is to prevent the infants from possible functional limitations or complications (e.g. ulceration). Usually, there is no indication for further treatment if there are signs of haemangioma involution.

Indications for treatment include haemangiomas that are objectively proliferating in the facial area, especially orifices of the body (eyes, lips and mouth, ears, nose). This is also valid for haemangiomas in the anogenital region, haemangiomas of the hands and feet, and extensive segmental haemangiomas. The possible treatment of haemangiomas in the cleavage region of girls should be discussed with the parents. There are also treatment indication for haemangiomas in the "beard area" and haemangiomatoses with organ involvement. Impending risks of a non-treatment are shown in Table 25.4.

Treatment options are available, ranging from topical ointments to plastic surgery. They are discussed below.

Cryotherapy

Cryotherapy destroys the proliferating angioma cells (endothelial tissue, rich of liquid). As the connective tissue and the keratinocytes are not affected, there are no scars when this treatment option is properly used. The penetration of the cryotherapy is about 3 mm, depending on the body region and the pressure that can be used; if situated above bone, penetration of 5 mm is possible with pressure. Superficial haemangiomas that are not larger than 2 cm in diameter can be treated by cryotherapy [4].

Cryotherapy with liquid nitrogen (−196 °C) has been nearly completely replaced by cryotherapy using cold metal elements (−32 °C) for 15–20 s, with much better outcomes and less adverse effects, like ulceration, hypopigmentation, and scarring. Application of local anaesthetics such as lidocaine for about 30–60 min before treatment minimizes pain associated with cryotherapy.

The cold applicator is pressed on the haemangioma with a constant pressure. In clammy body regions, one can prevent the applicator from adherence to the skin by rotating the applicator or by swabbing. The cryotherapy can be repeated as often as necessary, for example, every 2–4 weeks. In most cases, a single or two-time treatment is sufficient. Figure 25.3 shows a patient with a haemangioma before and after cryotherapy.

Laser Therapy

Laser treatment lost importance since there is propranolol as treatment option [6]. Only in exceptional cases, it is the therapy of choice. It is often used as a secondary treatment for residues.

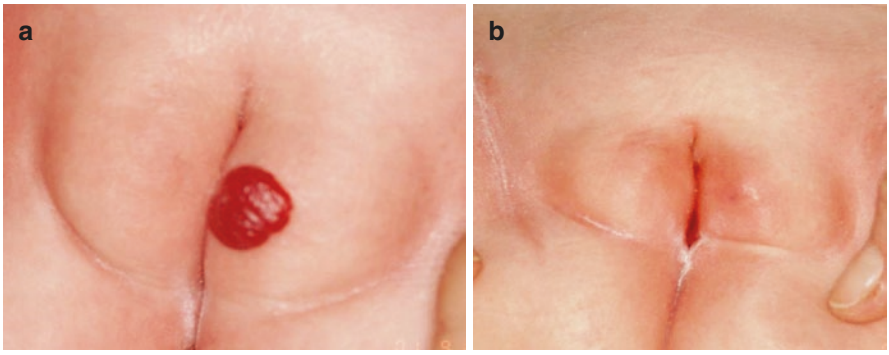

Fig. 25.3 Haemangioma of the genital area. (**a**) Before treatment, (**b**) 4 weeks after cryotherapy

Flashlamp-Pulsed Dye Laser (FPDL)

This dye laser (at a wavelength 585 nm) is absorbed almost completely by the haemangioma, leading to a selective photothermolysis of the intradermal vessels. The depth of penetration is quite low (2 mm). The FPDL is the therapy of choice for port-wine stains. Extensive superficial haemangiomas can also be treated by FPDL. Adverse side effects as hypo- or hyperpigmentation are possible. Depending on the extensiveness of the haemangioma and the duration of the treatment, a general anaesthesia may be necessary.

CW Nd/YAG Laser

This laser (at a wavelength of 1064 nm) can be used in haemangioma therapy in two ways: (a) In percutaneous Nd/YAG laser treatment with a preceding cooling using ice cubes, the laser beam is conducted through the ice cube. The depth of penetration is about 7 mm. (b) In interstitial laser treatment, through a puncture cannula, a glass fibre is placed inside the haemangioma. Deeper areas of massive haemangiomas can be treated without the risk of thermal skin damage. Anaesthesia is needed because both laser treatments are associated with pain.

Plastic Surgery Treatment

Plastic surgery is used in exceptional circumstances and is not the therapy of first choice [6, 7]. It is used to remove extensive haemangiomas in the ocular or lip/mouth region that do not show signs of involution. The aim is to prevent permanent loss of organ function.

Haemangiomas on the hairy portion of the scalp frequently lead to hair growth disorders and to scarred alopecia. After the involution phase, plastic surgery treatment can be done in these cases. It is also used as combination therapy to treat residual lesions after Nd/YAG laser treatment or cryotherapy.

Systemic Propranolol Treatment

The option of systemic treatment with propranolol for problematic haemangiomas has been in existence since 2008. This milestone created a revolution in the previously existing treatment concept for haemangiomas. Publications have demonstrated the impressive response of haemangiomas to treatment with propranolol [8–17]. Systemic therapy is an extremely effective treatment option with minimal side effects.

As a result of good tolerability and high responder rate in haemangiomas, systemic propranolol treatment has nearly completely replaced other drug therapies, such as cortisone, interferon or vincristine [18–21]. Since 2014, systemic propranolol treatment has received the seal of approval from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and is the gold standard for proliferating infantile haemangiomas requiring systemic therapy. Indications for propranolol treatment include life-threatening haemangiomas, haemangiomas with the risk of functional loss, ulcerated haemangiomas and haemangiomas with the risk of cosmetic complications.

Contraindications for propranolol treatment should be evaluated. Currently, the recommended dosage is 2–3 mg/kg per day, divided into two oral single doses. Oral administration of propranolol should be instituted under hospitalization for the first 2–3 days. The initial dose is 1 mg/kg per day, divided in two single doses. The interval between the single doses should be 9 h or more. On day 2, the dose is increased to 2–3 mg/kg per day, divided into two single doses. A diagnostic cardiological investigation (electrocardiogram and echocardiography) and continuous monitoring (respiratory rate, blood pressure, heart rate monitoring and blood glucose levels) should be performed on every patient during the patient's hospital stay.

For patients with diminished liver or kidney function, the elimination rate of propranolol is possibly lower. In these cases, a reduction of the dosage is necessary.

Usually, within a few days, the haemangiomas show involution to the treatment. The mode of action is still a matter of ongoing debate, but the suspicion is that there is a combination of vasoconstriction and enhanced apoptosis by the expression of VEGF. Exemplary clinical outcomes during systemic propranolol treatment are shown in Figs. 25.4 and 25.5.

The duration of treatment is set individually depending on the clinical course and possible side effects. Usually, there is a vast involution of the haemangioma within the first 6 months. In very extensive haemangiomas, the treatment may need to be continued until the 12th month of life. Similar to other haemangioma therapies, early intervention is crucial.

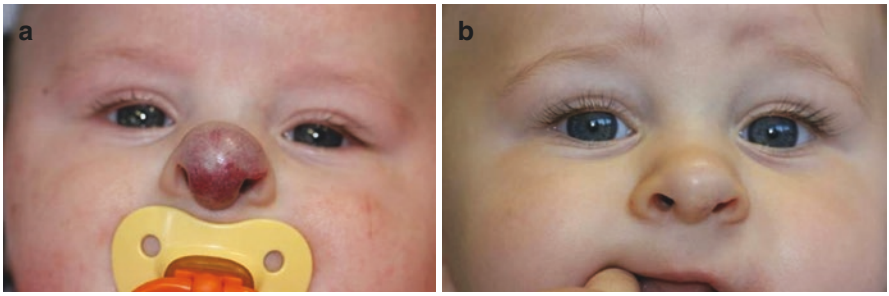

Fig. 25.4 Haemangioma of the nose. (**a**) Before treatment, (**b**) After 6 months of systemic propranolol treatment

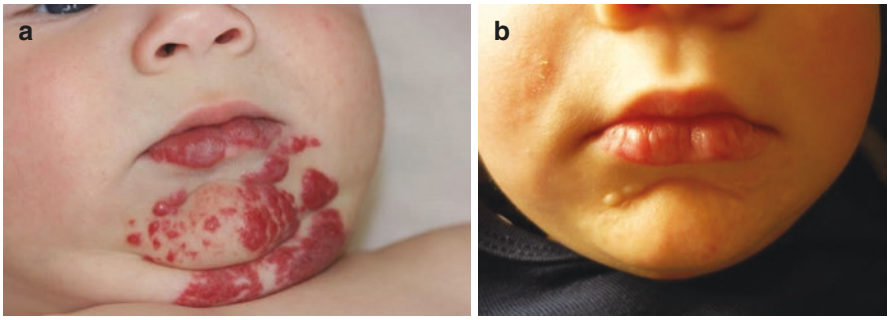

Fig. 25.5 Haemangioma of the "beard area". (**a**) Before treatment, (**b**) After 6 months of systemic propranolol treatment

In paediatrics, propranolol is the beta-blocker with the most and longest experience. For cardiac indications, propranolol has been used for more than 50 years in paediatrics. The spectrum of adverse effect is known, especially hypoglycaemia, hypotension and bradycardia. The overall experience in Europe and all over the world confirms the excellent tolerability of the treatment. Extensive provision of information to the parents is crucial. Propranolol should never be administered on an empty stomach because of the risk of hypoglycaemia. It is therefore recommended to take propranolol only during or after feeding. The time interval between single doses should never be less than 9 h. In case of severe gastrointestinal symptoms, pneumonia, bronchitis or any other severe illness, the treatment should be stopped and begun again only after consultation with the treating paediatrician and documented symptom resolution.

Topical Propranolol Treatment

Topical propranolol has been shown to be very successful. Timolol eye drops have the potential of clearing haemangioma in the eye [17]. Following this report, several formularies for topical propranolol were developed.

Possible indications for the use of topical propranolol are as follows:

1. Proliferating Haemangiomas that Can No Longer Be Treated with Cryotherapy
   Flat, extensive haemangiomas (> 2 cm in diameter).
   Deep haemangiomas (with a maximum depth of 6 mm on ultrasound)
2. Extensive haemangiomas that need to be treated and for which systemic treatment with propranolol is not yet indicated.
3. Localized and segmental haemangiomas with the exception of the face, especially:
   Haemangiomas in the gluteal and genital region.
   Haemangiomas on the hands and feet.
4. Treatment in Patients with Renewed Growth after Cryotherapy or Laser Therapy

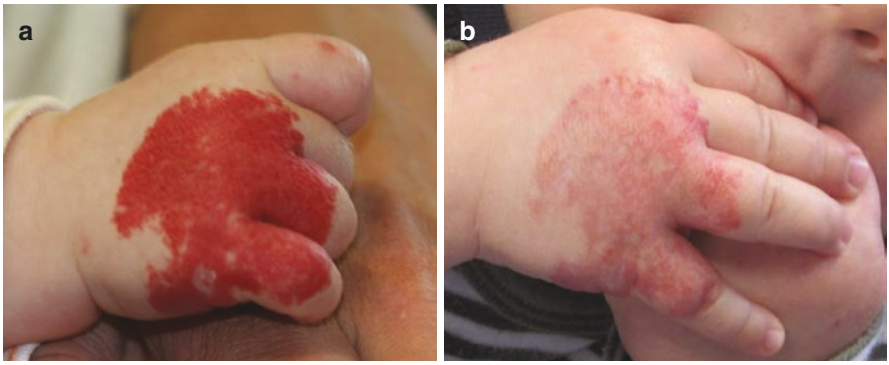

Fig. 25.6 Haemangioma of the right hand. (**a**) Before treatment, (**b**) After 3 months of topical propranolol treatment

Experience to date shows good response rates to the topical propranolol treatment with documentation of rapid and ongoing involution of the haemangioma (Fig. 25.6). The rate of side effects seems to be as less as with systemic propranolol [10, 20].

Actually, the topical propranolol treatment is only used in individual treatment attempts on an off-label base.

Other Drug Treatment Options

In the last few years, systemic propranolol treatment for haemangiomas has replaced other drug treatment options, like the use of cortisone, vincristine or interferon-alpha, nearly completely because of good tolerability and high response rate. Only in isolated cases or in non-responders to propranolol, systemic cortisone therapy is used. Therefore, this treatment option is only mentioned briefly. The possible indications for a cortisone treatment are identical with the indications for systemic propranolol treatment.

Initially, cortisone is started with a dosage of 2–3 mg (5 mg maximum) prednisolone equivalent per kg body weight daily for 2 weeks, followed by a reduction of the dosage and a slow wean over weeks to months. The response rate is about 60–85%.

Special Types of Vascular Tumours

Segmental Haemangiomas in the "Beard Area"

In this location (Fig. 25.5), there is a risk of up to 60% for airway obstruction because of the possibility of additional haemangiomas in the airways. Those infants should be monitored carefully. If there is the slightest suspicion for airway

haemangiomas (e.g. wheezing), a bronchoscopy is essential. If there is confirmation of an endotracheal haemangioma, systemic propranolol treatment or a laser therapy are recommended as early as possible.

Haemangiomatosis

If there is a disseminated haemangiomatosis with visceral involvement in infancy, shortly after birth, several small, mainly flat superficial haemangiomas may be visible on the skin. Only through sonography can a visceral affection (mainly in the liver) be detected. The prognosis has improved with systemic propranolol treatment.

In contrast, benign haemangiomatosis only appears on the skin. The haemangiomas look like little pearls, similar in appearance to pyogenic granulomas. Usually, there is spontaneous involution like in other haemangiomas, and there is no need for treatment. Especially during the proliferating phase, at least serial sonography of the liver should be performed.

Rapid Involuting Congenital Haemangioma (RICH)/ Non-involuting Congenital Haemangioma (NICH)

These tumour-like haemangiomas are completely developed at birth. The proliferating phase had already stopped in utero, and the maximum dimension is present at birth, or there may be signs of involution at birth already with no growth after birth. Usually, these dense grey/blue tumours are permeated with telangiectatic vessels and show a typical white rim. These haemangiomas usually show a rapid involution over a period of several months, leaving atrophic scars or excess skin (RICH). If there is no involution of the haemangioma, it is called NICH.

The knowledge about these special and not all that rare haemangioma forms is essential to prevent unnecessary diagnostic tests and treatment in affected infants.

In principle, critical monitoring is necessary to avoid missing rare forms of malignant tumours.

Haemangiomas in Association with Syndromes

Especially for segmental haemangiomas in the facial area (PHACE(S) syndrome, Fig. 25.7) and less often segmental haemangiomas in the gluteal region (PELVIS syndrome, Fig. 25.8), an association with possible combined malformations is potential (see Chap. 21).

Possible combined malformations in PHACE(S) syndrome are as follows:

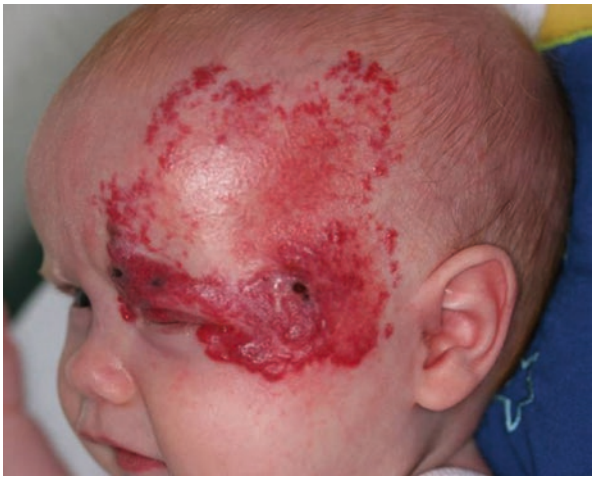

Fig. 25.7 PHACE(S) syndrome

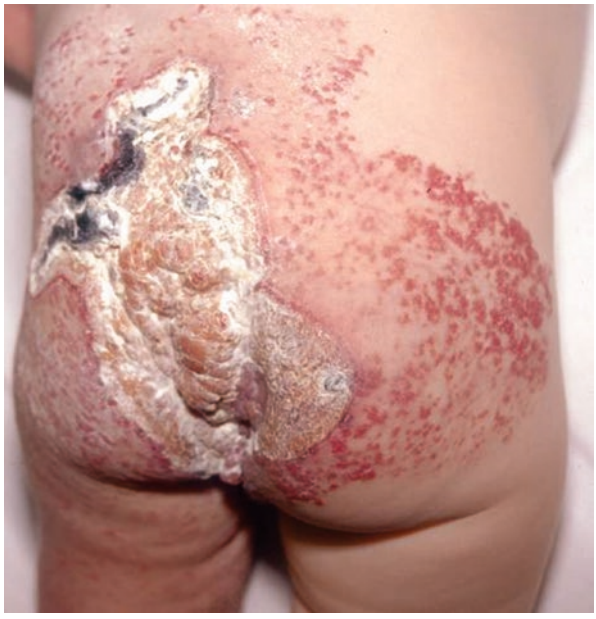

Fig. 25.8 PELVIS syndrome

Posterior fossa malformations (e.g. Dandy-Walker-malformation, hypoplasia of the cerebellum)
Haemangiomas (usually segmental in the facial area)
Arterial anomalies (malformations of the aorta like coarctation of the aortae, aneurysms)
Cardiac anomalies
Eye anomalies (cataract, hypoplasia of the optic nerve)
Sternal clefts

Possible combined malformations in PELVIS syndrome are as follows:

Perineal haemangioma (haemangioma in the gluteal region)
External genital malformations
Lipomeningomyelocele
Vesicorenal malformations
Imperforate anus
Skin tags (tethered spinal cord syndrome)

Vascular Tumours with Histological Specifics and/or Tendency to Develop Kasabach-Merritt Syndrome

The extremely rare tufted angiomas are located mainly in the upper trunk region or the head and cervical region. The clinical presentation is highly variable, ranging from single small tumours to extensive infiltrating plaques. Sometimes, there is a localized tenderness. Tufted angiomas can lead to the development of Kasabach-Merritt syndrome. A histological analysis is necessary. The therapy of choice is excision.

The kaposiform haemangioendothelioma is extremely rare. It is expressed as an invasive, locally aggressive but not malignant vascular tumour (no metastasis) located in the skin or the retroperitoneal area. Part of the affected infants show kaposiform haemangiomendotheliomas even at birth or shortly after birth. Those blue-violet skin lesions are usually located at the trunk and sometimes in the extremities. Frequently, a life-threatening Kasabach-Merritt syndrome develops. The Kasabach-Merritt syndrome results in disseminated intravascular coagulation (DIC) by activation of the coagulation system. Histological analysis is also necessary. For these tumours, the therapeutic options are limited but have improved during the last years because of new treatment strategies.

Vascular Tumours Acquired After Birth

Pyogenic granuloma is a tumour acquired after birth. It is the second most common vascular tumour in children older than 1 year and quite rare in the first 12 months of life. The aetiology is related to small vessel injuries (e.g. by scratching) or de novo development. Pyogenic granulomas are localized, dark red berry-like tumours mainly in the facial area. They tend to grow extremely fast and show an increased bleeding tendency. Therapeutic options include curettage, laser, cryotherapy or excision. The distinguishing factors between pyogenic granuloma, haemangiomas and port-wine stains are summarized in Table 25.5.

Table 25.5 Distinguishing factors between pyogenic granuloma, haemangiomas and port-wine stains

	Haemangioma	Port-wine stain	Pyogenic granuloma
Appearance	First weeks of life	At birth	After first year of life (rare during the first 12 months)
Size	Variable	Variable	Usually maximum pea-sized
Aspect	Papular, macular	Erythematous	Berry-like
Growth	Yes (rapid or slow, until the 9th–15th month of life)	No	Eruptive, very fast, within days
Localization	Every location possible	Frequently unilateral, often segmental	Frequently facial area (mainly periocular and lip region)
Bleeding Tendency	Very rare, sometimes in case of ulceration	Never	Very often
Combined malformation	Rare	Rare	Never

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Part III
Tumour Suppressor/DNA-Repair Disorders

Chapter 26
Neurofibromatosis I and II

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Neurofibromatosis I (NF1) (von Recklinghausen Disease)

History of NF1

Since the early thirteenth century, illustrations of patients with skin tumours are known of [1] and are thought to be the earliest documentation of the NF disease. Patients with NF1 have been mainly documented in the middle ages with disfiguring tumours. The condition itself was formally described by Daniel von Recklinghausen in 1882 [2]. He showed that tumours arise from the endoneurium of the peripheral nerve, and he described clinical features of NF1 in detail.

Till the end of the twentieth century, the term "von Recklinghausen disease" (Morbus Recklinghausen) was used because since the first description, it was thought that tumours arising from the nervous systems are a feature of the same disease. Formal diagnostic criteria were adopted in 1988 when the NF1 gene was cloned on chromosome 17q11.2 and consequently detailed descriptions of the NF disease emerged [3, 4].

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Epidemiology

NF1 is an autosomal dominant disorder affecting females and males and all ethnic groups equally. NF1 has an incidence between 1:2500 and 1:3000 [5] and a minimum prevalence of 1:4000–5000 [6]. Moreover, 50% of patients present as sporadic cases. The mutation rate of the NF1 gene is about tenfold higher than that of other disease genes [7].

Special Aspects of Inheritance: Microdeletions and Segmental NF1

In addition to the genetics of neurocutaneous disorders presented in Chap. 1 two particular genetic alterations in NF1 should be mentioned in more detail here:

Microdeletions are observed in approximately 5% of all patients with NF1. These patients show large deletions in chromosome 17q11.2, which include the NF1 gene and its flanking regions [8–10]. Large deletions are often termed "microdeletions" because they are too small to be detected by classical chromosome analysis. The phenotype in patients with microdeletions (1.4 Mb) is associated with facial dysmorphic features (90%), tall stature (46%), large hands and feet (46%), scoliosis (43%), joint hyperflexibility (72%), delayed cognitive development and/or learning disabilities (93%) and mental retardation (IQ < 70; 38%). As compared with the general NF1 patient population, significant increased frequencies of plexiform neurofibromas (76%), subcutaneous neurofibromas (76%) and spinal tumours (46%) were also noted. These patients are at high risk of developing MPNST (21%) [11]. These findings emphasize the importance of deletion analysis in NF1 since frequent monitoring of tumour presence and growth could potentiate early surgical intervention, thereby improving patient survival.

Based on our experience, support of personality in many regards is needed to optimize medical outcome and improve life quality.

Segmental NF1 results from mutations occurring in embryonic development. The timing and extent of the mutation relates to the extent of the disease. Genetic changes occurring early in embryogenesis may produce mild generalized phenotypes, which are not distinguishable from classical NF1. Later mutations result in segmental NF1, which is determined to have a prevalence of 1:36,000 (to 1 in 40,000), and signs are localized to one area or part of the body [12].

Diagnostic Criteria

The Institutes of Health Consensus Development Conference Statement devised the diagnostic criteria of NF1. Based on these criteria, confusion between NF1, NF2 and schwannomatosis is cleared up because the conditions represent different clinical features.

In order to establish the diagnosis of NF1 on clinical grounds, it is necessary to define two of the following criteria:

- A first-degree relative with NF1.
- Six or more café au lait patches (>0.5 cm in children and >1.5 cm in adults).
- Axillary or groin freckling.
- Two or more Lisch nodules (iris hamartomas).
- Optic pathway glioma.
- Two or more neurofibromas of any subtype or one plexiform neurofibroma.
- A distinctive bony dysplasia including sphenoid wing dysplasia or thinning of the long bone cortex with or without pseudarthrosis [13].

Clinical Characteristics of NF1 in Children

Café au lait patches are the first disease manifestation in almost all patients. They develop in the first 2 years of life, and the number and diameter increase in the early childhood (Fig. 26.1). The development of six café au lait spots (>0.5 cm in diameter before puberty or >1.5 cm after puberty) satisfies one of the diagnostic criteria for NF1. In the absence of a family history, most young children with café au lait spots as the only manifestation of NF1 will later develop other disease characteristics [14].

Axillary and inguinal freckling is in most children the second common criteria, which can be detected within the fourth year of life [15]. Freckles can also be found in other regions of the body, including the neck and the breasts of women (Fig. 26.2).

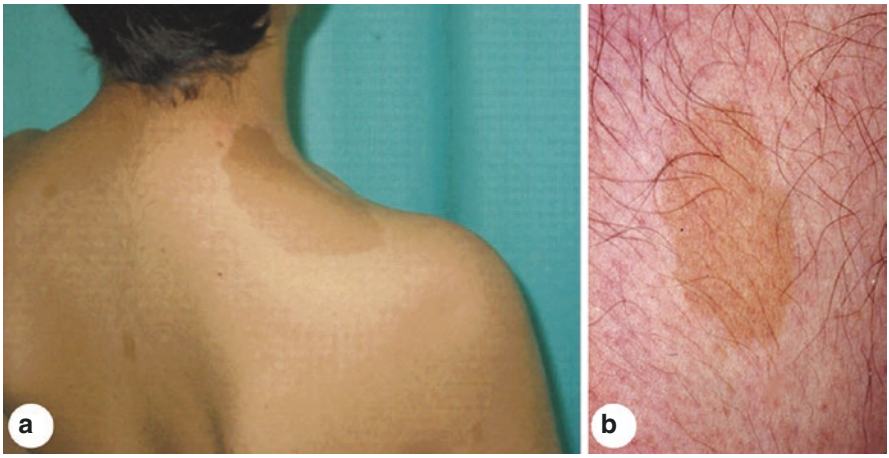

Fig. 26.1 Overview (**a**) and close-up (**b**) of café au lait spots. These alterations are present in almost all NF1 patients. The lesions impress as light brown discoloration of the skin, measuring ≥0.5 cm in children and ≥1.5 cm in adults. In children, café au lait spots are usually the first sign of NF1

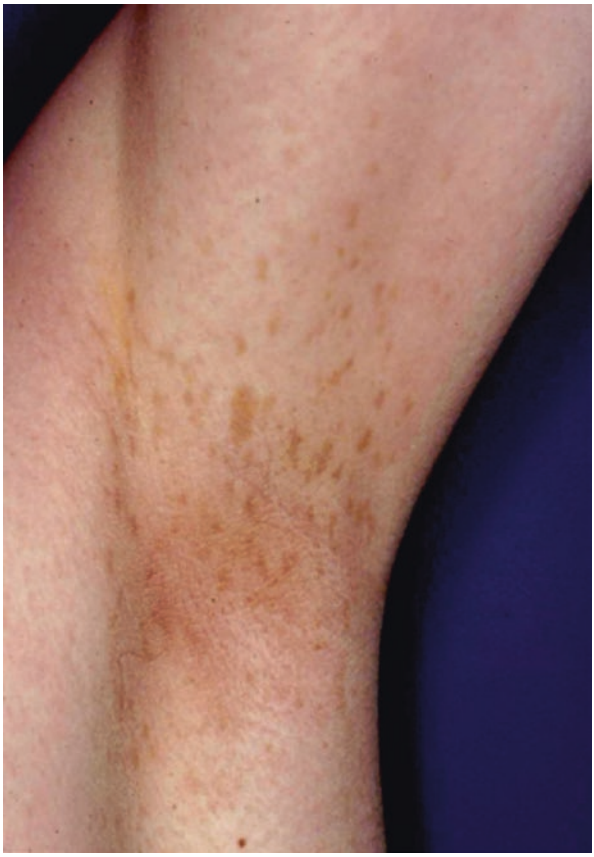

Fig. 26.2 Axillary or inguinal freckling is present in about 85% of NF1 patients

Lisch nodules were first described by an Austrian ophthalmologist who observed melanocytic hamartomas as a typical finding in NF1 patients [16]. Typically, they are first noted in children at age 5–10 years, and nearly all adults present with this ocular manifestation (Fig. 26.3). Lisch nodules do not impair vision and can be detected by slit lamp examination [17].

Neurofibromas manifest as cutaneous neurofibromas rarely prior to the age of 10 years (Fig. 26.4). They rather tend to develop in early adolescence. Because of mast cells being part of neurofibromas, these tumours can be responsible for local pruritus. Neurofibromas have no potential for malignant transformation. The tumour formation during adolescence may lead to a first "attack" on a healthy self-esteem and normal individualization, which might be influenced as well by learning difficulties and social problems. The adolescent needs sensitive education about his/her NF and, in some instances, psychological support.

Subcutaneous neurofibromas may become clearly visible in adolescence, and recent studies indicate that high numbers of these tumours indicate internal tumour burden [18]. Because the presence of subcutaneous neurofibromas was also

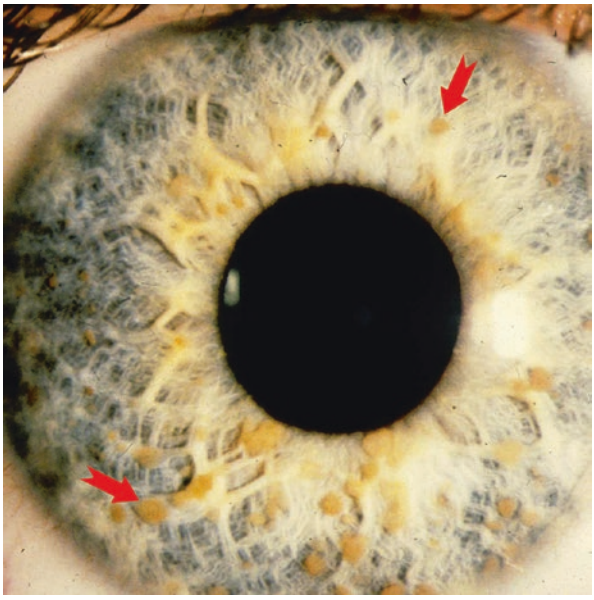

Fig. 26.3 Lisch nodules (arrows) are hamartomatous accumulations of melanocytes in the iris and may be demonstrated in 90–95% of NF1 patients

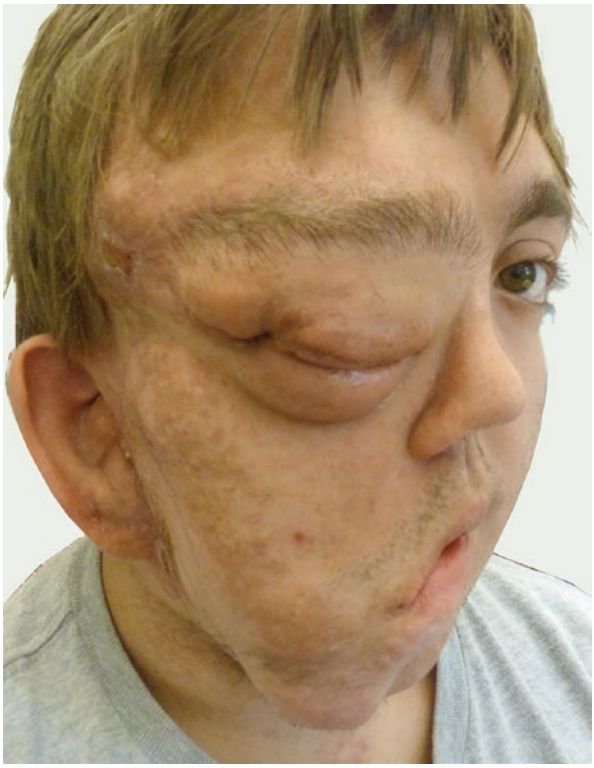

Fig. 26.4 Cutaneous neurofibromas first develop in adolescence in ≥95% of NF1 patients. Spurts of growth may be observed in puberty and pregnancy

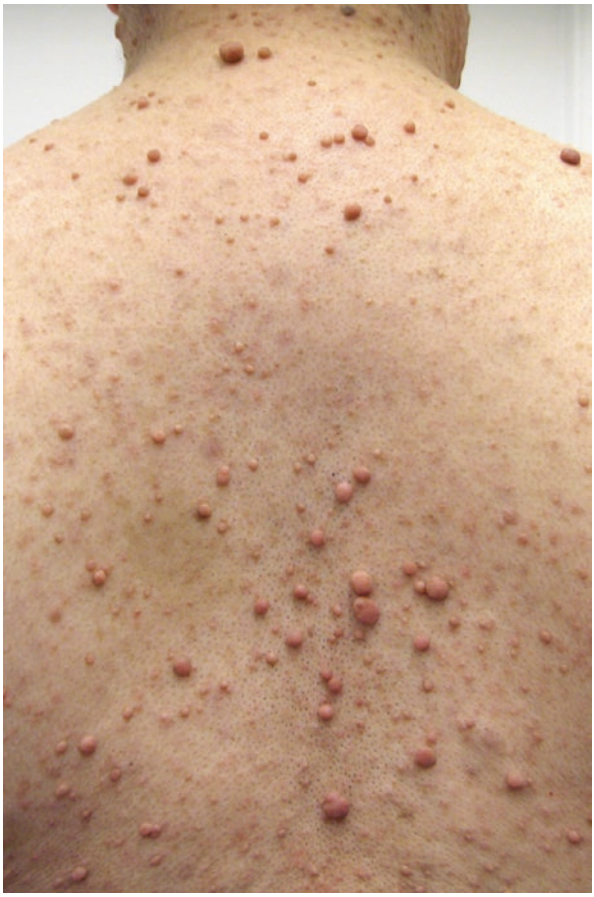

Fig. 26.5 Large plexiform neurofibroma causing severe facial disfigurement in an adolescent

associated with the occurrence of MPNST in adults, those patients might warrant more clinical attention [19, 20].

Plexiform neurofibromas (PNF) manifest almost all in the first years of life within any location of the body (Fig. 26.5). If externally visible, these tumours can be misdiagnosed as lymphangioma. The best therapeutic option for plexiform neurofibromas is the surgical removal, whenever possible [21, 22]. Due to their anatomic location and extension, surgery is sometimes impossible. PNF tend to show net-like growth patterns along nerve roots extending from a main nerve root to a small distal branch. These tumours can be divided in different growth types, which indicate the surgical treatment options: superficial, displacing and invasive [23]. Superficial tumours are frequently palpable and associated with hyperpigmentation, thickening and hypertrophy of the skin and/or hair excess. Each of these symptoms may be the only clinical sign of a superficial PNF that shows only skin involvement.

These tumours can cause disfigurement, pain and functional deficits. PNF are detectable internally in children and adolescents when those patients undergo

whole-body MRI (57%). The tumour burden correlates with specific complications or deficits. Therefore, those children and adolescents with internal PNF are in need of regular monitoring to estimate growth and upcoming complications. First follow-up whole-body examinations indicate that children without internal tumours do not develop internal tumour manifestations during longer follow-up periods (up to 5 years). Hence, children not burdened with internal tumours during first presentation probably belong to the low-risk group with regard to clinical deficits and to the development of PNF. PNF show an inverse growth correlation with age [24, 25].

Over the last few years, several agents, such as farnesyl transferase inhibitors, anti-angiogenesis drugs or fibroblast inhibitors, have been tested in clinical trials to inhibit or decrease PNF growth, without evidence for clinical efficacy [26].

Recent data from a phase l trial with pegylated interferon-alpha 2b showed a tumour shrinkage of 15–22% in a small subgroup of five patients. A tumour size reduction of 20% was observed in a trial with imatinib in a subgroup (6 out of 23) of patients with very small tumours [27].

Selumetinib has shown to shrink PNF in NF1 patients. The drug is indicated for symptomatic or high-risk or inoperable PNFs. The drug reduces size of PNF and improves pain and clinical outcome measures [24, 28]. Other MEK inhibitors like trametinib have also shown clinical benefit in the treatment of PNF [29].

Macrocephalus and short stature are common features of NF1. Macrocephalus is a minor disease feature which can be used to support the diagnosis of NF1 in children, if the diagnosis criteria are not satisfied.

Short stature is a typical feature in NF1 patients, and it may influence the personality development in adolescents. Even though growth hormone deficiency is not frequent, it has to be ruled out. In patients with a growth hormone deficiency, hormone replacement is considered safe, not contributing to accelerated growth of neurofibromas or plexiform neurofibromas or optic pathway gliomas (personal experience).

Pseudarthrosis and/or bowing of the long bones (particularly of the tibia) is observed in about 2% of patients with NF1 (Fig. 26.6). In most of these children, an incident of minimal trauma can lead to a bone fracture [30]. Congenital bowing is usually associated with thickening of the cortex of the long bones. Prophylactic splinting has been advocated in infants at risk in order to prevent fractures [31].

A population study demonstrated recently that children under 16 years of age compared to age-matched controls have a threefold increased risk of fracture [30]. The surgical management should be carried out by specialized orthopaedic surgeons. However, the surgical management of pseudarthrosis is frequently not satisfactory. Currently, there are two main options: the Ilizarov procedure as one treatment approach or, alternatively, treatment by transfer of a vascularized fibular graft from the contralateral extremity. Recently, successful treatment was reported by applicating recombinant human morphogenetic protein [32]. However, long-term follow-up is mandatory to document the positive outcome.

Scoliosis affects 10–26% [33] (Fig. 26.7) of NF1 patients and therefore requires annual follow-up examination during childhood and adolescence. Monitoring the spine is an important part of the clinical evaluation of NF1 patients. Patients with

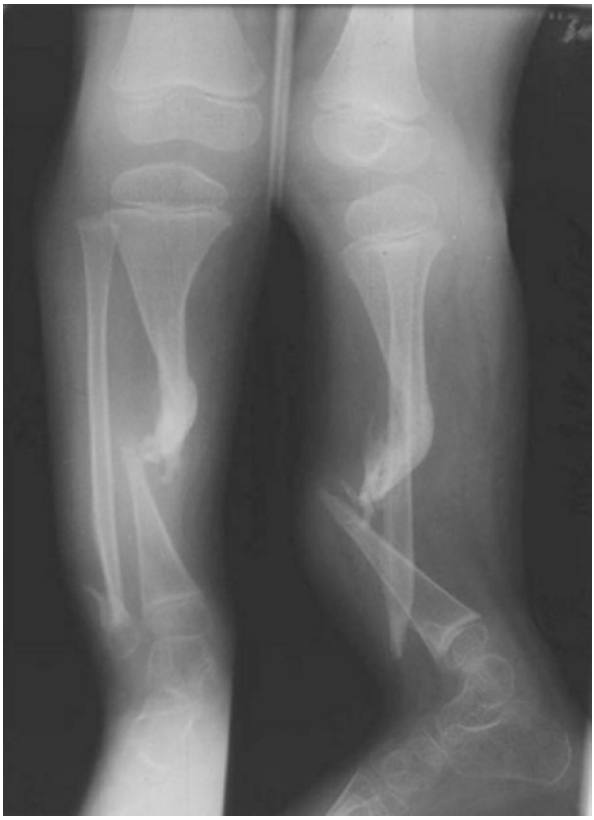

Fig. 26.6 Dysplasia with associated fracture of the tibia is seen in about 2% of NF1 patients

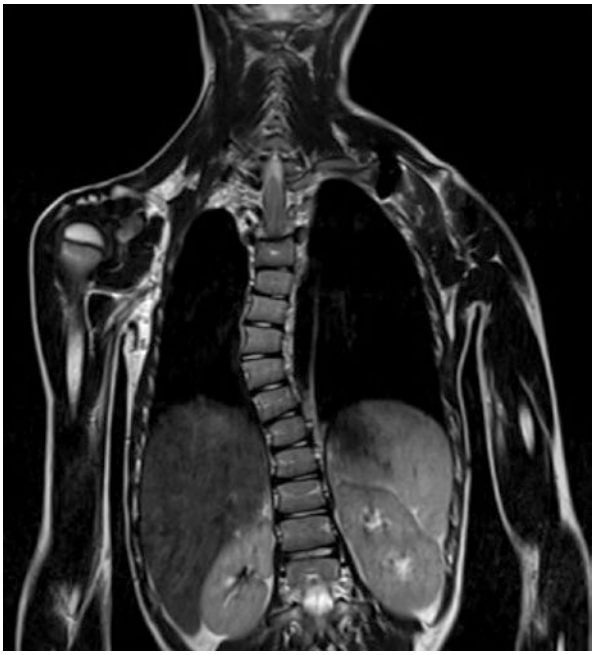

Fig. 26.7 Pronounced scoliosis with a Cobb angle ≥20% is observed in 10% of paediatric NF1 patients and together with short stature presents one of the most common skeletal alterations

clinical evidence of incipient scoliosis require regular monitoring of the progression of scoliosis every 6 months. Patients with mild curvatures do not require surgery. A real challenge is the early onset of rapid scoliosis, which is characteristic for NF1 and referred to as a dystrophic scoliosis. Dystrophic scoliosis commonly affects the lower cervical and upper thoracic spine; it may involve several segments and cause distortion of the vertebral bodies and ribs and requires early surgical intervention sometimes with less satisfactory outcome.

The vertical expandable prosthetic titanium rib (VEPTR) allows sequential correction of progressive scoliosis in immature NF1 children without fusion of the spine and permitting lung and spine growth [34].

Cardiovascular abnormalities in NF1 patients comprise congenital heart disease, vasculopathy and hypertension. Pulmonary artery stenosis accounts for 25% of congenital heart abnormalities. All children born with NF1 should undergo a thorough cardiac examination.

NF1-related vasculopathy includes renal and cerebral artery stenosis, aortic coarctation or arteriovenous malformations [35]. Hypertension should be excluded in children and adolescent patients, and any neurological deficit should be evaluated for cerebrovascular disease. About 6% of children had arteriopathy on neuroimaging studies [36].

Recently, an NF1 mouse model gave insight into the pathogenesis of NF1-related vasculopathy. Human endothelial cells have increased migration and proliferation in response to neurofibroma-associated growth factors by hyperactivation of RAS pathway [37].

Optic pathway gliomas are pilocytic astrocytomas (grade 1), which occur in 7–15% of children with NF1. But only 5% of these tumours become symptomatic, and only children under 7 years of age have a high risk of developing a symptomatic tumour. Since screening for asymptomatic optic tumours in children with NF1 typically does not produce any clinical consequences to the patient, MRI of the brain is not recommended as a routine examination. However, as these young children do not complain of visual problems, children should have visual assessment performed annually to assess for any unreported problems. Asymptomatic children should have one baseline assessment of colour vision and visual field at appropriate developmental age. A visual assessment in (very) young children who may have cognitive and attentional deficits is very difficult. Parents should be aware that visual problems of children, such as failing to pick up small toys or frequent dropping of toys, may be the first indicators of optic gliomas. A complete ophthalmological examination should be done on an annual basis for any child with NF1. The annual check-up should include assessment of visual acuity, colour vision, visual fields, ophthalmoscope and slit lamp examination. Ocular alignment and rotations, papillary light responses and refractive status with cyclopaedia examinations are recommended. Ophthalmoscopy should include indirect and, when possible, direct examination. Optical coherence tomography has been shown to be effective in identifying OPG early. In general, the measurement of visual acuity is the most important screening tool [38].

Accelerated linear growth in children may be the first manifestation of a chiasmatic glioma, even in the presence of a normal ophthalmological investigation. A

precocious puberty is frequently related to hypothalamic involvement of the tumour (see Chap. 47).

All patients under 13 years of age undergo annual ophthalmological examinations by an experienced neuro-ophthalmologist. Once an optic glioma has been identified, current recommendations include ophthalmologic and MRT evaluation every 4 months during the first year. This is followed by a lengthening of the intervals when ocular findings are unchanged. In case of a two-line decrease in visual acuity or a decrease in visual field, the patient is referred to a paediatric neuro-oncologist for treatment. The treatment of children depends on location and extension of the tumour; biopsy is rarely necessary. Chemotherapy is usually administered using vincristine and carboplatin [39]. In progressive paediatric low-grade glioma, treatment with MEK inhibitors leads to disease control. The data of a retrospective study with trametinib supports in-class efficacy of MEKI in progressive low-grade gliomas (LGGs) and necessity for upfront testing of trametinib against standard chemotherapy regimens [40]. Neurosurgeons are mostly involved when debulking of excessive gliomas is necessary (see Chap. 48). Even though there is evidence that radiotherapy will at least temporarily stop tumour growth, it is not suitable in young children because of the potential of secondary malignancy, vascular change, endocrine consequence and neuropsychological deficits [41]. The vast majority of optic gliomas in NF1 patients never progress once they have come to medical attention.

Astrocytomas outside optic pathways may occur in all parts of the central nervous systems. Most of them are histologically low-grade astrocytomas (pilocytic astrocytomas). Cerebellar LGGs have a good prognosis after neurosurgery. Brainstem gliomas are the most frequent tumour outside the optic pathway in NF1 patients. They tend to present later in the first decade of life. Cranial neuropathies, headache and gait instability may occur. In patients with symptomatic tumours, chemotherapy regimens are administered like in LGG paediatric population (SIOP-LGG).

Rhabdomyosarcoma is a non-neurogenic sarcoma, which is composed of cells that are likely to originate from neural crest [42]. Children have an increased frequency in developing these tumours [43]. Surgery is the best option with complete resection whenever feasible.

Leukaemia is observed more frequently in children with NF1 than in the general population. The risk of developing myeloid leukaemia is increased sevenfold. Currently, the increased risk for juvenile chronic myeloid leukaemia (JCML) is not conclusive and is certainly less than 1%. Furthermore, there is an increased risk for non-Hodgkin lymphoma (NHL) in individuals with NF1 [44, 45].

Malignancies are the leading cause of death in NF1 [46]. A patient with NF1 is four times more likely to develop a malignancy compared to the general population. NF1 patients have an increased risk of developing colon cancer, cancer of the oesophagus, stomach, lung, liver, thyroid, and ovary; and malignant melanoma. Furthermore, there is a higher likelihood to develop small intestine tumours and bone cancer [44].

Pain is found in about 7% of patients. Usually, classical manifestations, such as PNF and skeletal deformities, lead to chronic pain. Pain control follows the general pain management guidelines.

General or partial delay of development in the paediatric age group is frequently observed in different domains. The NF1 child can fail to reach normal developmental milestones in the expected time range. Frequently, parents report that their child moves slower than the siblings of the same age. The concentration span might be limited. Fine and gross motor deficits are characterized in part by clumsiness but also in problems with writing. Muscle hypotonia is characteristic, and frequently infants with NF1 have a protuberant belly. Also common is the impaired development of language. Speech problems can be found in 60% of children with NF1 [47], with characteristics such as voice quality, problems in regulating pitch, deviant nasality, misarticulation and disfluency. Muscular hypofunction may also lead to problems in articulation. In our experience, these deficits should be defined clearly, and appropriate physiotherapeutic interventions (occupational and logopaedic therapy) are recommended – similar to children with general learning and developmental deficits.

Deficits in cognitive function are without doubt the hallmark (most common) in children with NF1. Learning problems have been shown to be a whole complex, which is attributed to dysfunction of different brain regions. Impaired academic achievement occurs in up to 75% of children. This was defined by impaired performance (one standard deviation below grade of peers) in at least one academic performance test: reading, spelling and mathematics [48]. North et al. found that 65% performed more than 2 years below their chronologic age in at least one test of academic achievement [49]. Consequently, most NF1 children are at risk of class repetitions, underachievement, lower grades or even failing to graduate. These difficulties arise in elementary school but also cause problems later on in school. Contributing factors to the academic underachievement are learning disabilities, slightly below average IQ, NF1-specific cognitive deficits and behavioural problems. These factors, or a combination of these, also interact with problems in motor and speech impairments. Learning disabilities, defined by a significant discrepancy between intellectual ability and academic performance, can be found in 30% of children with NF1 without intracranial pathology [50]. The specific learning disabilities, dyslexia and dyscalculia, can be found in 20% of children with NF1 [51, 52]. Most children with NF1 show an IQ score within the average range compared to normative value, but the mean IQ seems to cluster around the low average to average range (reviewed in [53]). Children with IQ levels between 75 and 85 are particularly challenged, especially when they show additional cognitive deficits or behavioural problems. These children have problems integrating into a regular school system, and may not be challenged enough in lower/remedial school. Furthermore, there is a twofold increased risk (4–8%) for mild mental retardation (IQ < 70) in children with NF1 [49].

Some cognitive deficits seem to be specific for NF1. Decreased visual spatial function is a specific and highly frequent deficit in children with NF, mostly defined by the judgement of line orientation test in the past [54]. Also, visual constructive skills seem to be impaired [51, 52]. Children with NF1 also have deficits across a range of executive functions [55]. Working memory deficits occur with a high frequency and lead to problems in organizing and structuring tasks. In many NF1

children, strategies for problem-solving are poor, and they have difficulties in taking in information and expressing ideas.

Behavioural problems in children with NF1 are partially caused by attention-deficit hyperactivity disorder (ADHD). This is the most common diagnosis in children with NF1 with reported frequencies from 30 to 50% [56, 57]. Most NF1 patients with attention deficits show no hyperactivity but severe inattention deficits and impulsivity problems. Subclinical attention difficulties are present in 63% of children with NF1 [51]. Children with NF1 seem to internalize physical and behavioural problems, which lead to anxiety, depression and social withdrawal [57]. Children with NF1 also have problems in social interactions, which may cause further psychosocial problems [58]. Recent studies indicate that autism features are part of the NF1 phenotype [59–61]. This may be the main cause of the frequent social interaction problems in children with NF1.

In clinical practice, NF1-affected children should undergo neuropsychological evaluation at least once before school enrolment and/or when difficulties become apparent. This evaluation should be carried out by a multi-professional team. This team is ideally built up with paediatrics, psychologist and child psychiatrics and in close cooperation with educational specialists. Treatment and support should be performed by speech, occupational and physical therapists or those working together with the family to optimize the abilities of the children and to show ways how to overcome the deficits. In severe cases of behavioural problems, cognitive-behaviour therapy or social skill training should be considered.

Most children and adolescents with NF1 respond satisfactorily to systemic use of low doses (<15 mg) of methylphenidate (MPH) with a positive long-term effect on performance and behaviour [57]. Therefore, those children whose history and presenting symptoms suggest AD(H)D should be given an evaluation for sustained attention and impulse control. Recent studies show that NF1 with comorbid AD(H)D has a negative effect on intellectual development [62] and that treatment of AD(H)D with MPH may improve cognition in children with NF1 [63]. Mouse models show impaired spatial learning and impaired attention [64]. These deficits are due to hippocampal dysfunction and are reversible by farnesyl transferase inhibitors. However, the first statin trials finished recently showed no immediate benefit on these domains [65].

Structural abnormalities detected by MRI include focal areas of T2/FLAIR hyperintensity in deep white matter and basal ganglia or corpus callosum, which occur in most children with NF1 and may regress with age [66]. They are thought to present abnormal myelination, vacuolar changes and gliosis. It is unresolved if those structural abnormalities are linked to cognitive impairment. Frequently, it's recommended by physicians that children should undergo close monitoring of those hyperintensities, although follow-up examinations of those unspecific findings are not required [67].

Other minor clinical features in children and adolescents with NF1 are aqueduct stenosis (1.5%) with lifelong age of onset, epilepsy (6–7%) with lifelong age of onset and sphenoid wing dysplasia (1%) with age of onset at birth [68].

Clinical Characteristics of NF1 in Adults

Different disease domains have impact on the quality of life of NF1 patients. For many years, it was thought that the visibility of skin tumours and disfigurement are the leading factors for a decrease in life quality of adult NF1 patients. Our own studies revealed three main domains of associated impairment: (1) severity of medical complications of NF1, (2) visible disfiguring symptoms and (3) cognitive deficits [69]. Patients with higher disease severity burden and higher perceived disfigurement visibility reported a higher level of psychological distress. This was not reported by patients with cognitive deficits. But patients with persistent learning difficulties are impaired in their social and family life, partnership and sexuality.

This implies that besides medical treatment, including surgical removal of disfiguring skin tumours, it is important to recognize cognitive impairment in adults. Close cooperation among medical professionals, psychologists and social workers is required to decrease the burden of the various domains. It is unresolved to which extent impaired visual-spatial ability, poor fine motor skills, reading and writing difficulties, reduced long-term memory, attention deficit and executive function problems persist in adults with NF1.

Treatment of cutaneous neurofibromas is indicated if the tumours are symptomatic. Neurofibromas can lead to transient stinging and itching. Sometimes these tumours induce pain and cause problems by wearing of clothing. Multiplicity of these tumours may cause a disfigurement, which may have a psychological impact in the individual "self-image", partnerships and social relations.

Therefore, referral to surgeons skilled in the removal of neurofibromas is indicated, and plastic surgeons should be consulted whenever disfigurement is present. This is especially true for neurofibromas of the face and neck. The result of surgery is dependent on dimension of tumour, its localization and its structure (diffuse, nodular or pedunculated) and the skin texture. Pedunculated neurofibromas can be excised with very satisfactory results. Neurofibromas can be removed by different techniques: by scalpel, laser or electrocauterization. In our experience, the scalpel is useful for the larger, exophytic tumours. The use of laser and electrocauterization is helpful for tumours with intracutaneous localization containing a great amount of blood vessels. Completely resected tumours typically do not relapse. There is no proven benefit of carbon dioxide laser treatment in comparison to the removal of neurofibromas by scalpel [70]. There is also no evidence that dermal neurofibromas tend to have a malignant change. The itching of neurofibromas can be very troublesome to patients, and the effect of antihistamines is not always satisfactory in resolving the itching problem.

Plexiform neurofibromas and surgery are important topics in clinical care. Although longitudinal growth studies demonstrated that PNF progression slows down with increasing age, a small subgroup of adults with PNF show growth spurts, which are highly suspicious for MPNST. However, external tumours may loosen their texture and therefore seem to extend.

The fact that many tumours are large, irregular in shape, highly vascular and difficult to dissect from the surrounding tissue makes surgery challenging. In general, surgery in patients with small and superficial PNF can be performed without difficulty, and no regrowth is observed. In adults, complete removal is limited according to the topography, extension and growth patterns of the tumour. However, subtotal removal of large tumours performed continuously at intervals can lead to a satisfactory outcome. First, studies have shown that surgery can lead to an improvement of disfigurement, pain relief and decrease of functional deficits [22].

Spinal neurofibromatosis may be observed in a small subgroup of NF1 patients with and without pigment abnormalities, absence of typical dermal neurofibromas and different degrees of subcutaneous lesions. These patients frequently come to clinical attention by back pain or peripheral neuropathy. When these patients undergo spinal MRI, bilateral spinal tumour involvement is frequently detected. Multiplicity of tumours makes it sometimes impossible to determine which tumours are responsible for neurological deficits, so neurosurgical intervention is impossible [71]. Selumetinib showed improvement of spinal neurofibroma burden on imaging. This observation suggests that the MEKI may prevent or reduce neurological symptoms in these patients [72].

Malignant peripheral nerve sheath tumours (MPNST) are the most common malignancy in NF1 patients and the main cause of early death. The lifetime risk of MPNST in NF1 patients is 8–13% [73]. The analysis of proportionate mortality ratios demonstrated that NF1 patients were more likely to have a malignant connective or other tissue neoplasms listed on their death certificate than those without NF1 [74]. Predominantly, the transformation from PNF to MPNST occurs in individuals aged 20–35 years. 10–20% are of even younger ages (1–19 years) [75]. When diagnosed, the MPNST in NF1 patients tend to be large (<5 cm diameter in 5 patients, 5–10 cm in 13 patients, >10 cm in 21 patients) [76]. Clinical indicators of malignancy are persistent or increasing pain, swelling and increase in size and/or neurological deficit. NF1-associated MPNSTs are more frequently located in the trunk [76].

MPNST are at high risk for local recurrence (43%) and distant metastasis (40%) [77]. The majority of MPNST metastases in adults are pulmonary, followed in decreasing order of frequency by the soft tissue, bone, liver, abdominal cavity, adrenal gland, diaphragm, mediastinum, brain and retroperitoneum [78].

Some risk factors have been identified in the last years. The presence of internal tumour load is strongly associated with the development of MPNST [18], which was confirmed performing whole-body MRI in NF1 MPNST patients. Annual growth rates.

(>20%) determined by volumetric analysis in adults are highly suspicious for MPNST [22]. The NF1 microdeletions patients are at high risk for developing MPNST [11, 79]. The most important factor in effective treatment of MPNST is an early diagnosis and complete surgical resection with wide margins. However, the challenge of early diagnosis is not satisfied in most cases. In our experience, it is helpful to identify those patients with high internal tumour burden by MRI and

perform sequential follow-up investigations to identify lesions which show abnormal growth patterns. As MRI does not always indicate definitive malignant degeneration, another imperfect tool for the detection of MPNST in NF1 is 18-fluorodesoxyglucose positron emission tomography (FDG-PET). By measuring the standardized uptake value (SUV) as a parameter for metabolic activity of tumours, PET-CT differentiates between benign (SUV 1.5–2.0) and malignant tumours (SUV >5.0). But there is a range of SUV values between 2.5 and 3.5, where malignant and benign lesions are found by histology. On the other hand, rare cases of atypical neurofibroma may show SUV values >5 [80]. Thus, the final preoperative diagnosis of MPNST is usually archived by histopathology and immunohistochemistry on open biopsy or fine-needle aspiration. It has been shown recently that the traditional chemotherapy with doxorubicin in combination with ifosfamide has low response rate (<20%) in NF1 MPNST [81] and that radiation may improve local control, but not survival rates.

Glomus tumours are small benign neoplasms that arise from the glomus body, a thermoregulatory shunt in fingers and toes. (The glomus body is an arteriovenous anastomosis comprised of vascular structures, naeve cells and smooth muscle-like cells.)

The diagnosis of a glomus tumour is based on clinical suspicion. Patients complain about a typical triad of symptoms: severe pain, point tenderness and cold hypersensitivity. There is a high diagnostic probability of a glomus tumour by inducing pain with a pencil tip or a pin at the location of the tumour, whereas the same procedure carried out adjacently causes no pain. The average age of diagnosis in NF1 patients is 36 years, but those tumours have come to clinical attention in children also. Most glomus tumours can be excised without problems and do not reoccur. Symptoms from glomus tumours may be attributed erroneously to pain from a subcutaneous neurofibroma.

NF1 patients are more likely to develop gliomas, which require treatment in a similar fashion as their sporadic counterparts. Adults with NF1 develop glioma of the brain at a frequency of about 4% [82], and the lifetime risk of dying due to NF1-related brain tumours is between 3 and 9% [83]. Most tumours are pilocytic astrocytomas, which have a better prognosis than their sporadic counterparts.

Mortality in neurofibromatosis is increased by the occurrence of glioblastoma multiforme (GBM) based on analysis using US death certificates [74]. There is a fivefold increased risk of developing WHO grade IV astrocytoma (= GBM). The treatment does not differ from the sporadic counterparts. They may arise in the setting of previous cranial radiation.

Gastrointestinal stromal tumours (GIST) are seen more frequently in persons affected by NF1 than the general population. The prevalence of GIST is not really known. We identified 3 patients with GIST while performing 400 whole-body scans. The most common symptoms are abdominal pain, bleeding, perforation and intestinal obstruction [42, 84]. NF1 patients often show multiple GISTs, and GISTs of the small intestines outnumber gastric GISTs.

NF1 GISTs do generally stain positive for KIT protein (CD117) like most other GISTs. Compared to sporadic GISTs, NF1 GISTs are more likely to show S-100

reactivity (a marker of neural differentiation), entrapped myenteric nerves within the tumour [85].

NF1 GISTs rarely metastasize [86]. Follow-up of our NF1 GIST cohort showed that patients have a good prognosis after surgery. This is confirmed by a follow-up study in nine patients up to 32 years [87]. NF1-associated GIST typically do not overexpress c-KIT or PDGFRA(α). Therefore, the use of imatinib in this population is limited.

Breast cancer occurs with a fivefold risk in patients with NF1, primarily affecting women younger than 50 years of age [88–91]. Current data indicate that the cumulative risk for breast cancer by the age of 40 years is 4.7%, which is over ten times higher than in the general population [83]. The risk for a second breast cancer is 26% during the first 20 years after the first breast cancer [92]. It is recommended that all young women perform self-examinations monthly and undergo regular mammography screening. It is unclear at which age initial mammograms should be carried out because radiation may trigger benign lesions to transform into malignant tumours in NF1. Current data indicates that breast cancer screening guidelines should be evaluated for this potentially high-risk group.

Pheochromocytoma should be suspected in NF1 patients who present with sustained or paroxysmal hypertension, unexplained agitation and anxiety, tachycardia, palpitation, headache, perspiration and flushing.

Pregnancy and hormones contribute to the growth of neurofibromas, as neurofibroma growth is stimulated by puberty and pregnancy. A recent study has shown that 75% of neurofibromas carry progesterone receptors. However, there is no evidence that the combined oral contraceptive pill or progesterone-only pill may contribute to neurofibroma growth [93]. During pregnancy, obstetricians and NF clinicians should be aware that spinal and pelvic neurofibromas may progress rapidly, and these neurofibromas should be monitored closely. Recently, it was shown that pregnancy does not induce PNF growth [94]. According to a population-based study, NF1 was associated with increased maternal morbidity in pregnancy (including hyperintensive and cerebrovascular complications) but not increased maternal mortality. Obstetricians should be aware of the potential for increased antenatal and peripartum complications among women with NF1 [95].

Decreased bone mineral density was suspected from surgical treatment of patients with scoliosis, which revealed that the bony structures are frequently affected. These observations led to mineral density studies, which have shown that bone mineral density (BMD) is frequently decreased in adult NF1 patients [96]. Population studies determining the risk of fractures in NF1 patients recently showed that adults with NF1 have a 5.2-fold risk for bone fractures [30]. Recent studies revealed that serum vitamin D3 levels among NF1 adult patients are much lower than in controls, and this might be pathogenetically related [96]. In a retrospective study, it was demonstrated that oral vitamin D supplementation improves BMD significantly [97]. In our practice, we substitute low vitamin D3 levels according to international guidelines.

Clinical Management

NF1 clinic calls for an interdisciplinary approach to assure an optimal treatment of patients with NF1. A specialized centre should provide the expertise that covers the different aspects of the disease. The role of these experts is to monitor complex cases, to give advice to the general practitioners and to educate patients and their families.

Surgery plays a pivotal role, both in the management of tumours and skeletal deformities as outlined above.

Genetic counselling is a further central aspect in NF1 patient care since there is a 50% risk of passing the NF1 gene onto the offspring. The chance of having an infant with severe problems is 1 in 12, and the disease is fully penetrant [15]. The disease diagnosis is based on clinical grounds, and mutation analysis should be carried out only in patients with unusual phenotype and when the diagnostic criteria are not satisfied (after the age of four). Prenatal testing and genetic diagnosis are available for patients with NF1. Current techniques detect the causative mutation in up to 95% of cases. But, a negative patient test does not exclude an NF1 diagnosis because the mutation can be present in the noncoding region of the NF1 gene. In patients with segmental NF1, mutation analysis may not be necessary because the mutation is usually not present in the blood DNA [98].

Differential Diagnostics of NF1

NF1 has to be distinguished from other syndromes associated with pigment abnormalities (1), overgrowth conditions (2) and tumour conditions (3).

1. Legius syndrome: café au lait spots and axillary and inguinal freckling (se. McCune-Albright syndrome, irregular café au lait patches, polyostotic fibrous dysplasia (see Chap. 42)).
2. LEOPARD syndrome: multiple lentigines, deafness, ocular hypertelorism, congenital heart disease (see Chap. 17).
3. Klippel-Trenaunay-Weber syndrome: cutaneous haemangiomas, varicose veins, hemihypertrophy (see Chap. 9)
4. Proteus syndrome: hyperostosis, hamartomatous overgrowth, epidermal naevi (see Chap. 22).
5. Lipomatosis: multiple subcutaneous lipomas affecting all parts of the body. Fibromatosis: multiple tumours of the muscles, skin, bones and internal organs Multiple endocrine neoplasia type 2B: phaeochromocytoma, mucosal neuromas, medullary carcinoma of thyroid, gastrointestinal ganglioneuromatosis and marfanoid habitus
6. Mismatch repair syndromes: hereditary nonpolyposis cancer of the colon—café au lait spots, affected siblings but normal parents (caused by homozygosis for one of the genes) [99].

Neurofibromatosis II (NF2)

History of NF2

In 1820, JM Wishart documented a case report of a 21-year-old man with a history of amblyopia and multiple brain tumours. After death, the autopsy of the deaf man revealed bilateral cranial nerve tumours, multiple dural-based tumours and tumours of the skull base [100]. The multiplicity of cranial nerve and brain tumours was described in autopsies in this century [101]. Henneberg and Koch [102] observed that a clinically distinct form of NF existed, which lacked the skin affection typical for von Recklinghausen disease but included bilateral eighth cranial nerve tumours. They referred to this disorder as "central" neurofibromatosis in contrast to the "peripheral" features of von Recklinghausen disease [102]. Cushing published the association of vestibular schwannomas and meningiomas in 1917 [103].

Spinal tumours were observed in children in different locations [104, 105]. Differentiated descriptions of hearing loss and deafness by bilateral schwannomas were reported since 1905 [106–108].

Ocular symptoms such as double vision, amaurosis and cranial nerve palsy were attributed to tumours of the cranial nerves [102, 107, 109]. Since 1886, skin tumours have been recognized as being part of the disease [104]. Histological description of the tumours occurring in NF2 was no different to current understanding. Glial proliferation, neurofibromas, meningiomas, neurinomas and ependymomas were diagnosed [110].

Despite this knowledge, the confusion between NF1 and NF2 was unresolved until the separate locations of the NF1 and NF2 genes were identified.

Epidemiology

On ground of population-based data, the incidence at birth was estimated to be 1:40,000 [111]. The awareness of the disease has slightly increased due to the improved diagnostic options by magnetic resonance tomography and early genetic identification of NF2 mutations in young patients with early onset of the disease. Recently, the birth incidence was estimated to be approximately 1:25,000 [112].

Genetics

NF2 shows autosomal dominant transmission with nearly full penetrance determined by the presence of bilateral vestibular schwannomas (VS) by age 30. Incomplete expression is observed in children aged younger than 10 years and rare

cases with very mild clinical course. About half (50–60%) of all patients present with no family history. The high rate of sporadic NF2 reflects a high mutation rate at the NF2 locus and low reproductive fitness, especially in the severely affected patients (see Chap. 1).

In sporadic NF2 presenting with bilateral VS, only 70% of mutations are detected by mutation analysis in blood DNA. The reason being that somatic mosaicism is a typical phenomenon in NF2 and is more common than in all other inherited disorders with a frequency of >50%. Mosaicism in NF2 has been proved to occur in about 60% of sporadic cases in an age-dependent manner (80% >60 years, 22% <22 years) [113]. Those patients have mostly a milder course of disease compared to their offspring [114]. These findings have important implications for genetic counselling. Patients presenting with unilateral cerebral tumour formation and no ocular manifestation have a higher probability (60%) of mosaicism [115]. NF2 patients can also present without vestibular schwannomas and share the same clinical features as schwannomatosis patients do. Identical somatic NF2 mutations in two independent schwannomas (tumours) are needed to verify the diagnosis of NF2 mosaicism.

Sporadic NF2 patients with mosaicism presenting with bilateral VS have a 1:8 risk of passing the disease on to their children. In patients with unilateral VS, the risk decreased to 1:12 [115, 116].

Genotype-Phenotype Correlation

Mutation analysis revealed many different mutation types in NF2. Nonsense and frameshift mutations result in truncated protein product and are associated with more severe phenotype. This is due to the early onset of initial tumour manifestation and the multiplicity of tumours [117, 118]. In cases with the mutations in the splice acceptor region, there is a variable course of the disease [114, 119]. Large deletions (and missense mutations) are associated with milder disease. Cross-sectional genotype-phenotype correlation studies have led to consistent findings of association between clinical indices of NF2 disease severity and type of constitutional NF2 mutation. However, in the longitudinal study of NF2 tumour growth rates, this correlation is not significant anymore. Genes other than NF2 may affect NF2 disease severity, schwannoma and meningioma tumorigenesis. The role of modifying genes and epigenetic factors is unresolved so far [120] (see Chap. 1).

Diagnostic Criteria

The diagnosis of NF2 has been based on the diagnostic criteria defined by the NIH Conference in 1987, which were then modified in 1997 to include presumptive or probable NF2. The so-called Manchester Criteria are as follows:

1. Bilateral vestibular schwannomas or family history of NF2 plus
2. Unilateral vestibular schwannoma
3. Any two of meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities

Additional Criteria Are as Follows
- Unilateral vestibular schwannoma plus any two of meningioma, glioma, neurofibroma, schwannoma and posterior subcapsular opacities
- Multiple meningiomas (two or more) plus unilateral VS or any two of glioma, neurofibroma, schwannoma and cataract

The Manchester Criteria identify higher proportions of patients of both time points (most recent, 93%; initial, 14%). However, the existing set of criteria has limitations with regard to adequate diagnosis at initial assessment for diagnosing patients without bilateral VS as having NF2, particularly people with a negative family history of NF2. In a retrospective study, it was established that the typical gliomas in NF2 are spinal ependymomas [121]. Furthermore, neurofibromas rarely occur in NF2 patients and should not be part of the diagnostic criteria [122].

Clinical Characteristics

The clinical course is extremely variable depending on tumour burden and associated complications. NF2 can be divided into a severe form with early presentation and fulminant course and a milder variance with late age of onset and much less rapid course. This division into a severe course [100] and milder affection [123] is helpful for counselling and decisions regarding surgical interventions because patients with an early age of onset tend to have a more aggressive course of disease [119]. However, this classification shows many transitions, and therefore many patients don't fit exactly to these criteria. The main problems in the long-term follow-up are the decrease in hearing, motoric disturbances either after surgical intervention or due to polyneuropathy and visual impairment.

Skin tumours are a common sign in children suffering from NF2. Patients present with at least one skin tumour with minimal elevation and roughing. The changes differ from neurofibroma and are more subtile. Skin schwannomas are an early indicator of the diagnosis. Careful skin inspection allows the diagnosis of NF2 at an early age [124, 125].

Most patients with severe course of the disease present with some skin tumours. The lesions were the first sign on presentation in 27% of the patients. Patients with more severe disease have a significant greater prevalence of skin tumours. Tumours appear mostly as flat dysplastic or subcutaneous spherical nodular lesion. Histology

revealed predominantly schwannomas, rarely neurofibromas or mixed tumours [122].

Ocular abnormalities in children with NF2 are another important clue for diagnosis based on clinical examination. Subcapsular bilateral cataract and/or additional ocular abnormalities such as optic meningioma, epiretinal hamartoma, epiretinal membrane, strabismus and amblyopia belong to the presenting features of these patients and are quite common.

Cataracts occur with a frequency of 90% and are the most frequent ocular manifestation in NF2 patients. They may occur at an early age but can be detected also in most patients during follow-up investigations. These lesions are often posterior, subcapsular or peripheral cortical located. Retinal abnormalities in NF2 patients include epiretinal membrane in the macular or perimacular area and combined pigment epithelial and retinal hamartomas. The epithelial and retinal hamartomas occur in up to 25% of the patients. Amblyopia has been observed in 10% of all NF2 patients and is frequently recognized prior to diagnosis of NF2 itself [126]. Strabismus was found in a larger patient sample in 52% of the patients. Refractive errors (myopia 33% and hyperopia 8%) were frequent, and an increased incidence of vestibular nystagmus was detected [127].

Facial nerve palsy is a common consequence of VS surgery, leading to conjunctivitis and corneal injury. Therefore, techniques for conserving the lacrimal gland fluid, which lubricates the cornea, are part of the ophthalmological care. Intracranial pressure caused by multiple tumours can lead to choked disc and decrease of vision, which makes shunting necessary (see Chap. 47).

Hearing problems are a typical feature of NF2. In most patients with unilateral decrease in hearing, a vestibular schwannoma (VS) is the cause (Fig. 26.8). When these tumours are present bilaterally, they often differ in size. Deterioration of hearing differs between patients; in some, a rapid progression is observed with sudden hearing loss. Usually, hearing deceases about 5 dB/year [128]. There is no straightforward correlation between hearing loss and tumour size or growth [128].

The average age of hearing loss is 24 years and is associated with other otological symptoms, such as tinnitus or imbalance. VS initiate from the internal auditory canal from where they expand into the cerebellopontine angle. VS can be detected by MRI frequently in children at the age of 10 years, and a vast majority grows at least 5 mm^3/year [120, 129]. Because there is still a significant delay in diagnosis of the disease, the majority of patients underwent surgery of VS with a diameter of more than 2.5 cm. The time of diagnosis is crucial because there is no doubt that successful surgery and hearing preservation depends on tumour size and audiological functional nerve integrity.

Hearing loss in neurofibromatosis type 2 is not closely correlated to tumour volume and/or neurological/neurophysiological findings as prolongation of latencies in brainstem evoked potentials. Different mechanisms seem to contribute to the complex process of hearing loss in patients with bilateral vestibular schwannomas. Recently, it was shown that elevated intralabyrinthine protein was identified frequently by FLAIR MR imaging and associated with the presence of hearing loss. This observation supports the model in which hearing loss develops as a result of cochlear aperture obstruction and the accumulation of intralabyrinthine protein [130].

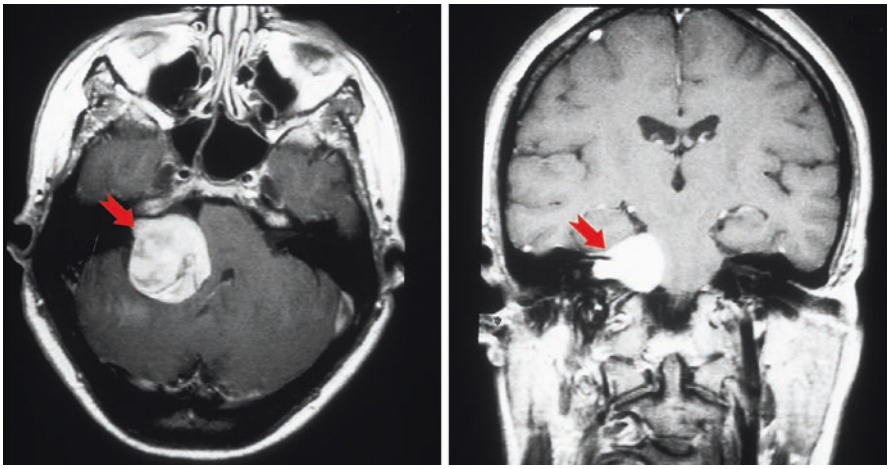

Fig. 26.8 Unilateral schwannoma in the cerebellopontine angle (arrows)

The temporal bone histopathology in NF2 was investigated to prove tumour origin. Light microscopy revealed a multicentric origin in 19 out of 26 ears. Tumours were seen to arise within the internal auditory canal and from various locations within the labyrinth. Most cases showed significant degrees of degeneration of sensory and neural elements within the cochlea. The study demonstrated that NF2 is a multifocal process associated with secondary degeneration within the cochlea and explain that total removal of these tumours might be impossible. Furthermore, these findings make clear that clinical abnormalities and decrease of hearing are not straightforwardly correlated with a single tumour [131].

The intracanalicular bone invasion of the vestibular schwannoma is another factor, which contributes to the natural history and the surgical outcome of NF2 patients. The two clinical phenotypes of NF2 [100 vs. 123] show distinctive differences regarding invasion of the internal auditory canal wall, which was predominantly in the Wishart phenotype.

In sporadic vestibular schwannomas, it was found that the severity of hearing loss is associated with tumour secretion of proteins with ototoxic or otoprotective potential [132]. This indicates that secretion of fibroblast growth factor 2 (FGF2) also plays an important role in the hearing process irrespective of tumour size. Studies are being carried out to investigate the meaning of FGF2 in neurofibromatosis type 2.

Involvement of other cranial nerves is frequently observed. According to own unpublished studies, trigeminal tumours occur in about 26% of patients which can lead to sensory deficits but rarely induce motoric dysfunction. Different degrees of ocular motoric deficits are attributed to trigeminal tumours. Tumours of all cranial nerves occur in NF2 tumours, including optic nerve meningioma and the lower cranial nerves. The hypoglossal nerve is the most frequent affected nerve of the caudal nerves.

Meningiomas appear in about 50% of all patients with NF2, with the majority being intracranial. The majority of meningiomas occur in the convexity (66%), the

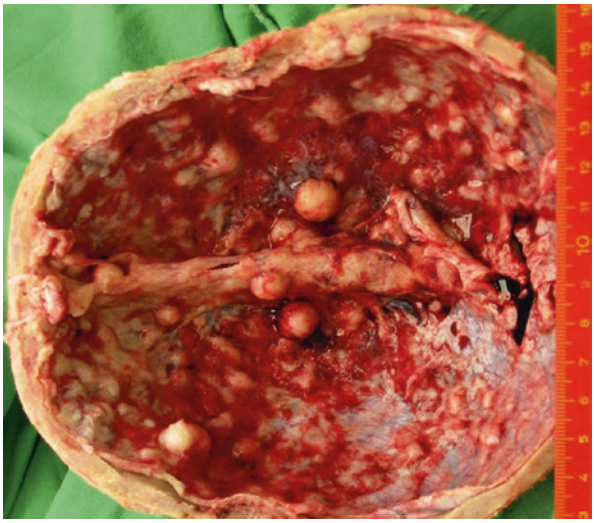

Fig. 26.9 Postmortem investigation of a NF2 patient demonstrating multiple cranial meningiomas

falx (54%) and the sagittal sinus (23%) and grow large before becoming symptomatic (unpublished own data cross-sequentially). The challenge for surgical treatment is the frequent multiplicity and in the course of progression sinus infiltration and increased intracranial pressure. Limited treatment options, such as shunt application, are a cause of reduced life expectancy in NF2 patients [133].

Spinal tumours develop in about 90% of NF2 patients without any preferred location. The majority of patients present with meningiomas or schwannomas (Fig. 26.9). Neurofibromas occur rarely. According to own experience, about 30% of tumours become symptomatic in cross-sectional analysis, and the majority is resectable with neurological deficit. Opposed to this, ependymomas are asymptomatic in most patients and show only slow progression over longer time periods [134].

Asymptomatic spinal and cerebral tumours may be found in patients who undergo MRI of the brain and spine [135–137].

Polyneuropathy may be detected in at least 40% of adults with NF2 on nerve conduction studies even without evidence of compression of the nerves by tumours [138]. Tumourlets were identified as one reason for the occurrence of polyneuropathy beside schwannomas compressing the nerve itself. But peripheral nerve involvement with subclinical neuropathy is more frequent as shown by electrophysiological investigation [139] or areflexia. Sural biopsy from NF2 patients showed a loss of nerve fibres and coreless onion bulbs formed of abnormal Schwann cells.

The underlying mechanism is complex. Nerve compression is caused by spinal root tumours, involvement of peripheral tumours by tumourlets and macrolesions, a primary defect of the heterozygous Schwann cell and, as recently shown, dysfunction of the axon itself [140, 141]. A recent study using high-resolution MR neurography found a close correlation between the number of non-compressive microlesions and the severity of NF2-PNP symptoms. Further studies also revealed distinct hypertrophies of the dorsal root ganglia (DRG) and identified primary sensory

neurons as a possible vulnerable site in origination of areflexia and sensory loss in NF2-PNP as well as a potential pathognomonic marker in the differentiation to schwannomatosis.

While DRG hypertrophy and peripheral nerve lesion occur very early in NF2, these findings seem to be relatively constant in the later course of the disease. Thus, secondary long-term processes might be responsible for the development of NF2-related neuropathy, with symptoms only occurring if a certain threshold is exceeded. Recent histological ex vivo sections revealed severe Schwann cell hyperplasia nearby primary sensory neurons as the structural correlate of DRG hypertrophy in human NF2.

Differential Diagnosis

Without doubt, the main differential diagnosis is schwannomatosis. Patients with schwannomatosis present with multiple peripheral schwannomas and do not develop vestibular tumours [142]. In a subgroup of patients with Schwannomatosis, meningiomas and lower cranial nerves tumours are observed. Most patients show first clinical symptoms in the age range between 30 and 40 years, and tumours rarely can become symptomatic in the paediatric age group. In contrast to NF2 patients, no ocular or cutaneous abnormalities are found, and no NF2 mutation is detected in the blood DNA. SMARC B1 and LTZR1 mutations have been identified to be causative [143–145], but for the majority of patients, the mutational background is unresolved so far. Patients with multiple meningiomas have some overlap with NF2. But in most patients with multiple meningiomas or meningiomatosis, these occur isolated with no other NF2 features.

Management and Therapy

In patients with confirmed clinical or genetic disease, it is important to label the clinical course of the condition. In children with early onset of symptoms, clinical follow-up is recommended every 6 months and at least annual screening at the age of 10 with cranial and spinal MRI and audiological assessment including brainstem evoked potentials. Patients with NF2 should have clinical follow-up examinations annually between 18 and 30 years. In our experience, annual clinical investigation of NF2 patients is recommended in general. Because growth rates of vestibular schwannomas, cranial nerve and spinal tumours in a single patient are independent and have a high variability, a tailored approach must be taken for each patient with multidisciplinary assessment from otolaryngology, neuro-otology, neurosurgery and neurology in planning the timing of surgical interventions.

Tumour size, tumour growth rates, degree of hearing, personality and psychological implications must be taken into account. Surgery with the aim to preserve

hearing is considered if the tumour is below 2 cm in diameter and if there is cerebral spinal fluid at the lateral end of the internal auditory channel. Preservation of serviceable hearing is possible in 30–65% of patients [146, 147]. If useful hearing (>70% speech discrimination) is preserved, the second tumour may also be removed by a hearing preservation approach.

If hearing is not successfully preserved in the first year, but the cochlear division of the eighth nerve is preserved anatomically, the second year is monitored for tumour growth or hearing loss, allowing preservation of hearing as long as possible before a second surgery is performed [147, 148]. So far, the issue of long-term recurrence of vestibular schwannomas after successful surgery with hearing preservation remains open. According to own observations (unpublished), at least 50% of patients develop a tumour recurrence during follow-up period of 15 years (see Chap. 48).

When hearing is declining in the only functional ear, internal auditory canal depression is an approach that may preserve hearing for a period of time [149]. If hearing is lost completely, hearing restoration approaches, such as cochlear nerve implant (CNI) or auditory brainstem implant, should be considered. To assess the utility of CNI, the patient is referred for promontory stimulation [150]. It was shown that the timing of brainstem implantation after hearing loss is a main factor favouring potential auditory improvement [151].

The role of any form of radiosurgical therapy for NF2 tumours remains controversial. Radiotherapy (stereotactic radiosurgery) or intensity-modulated radiation therapy has been used in a subset of NF2 tumours that progress in spite of surgical treatment or in individuals at high risk for operative complications with significantly less success than in sporadic tumours [116, 152]. From the radiosurgical perspective, the reason for the reduced effectiveness is the large tumour size. Many clinicians are hesitant to recommend radiation for NF2 patients with tumours of any size. Radiation should be used with caution in a setting of NF2 since – though the prevalence of nervous system malignancy is very rare in NF2 population studies – secondary malignancies after radiotherapy treatment have been reported [153]. To date, more than 20 cases of malignancies (i.e. glioblastoma, rhabdomyosarcomas or malignant meningiomas) have been reported in patients with NF2 after radiation therapy [154]. Radiotherapy may also lead to more difficult surgical intervention than primary surgery [155], which is necessary because tumours grow despite radiation.

The management of patients with incomplete expression of symptoms, like children where expression of clinical symptoms is incomplete and no NF2 mutation identified, comprises mandatory ocular investigation and annual cranial and spinal MRI. Under the age of 20, scanning should take place in alternation. After the age of 20 when tumour growth rate slows down, scanning every 3–4 years is sufficient. Scanning can be discontinued by the age of 40. In case of an individual having proven NF2 mutation and no displayed clinical symptoms [156], clinical investigation should be performed every 3 years.

Patients with features of NF2, such as unilateral vestibular schwannoma under the age of 20 or isolated cranial meningiomas or schwannomas, are at risk for

NF2 > 20% [157]. The risk of NF2 decreases significantly with occurrence unilateral vestibular schwannoma between the age of 20 and 30. Clinical evaluation should include cranial and spinal MRI, audiology, ocular and dermatological investigation initially and at age 20. Afterwards, investigations can be performed in large intervals.

Medical Treatment

Since 2008, the antiangiogenic drug bevacizumab has been introduced to treat NF2 patients with progressive VS and unilateral hearing loss, who are at risk of hearing loss by surgery or tumour progression. Out of ten patients with progressive VS treated with bevacizumab, eight showed tumour shrinkage with a median best response rate of 26%. Hearing improved in some patients. At the same time, two patients treated with bevacizumab showed 40% tumour reduction along with significant hearing improvement in one patient [158]. In a retrospective review of 31 patients [159], who showed annual growth rates of 20%, 90% of patients showed improved or stable hearing after 12 months; during the observation period of 36 months, there was a decrease of stable hearing or hearing improvement in 61% of patients.

Furthermore, the volume reduction of 88% achieved in the first year declined significantly during 36 months of treatment to 54%. Discontinuation of treatment led to regrowth of the VS within a timeframe of 3–6 months [160]. Especially, cerebral meningioma growth or spinal tumour progression necessitating surgery leads to discontinuation of treatment with bevacizumab. But, side effects such as proteinuria and hypertension can also cause discontinuation. According to our own observations, dose reduction of bevacizumab during treatment might partially overcome serious side effects. In comparison to other targeting agents such as sorafenib, everolimus [161], erlotinib [162] and lapatinib [163], the monoclonal antibody bevacizumab inhibiting the angiogenic effects of VEGF is significantly more effective. Bevacizumab leads to improved life quality in adult patients with progressive VS. In general, paediatric patients do not experience tumour shrinkage of vestibular schwannomas by bevacizumab medication [164].

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Chapter 27
Tuberous Sclerosis (Bourneville Disease)

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Introduction

The first description and nomenclature are credited to Bourneville 1880 [1]; in 1890, Pringle reported adenoma sebaceum, but in 1862, Friedrich Daniel von Recklinghausen was the first person to recognize the condition [2, 3]. Between 1880 and 1900, Bourneville and Brissaud summarized the clinical findings in ten additional cases of TSC and correlated the cutaneous abnormalities with renal lesions [4, 5]. The relationship between Bourneville and Pringle syndromes was published

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for the first time in 1908 by Vogt [6], who was also the first to define and link adenoma sebaceum (now more appropriately termed "facial angiofibroma") to mental insufficiency and epilepsy. Later, Van der Hoeve detailed the histology of autopsy tissue derived from the optic nerve and retina in patients with TSC [7].

Tuberous sclerosis complex does not show a geographic, racial or sexual predilection. It carries a prevalence of approximately 1:6000. Approximately 20–30% of the cases show a familial autosomal dominant inheritance, and the remaining 70–80% are caused by de novo germline mutations. TSC is a multisystem genetic syndrome that can present at any age, affecting almost all organ systems of corpus (central nervous system, heart, kidneys, eyes, skeletal and lungs).

In 1998, the National Institutes of Health sponsored the first TSC Consensus Conference to develop recommendations for the diagnosis and clinical management of patients affected by TSC [8]. The International Tuberous Sclerosis Complex Consensus Conference updated the diagnostic criteria in 2012 to include pathogenic mutations of the TSC1 and TSC2 genes in establishing a diagnosis [9].

Genetics (Also See Chap. 1)

Although the hereditary nature of tuberous sclerosis was reported in 1910, causative gene mutations were not identified until the 1990s when multilinkage analysis of multigenerational families with TSC led to the identification of two genes, TSC1 and TSC2. Reviewing more than 4200 individuals with TSC and their families in whom disease-causing mutations have been identified, about 31% had a mutation in TSC1, and the majority of others possess a mutation in TSC2 [9]. Located on chromosome 9q34, TSC1 comprises 23 coding exons [10], while TSC2 is located on 16p13 and has 41 exons [10, 11]. Both genes are considered as tumour suppressors and follow Knudsons two-hit hypothesis for carcinogenesis: inactivation of both alleles is necessary for tumour development [12].

Most of the mutations in TSC1 yield premature protein termination. In TSC2, the mutational spectrum covers missense, nonsense, frameshift and large genomic deletions [10, 13]. Loss of heterozygosity in the tuberous sclerosis lesions has been demonstrated for both the 9q34 and 16p13 regions [14]. Some degree of mosaicism also has been reported, which has potential implications in molecular diagnosis and genetic counselling [15, 16]. Approximately 15% of patients with TSC do not have identifiable mutation in either gene. Disease severity can be variable, even within families, and may reflect differential expression of normal and mutant TSC alleles.

Signalling Pathways Affected in TSC

TSC1 and TSC2 encode for hamartin and tuberin, respectively. These proteins were noted early to interact [17] and contribute to cell cycle regulation. The current understanding supports both proteins form a TSC protein complex, mTORC1,

which functions as a tumour suppressor. Inactivation of either gene results in overactivation of the mTOR pathway. This signalling mediates cellular activity as a serine-threonine protein kinase that activates the GTPase activity of RHEB (Ras homolog enriched in brain) [18, 19].

Clinical Characteristics

Tuberous sclerosis complex features often are present in early infancy but may not be recognized as part of the syndrome. Over the life span, there can be varying and progressive involvement not only of the skin and CNS but also other organs and systems, such as the heart, kidneys, eyes, skeletal system and lungs. Skin lesions of TSC include hypomelanotic macules, also known as ash-leaf spots (85–97% of patients), shagreen patch (20–80%), facial angiofibromas (75%) and ungual fibromas (17–87%) [13, 20]. Hypomelanotic spots (Fig. 27.1) range from a few millimetres to centimetres in diameter and can be scattered across the body. In fair-skinned individuals, these are more visible under Wood's lamp of ultraviolet light.

Isolated small spots, "confetti" lesions, are a minor rather than a major criterion. Some patients with TSC have a tuft of white hair (poliosis). The characteristic facial angiofibromas are located on the nose and symmetrically on the cheeks and chin (Fig. 27.2). They consist of small, red and brown nodules that appear during early childhood (1–4 years). Initially, these can be flat and later raised; they are present in 40–90% of the patients with tuberous sclerosis. Fibrous cephalic plaque can be a finding specific to TSC. Shagreen patches appear as large and discoloured plaques to the lower back or flank. Fibromas under or around the nails are encountered in

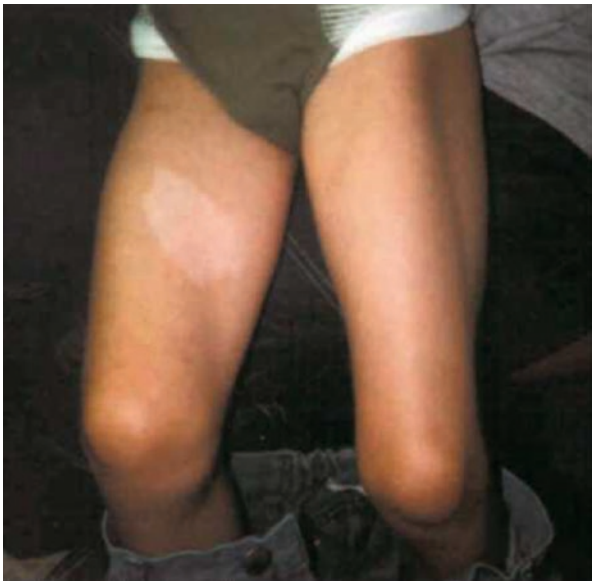

Fig. 27.1 Hypomelanotic spot on the right leg in tuberous sclerosis

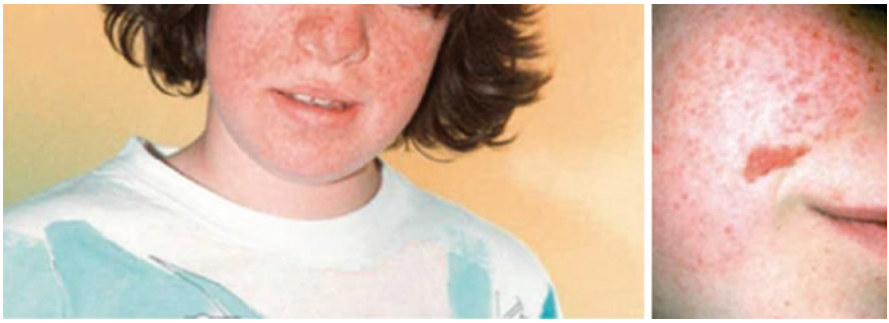

Fig. 27.2 Facial angiofibroma on the cheek

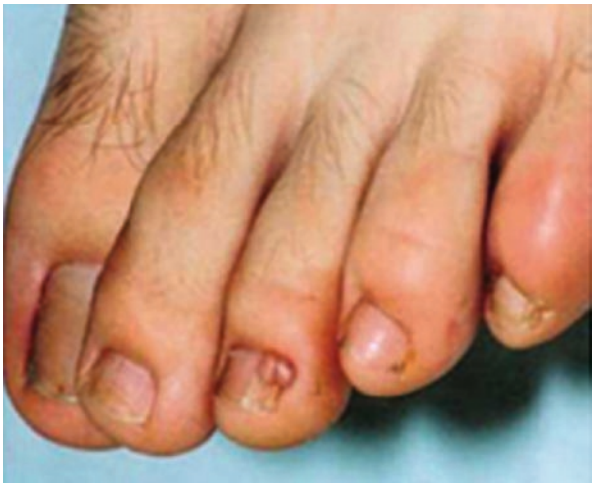

Fig. 27.3 Fibromas over the nail of the middle toe of the left foot in tuberous sclerosis

15–50% of the adult patients, more commonly found in the feet than in the hands (Fig. 27.3). Oral fibromas of the gums occur in 10% of the patients. Erosions of the enamel manifest as dental pits in 70–100% of the adult patients.

Neurological involvement includes epilepsy, and the identification of early-life seizures often is the presenting sign contributing to diagnosis. About 80% of TSC patients will present with seizure onset in the first 3 years of life and 2/3 of them in the first 12 months. Neonatal epilepsy seems to be quite rare, but it has been reported as well [21]. The age at seizure onset, the timing of appearance of epileptiform abnormalities on the EEG and the localization of abnormalities might relate to the location of cortical tubers detected on MRI in up to 90% of cases and may coincide with functional maturation of the cortex. An earlier expression has been demonstrated for temporo-occipital regions compared to frontal [22, 23]. In the same child, focal seizures may precede, coexist with or evolve into epileptic spasms [24]. Subtle focal seizures can occur, such as unilateral tonic or clonic phenomena mainly localized in the face or limbs, tonic eye deviation, head turning and unilateral grimacing. These may be missed by the parents until the third or fourth month of life when

epileptic spasms occur. Therefore, every effort should be made to diagnose TSC before the onset of epilepsy, thus having the opportunity to educate parents in recognizing subtle focal seizures.

EEG monitoring every 4 weeks in the first 6 months of life, and later every 6 weeks, has been studied for the appearance of epileptiform abnormalities or even ictal activity before the development of clinical seizures [25]. Trials of vigabatrin for the prevention of or delay in seizure onset have been under way in Europe [26] and in the United States with promising results. The vast majority of TSC children with early onset seizures will later develop refractory seizures, often associated with multifocal EEG abnormalities (see Chap. 50) [23, 27]. In particular, almost all children presenting with infantile spasms will have other seizure types, and precise electroclinical differential diagnosis between Lennox-Gastaut syndrome (LGS) and focal symptomatic epilepsy arising from the frontal lobe may be extremely difficult.

For some, long-term video-EEG monitoring can reveal subtle electroclinical abnormality suggestive of a focal seizure onset. In these patients, high time-resolution topographic EEG analysis and dipole localization methods may detect secondary bilateral synchrony (SBS), often originating in frontal regions and corresponding to prominent cortical tubers detected by MRI in the mesial surface of the frontal or the anterior temporal lobes.

Epilepsy surgery can provide short-term or long-term seizure remission, and even incomplete reprieve of seizure burden can improve quality of life and comorbidities (see Chaps. 48 and 49). Although epilepsy in TSC is usually a paediatric issue, about 12% of patients with TSC will experience their first seizure during adulthood, highlighting that the risk for seizure is high during the entire life span [21]. Although refractory epilepsy is a major concern in TSC patients, approximately a third of patients become seizure-free, in some cases even after experiencing early onset seizures and infantile spasms [28].

Even if prognostic factors have been proposed, predicting the course of epilepsy in TSC remains a major challenge. However, seizure onset in the first 3 years of life, the presence of frequent and multiple seizure types, an incomplete response to antiepileptic agents, the presence of multifocal EEG abnormalities with the occurrence of new EEG foci over time as well as a high tuber burden or the presence of cystic tubers should be considered as unfavourable prognostic factors, indicating a high risk of developing refractory epilepsy [24].

Neurocognitive and psychopathological manifestations are a common feature in TSC and may show striking variability [29] with possible combinations of psychomotor delay, cognitive delay, behavioural disturbances, autism spectrum disorders (ASD) and attention-deficit hyperactivity disorder (ADHD). In adults, additional psychiatric problems might present, such as anxious and/or depressed mood [30, 31]. Some individuals in the same family can be impaired and have severe autism and challenging behaviours, whereas others lead normal lives. A bimodal distribution of intelligent quotient (IQ) exists between a population with severe intellectual disability (30%, mean IQ = 30–40) and a population with less severe intellectual disability (>50%, mean IQ = 93) [32]. Patients with TSC who display average intelligence may, however, be prone to specific cognitive deficits of memory, attention or executive skills [33, 34].

An early age at seizure onset is one of the most important risk factors for a subsequent cognitive impairment [23, 33], and early seizures may also increase the risk for autism spectrum disorders. Children with tuberous sclerosis may manifest epilepsy prior to the onset of autism, raising the issue of a causal relationship with seizures disrupting the developing brain and specifically cognitive and social skills. Early-onset epileptiform EEG activity within the temporal lobes, and perhaps in other locations, might have a deleterious effect on the development and establishment of key cognitive representations concerned with the processing of social information [35]. Therefore, prompt treatment of epilepsy is mandatory in order to reduce the severity of cognitive and behavioural impairment, although this does not guarantee a normal mental outcome [36]. There is also study regarding the impact of vigabatrin on long-term intellectual ability if implemented on the basis of epileptiform abnormalities present before the onset of epilepsy [37]. However, further randomized studies are needed to clarify this point.

Frequency of autism in infants with tuberous sclerosis might be significantly higher than frequency of cardiac or renal abnormalities, for which screening is routinely done. Children with cognitive impairment are significantly more likely to have autistic spectrum disorder and attention-deficit hyperactivity disorder [29]. Since an early diagnosis of TSC is increasingly possible, children should be monitored not only for the appearance of seizures but also for early signs of autism spectrum disorder, thus making an early intervention during the period of brain plasticity possible [35]. Children with TSC and epilepsy are at higher risk for other behavioural disturbances such as attention-deficit hyperactivity disorder (ADHD) [38]. In particular, those with frontal epileptiform EEG foci show deficits on tasks assessing impulse control and planning, as well as impaired inhibition and set shifting. Side of the seizure focus may contribute to executive dysfunction in patients with epilepsy; particularly, a left frontal focus can interfere with inhibitory processes [39]. Moreover, 90% of patients with TSC exhibit supratentorial brain lesions, including cortical tubers, subependymal nodules (as calcified tumours), subependymal giant cell astrocytoma (SEGA), white matter linear migration lines, corpus callosum agenesis or dysplasia and transmantle cortical dysplasia (see also chapter on neuropathology). Infratentorial brain lesions are less common (<2% of patients) and can include linear and gyriform cerebellar folia calcification, cerebral nodular white matter calcifications, agenesis and hypoplasia of the cerebellar hemispheres and vermis, enlargement of the cerebellar hemispheres and subependymal nodules and tubers in the brainstem and fourth ventricle [40].

Cortical tubers are characterized by proliferation of glial and neuronal cells and loss of the six-layered structure of the cortex. The most prominent abnormal cell types in tubers are large dysplastic neurons, giant cells and bizarrely shaped astrocytes. Dysplastic neurons have disrupted radial orientation in the cortex and abnormal dendritic arborization, showing γ-aminobutyric acid (GABA) transporter defect and low GABAergic inhibition [41]. Subependymal nodules are hamartomas, typically seen in the subependymal wall of the lateral ventricles. Some nodules protrude into the ventricular cavity. Subependymal nodules develop during foetal life, are present in most patients with tuberous sclerosis and are usually asymptomatic. Nodules bigger than 5 mm, which are located near the foramen of Monro, not calcified and enhanced by gadolinium, have a high probability of evolving into SEGA,

particularly in familial cases of tuberous sclerosis [42]. Transformation of a subependymal nodule into SEGA is usually a gradual process, of which the highest rate is in the first two decades of life. Rapid growth over 12 months has been reported rarely [42]. Occurring in about 10% of cases, these slow-growing tumours demonstrate mixed glioneuronal lineage, and they are the most common brain tumours in patients with tuberous sclerosis [42, 43]. Growth of these lesions at the foramen of Monro can block the flow of the cerebrospinal fluid, leading to progressive lateral ventricular dilatation and increased intracranial pressure.

Neonatal SEGA are extremely rare; however, large SEGA have been identified in utero as early as 19 weeks of gestation [44]. The clinical diagnosis of a SEGA can be extremely difficult. They often present insidiously with subtle changes in behaviour, cognitive function or seizures long before clearcut symptoms of increased intracranial pressure, including headache and vomiting [45]. Obstructive hydrocephalus (in some cases) with clinical signs of intracranial hypertension or progressive hydrocephalus without obvious signs of increased intracranial pressure and new neurological deficits, such as blindness or worsening of a preexisting deficit, are considered indications in favour of prompt surgical resection [46]. Enlarging SEGAs alternatively can be treated with mTOR inhibitors such as everolimus, especially in cases when surgical intervention threatens eloquent cortex [47, 48].

SEGA are responsible for an estimated 25% of mortality attributable to TSC [42]. The potential for poor outcome from these lesions has led to recommendations to use cranial imaging to help identify SEGA at a presymptomatic stage [49]. According to guidelines of the NIH Consensus Conference, children with a diagnosis of TSC should have a brain MRI performed every 1–3 years, generally up to the age of 21 years [50, 51]. This recommendation is based on evidence that neuroradiological surveillance, early detection and early intervention for SEGA in TSC are associated with better neurological, cognitive and behavioural outcomes than in children with TSC who did not have surveillance for SEGA.

The kidneys can harbour angiomyolipomas (AMLs), single or multiple cysts, renal cell carcinoma and oncocytomas in 75–80% of the patients over the age of 10 years [52, 53]. Angiomyolipomas are histologically benign tumours made of blood vessels, connective and lipoid tissues and smooth muscle fibres (Fig. 27.4). They can replace renal parenchyma. Cysts may be present at any age, and renal tumours tend to grow mainly in older children and adults (Fig. 27.5). Symptoms usually occur during adulthood when the tumours grow beyond 4 cm in size. They can cause major bleeding and renal failure, especially when both kidneys are affected [54]. The symptoms include haematuria, hypertension, lumbar pain and renal insufficiency. Occasionally, some adults are diagnosed with tuberous sclerosis complex as a result of renal or pulmonary presentation. Tumours rarely become malignant. The combination of renal cysts (20–30% epithelial cysts) and angiomyolipomas is another characteristic of TSC [55]. A particularly aggressive phenotype occurs with contiguous gene deletion of the adjacent TSC2 and PKD1 genes, resulting in multiple renal cysts from infancy. Renal failure is a leading cause of early death [56]. Extrarenal angiomyolipomas (AMLs) are rare. In a retrospective study of sonographic and CT images, Fricke et al. [57] found 8 hepatic AMLs in 62 patients with TSC and bilateral diffuse renal angiomyolipomas.

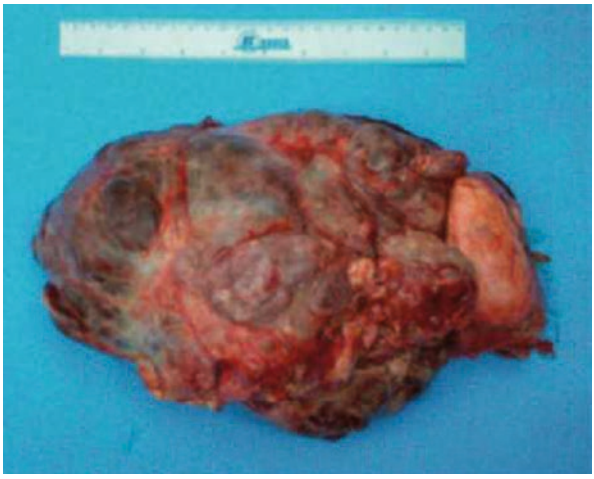

Fig. 27.4 Angiomyolipoma of the kidney in tuberous sclerosis

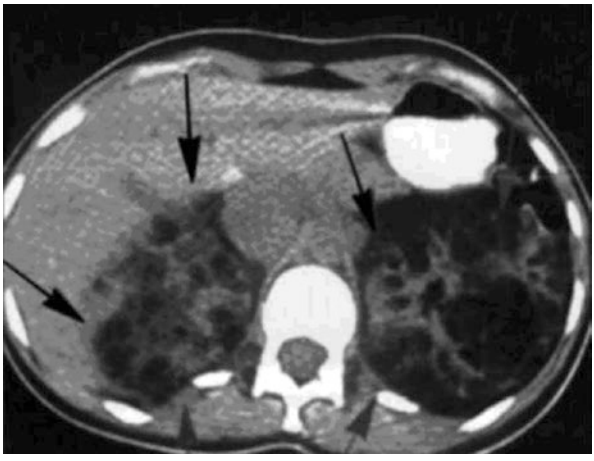

Fig. 27.5 Bilateral renal angiomyolipomas in a patient with tuberous sclerosis and large renal masses in CT scan (arrows)

Rhabdomyoma of the heart (Fig. 27.6) represents (along with hypopigmented skin spots) the earliest signs of TSC, preceding the onset of seizures [58]. Rhabdomyomas are observed in 43% of TSC patients and may sometimes be seen on prenatal ultrasound studies. Foetal rhabdomyoma (giant cardiac rhabdomyomas) is the most common foetal cardiac tumour and is often associated with tuberous sclerosis. Usually the tumours are relatively small and show no mediastinal shift. Foetal hydrops and pericardial effusion are rarely seen. The tumours may remain clinically insignificant and they tend to shrink as time passes. Cardiac dysfunction, when it does arise, can present as heart failure soon after birth. The tumours are responsible for interruption of the electrical conduction or cardiac arrest, depending on their size. Even after involution of the visible rhabdomyoma on imaging, electrocardiogram can demonstrate arrhythmia [59]. Diagnosis usually is made by ultrasound. The echocardiogram of the heart provides longitudinal follow-up of the tumour, and surveillance electrocardiogram also is recommended.

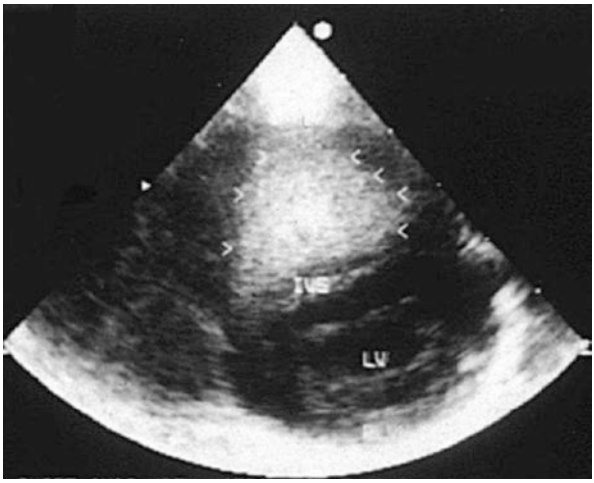

Fig. 27.6 Demonstration of a rhabdomyoma of the heart in an infant with tuberous sclerosis by sonography

Another cardiovascular complication of TSC is aortic aneurysm. Arterial aneurysms, mostly aortic and intracranial, probably through dysfunction of smooth muscle cells, have been reported sporadically in TSC. Kimura et al. [60] reported a case of a 2-year-old boy with a descending aortic aneurysm, and Boronat et al. [61] found three cases of intracranial aneurysm in a cohort of 404 patients.

Pulmonary involvement carries high morbidity and mortality when present and symptomatic. The diagnosis of lymphangioleiomyomatosis (LAM), which consists of reticular infiltration, multicystic formation and micronodular pneumocyte hyperplasia, is age-dependent. It is estimated that LAM occurs in 30–80% of women with TSC in 10–12% of men; the involvement increases with age and men rarely are symptomatic [47]. The mean age of diagnosis for TSC-associated LAM is 28 years compared to 35 years for sporadic LAM. The tumour suppressor genes TSC1 and TSC2 have been implicated in the aetiology of LAM, as mutations and loss of heterozygosity in TSC2 have been detected in LAM cells [62]. LAM manifests as dyspnoea, haemoptysis and spontaneous pneumothorax [63]. Multifocal micronodular pneumonocyte hyperplasia may be detected by CT of the chest, revealing numerous thin-walled cysts. Tissue biopsy with special stains (HMB-45) should be reserved for cases with atypical presentations. Preventive strategies include avoidance of cigarette smoking and estrogen-containing medications; for moderate to severe disease, mTOR inhibitor sirolimus has been indicated to stabilize lung function [64].

Skeletal system involvement includes cysts in the long bones and metacarpal and metatarsal joints. The association between tuberous sclerosis and macrodactyly is very uncommon [65].

The visual system is affected in the majority of TSC patients (see Chap. 47). On fundoscopy, retinal lesions (Fig. 27.7) are seen in 87% of the patients, which may be missed without proper pupillary dilation, especially in small children. The retinal lesions of TSC are astrocytic hamartomas and achromic patches, similar to the hypopigmented skin lesions [58]. The lesions consist of whitish or yellowish elevated areas resembling mulberries, often near the optic discs (retinal astrocytomas). The frequency of retinal hamartomas in TSC varies (about 50% of cases). The

ophthalmic findings seldom include hypopigmentation of the iris. Retinal astrocytic lesions of TSC generally are nonprogressive but may also grow relentlessly and cause severe ocular complications [66].

Diagnosis

The diagnosis of TSC is based on clinical findings. Diagnostic criteria of the disease have been established by the Subcommittee of the Professional Advisory Board of the National TS Association revised by Roach and Sparagana [50, 52] and in 2012 by the International Tuberous Sclerosis Complex Consensus Group [9, 59]. Definite TSC is diagnosed when at least two major (or one major plus two minor) features are present. Probable tuberous sclerosis complex includes one major and one minor feature. Possible tuberous sclerosis complex includes one major or two or more minor features.

- Major features include skin manifestations (i.e. facial angiofibromas, ungual fibroma, more than three hypomelanotic macules and shagreen patches).
- Brain and eye lesions (i.e. cortical tubers, subependymal nodules, subependymal giant cell astrocytoma, multiple retinal nodular hamartomas).
- Tumours in other organs (i.e. cardiac rhabdomyoma, lymphangioleiomyomatosis, renal angiomyolipoma).

An early prenatal diagnosis, such as based on foetal rhabdomyoma, may help for an adequate planning of perinatal monitoring and treatment with involvement of a multidisciplinary team.

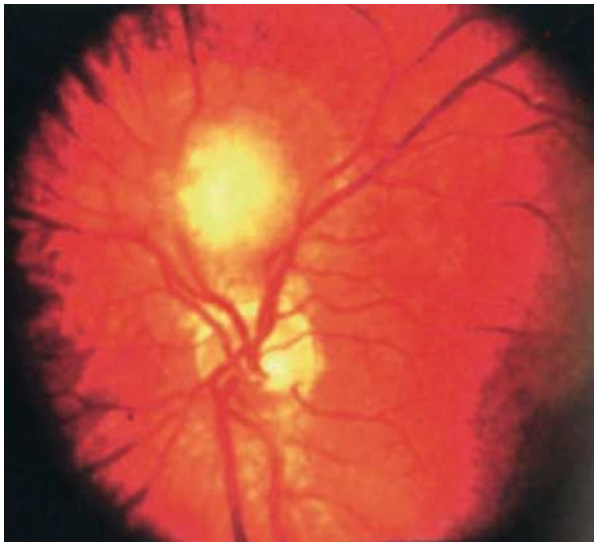

Fig. 27.7 Fundoscopy demonstrating retinal lesions

- Minor features include multiple randomly distributed pits in dental enamel
- Rectal polyps
- Bone cysts
- Cerebral white matter migration abnormalities on brain imaging
- Gingival fibromas
- Nonrenal hamartomas
- Retinal achromatic patches
- Confetti skin lesions and multiple renal cysts

Though not part of the diagnostic criteria, associated neurological features at the time of diagnosis and during disease surveillance also include seizures, autism or pervasive developmental disorders, mental retardation and various learning and behavioural disorders [40].

Early recognition of the disease demands genetic counselling of the parents, dermatologic and ophthalmologic examination, echocardiogram and electrocardiogram, brain and kidney imaging studies and developmental assessment. EEG is warranted depending on whether the patient has manifest seizures or is at a developmental age vulnerable to seizures. CT or MRI scans of the brain show hypodense/hypointense subependymal nodules (Fig. 27.8) (see Chaps. 3 and 4). Calcified nodules are readily demonstrated with CT scanning; MRI better delineates the

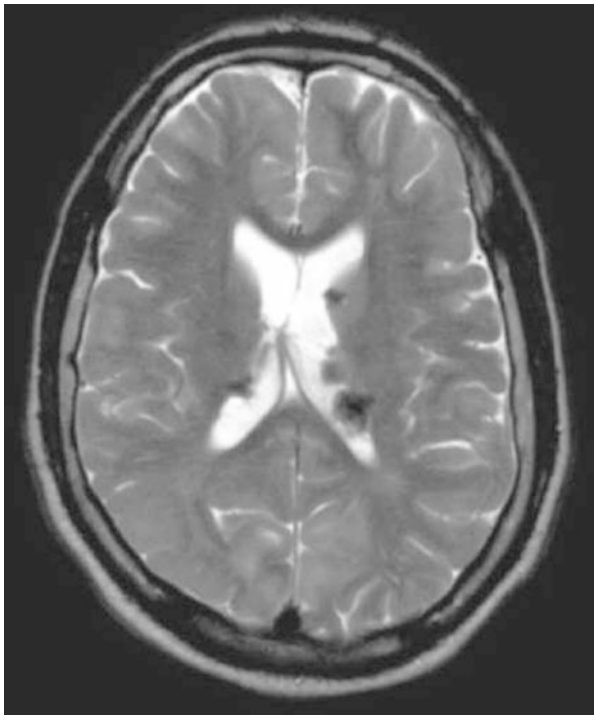

Fig. 27.8 MRI demonstrating SEGA and subventricular nodules in tuberous sclerosis

parenchymal lesions. White matter changes are hyperintense on T2-weighted sequences with a radial distribution from the ventricular ependyma to the normal cortex.

Extensive studies show variable EEG findings with epileptiform abnormalities and, rarely, with no abnormalities at all. The EEG may show multifocal hypersynchronous activity, while the primary characteristic of the infantile-type spasms is hypsarrhythmia and spike-and-wave discharges. Later, focal and generalized spikes and spike-and-slow-wave complexes may be shown. Visual recording techniques have led to significant progress in the classification of seizures associated with TSC, demonstrating that they have a focal or multifocal origin in the vast majority of the cases. In most cases, an awake interictal EEG shows focal or independent multifocal spike-and-slow-wave activity at onset and later a pseudo-hypsarrhythmic pattern. Although the pathophysiological mechanisms responsible for the co-existence of focal seizures and infantile spasms (IS) are still unclear, the latter may be the result of a rapid secondary generalization. Focal discharges are often associated with tumours within the cerebral parenchyma. It seems that the type of the initial seizures may be a significant prognostic factor.

As clinical features vary across the lifetime, surveillance testing at the time of diagnosis and at regular intervals is an important feature of comprehensive TSC care.

Management

A multidisciplinary team is necessary for achieving optimal patient therapy and outcomes.

Surgery management: As SEGAs are benign lesions, the surgical goal in the management of SEGAs is to perform a gross total resection whenever possible, which means an almost complete cure for many [67]. Therefore, previous attitudes towards operating on only symptomatic patients evolved towards a more aggressive approach to avoid the sequelae of raised intracranial pressure and hydrocephalus [68].

The surgical approach depends on tumour extension and the presence of hydrocephalus (see Chaps. 48 and 49). Transcortical, transventricular and transcallosal interhemispheric routes remain the most used approaches to the foramen of Monro [67]. However, new surgical strategies have evolved with time, and tools such as endoscopic procedures allow a less aggressive approach and lower morbidity [68, 69].

In the majority of children operated on early, the surgical outcome fluctuates between good and excellent. Some studies confirm the benefits of early surgical removal of SEGAs, especially when the tumour's diameter is less than 3 cm [43, 70]. Complications after surgical removal of SEGAs reflect those of any tumour surgery within the cerebral ventricles and around the foramen of Monro. Transient or permanent motor deficits, haemorrhage or compressive subdural collection have

been reported in about 10–20% of surgical patients [67, 70]. Major complications tend to occur more frequently in patients who are symptomatic for raised intracranial pressure or major hydrocephalus before surgery [71], such that a SEGA should be removed as soon as clear evidence of growth on two subsequent images has been determined [68]. Early resection of the tumour before the onset of irreversible neurological deficit is critical to improve the quality of life of this population, and it is associated with a low recurrence rate and low morbidity.

Symptomatic renal tumours previously have been treated surgically with nephrectomy or selective embolization for size greater than 4 cm. With the availability of medical interventions that may slow growth of angiomyolipomas and preserve renal function, embolization or resection is reserved for acute situations of haemorrhage [72].

In a meta-analysis of the literature for cardiac rhabdomyomas, Verhaaren et al. [73] concluded that surgical intervention immediately after birth is only necessary when severe cardiac outflow obstruction occurs. This tumour is generally believed to have no haemodynamic effects in the majority of cases. Exceptions may surface such as a report case of severe obstruction of the left ventricular outflow tract by a solitary tumour during pregnancy. Cardiac arrhythmias can be treated by medication or ablative surgery.

Medical treatment: In animal models, mTOR inhibitors showed that mTORC1 blockade alone and PI3K-mTOR blockade lead to suppression of tumour development and a longer survival of the treated animals [74]. Rapamycin, the first mTOR inhibitor used in individuals with TSC-associated lesions, was able to cause regression of SEGAs [75]. Its efficacy has been subsequently confirmed in later studies and even in lesions other than SEGAs, such as angiomyolipomas [76–79].

Actions of mTOR inhibitors within the mTOR pathway result in decreased protein synthesis and cell-cycle arrest, as well as decreased angiogenesis. EXIST-1 (examining everolimus in a study of TSC) was a phase III international, multicentre, double-blind, randomized, placebo-controlled trial that evaluated the efficacy and safety of everolimus in 117 patients (median age 9.5 years; range 0.8–26.6 years) with SEGA associated with TSC [80]. Everolimus was associated with a significantly greater overall SEGA response rate to shrink or stabilize growth, compared with placebo (35% vs. 0%; $p < 0.0001$); this benefit was consistent across all patient subgroups analysed [80]. Medical management with mTOR inhibitor such as everolimus can be considered for tumours that are multiple, recurrent or not amenable to gross total resection based on location or size [69, 81].

Common, typically self-limited, side effects are mostly linked to the immunosuppressive action of mTOR inhibitors and include aphthous ulcers, acneiform rash, diarrhoea, arthralgias, thrombocytopenia and non-infectious pneumonitis and may require temporary dose reduction or cessation. Severe adverse events may include upper respiratory tract infections and a potentially dramatic elevation of serum cholesterol and lipoproteins, sometimes requiring dietary adjustment or even an adjunctive pharmacological treatment [81].

Cutaneous manifestations in the form of facial angiofibromas can warrant intervention such as pulsed dye laser therapy. Systemic mTOR inhibitors have not been

approved for primary cutaneous indication, but patients with TSC taking these treatments for other indications report improvement in skin findings. Nonsystemic formulations of topical mTOR inhibitors have been compounded but are not commercially available. In topical formulation, localized irritation is a possible side effect. Ungual fibromas and cephalic plaques may warrant surgical intervention [82]. The Tuberous Sclerosis Association has released clinical guidelines for the care of patients and families with TSC (www.tuberous-sclerosis.org). In the United States, similar guidelines and resources are available through the Tuberous Sclerosis Alliance (www.tsalliance.org). In addition to medical surveillance, families with TSC and their care providers should screen for TSC-associated neuropsychiatric disorders (TAND) as these comorbidities often are underrecognized. Early recognition can facilitate interventions in homes, schools and communities [83].

Prognosis

The prognosis varies depending on the type and severity of the disease but generally reflects poorly on the psychomotor progress of the child. In oligosymptomatic cases, the prognosis is encouraging. Early screening for a diagnosis of autism is necessary [84, 85]. The onset of seizures in the neonatal period predicts moderate to severe developmental delay in more than 1/3 of cases. Most patients develop partial focal seizures that secondarily generalize or advance to Lennox-Gastaut syndrome during the course of the disease. The presence of infantile spasms due to TSC strongly correlates with the number of cortical tubers. Infants with transient IS and isolated cortical tubers located in the parietal and Rolandic regions may have normal intelligence. In contrast, children with persistent IS preceded or followed by focal seizures and with multiple bilateral tubers often develop refractory epilepsy and severe intellectual disability. Intellectual disability is a common comorbidity accompanying leading causes of death such as CNS tumours, renal insufficiency or epilepsy as in the cases of status epilepticus or sudden, unexpected death in epilepsy (SUDEP). Renal complications evolve over the lifespan. Female patients in particular are vulnerable to fatal complications of LAM [56]. Early recognition of these distinctive features appears worthwhile for therapeutic and prognostic implications [25, 86, 87].

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Chapter 28
Angiomatosis of the Retina and the Cerebellum (von Hippel-Lindau Syndrome)

Christos P. Panteliadis and Ramsis Benjamin

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Introduction

The autosomal dominant von Hippel-Lindau syndrome is a systemic cancer syndrome. The most common neoplasms are cerebello-retinal haemangioblastomas and endolymphatic sac tumours. It has a prevalence of approximately 1 in 36,000–40,000 people. Its penetrance reaches 95% by the age of 60.

The eponym is named after Eugen von Hippel, who in 1895 presented at the Heidelberg Ophthalmologic Society a 25-year-old patient with unusual retinal findings [1]. In 1904, he followed it with the histological description of the disease [2] similar to the cases in the literature by Collins [3] and Czermac [4]. In 1911, von Hippel documented another case of congenital haemangioblastoma in the retina and subsequent autopsy-proven tumours and cysts within the CNS, kidneys, pancreas, spleen and epididymis [5]. The Swedish pathologist Arvid Lindau linked the retinal

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lesions with cerebellar tumours and published in 1926 and 1927 a detailed description of 40 patients [6, 7].

The spectrum of tumours associated with von Hippel-Lindau (VHL) syndrome includes benign haemangioblastoma, retinal angioma, phaeochromocytoma (phae), paraganglioma (parag), pancreatic cysts and islet cell tumours, endolymphatic sac tumours in the inner ear and malignant clear-cell renal carcinoma (ccRC) [8–10]. VHL types 1 and 2 have been distinguished by low (5%) versus high (60%) rates of phae/parag, while VHL type 2 has been further classified into type 2A (rare ccRC), type 2B (frequent ccRC) and type 2C (strictly phae/parag) [11].

VHL gene is mapped to chromosome 3p25–26, producing a 30 kDa protein of 213 amino acids, pVHL, which possesses no enzymatic activity but is able to inhibit transcription elongation by binding to two proteins, elongin B and elongin C [12]. A second wild-type isoform of 160 amino acids is also expressed in human cells.

VHL regulates the production of vascular endothelial growth factor (VEGF) through a VHL-responsive element in the promoter region of VEGF and the ubiquitination of the hypoxia-inducible factor-1, HIF-1 [13]. An interaction also exists between the pVHL and a negative regulator of Mdm2, the programmed cell death 5 (PDCD5) protein [14]. The function of VHL is to control the ability of cells to exit cell cycle (Fig. 28.1).

Mutational analysis in the VHL gene shows important genotype/phaenotype correlates. More specifically, mutations that cause premature protein termination (nonsense, insertion and deletion) are most common in VHL cases without phaeochromocytoma. Mutations in type 1 VHL are predominantly large deletion or truncation that result in an encoded protein with very little or no activity. It is associated with retinal and CNS haemangioblastoma and clear-cell renal carcinoma. Missense mutations, on the other hand, are most prevalent in type 2 VHL [16, 17].

Mutational research has demonstrated that 20% of the patients exhibit germline deletions but lack correlation with phaenotypic characteristics. Loss of heterozygosity (LOH) has been demonstrated in all tumour types occurring in VHL patients. Hypermethylation of the VHL gene is detected in 1/3 of the tumours that do not have LOH.

Clinical Characteristic

Haemangioblastoma

VHL disease is characterized by haemangioblastomas in the brain, spinal cord and retina. The basic pathologic anomaly is capillary angioblastoma. The disease is diagnosed based on disseminated haemangioblastomas or in patients with a single lesion and a strong family history [18–20]. In addition, angiomas in the spinal canal have been observed, associated with syringomyelia and cystic tumours in the pancreas, kidneys and epididymis (cystadenoma) in up to 80% of the cases.

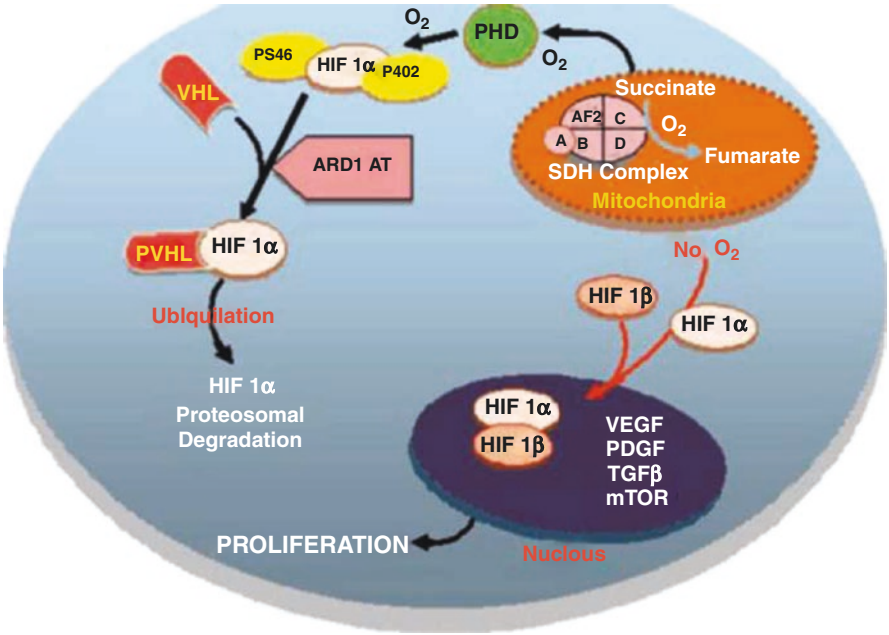

Fig. 28.1 The VHL tumour suppressor gene targets the hypoxia-inducible factor (HIF) as a major regulator of the hypoxic response. Ubiquitylation represents an efficient mechanism of tagging proteins for degradation by the 26S proteasome. VHL forms a multi-protein complex with elongins B and C, cullin 2 and Rbx-1. The ECV (elongin/cullin/VHL) complex displays E3 ubiquitin ligase activity, which acts to polyubiquitylate protein substrates. Within this complex, pVHL acts as a substrate recognition subunit. Abbreviations: HIF, hypoxia-inducible factor; SDH, succinate dehydrogenase; VEGF, vascular endothelial growth factor; PHD, prolyl hydroxylases [12, 15]

Haemangioblastomas involve 2/3 of the time the cerebellum (Fig. 28.2), 1/4 the spinal cord, 1/10 brainstem and rarely the pituitary gland [22, 23]. Cerebellar haemangioblastomas may be associated with headache, vomiting, gait disturbances or ataxia. Spinal haemangioblastomas and related syrinx usually present with pain. Sensory and motor loss may develop with cord compression [18]. These lesions most commonly present during adulthood; however, imaging surveillance should begin in childhood [24].

Phaeochromocytoma and Other Tumours

Patients with VHL are predisposed to a variety of tumours occurring in 14 different target organs. Bilateral phaeochromocytomas have been documented in greater than 40% of VHL cases and are typically associated with a positive family history [25]. The prevalence of phaeochromocytoma overall reaches 53%. Symptoms of phaeochromocytoma include intermittent bouts of diaphoresis, headache, palpitation and

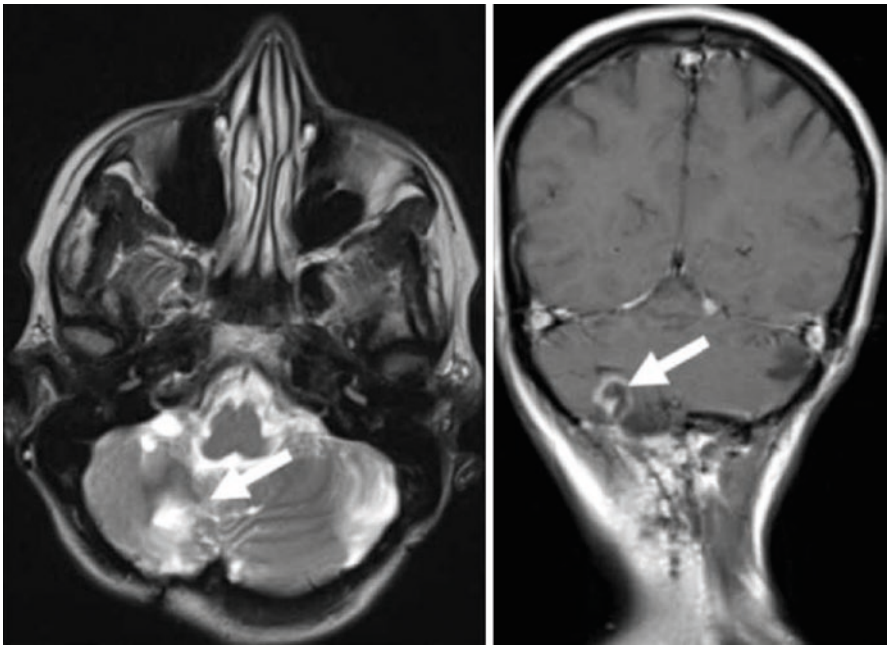

Fig. 28.2 MRI disclosing cerebellar haemangioblastoma in von Hippel-Lindau syndrome; left, T2-weighted axial view of a paramedian cerebellar tumour; right, coronal section showing a cystic irregular rim-enhancing mass (with kind permission from Saara Metso [21])

hypertension (The "4 Hs" of phae: hyperhidrosis, headaches, high heart rate, HTN), the last unremitting to antihypertensive medications. The levels of 3-methoxy metabolites, normetanephrine and metanephrine in the serum and urine clinch the diagnosis of phaeochromocytoma. The lesions are almost always located in the adrenal glands. Malignant hypernephroma is very common (1/3 of the cases) and is a significant cause of death [26]. Moreover, 60% of the affected males also have a VHL-associated tumour known as epididymal cystadenoma. Pancreatic lesions are common, most often benign cystadenomas, which occur in at least 50% of patients with VHL [9, 27]. Mutations in the VHL gene can also upregulate expression of the central angiogenic factor, VEGF, which drives abnormal angiogenesis in clear-cell renal carcinomas (ccRC). Endolymphatic sac tumours of the inner ear occur in approximately 15% of patients, which may cause irreversible hearing loss if left untreated.

Retinal Angiomas

With careful and diligent examination, capillary haemangioblastoma in a child can be visualized by the aid of an ophthalmoscope as a cystic mass in the peripheral aspect of the retina (Fig. 28.3). Only 5% of patients with VHL present with retinal

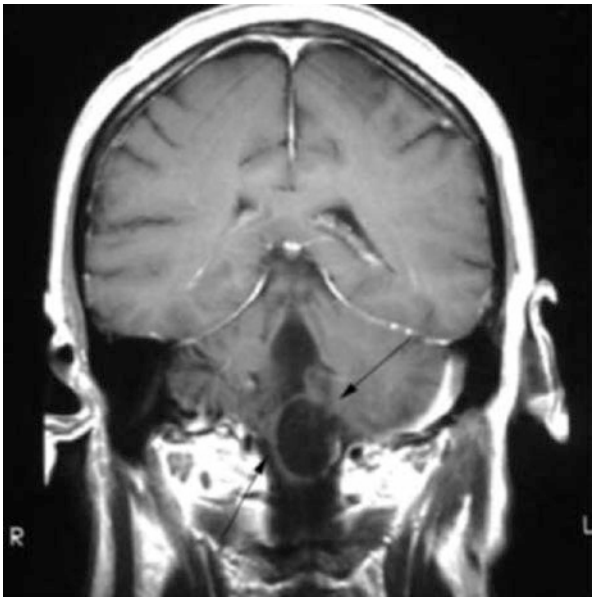

Fig. 28.3 50-year-old woman with the syndrome. Coronal postcontrast T1-weighted image shows a haemangioblastoma as a pure cystic lesion involving the medulla (arrows)

capillary hemangioma before the age of 10 years; most patients present between the ages of 10 and 40 years [28]. VHL disease can be associated with Goldenhar syndrome, a rare congenital maldevelopment of the ear, nose, soft palate, lip and mandible. Examination of the retinal structure using optical coherence tomography shows a significant decrease in retinal thickness in all patients when compared to controls [29]. Further, 25–80% of the patients with retinal haemangioblastoma will have VHL disease. Visual disturbances, floaters, metamorphopsia and strabismus constitute some of the ophthalmological complaints. Frequently, there is progressive accumulation of fluid behind the retina resulting in its detachment (Fig. 28.4).

Complete visual loss in one or both eyes occurs at a young age. Retinal capillary haemangioblastoma occurs sporadically or as the sole manifestation of VHL disease. Neither the prevalence nor the number of angiomas increases with age. The tumours are often multiple and bilateral in more than 50% of the patients and may exist anywhere in the retina. Many tumours are progressive, often reaching stage 3 or greater retinopathy (i.e. exudation and vitreous haemorrhage).

Diagnosis

The clinical diagnosis of VHL disease hinges on the family history [9, 30]. With no family history, the patient must harbour two or more of the following criteria for the diagnosis to be made:

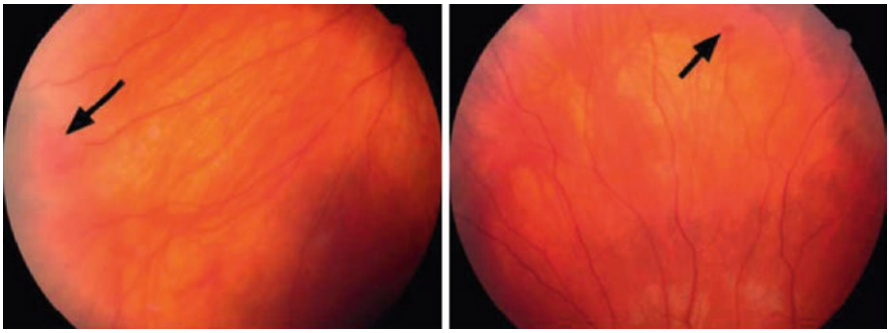

Fig. 28.4 Funduscopy in a patient with von Hippel-Lindau syndrome revealing small haemangioblastomas (arrows) (with kind permission from Saara Metso [21])

1. Multiple haemangioblastomas within the oculo-cerebrospinal axis or a solitary haemangioblastoma in the presence of renal or pancreatic cysts
2. Clear-cell renal carcinoma
3. Phaeochromocytoma
4. Endolymphatic sac tumours, papillary cystadenomas of the epididymis or broad ligament or neuroendocrine tumours of the pancreas

In the presence of a family history of VHL disease, the clinical diagnosis is established by at least one of the following:

1. Retinal angioma
2. Spinal or cerebellar haemangioblastoma
3. Phaeochromocytoma
4. Clear-cell renal carcinoma
5. Multiple renal and pancreatic cysts

Cerebellar symptoms start after the second decade of life. Patients suspected of having VHL require annual ophthalmologic examination with fluorescein angioscopy or angiography from infancy onwards. Urinary catecholamines (VMA and noradrenaline) should be obtained every 1–2 years, along with yearly abdominal ultrasonography or magnetic imaging after the age of 10 years. Cranial and spinal MRI scans are needed every 2 years from age 11 and every 3–5 years after age 60. Vascular tumours like haemangioblastoma reveal high intensity on T2-weighted sequences. In comparison with CSF, the cystic part of the tumour is of slightly higher intensity on T1-weighted and significantly higher intensity on T2-weighted images, indicative of proteinaceous substance [31]. Diffusion weighted images could distinguish between cystic and non-cystic lesions. Visualization of feeding vessels may differentiate this neoplasm from other cystic tumours, such as cystic astrocytoma or medulloblastoma. In comparison, MRI is superior over CT in delineating lesions in the posterior cranial fossa. Unfortunately, endolymphatic sac tumours of the inner ear may go undetected by MRI, and some advocate for annual audiometry to screen for a distinct pattern of low-frequency hearing loss seen in

these cases prior to MRI changes [32]. In patients with VHL syndrome, phaeochromocytoma cannot always be diagnosed by biochemical catecholamine analysis, requiring CT or MRI scanning of the abdomen.

Gad DOTANOC PET/CT helps in the diagnosis of VHL syndrome by discovering occult tumours that are clinically silent [33].

Prenatal diagnosis for pregnancies at 50% risk is possible by analysis of DNA extracted from foetal cells via amniocentesis (at 15–18 weeks gestation) or chorionic villus sampling, usually performed at 10–12 weeks of gestation [9].

Therapy

The best management of the disease is early diagnosis and close monitoring. Mutational analysis of at-risk family members with VHL should allow screening for complications in asymptomatic individuals and for routine diagnostic surveillance. Anticipation related to the shortening of telomere length is present in families with VHL disease and may be helpful for genetic counselling [19, 34].

Early detection and treatment of peripheral retinal angiomas is imperative to help prevent visual loss. Similarly, changes in annual audiometry of low-frequency hearing loss may herald the finding of endolymphatic sac tumour, amenable to microsurgical intervention or stereotactic radiosurgery (SRS), with probable hearing preservation subsequently [35].

Stereotactic radiosurgery can achieve a high local control rate of above 60% for over a decade without radiation-induced complications in patients with intracranial tumours [10, 36].

Combination of bevacizumab and interferon-α is an effective strategy for initial therapy of metastatic RCC [37, 38]. Antiangiogenic agents such as sunitinib, an inhibitor of tyrosine kinase receptor that mediates the effects of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and erythropoietin, have shown promise in controlling metastatic ccRC [39, 40]. In patients with sporadic, recurrent or progressive renal cell carcinoma as a result of dysregulation of VHL-dependent pathway, sunitinib can achieve a partial RECIST response in nearly 2/3 [41]. Several other targeted therapies have been approved for the treatment of metastatic renal carcinoma, which may have strong potential for ccRC as well, such as tivozanib, cediranib, VEGF Trap and temsirolimus [42, 43].

Radiofrequency ablation is a minimally invasive treatment for small hereditary renal carcinomas. It has low complication rate and minimal decrease in renal function [44, 45].

LASER therapy is successful at an early stage of retinal angioma. Other options include cryotherapy, radiotherapy, photodynamic therapy and en bloc resection for advanced cases. None of these therapies, however, has achieved a general consensus. Other approaches could be considered, such as transvitreal endoresection after ligating the feeder vessels [46].

Prognosis

Prognosis is good following conventional surgical removal of cerebellar haemangiomas. Stereotactic radiosurgery has been shown to provide actuarial tumour control rates of 94% and 80% after 5 and 10 years, respectively [47]. Perhaps in the future, minocycline could be rendered concurrently with radiosurgery, as it induces the oxygen-labile transcription factor hypoxia-inducible factor-1 alpha (HIF-1α) proteasomal degradation under hypoxia by increasing the expression prolyl hydroxylase-2 and HIF-1α/von Hippel-Lindau protein interaction, thereby overcoming hypoxia-induced HIF-1α stabilization [48].

Visceral manifestations of VHL are often asymptomatic, and their early detection, much like haemangiomas, is of considerable help in the treatment. Longitudinal imaging scans for renal manifestations of VHL disease should commence in the second decade of life. The proangiogenic, proinflammatory cytokine CXCL7 is an independent prognostic factor for overall survival for ccRC, at least in nude mice [49], which may have future utility in humans. Serial screening imaging studies for the early detection of VHL-associated neuroendocrine tumours are necessary in individuals at risk of VHL disease.

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Chapter 29
Gorlin-Goltz Syndrome (Nevoid Basal Cell Carcinoma Syndrome)

Christos P. Panteliadis and Reinhard E. Friedrich

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Introduction

Epidemiological analyses estimate the incidence of GGS to be 1 per 50,000–150,000 in the general population. The causative gene is the analogue to the patched (PTCH) gene of the fly.

Drosophila. PTCH1 maps to chromosome 9q22.3–31 [1]. In addition to the mutations of PTCH1, mutations in the genes PTCH2 [2] and suppressor of fused (SUFU) [3] were also detected in GGS patients. There are differences in the phenotype of the GGS patient in relation to the site of mutation [4]. Therapy is symptomatic.

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History. In the late nineteenth century, Jarisch and White made the first descriptions of patients with findings corresponding to the current diagnostic criteria of GGS [5, 6]. Gorlin and Goltz coined their names to the condition in 1960 after presenting an accurate description of the hereditary nature of the disease, phenotype, and main clinical characteristics [7]. Soon after the description of the syndrome, Satinoff and Wells described two Egyptian skeletons of the Dynastic Period with skeletal anomalies compatible with findings recorded in GGS. The skeletons (Istituto di Antropologia, University of Turin) showed mandibular cysts and multiple bony cavities in maxilla, bifid ribs, os sacrum with incomplete fusion of the caudal laminae, and slightly enlarged sella turcica [8].

Terminology. GGS is mislabelled at times as "basal cell nevus syndrome" [9, 10]. The term "nevus", however, is a misnomer in terms of describing the biological quality of the syndrome's skin lesions because the cutaneous lesions frequently represent aggressive basal cell carcinoma (BCC) as seen in GGS, rather than a benign lesion as the term "nevus" implies. According to Gorlin, the general term "nevoid basal cell carcinoma syndrome" describes more precisely the potential risk of the affected patients from skin neoplasms [11]. GGS patients are at risk of more non-cutaneous neoplasms than the general population, so the medical assessment of the patient must include many functions and organs. Patients with this rare syndrome often have anomalies in multiple organs, many of which are subtle.

Clinical Characteristics

General characteristics. General characteristics in GGS are BCC, jaw keratocysts, and cerebral calcifications [12, 13] (Fig. 29.1a, b, c). However, general body characteristics are often of decisive importance for the first examination of patients in order to establish the diagnosis, in particular in young individuals [14–18]. The main visible facial feature frequently is a "coarse face" with an enlarged head, frontal bossing, hypertelorism, and broad nasal root [16, 19, 20]. About 70% of patients with this syndrome have some degree of craniofacial anomalies. GGS patients are often tall in relation to their next of kin. This finding is often noticed already in childhood.

Skin

Whereas life expectancy in NBCCS is not significantly different from average, the neoplastic alterations can be a dominant burden in the patient's life. The patients usually bear pronounced skin sensitivity to ionizing radiation, including ultraviolet light [21, 22]. They have an increased rate of BCC compared to the general population. BCCs may appear as early as 2 years of age, but the first manifestations usually appear between puberty and 35 years of age [23]. The majority (90%) of GGS

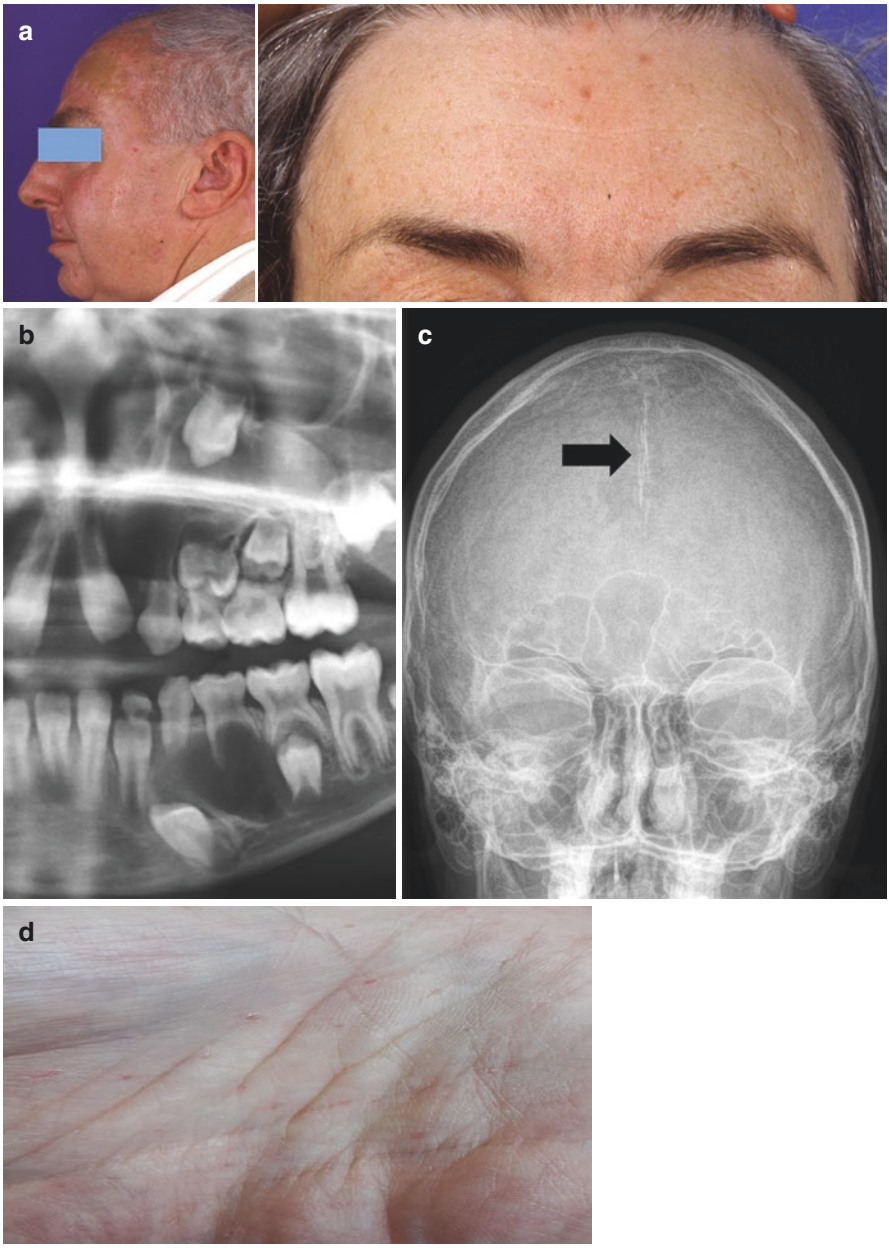

Fig. 29.1 (**a**) Left: Profile of a patient with GGS. Multiple scars and skin transplant resulting from uncounted surgical procedures for BCC excision. Note two scabbing ulcerations of pinna. Right: Frontal bossing and multiple nevi in a patient with GGS. (**b**) Orthopantomography of jaws of a young patient with GGS (cropped image, left body side). Note multiple cystic lesions in both jaws and retained permanent teeth. All cystic lesions proved to be odontogenic keratocysts (OKC). While the X-ray findings of solitary keratocysts are ambiguous, syndromic lesions mostly present as multiple OKC. (**c**) Posterior-anterior skull radiograph of a child with GGS. Note bilamellar ossification of falx cerebri (arrow). (**d**) Palmar pits in a GGS patient

patients develop BCC at age 30 years and older [24], which correspond strongly with increased exposure to the sun [25]. Bhattacharjee et al. [26] reported the first primary cutaneous carcinosarcoma associated with NBCCS. Reports on BCC in GGS are predominantly from Western countries. The early development of BCC in Caucasians with GGS is possibly facilitated due to their lower light protection of skin [15]. However, exposure of the skin to sunlight is not mandatory for the frequent development of BCC in GGS [25]. GGS was noted as a rare genetic disorder worldwide [27]. In addition to BCC, other skin findings like basal cell nevus, epidermal cysts [28], facial milia [29], and palmar and plantar pits are typical in GGS (65–80% of patients) (Fig. 29.1d).

Genetics

Epidemiological analyses estimate the GGS incidence to be 1 in 50,000–150,000 [30]. The disorder carries an autosomal dominant trait [14] and has been described equally in number in both sexes. Mutation of a candidate gene was identified on chromosome 9 [30] and finally characterized as the human homologue to the Drosophila patched gene (PTCH) [31]. Patched is part of the highly conserved hedgehog signalling pathway, important in determining embryonic patterning and cell fate in multiple structures of the developing embryo [32–36]. The gene causing GGS in humans is located on chromosome 9q22.3–9q31 and termed "PTCH1" [11, 37–42].

However, recent studies have shown that, in addition to PTCH1, mutations in PTCH2 (chromosome 1) can also cause GGS, although the importance of PTCH2 mutations for the development of the GGS has so far been controversially discussed [43]. Mutations in a third gene, named suppressor of fused (SUFU; chromosome 10 [44]) are relevant in determining the genetic basis of neurogenic tumours in GGS [45]. Apparently, no OKC occurs with mutations of SUFU [45]. There are obviously differences in GGS phenotype depending on the particular mutation [46].

Radiology. Radiological findings in GGS are very numerous and variable [47]. Some findings are of diagnostic relevance; others are also of functional importance. Frequent clinical and radiological manifestations include (multiple) odontogenic keratocysts (OKC; up to 75%), macrocephaly, hydrocephalus, and agenesis of the corpus callosum, bridging of sella turcica, calcification of the falx cerebri (37–79%), skeletal abnormalities such as Sprengel deformity (elevation of the scapula with rotation of its lower angle towards the spine), marked pectus deformity (about 43%), bifid ribs (40%), short fourth metacarpal bone, and syndactyly of the digits. Cleft lip and/or palate occur in 3–8% of the cases [48, 49].

The first radiological indications for a GGS can often be seen on plain radiographs. On radiographs of the thorax and spine, spina bifida occulta, and congenital abnormalities of ribs and of the shoulder(s) were found in a large proportion of patients [50]. A variant of the first cervical vertebra, the ponticulus posticus, was demonstrated by lateral cephalograms to develop in many patients with GGS [51].

However, the diagnostically relevant sella turcica bridge is a much better known radiological sign on lateral cephalometry in patients with GGS [52].

Orbit and Eye

The most frequently reported orbital and ocular findings in GGS are hypertelorism (45.5%), congenital cataract (18%), nystagmus (9%), colobomas (9%) and strabismus (63%), epiretinal membranes (36%), and myelinated optic nerve fibre layers (36%), highlighting the value of ophthalmological investigation in this patient group [53].

Jaw Cysts

OKC can be the first finding of the syndrome, which is why the treating dentists are of particular importance when introducing the differential diagnosis of GGS in patients with OKC, especially when young patients are affected without further diagnostically relevant findings being evident. OKC is a locally aggressive osteolytic jaw lesion that occurs sporadically or in association with NBCCS. Indeed, only a few patients with OKC have GGS. Recurrence of OKC is a frequent finding both in sporadic and syndromic lesions. In contrast to cutaneous cysts, the morphological and immunohistochemical profiles of syndromic and sporadic jaw cysts show no significant differences [54, 55]. Sporadic OKC rarely appears in childhood. Careful examination of children and adolescents with OKC is therefore indicated in order to rule out GGS. In a retrospective study of 50 children up to 18 years of age presenting with first diagnosis of OKC and so far not diagnosed as GGS patients revealed a high frequency of new GGS cases. Hence, clinicians should have a low threshold for referral to complete examination or genetic testing in children with even a single OKC [56].

Other Findings

Reports of other findings, particularly dysplasias and tumours, are numerous, for example, ovarian calcification, fibromas of the ovaries (20%) or heart (2%), medulloblastoma (5%), and other tumours [57, 58]. The proportion of syndromic medulloblastomas in a larger case series (n = 129) is less than 10%. Both PTCH1 and SUFU germline mutations were detected in GGS cases (2/129) [59]. In an earlier evaluation of GGS-associated findings, the proportion of patients with medulloblastomas was 3.8% (4/105) and is currently estimated at around 5%. There are assessments of the genotype-phenotype ratio of the GGS that expect a significantly higher risk of medulloblastoma in cases with SUFU mutations (33%) in contrast to PTCH1 mutations (<2%) [60].

Diagnosis

Kimonis et al. [60, 61] have proposed that diagnosis of GGS can be made in an individual suspected of being affected by GGS if two major criteria, or one major and two minor criteria, are revealed.

The major criteria consist of two or more BCC in individuals younger than 20 years; OKC of the jaw (Fig. 29.1b); three or more palmar or plantar pits (Fig. 29.1d); bilamellar calcification of the falx cerebri (Fig. 29.1c), bifid, fused, or markedly splayed ribs; and a first-degree relative with GGS.

The minor criteria comprise macrocephaly, congenital craniofacial malformations (frontal bossing, coarse facies, cleft lip/palate, moderate or severe hypertelorism), Sprengel deformity and other skeletal abnormalities, syndactyly of the digits, ovarian or cardiac fibromas, and medulloblastoma. Genetic diagnostics plays an increasingly important role in differential diagnosis, especially in oligosymptomatic cases.

Imaging techniques may be necessary to establish the diagnosis and in-patient monitoring, such as MRI of the brain, echocardiography, abdominal ultrasonography, dental radiography, and skeletal survey, however, with the goal of minimizing the amount of ionizing radiation rendered at any given period. The rate of meningioma and medulloblastoma may increase post-irradiation in these patients. The combination of clinical, regular skin examinations, imaging, and histological findings is indispensable in identifying patients at risk and establishing diagnosis [61]. Patients suspected of having GGS should have biopsies obtained from several suspicious skin lesions. Obviously, if an infratentorial mass is detected by cranial MRI, it should be biopsied to rule out medulloblastoma.

Therapy and Prognosis

Patients with GGS may need to be treated by a wide range of specialists, including dermatologists, dentists, cardiologists, radiologists, oncologists, and orthopaedic surgeons [62–64]. Frequent clinical and dermatologic surveillance is necessary for individuals with established GGS, and sun protection is an important preventative measure. The colloquium group for NBCCS consists of individuals with research interest in this syndrome and additionally serves as the medical advisory board of the NBCCS Life Support Network [9, 19].

Skin Surgical excision of neoplastic skin lesions is the therapy of choice [65]. In superficial and well-defined lesions, ablative surgery, cryosurgery, laser ablation, and electrocautery successfully may be applied [66]. However, the multiplicity of many lesions and difficult anatomical localizations of the lesions, especially in the face, place considerable demands on surgical therapy. In individual cases, the size and number of tumours may prompt the use of alternative therapies, e.g. cryotherapy or nonsurgical measures [65].

Topical therapies, such as 5% imiquimod or 5% fluorouracil, are recommended in patients with low-risk superficial BCC, in cases with nodular BCC possibly combined with phototherapy [65, 67]. In locally advanced and/or metastatic BCC, application of hedgehog inhibitors, e.g. vismodegib or sonidegib, should be considered. However, the rate of dropouts due to drug intolerance is very high in patients with BCC participating in clinical studies. After stopping the medication, further tumour development must be expected [29, 30]. New immunotherapies are currently being tested in clinical studies, e.g. medication with anti-programmed cell death 1 (PD-1) antibodies [65]. However, the study results have so far been unsuitable for developing general recommendations for PD-1 in BCC [68].

Odontogenic keratocyst (OKC) Treatment of OKC is surgical [69]. The use of locally applied toxic agents such as Carnoy's solution to prevent relapses is controversial [70]. In individual cases, conservative treatment strategies have been successful that have reduced the rate of loss of teeth and parts of the jaw [71]. Case reports detailed treatment results with vismodegib for BCC in GGS patients and showed remarkable shrinkage of osseous lesions in some patients with syndromic OKC [72].

Prevention

Adherence to effective measures to protect the skin from light and regular dermatological examinations is essential for patients with GGS. Siblings of GSS patients should be clinically and possibly genetically investigated for evidence of this syndrome. Early diagnosis and therapy may reduce the severity of the long-term sequelae of GGS, including malignancy and oromaxillofacial deformation and destruction. Annual screening for medulloblastoma (in patients younger than 8 years) and orthopantomography of the jaws for OKC (in patients older than 8 years) is recommended. The risk of developing neoplasm in the radiation area has been proven in patients with GGS, so radiation therapy should be avoided whenever possible [73].

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Chapter 30
Cockayne Syndrome

Christos P. Panteliadis

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Introduction

Cockayne syndrome (CS), or Neill-Dingwall syndrome, is a rare autosomal recessive, multisystem disorder characterized by a variety of clinical features, such as hypersensitivity to UV light (but not all patients), microcephaly, degeneration of multiple organ systems including the eye and ear, cataracts, severe growth failure and cachexia (also termed cachectic dwarfism), short life span and progressive nervous system abnormalities. The first two patients were described by Cockayne in 1936 [1], who also published a follow-up report in 1946. The syndrome is characterized by dwarfism with prognathism, thickening of the skull bones and other skeletal changes, a peculiar form of retinal pigmentation, optic atrophy, cataract, deafness and mental deficiency [2]. In 1950, Neil and Dingwall published two brothers with dwarfism, microcephaly, a fine diffuse characteristic "pepper and salt" chorioretinitis, intracranial calcification and developmental deficit [3]. The elder

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brother developed deafness. The appearance of the patients was exactly similar to that of Cockayne's cases and overlapped xeroderma pigmentosum (see Chap. 31) [4].

Some patients have been reported to have CS in combination with symptoms or signs of other rare genetic disorders, such xeroderma pigmentosum (XP) or Refsum disease. The growth failure is profound and generally begins within the first year of life. All patients with CS eventually develop neurologic dysfunction and have cognitive deficiency. The mean age of death in reported cases is 12 years. The clinical heterogeneity of Cockayne syndrome shares similarities with other DNA repair disorders [5]. The molecular mechanisms underlying CS have been linked to two genes ERCC6 and ERCC8 in the pathway of nucleotide excision repair (NER). Patients with CS have a defect in a sub-pathway of NER, referred to as transcription-coupled nucleotide excision repair (TC-NER). Patients with the genetic disease CS are highly sensitive to sunlight exposure and have a greater risk of cancer on sun-exposed areas of the body [6].

Epidemiology

The incidence of CS in Japan is estimated at 2.7 per 1,000,000 births (95% CI: 2.19–3.11), and the prevalence approximates 1/2,500,000. Moreover, 90% of the cases belong to type I (see below [7, 8]). In all populations, CS has an incidence of 1 in 250,000 live births and a prevalence of 2.5 per million, the numbers being remarkably consistent across various regions globally [7, 8]. CS usually begins in early infancy, and up to now, more than 200 cases of CS have been published. It is characterized by postnatal growth failure and progressive multiorgan dysfunction.

Clinical Characteristics

Clinical features comprise of severe growth failure (stooped posture), progressive multiorgan dysfunction, renal disease, increased blood pressure, beaked nose, microcephaly, loss of subcutaneous fat, hearing loss (sensorineural), cataracts, pigmentary retinopathy, photosensitivity and sunburn after brief exposure. The mean age of death in reported cases is 12 years and 3 months.

Photosensitivity occurs in 75% of patients with CS, characterized by sunburn after brief sun exposure (Fig. 30.1) [9]. Cyanotic acral oedema of the extremities was also present in 75% of CS patients along with hair anomalies and nail dystrophies [9]. Patients show the appearance of premature aging [10]. When cardinal features are lacking, the diagnosis of CS should be considered in infants with growth retardation at birth, microcephaly, kyphosis, scoliosis and one of the suggesting features, such as enophthalmia, limb ataxia, abnormal auditory-evoked responses or ventriculomegaly on cerebral imaging [8, 11, 12].

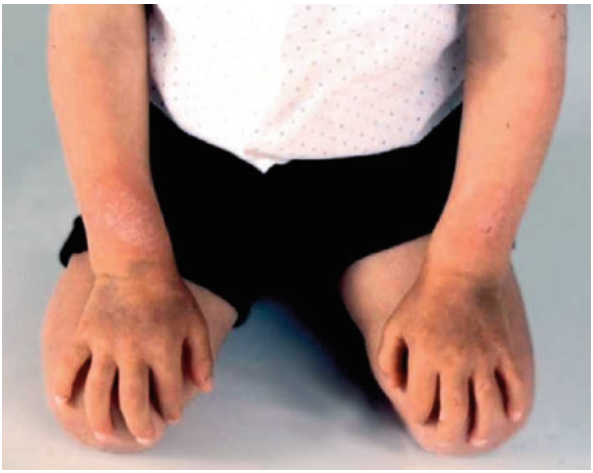

Fig. 30.1 Photosensitivity characterized by sunburn after brief sun exposure

Nance and Berry reviewed 140 patients (75 male, 60 female, 5 undetermined) with CS and provided detailed information on many of the clinical features [12, 13]. They differentiated between major and minor criteria for the diagnosis and proposed a classification of CS into three types.

CS type I (classical type) patients show normal developmental milestones in the first months of life but begin to show growth and developmental abnormalities by 1–2 years of age. Motor and speech delay can be observed at the end of the first year or during the second year of life. CS type I patients usually learn to walk but often lose this ability as the disease progresses. These patients can understand and make simple sentences. However, progressive impairment of vision, hearing and central and peripheral nervous system function leads to severe disability and death typically in the first or second decade of life [14, 15].

CS type II (congenital or severe type) shows an early onset or is already apparent at birth. Type II is the most severe form, shows prenatal growth retardation, and is therefore affected at birth. Death usually occurs by the age of 5 years [7].

CS type III (late-onset or adult-onset type) patients may only have mild intellectual disability and learning difficulties in primary school. Some patients have even been reported to have normal intellectual capacities and should probably be considered as yet another subgroup of severity. CS type III is a phaenotype in which major clinical features associated with CS only become apparent after the age of 2 years; growth and/or cognition exceeds the expectations for CS type I. Cognitive decline and early dementia in adulthood are often reported in the oldest patients of these categories, typically after 30 or 40 years of age [7, 14].

The distinction between these three types is not absolute and is becoming less distinct as additional patients are identified. Dense or punctuate, symmetrical calcifications in the putamina are usually predominant in types I and III patients, and there can be associated calcifications in the dentate nuclei in later stages [14].

Symptoms in CS include a characteristic aged facial appearance with protruding nose and sunken eyes (designated bird-like face) and thin hair, musculoskeletal abnormalities (contractures, kyphosis), progressive neurological and cognitive dysfunction, sensory-neural hearing loss and eye abnormalities, such as congenital cataract and retinal degeneration [16]. The characteristic facial appearance of CS patients is mainly due to the loss of subcutaneous and orbital fat. The resulting enophthalmia is one of the most specific hallmarks for clinical diagnosis. CS is a progressive disorder and most symptoms appear and worsen with time. All CS patients show very similar features, but the time of onset and the rate of progression vary widely among the subgroups. With hundreds of CS patients having been identified and clinically characterized, it has become clearer that CS has a spectrum of severity and that there is no clear threshold between the largely overlapping subgroups [14].

Pathology

CS can result from mutations in any of the five genes (CSA, CSB, XPB, XPD, XPG). The CSA and CSB genes code for proteins that interact with components of the transcriptional machinery and with DNA repair proteins. The abnormalities in CS are caused by mutation in two gene regions of chromosomes 5 and 10, CKN1 (for CSA patients) and ERCC6 (for CSB mutation), respectively [17, 18].

In the majority of CS cases, the defect is located in group B (CSB) protein, and approximately 80% have a mutation in the CSB gene [19, 20]. Indeed, because various repair pathways are compromised, CS is widely considered a genome instability syndrome. It seems that dysregulation rather than DNA repair defects is the main cause of neurological symptoms in CS [21, 22].

Diagnosis

The diagnosis of CS is established by identifying biallelic pathogenic variants in ERCC6 or ERCC8 on molecular genetic testing. Neurological abnormalities such as brain demyelination with calcium deposits and medically intractable movement disorders are present [1, 19] (see Chap. 4). The neurologic defects observed in CS patients are quite complex and multifaceted. The extremely small size of the brains of CS patients at the time of death is one of the most striking features of brain growth defects and atrophy. Clinically patients develop dementia and show progressive deterioration of brain function [20]. There exists absence of electrophysiological signs of cochlear or retinal involvement; nerve conduction studies show severe demyelinating peripheral neuropathy [23]. Neuroimaging studies have shown that cerebral and cerebellar atrophy, brain calcifications (can be located in the basal ganglia and in the dentate nuclei) and white matter anomalies are cardinal features

of CS, which progress with time and are very severe in these patients [5, 24, 25]. White matter loss and ventricular enlargement are probably the earliest detectable signs of CS on brain imaging and are present at the onset of neurological symptoms in all clinical subtypes. White matter signal anomalies on MRI are mainly related to primary hypomyelination; calcifications (putamen), less often in the cortex; and brain atrophy [25]. Secondary demyelination and astrogliosis are present in some cases and have been previously demonstrated in neuropathological reports of CS cases [26].

The diagnostic criteria are based on two categories: major criteria such as postnatal growth failure (<fifth percentile by age 2; early developmental delay), progressive microcephaly (may be present at birth), neurologic dysfunction, progressive deterioration of behaviour and intellect (all individuals), leukodystrophy on brain MRI (abnormal myelination reported in 93% of patients) and intracranial calcifications (in 63% of patients) and minor criteria such as cutaneous photosensitivity; demyelinating peripheral neuropathy (by electromyography, nerve conduction testing and/or nerve biopsy); pigmentary retinopathy (67% of the cases, and/or cataracts in 47% of patients); sensorineural hearing loss (86% of patients); dental anomalies, including carious teeth; cachectic dwarfism with thinning of the skin and hair; sunken eyes; and a stooped standing posture [14, 15].

Management

Prenatal diagnosis of CS by foetal amniocytes has been performed. Prenatal growth failure, congenital structural eye anomalies, severe neurologic problems from birth and the presence of cataracts within the first 3 years of life are predictors of severe disease and early death. Therapeutic measures are generally symptomatic and differ between the three types of CS. If indicated, patient management includes physical therapy, cochlear implants, cataract surgery, sunscreen and artificial feeding [4, 13].

The management of CS type I is purely symptomatic and complicated. No metabolic defect responsive to dietary, drug or hormonal therapy has yet been defined. Gastrostomy and tube placement may help to avoid malnutrition in patients with poor oral intake. Patients should be monitored for treatable complications of the condition, such as hypertension, hearing loss and dental caries. Those with cutaneous photosensitivity should avoid excessive sun exposure and use sunscreens when outdoors [4, 13]. In addition, the management of renal failure and nutrition are very important for ensuring good quality of life throughout the long-term course of CS [27].

The therapy with stem cell-based replacement holds great promise towards restoring tissue homeostasis, e.g. for premature aging disorders [28]. The isogenic CS stem cell models established in diverse studies provide a valuable platform for studying CS pathogenesis, discovering innovative drugs and the development of new cell replacement therapies [21, 29].

Hebb et al. [30] used stimulation of the ventral intermediate nucleus of the thalamus in a young man with CS to manage severe motor symptoms. They found a marked and progressive response to thalamic stimulation within weeks of surgery (see Chap. 4). These results suggest that patients with CS can be considered for deep brain stimulation to treat refractory movement disorders.

Prognosis

The prognosis in type II is much worse than that of the "classical" CS patient, and death usually occurs by the age of 6 or 7 years. Dental, auditory and cutaneous complications are less commonly noted in these patients, perhaps because of the severe neurologic illness or early age of death. Type III includes patients with normal intelligence, normal growth and/or normal reproductive capacity.

For all patients, a regular annual follow-up is recommended, which should include eye examinations, such as fundoscopy, evaluation for cataracts and visual evoked potentials. Further, hearing tests like audiometry tests and evoked potentials should be performed. Periodic evaluation of renal and liver function is recommended as well as regular blood pressure and blood glucose testing to reveal abnormal metabolism [7, 12, 22].

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Chapter 31
Xeroderma Pigmentosum (Kaposi Dermatosis)

Ramsis Benjamin

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Introduction

A condition with conspicuous findings of parched pigmented skin was first introduced in 1874 by the Hungarian dermatologist Moritz Kohn Kaposi in a textbook published with his father-in-law, Ferdinand Ritter von Hebra, at that time the department chair of dermatology at Vienna University [1]. The disease was later labelled as "xeroderma pigmentosum" to connote the dry pigmented skin seen in these patients, but perhaps a misnomer as cranio-ocular abnormalities also surface with high frequency, along with various carcinomas. XP can be referred to as Kaposi dermatosis, not to be confused with Kaposi sarcoma seen in immunosuppressed individuals. The heterogeneity in XP genes that span several chromosomes makes

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the condition markedly complicated to diagnose and treat. Therapeutic options are being created to counter the defective DNA repair pathway. This chapter discusses the clinical features and pathophysiology of xeroderma pigmentosum.

Clinical Characteristics

The prevalence of xeroderma pigmentosum (XP) is the highest in Japan at 1 in 20,000 compared to 1 in a million in the United States [2]. Certain regions in the world carry a higher prevalence, such as Japan, North African countries and the Middle East, where consanguinity might be higher. Cases of XP occur in all races without sexual bias. The disease is usually detected within the first 2 years of life. The skin, the eye and the nervous system could be involved simultaneously or at different stages of the disease. The triad of cognitive deficit, short stature and hypogonadism in children with XP is referred to as De Sanctis-Cacchione syndrome [3].

Cutaneous Involvement

The skin is normal at birth, but the first stages of abnormalities begin at 6 months. Minimal UV exposure leads to profound sunburn reaction with blistering or persistent erythema in half of the individuals. In all children, numerous hyperpigmented patchy freckling (solar lentigines) on the face appears, a sign of unrepaired DNA damage. Without aggressive sunblock usage and UV light avoidance, the skin progressively becomes parched (xerosis), pigmented like salt-and-pepper (Fig. 31.1) and atrophic (poikiloderma) [4]. Telangiectatic skin lesions are also noted. Premalignant keratoses soon develop and convert into basal cell carcinoma, squamous cell carcinoma or melanoma by the age of 8 years. Children with XP have a 10,000-fold increased risk of developing cutaneous cancers than the age-matched population. Skin tumours tend to be multiple, and as many as 100 mixed tumours have been reported. This may result in disfigurement in severely affected subjects.

Ocular Involvement

Ocular problems arise in nearly 80% of children with XP. Photophobia often exists along with conjunctivitis, vascular pterygia and fibrovascular pannus of the cornea. Symblepharon (a partial or complete adhesion of the palpebral conjunctiva of the eyelid to the bulbar conjunctiva of the eyeball) with ulceration and atrophy of the eyelids results in ectropion, entropion or complete loss of the lids in severe cases. Keratitis, corneal opacification and tumours (squamous cell carcinoma, basal cell carcinoma, sebaceous cell carcinoma, papilloma, fibrosarcoma,

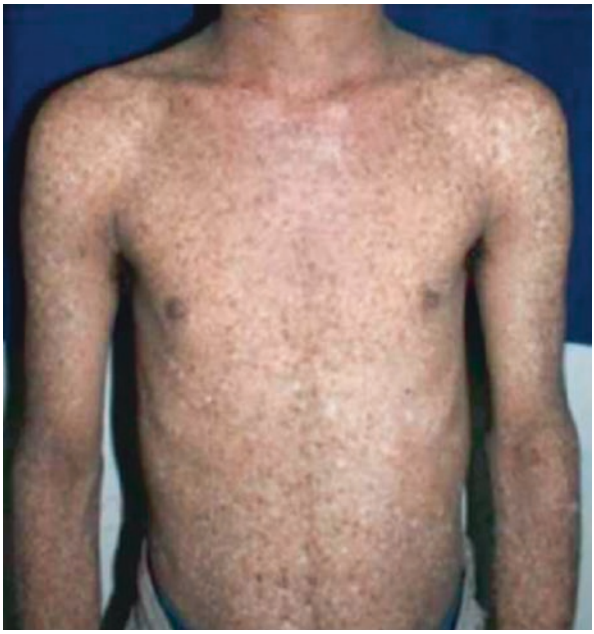

Fig. 31.1 Hyper- and hypopigmented skin resembling salt-and-pepper appearance. (From Mareddy et al. 2013, with kind permission [4])

melanoma and epithelioma) of the conjunctiva and corneo-conjunctival junction are the major source of ophthalmological morbidity. Patients with XP are at 2000-fold higher risk of developing cancer of the eyes. The ocular features appear as commonly as the cutaneous abnormalities, but may be more severe in black individuals. The retina is shielded by the anterior structures and, therefore, is usually not involved.

Neurological Involvement

Neurological involvement is often part of the phenotypic spectrum, and the symptoms could be quite protean. The presence of progressive neurological deficit and the age of onset correlate with the degree of defect in the DNA repair. Early onset of symptoms in infancy has been observed, or it could be delayed until the second decade. Neurological symptoms (in 20–30% of the cases) are progressive and may result in severe disability. The majority exhibit cognitive impairment, having a median intelligence quotient score of 45. Spasticity, ataxia and acquired microcephaly also exist.

Other neurological abnormalities include choreoathetoid movements, seizures, polyneuropathy with segmental demyelination, sensorineural deafness and supranuclear ophthalmoplegia. The neurological problems may overshadow the cutaneous manifestations in some patients with XP. Rarely, in some patients, dysphagia or vocal cord paralysis may develop during a respiratory infection [5].

Other Neoplasia

An approximate 10–20-fold increase in cancers of the internal organs have been observed in XP patients. Carcinomas of the lung, tongue, breast, stomach and testicles, among others, have been reported, as well as gliomas of the brain and spinal cord [6, 7].

Pathogenesis

Early histological findings include hyperkeratosis and increased melanin in the basal cell layer. Atrophic or elongated rete ridges could be observed, along with chronic inflammatory processes in the upper dermis. Later, the skin develops features indistinguishable from actinic keratosis, having atypical and elastic architecture.

UV light naturally depletes Langerhans cells in the epidermis. In normal circumstances, UV radiation induces cross-link photoproducts (dimerization) between thymine nucleotides that require excision and insertion. This repair process, known as nucleotide excision repair (NER), is deficient in XP [8]. Two overlapping pathways for NER have been proposed: the rapid transcription-coupled (TC) repair directed at the transcribed strand and a slower global genome (GG) repair [9].

There are nine specific XP repair genes, eight of which constitute the NER pathway. They include ERCC1 and ERCC2 (XP-D) on the long arm of chromosome 19, ERCC3 (XP-G) on chromosome 2, ERCC4 (XP-F) on 16p, ERCC5 (XP-B) on 13q, XP-A on 9q, DDB2 on 11p, POLH (XP-V) on 6p and XP-C on 3p. The ninth gene bypasses unrepaired damage. The seven complementary groups A through G are defective in both pathways for NER [10]. Complementation refers to different molecular abnormalities in XP that when combined could reverse the DNA repair defect [11, 12]. These entities vary significantly in frequency and in populations. For example, XP-A accounts for up to 40% of all cases in Japan. In the United States, XP-C and XP-D complementation represent 30% and 20% of all XP cases, respectively, whereas XP-A is rare. The XP-G carries a severe form; on the flipside, XP-F is mild.

Neurological problems are seen more commonly in groups XP-A and XP-D [13]. Up to 50% of XP-D patients may show neurological deterioration. The presence of neurological abnormalities correlates with the degree of NER repair defect; patients with greatest impairment of DNA repair are more prone to developing neurodegeneration. Pathologic studies have shown neuronal loss without other histological hallmarks. Diffuse axonal loss with secondary demyelination has been determined in patients with clinical evidence of polyneuropathy [14].

Differential Diagnosis

The differential diagnosis is broad and includes cortical basal ganglionic degeneration, malignant astrocytoma, Hallervorden-Spatz disease, inherited metabolic disorders, multiple sclerosis, multiple system atrophy, olivopontocerebellar atrophy, thyroid disease, Bloom syndrome, LEOPARD syndrome, Osler-Weber-Rendu syndrome, Werner syndrome (progeria) and Hartnup disease. Other conditions also host mutations in the NER pathway, but with different symptoms, such as Cockayne syndrome (see Chap. 30), cerebro-oculo-facio-skeletal syndrome (COFS) and trichothiodystrophy.

Diagnosis

The diagnosis of XP is made clinically based on skin, eye and neurological manifestations. Cranial imaging studies typically reveal ventriculomegaly, along with cortical and brainstem atrophy in most patients, although the white matter is usually preserved. Nerve conduction velocities are reduced and may show axonal (or mixed) polyneuropathy. Audiometry usually reveals early high-tone hearing loss. Laboratory abnormalities are absent in XP patients. Genetic testing is not readily available, which involves cell-fusion techniques, followed by DNA repair analysis or gene sequencing. Amniocentesis or chorionic villi sampling is possible in the third trimester via unscheduled DNA synthesis or the alkaline comet assay [15].

Therapy

Patients with XP need to be monitored every 3–4 months for various dermatological and ophthalmological conditions. Consultation with a geneticist may help to differentiate XP from other related conditions, such as Cockayne syndrome and progeria. Patients must avoid the sun at all times, even fluorescent lights that emit radiation below 320 nm. If sun exposure cannot be entirely avoided, patients should wear full clothing, use sunscreen with SPF 50 or greater and wear dark glasses. A UV light meter can be used at home, in vehicles and classrooms to measure the amount, and window filters applied. Some families reverse their day/night cycle to eliminate sun exposure entirely. Methylcellulose eye drops or soft contact lenses have been used to keep the cornea moist and to protect against mechanical trauma in individuals with deformed eyelids.

Premalignant lesions such as actinic keratoses may be treated with topical 5-fluorouracil or by freezing with liquid nitrogen. Cutaneous neoplasms are treated in the same manner as in individuals who do not have XP. This involves electrodesiccation and curettage, surgical excision or chemosurgery. Oral isotretinoin at 2 mg/kg/d is rendered only to those with multiple skin cancers. It may produce hepatotoxicity and dose-related irreversible calcification of ligaments and tendons [16]. The combination of 5% imiquimod cream and oral acitretin in a few cases of XP-related cutaneous neoplasms has shown some promise anecdotally [17, 18].

Neurological care is mostly supportive. Seizures can be treated like other complex partial seizures. Spasticity is usually mild. If it interferes with mobility, baclofen or botulinum neurotoxin could be beneficial.

New approaches are being investigated and utilized to engineer mega-nucleases, zinc-finger nucleases or TALE nucleases to accurately generate a double-strand break at a specific locus and to insert an exogenous DNA repair matrix [19].

Prognosis

Fewer than 40% of patients survive beyond the age of 20 years. Individuals with milder disease may survive beyond middle ages. Neoplasms are usually the chief cause of death. Many patients become bedridden and incontinent. Some develop significant cachexia in the terminal stages despite adequate caloric intake.

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Part IV
Defects of Enzymes and Structural Proteins

Chapter 32
Cerebrotendinous Xanthomatosis

Ramsis Benjamin

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Introduction

Since van Bogaert's description in 1937 of two cousins with cerebello-pyramidal signs, cataracts and tendon xanthomata, over 300 cases of cerebrotendinous xanthomatosis have been identified. The prevalence could reach one in 50,000 Caucasians [1]. The incidence is higher in East and South Asians (<1:75,000) than in Europeans (<1:500,000). In the Israeli Druze community, the incidence is 1:440 [2].

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive inborn error of acid bile synthesis and sterol storage, caused by a deficiency in the mitochondrial enzyme sterol 27-hydroxylase (CYP27). It is characterized by xanthomas within the tendons, juvenile cataracts, early atherosclerosis and progressive neurological disorder with cerebellar ataxia and dementia.

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Clinical Characteristics

Chronologically, neonatal cholestatic jaundice and continuing diarrhoea during infancy present first, followed by the development of juvenile cataract that affects 75% of the children by the age of 5 years. The combination of diarrhoea and cataracts is virtually pathognomonic for the disease [3, 4].

Tendon xanthomas (yellowish deposits on tendons, especially the Achilles and the extensor tendons) occur in young adulthood (Fig. 32.1). Large deposits of cholesterol and cholestanol are found in almost every tissue, particularly the brain, bones and lungs. With more advanced age, neurological regression takes precedence, including neuropathy, psychosis, progressive dementia, atypical parkinsonism, seizures including infantile spasms as presenting signs, and cerebellar and pyramidal signs [5–7].

Pathogenesis

Xanthomas possess birefringent crystalline material that deposits in the cerebellum, basal ganglia and cerebellar peduncles. Although morphologically normal by electron microscopy, paracrystalline inclusions and an increased number of peroxisomes are seen within the foamy cytoplasm of mitochondria. A single gene located on chromosome 2, CYP27A1, is known to be associated with CTX. Base-pair deletion of CYP27A1 alters the amount of vinculin, ABP-280, TALIN and vimentin in leukocytes of CTX patients, impairing membrane cholestanol moiety [9]. Mutation

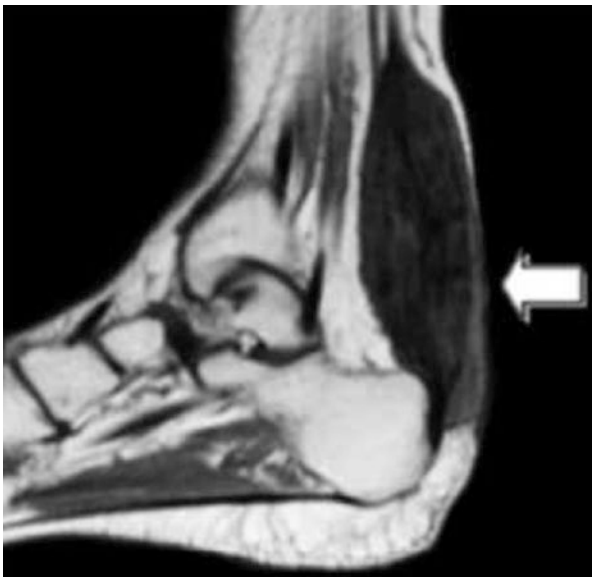

Fig. 32.1 Sagittal T1-weighted MRI showing xanthoma of the Achilles in a patient with CTX. (From Cerqueira et al. 2010, with kind permission) [8]

in this gene also causes a deficiency in its protein, sterol 27-hydroxylase, which is a mitochondrial cytochrome P450 that acts as a rate-limiting step in bile acid synthesis pathway [10, 11]. As a consequence, increased by-products of cholestanol, the 5-α-dyhydroderivative of cholesterol, occur (Fig. 32.2).

Diagnosis/Differential Diagnosis

The closest differential diagnosis to CTX is lecithin-acryl cholesterol transferase (LACT) deficiency, which also manifests in young adulthood. The distinguishing clinical features are corneal opacities, haemolytic anaemia, renal insufficiency and premature atherosclerosis in LACT. The total plasma cholesterol levels vary in LACT deficiency, with a marked decrease in esterified cholesterol and increased unesterified cholesterol. There is an increase in VLDL, and all lipoprotein structures are abnormal. Other disorders of lipid metabolism worth mentioning include Tangier disease, familial hypercholesterolaemia, abetalipoproteinemia, sitosterolaemia (another autosomal recessive condition with elevated serum levels of plant sterols, sitosterol and campesterol) and Smith-Lemli-Opitz syndrome.

The biochemical abnormalities that separate CTX from other conditions with xanthomas include high plasma and tissue cholestanol concentration, normal-to-low plasma cholesterol levels, decreased chenodeoxycholic acid (COCA) and increased concentrations of apolipoprotein B in the cerebrospinal fluid. Cranial

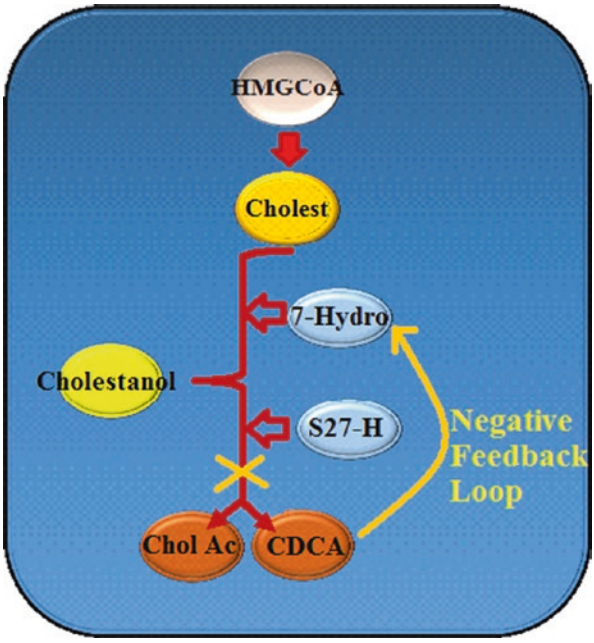

Fig. 32.2 The production of cholic (Chol Ac) and chenodeoxycholic acids (CDCA) is interrupted by the enzymatic defect of sterol 27-hydroxylase (S27-H). Cholestanol thus accumulates and deposits in lipophilic tissues of the brain and tendons. *Cholest* cholesterol, *HMG-CoA* hydroxymethylglutaryl-coenzyme A, *7-Hydro* 7-hydroxylase

imaging studies reveal bilateral hyperintense dentate nuclei and diffuse atrophy of the cerebral and cerebellar white matter. In keeping with widespread mitochondrial dysfunction in the brain, magnetic resonance spectroscopy illustrates diminished N-acetylaspartate (NAA) and elevated lactate peak [12].

Measurement of sterol 27-hydroxylase enzymatic activity is no longer necessary for the diagnosis due to the near 100% sensitivity of sequence analysis for the CYP27A1 gene. Inclusion of CTX to the uniform screening panel of disorders in newborns is being considered [13].

Therapy

Replacement of the bile acid pool with oral chenodeoxycholic acid is the mainstay of treatment [14–16]. Long-term administration of CDCA (750 mg/day) in patients with CTX normalizes plasma and CSF concentrations of cholestanol, with an improvement in neurophysiologic deficits. Chenodal has received an orphan drug designation from the FDA in the USA.

The most effective drug regimen appears to be a combination of CDCA with a β-HMG-CoA reductase inhibitor, resulting in a decline in the serum cholestanol concentration and eliminating its accumulation in the central nervous system [17]. Parkinsonian features respond more favourably to diphenylpyraline than to levodopa [18].

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Chapter 33
Chédiak-Higashi Syndrome

Ramsis Benjamin

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Clinical Characteristics

Approximately 500 cases have been reported worldwide in the past two decades [1]. Classic and atypical forms exist—the former is more likely to develop an accelerated lymphohistiocytic phase, whereas the latter lacks severe infections, but increased neurologic impairment. Symptoms of CHS appear shortly after birth or before the age of 5 years, on average slightly before 2. Infants born with CHS have a patchy distribution of nonpigmented skin. Blonde, silvery, sparse hair (Fig. 33.1) and pale eyes are the typical characteristics [2, 3].

Along with hypopigmentation, most infants exhibit adenopathy, bleeding diathesis, hyperhidrosis, variable hepatosplenomegaly and jaundice. Fever of unknown origin, frequent and severe pyoderma, sinopulmonary infections and subcutaneous abscesses from Staphylococcus aureus soon follow. Neurologic abnormalities occur late and may present as gait and limb ataxia, epilepsy, paraesthesia, cognitive delay and peripheral neuropathy. Generally, at the time of CNS manifestation, the child with CHS has already entered an accelerated lymphoproliferative phase, causing

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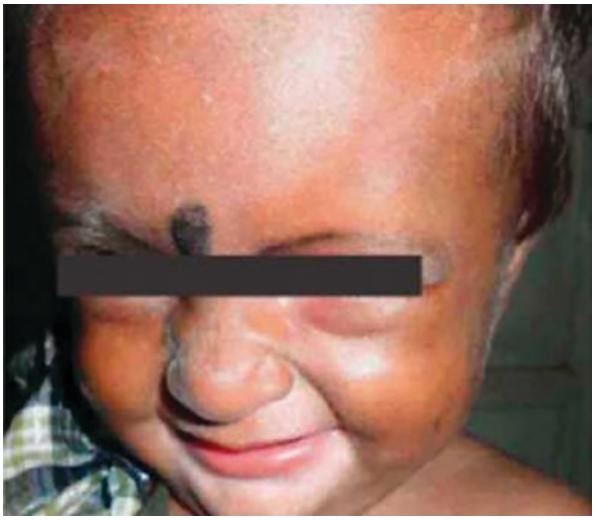

Fig. 33.1 Silvery grey hair with hypopigmented macule on the face. (From [2], with kind permission)

rapid hepatosplenomegaly, lymphadenopathy, profound leukopenia and thrombocytopenia and ultimately death [4]. This lymphoproliferative stage occurs in over 80% of the patients in response to an infection such as Epstein-Barr virus. About half of the children will develop haemophagocytic lymphohistiocytosis, which is usually fatal [2]. If the patient matures to late childhood, parkinsonism, spinocerebellar degeneration and peripheral neuropathy form the basis of the neurologic sequelae [5]. Levodopa may show some benefit in controlling the parkinsonian features [6].

Pathogenesis

Chédiak-Higashi syndrome is a rare autosomal recessive, immunodeficiency disease that has been mapped to human chromosome 1q42.1-q44, afflicting all race groups [7]. Parental consanguinity often exists. The CHS gene normally encodes for lysosomal trafficking regulator, formerly called LYST that has been relabelled as CHS1 [8, 9]. The gene contains 53 exons, 51 of which possess coding capability. Although the precise function of the gene is unknown, it seems to involve the regulation of phospholipase D activity, fission and secretion of lysosomes [10–12]. About 75 homozygous variants, mostly nonsense/frameshift and less frequently missense mutations, have been identified [1].

The disease is characterized by abnormal intracellular vesicle formation, delayed phagolysosomal fusion and large and irregular lysosomes that reside within leukocytes and fibroblasts (Fig. 33.2). The large inclusions exhibit azurophilic and granular markers [13]. Defective melanization of melanosomes occurs in oculocutaneous albinism associated with CHS.

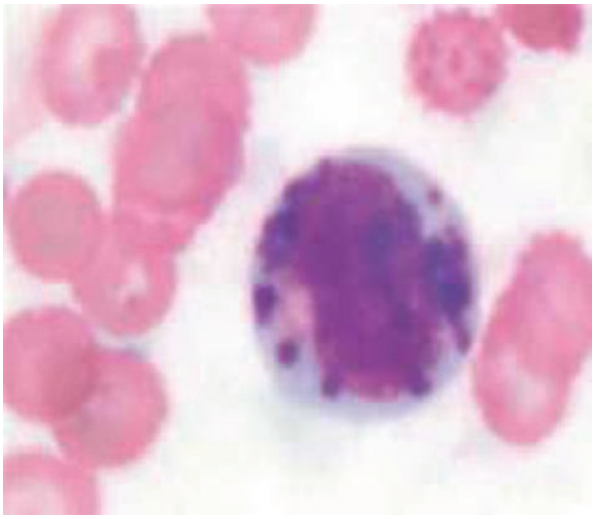

Fig. 33.2 Large intracytoplasmic granules in a granulocytic cell (Giemsa-stained bone marrow aspirate film; 1000×; from [4], with kind permission)

In the early stages of neutrophil maturation, normal azurophil granules fuse to form megagranules, whereas in the later stages (i.e. during myelocyte stage), normal granules develop. The mature neutrophils contain both populations. A similar phenomenon occurs in monocytes. The impaired function in the polymorphonuclear leukocytes may be related to abnormal microtubular assembly. The dysfunction leads to neutropenia, which may be profound, impaired chemotaxis and fusion, resulting in lessened bactericidal activity.

Diagnosis

Serum analysis of a child with CHS reveals hypergammaglobulinemia and neutropenia. Diagnosis can be made by detecting giant granules within neutrophils, eosinophils and granulocytes under light microscopy. These giant inclusion bodies are further observed in leukocyte precursor cells during bone marrow smears. The granules stain heavily for peroxidase, suggesting large clumps of lysosomal enzymes, or in the case of melanocytes, giant melanosomes. Prenatal diagnosis can be made by biopsying the foetal scalp or sampling the foetal blood.

In older children, extensive loss of alveolar bone and tooth exfoliation are noted. Microscopic evaluation of periodontal tissue illustrates extensive bacterial infiltration [14]. Finally, CT and MRI scans demonstrate diffuse brain and spinal cord atrophy. The differential diagnosis includes spinocerebellar degeneration, cutaneous T-cell lymphoma, Griscelli syndrome (caused by a defect in the RAB27A gene), Elejalde syndrome and Hermansky-Pudlak syndrome.

Therapy

The primary goal of pharmacotherapy, as for many other neurocutaneous diseases, is to reduce morbidity. Because of haemorrhagic tendency, certain activities are to be avoided. Drainage of cutaneous abscesses and debridement may be necessary. Seizures, if present, are preferably treated with the newer antiepileptic agents such as levetiracetam, lacosamide or lamotrigine. Interferon may partially restore the function of natural killer cells. Acyclovir, high-dose intravenous immunoglobulin (IVIg) and colchicine are effective in managing the lymphohistiocytic infiltration. The paediatric dose of acyclovir is 10 mg/kg IV every 8 h for 2–3 weeks, with adequate hydration to offset renal compromise; IVIg is 100–200 mg/kg every 4 weeks, not to exceed 1 g/kg/dose; and colchicine is 0.5–0.6 mg orally twice or three times a day (adult dose).

Alemtuzumab, an anti-CD52 monoclonal antibody, is a second-line treatment after etoposide-based regimen in pre-transplantation for HLH [15, 16]. The role of experts in haematology-oncology cannot be overemphasized in the management of these patients as the child with CHS will require allogeneic bone marrow transplantation (BMT) early in the course of the disease. Those children who cannot undergo BMT will usually die before the age of 10 years. An HLA-matched family donor would be most suitable; otherwise, one must seek an unrelated donor or placental blood graft [17]. Although the immune system strengthens with BMT, hypopigmentation and neurologic symptoms worsen as the child ages.

Prognosis

Morbidity and mortality result from frequent cutaneous, mucosal and respiratory bacterial infections, haemorrhagic diathesis or from lymphocytic infiltration and destruction of major internal organs. Survival beyond the first decade leads to enlargement of the lymph nodes, spleen and liver. Bone marrow transplantation further extends the survival rate into the second and third decades, but neurologic symptoms heighten. These patients develop progressive and severe demyelinating and axonal peripheral neuropathy, compromising motor function.

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Chapter 34
Child Syndrome

Christos P. Panteliadis

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Introduction

Otto Sachs in 1903 is attributed to having published the first case of an 8-year-old girl with *xanthoma-like naevus* involving the right axillary region and weakness in the ipsilateral upper arm [1]. The condition remained obscure until 1948, when the Swiss-American paediatrician Dr. Hans Zellweger and Üehlinger reported a patient with "half-sided osteochondrodermatitis and naevus ichthyosiformis" [2].

About hundred sporadic cases have been reported in the literature under a number of designations, including unilateral ichthyosiform erythroderma, unilateral erythrokeratoderma, unilateral epidermal naevus, unilateral ectromelia, inflammatory epidermal naevus and unilateral limb and skin deformities with congenital heart disease [3–5]. For unclear reasons, the right side of the body is twice more likely to be affected.

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CHILD syndrome (OMIM 308050) follows a dominant X-linked pattern with a female-to-male ratio of 19:1, invariably lethal to male trait [6]. All three types of mutations (missense, nonsense and stop mutations) in the *NSDHL* gene have been identified. The gene is located on the long arm of the X chromosome at position 28. It encodes for 3-β-hydroxysterol dehydrogenase (sterol-4-α-carboxylate 3-dehydrogenase) found in endoplasmic reticulum and intracellular lipid storage droplets, which catalyses the biosynthesis of steroid progesterone and androstenedione from dehydroepiandrosterone (Fig. 34.1). It is the only enzyme in the corticosteroid synthesis not belonging to the cytochrome P450 family [7, 8].

Pathogenesis

Peroxisomes play a key role in the pathogenesis of CHILD syndrome as they are intimately involved in the catabolism of prostaglandins and hydroxyeicosatetraenoic acid [9]. Skin fibroblasts from *CHILD* naevus exhibit a decrease in both the peroxisome number and the activity of two specific peroxisomal enzymes – catalase and dihydroxyacetone phosphate acyltransferase [10], specifically centred in the areas of cutaneous involvement without systemic manifestations. Peroxisomal deficiency in the involved naevus leads to the accumulation of *PGE2* and keratinocyte growth, which consequently may contribute to the epidermal hyperproliferation. Markers of keratinization possess the typical patterns of hyperproliferative skin diseases, defined by expansion of the basal layer keratins (*K5/K14*), thickening of filaggrin, involucrin-positive (the differential marker of human keratinocytes) upper epidermal layers and expression of hyperproliferative keratins (*K6/K16*) [11]. The genotype in *CHILD* naevus is explained by the *Lyon* hypothesis; i.e. random inactivation of one of the X chromosomes in female cells and daughter clonal populations results in mosaicism that manifests in *Blaschko* lines [12] (lines that represent dorsal-to-ventral migration tracks of precursor cells from the primitive streak). The lateralization of all associated abnormalities could be hypothesized by the hypothesis that the X chromosome inactivation coincides and interferes with a clone of organizer cells that control a large morphogenetic field [13, 14]. The NSDL protein product is a 3-β-hydroxysterol dehydrogenase, an oxidoreductase, that is involved in the removal of two C-4 methyl groups with $NAD(P)^+$ as acceptor in one of the end steps of cholesterol biosynthesis [15, 16]. There is absolute requirement for cholesterol synthesis in situ once the blood-brain barrier is formed in the foetus [17].

Clinical Characteristics

CHILD syndrome is an exceedingly rare disorder. It affects the ipsilateral skin, viscera, musculoskeletal and central nervous system. Cutaneous naevi are described as waxy, yellow scaly (*ichthyosiform*), erythematous plaques, having a sharp

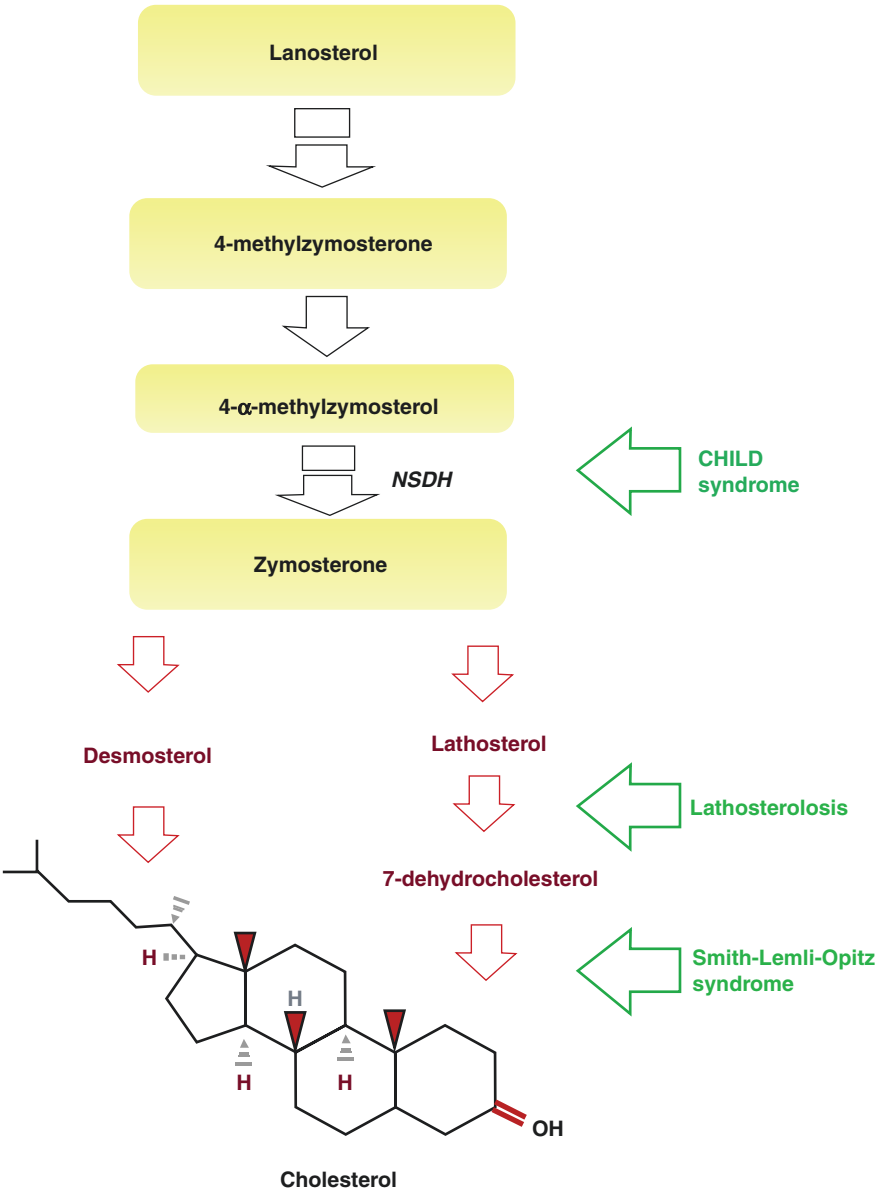

Fig. 34.1 3-β-Hydroxysterol dehydrogenase is involved in step 4 subpathway that synthesizes zymosterol. CHILD syndrome, shown in relation to other metabolic disorders, involves mutations in *NSDH* gene

unilateral midline demarcation [18]. About 80% of the cases occur on the right side. This distinct unilateral pattern may be diffuse and/or linear, with streaks following the *lines of Blaschko* within the diffuse erythema. On the other hand, partial

resolution or spread to uninvolved areas has been observed during the early years of life. There is impaired hair growth and streaks of alopecia on the ipsilateral side [19]. The nails often exhibit hyperkeratosis and dystrophic changes (*onychodystrophy*). Punctate calcifications of the cartilage are often evident on radiographs and may disappear during the early years of life [14]. Cognition is usually in the normal range.

Anomalies in *CHILD* syndrome consist of homolateral (*ipsilateral*) limb defects ranging from hypoplasia of the phalanges to defects of the long bones and absent extremity. Ipsilateral hypoplasia of the axial skeleton, including the calvarium, mandible, scapula, ribs and vertebrae, which can lead to scoliosis, is also present, along with cardiac malformations and ipsilateral hypoplasia of the brain, lungs, thyroid, kidney and reproductive tract [20, 21]. The cardiovascular malformations are the most common causes of early death [22]. Although *CHILD* syndrome is an ipsilateral condition, abnormalities on the contralateral side may be seen. A case of bilateral involvement has been described in a 16-year-old girl [13]. In familial cases with atypical or minimal findings, the importance of molecular analysis to confirm the diagnosis cannot be overstated [23].

An associated naevus, known as *CHILD* naevus, shows a marked preference for the body folds (*often by dermatomes*), which is defined as ptychotropism [24]. The expression is derived from the *Greek words* ptyche/πτυχή (fold) and trope/τροπή (*a turning*). The most frequently affected areas are the vulva, axilla and gluteal folds [6, 24]. Most often, the extent of skin involvement remains constant in the affected side, contrary to *Conradi-Hünermann* syndrome (or CDPX2) that has the characteristic ichthyosiform erythroderma (psoriasiform epidermis with hyperkeratosis), chondrodysplasia punctata and orthokeratosis [25]. Other features of the latter syndrome are waxy, yellowish naevi as well as scaly and microscopic changes within the verruciform xanthomas.

Diagnosis

Diagnosis of CHILD syndrome is based on clinical and radiological findings of the pelvis, ribs, vertebrae and extremities in infancy. Skin biopsy from the involved and uninvolved areas is necessary. Histologically, the epidermis shows acanthosis with alternating orthokeratosis, hyperkeratosis, parakeratosis and mild hyperplasia [21, 26]. Patchy hypergranulosis may also be observed, and the biopsy shows suggestive of an ichthyosiform dermatosis [7]. Radiographic examination of the head, trunk and extremities is essential in detecting skeletal abnormalities. Computerized tomography of the head and trunk may reveal progressive hypoplasia or aplasia of the cerebral cortex and hippocampal neurons [17].

Echoencephalography is needed to examine the size and flow of the ventricles. Sleep electroencephalography may elucidate the diagnosis of a predisposed seizure disorder. A distinctive phenomenon of verruciform xanthoma, which is characterized by enlarged papillae filled with foamy histiocytes, has been reported when

biopsy samples are obtained from the body folds. On electron microscopy, the parakeratotic corneocytes and basal cells contain lipid vacuoles and numerous intercellular vesicular structures.

Abnormal cementsomes (lamellar granules) with electron-dense bodies have also been reported. The papillary dermis is thickened and filled with histiocytes containing large lipid vacuoles. Fibroblasts are similarly filled with lamellated structures. In fact, combining clinical and molecular examination could determine the diagnosis of CHILD syndrome with milder features [23], and to distinguish CHILD from other conditions such as *Conradi-Hünermann-Happle* syndrome (*X-linked dominant*) caused by mutations in EBP. The latter harbours *ichthyosiform* erythroderma as well as linear or whorled pigmentary lesions, striated ichthyosiform hyperkeratosis and patchy cicatricial alopecia.

Therapy

No curative therapy exists, only symptomatic relief based on the severity of clinical presentation. A multidisciplinary approach of experts in the fields of dermatology, orthopaedics, cardiology, physiotherapy and psychology is imperative for effective management. Patients with milder forms carry a normal life.

The management of ichthyosiform erythroderma includes oral and/or topical steroids, such as 2% lovastatin emollients, or with lactate-based creams (topical retinoids and keratolytics). Alternative therapy with oral or topical ketoconazole is possible [5, 27]. The use of topical lovastatin leads to complete healing of the inflammatory CHILD naevus in a few cases [28, 29]. Scoliosis or other bone problems, e.g. contractures, are treated with orthopaedic braces and/or corrective surgery. Although the right side of the body is invariably affected, patients with left-sided symptoms harbour a more dire prognosis, usually succumbing to cardiovascular complications.

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Chapter 35
Dorfman-Chanarin Syndrome

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Introduction

Dorfman-Chanarin syndrome (at times stated in reverse order) is a multisystem autosomal recessive lipid storage disease that was first described in 1974 by *Dorfman* and colleagues [1]. Within a year, *Chanarin* published another patient with generalized accumulation of neutral lipid droplets in the body that differed from known lipid storage disorders [2]. It is characterized by ichthyosis (*non-bullous erythroderma*), deafness, cataract, myopathy, hepatomegaly, liver cirrhosis, poor cognitive faculties and accumulation of lipid vacuoles in neutrophils [3, 4]. The majority of patients reside in the Mediterranean or the Middle East [5].

Patients with *Dorfman-Chanarin* syndrome (OMIM 275630) often have mutations in *ABHD5/CGI-58* gene, which encodes α/β-hydrolase domain-containing 5 (ABHD5), an activator of adipose triglyceride lipase (lipid metabolism), leading to

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intracellular accumulation of triglycerides (triacylglycerol) in the skin and liver [6]. Lipid storage occurs in granulocytes at various sites in the human body. *CGI-58* is expressed and packaged into lamellar granules and is likely associated with intercellular lipid layering in the stratum corneum (the outermost layer of the epidermis). It thus plays a crucial role in keratinocyte differentiation [7, 8]. This gene is located on chromosome 3p21 and contains seven exons that encode for the α/β-hydrolase domain-containing protein 5 (an esterase protein), lipase and thioesterase subfamily [9].

Clinical Characteristics

Dorfman-Chanarin syndrome is a multisystem, autosomal recessive disease characterized by ichthyosis, deafness, cataract, myopathy and hepatomegaly [3–5]. The liver is most frequently involved in CDS, clinically presenting as hepatomegaly (*fatty liver*). Other clinical features include ataxia, renal anomalies (rare), oedema, proteinuria, strabismus and mental impairment [10].

Eleven different mutations causing truncated proteins have been described in children younger than 6 years and in 21% of patients on whom molecular diagnosis was obtained [11]. Lipids can accumulate in the white cerebral matter, cortex and basal ganglia [12].

The neurologic findings vary widely from being asymptomatic to myopathy, deafness, disequilibrium, mental slowing, subcapsular cataracts and nystagmus [13, 14]. Homozygous *ABHD5* splice site mutation that skips exon 6 may result in cutaneous manifestation without cognitive impairment [15].

The skin exhibits an erythrodermic-type of non-bullous congenital ichthyosis. Neutral lipids deposit in the cytoplasm, but the biochemical defect that leads to lipid deposition remains elusive [16].

The functional deficiency of TAG lipase is believed to cause impairment in intracellular TAG metabolism [15]. Lipid droplets have been detected in various cells such as fibroblasts, in both myelinated and unmyelinated nerves, smooth muscle cells and sweat glands [17].

Diagnosis

The clinical diagnosis is based on the characteristic features and can be easily established by a simple blood smear showing polymorphonuclear cells (*granulocytes*) harbouring lipid vacuoles (*cytoplasmic vacuoles*) called *Jordans' bodies* [18]. The lipid vacuoles can also be observed in smears of heterozygous subjects and can serve as a screening test.

Abdominal ultrasonography generally shows mild hepatomegaly with fatty infiltration. Liver biopsy can detect steatohepatitis, and a smear would confirm *Jordans'*

anomaly, a permanent finding in Dorfman-Chanarin syndrome. Skin biopsy reveals hyperkeratosis, prominent granular layer and mild lymphocytic infiltration [19, 20].

Therapy

The degree of treatment relies on the severity of clinical characteristics. A multidisciplinary approach of various specialties, including internal medicine, dermatology, ophthalmology and gastroenterology, should contribute to the management of the patient [3, 4]. Diet is one of the most important therapeutic components. A diet devoid of long-chain fatty acids and rich in medium-chain fatty acids is recommended. Long-term topical therapy is administered for bilateral punctate keratopathy. Oral formulation of ursodeoxycholic acid and local therapy for ichthyosis provide additional support.

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Chapter 36
Ehlers-Danlos Syndrome

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Introduction

Ehlers-Danlos syndrome comprises a group of heterogeneous diseases characterized by connective tissue fragility. Although the disorder was recognized even during the time of *Hippocrates,* the first detailed clinical description of the syndrome is attributed to the dermatologist Dr. A *Tschernogobow* in 1892, where in Russia the disease continues to bear his name [1]. Dr. *Edvard Ehlers,* a Danish dermatologist, published a patient with the characteristic hyperelastic skin in 1901 and established the condition as a unique entity. *Henri-Alexandre Danlos* in 1908 *challenged a previously misdiagnosed case of "juvenile pseudodiabetic xanthoma"*; the individual possessed hyperextensibility of the skin, *joint* laxity and hypermobility, along with involvement of blood vessels and other organs [2–5]. In 1936, *Frederick*

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Parkes-Weber suggested that this particular connective tissue disorder should be given the eponym *Ehlers-Danlos* syndrome.

The first molecular defect (lysyl hydroxylase deficiency) was discovered by two separate groups in 1972 [6, 7]. Fatigue could be the chief complaint in the hypermobile type of the disease [8].

Pathogenesis

Skin biopsies examined by electron microscopy have revealed abnormal collagen fibril structure [9, 10]. Reduced electrophoretic mobility of type V collagen has also been detected in some families [9], which explains the difference in the way these collagen proteins migrate under electrophoresis.

The *gene defect* has been recognized for all the subtypes of EDS, with the exception of hypermobility EDS [9, 11]. Mutations in the *COL5A1* (collagen, type V, alpha 1) and the *COL5A2* gene, encoding the α-1 and the α-2 chains of type V collagen, respectively, have been shown to cause the disease, but it is unknown to what proportion classic EDS patients carry these mutations as others in *FLNA* have also been detected in EDS patients with periventricular heterotopia [12–14]. The inheritance pattern in periventricular heterotopia and EDS follows an X-linked dominant disorder, having a presumptive hemizygous male lethality. Initial studies suggest linkage to chromosome Xq28, the FLNA locus.

Clinical Characteristics

Ehlers-Danlos syndrome is a clinically and genetically heterogeneous group of heritable connective tissue disorders characterized by joint hypermobility, skin hyperextensibility and tissue fragility [5, 15]. Collagen of multiple forms constitutes the most copious protein in the body. About 30 different genes belonging to 15 different chromosomes contribute to the formation of collagen. Therefore, it is not surprising to see an array of syndromes arising from the mutation of these genes. The gender ratio is equal, and the syndrome has no geographical boundaries. EDS is caused by gene mutations in different collagen and collagen-modifying enzymes that affect the mechanical properties of the skin, joints, ligaments and blood vessels [16]. The current classification is based on the clinical signs and symptoms.

Six subtypes of EDS have been identified based on the molecular and biochemical findings and on the extent to which joints, skin and other tissues are involved. A descriptive term has been introduced to define each subtype (the former classification is presented in parenthesis): *classic* (**I, II**), *hypermobility* (**III**), *vascular* (**IVa–c**), *kyphoscoliosis* (**VI, VIa,b**), *arthrochalasis* (**VIIa,b**) and *dermatosparaxis* (**VIIc**).

Former *EDS* types **V**, **VIII** and **X** have been classified as "*Others*", and type **IX** is no longer considered an EDS phenotype [9]. The characterization of several new

EDS variants has broadened the horizon into the molecular pathogenesis of EDS by implicating genetic defects in the biosynthesis of other extracellular matrix molecules, such as proteoglycans and Tenascin-X, or genetic defects in molecules involved in intracellular trafficking, secretion and assembly of extracellular matrix proteins [17].

Subtypes 1–6

1. **Classic EDS.**
   The majority of classic EDS cases have an autosomal dominant inheritance. Missense and splice-site mutations in type V collagen gene have been observed, but other mutations may play a role, including the Tenascin-X gene [18]. The **major** diagnostic criteria consist of skin hyperextensibility, joint hypermobility and widened atrophic scars. A velvety skin, easy bruising, subcutaneous spheroids and molluscoid pseudotumours form the minor diagnostic criteria. Other manifestations of tissue extensibility and fragility (e.g. hiatal hernia, anal prolapse in childhood, cervical insufficiency), surgical complications (postoperative hernias), joint hypermobility (sprains, dislocations/subluxations, pes planus, etc.), hypotonia due to hypermobility and delays in the development of motor skills are seen. Patients with *Ehlers-Danlos* syndrome need to be evaluated carefully for the presence of renal anomalies [19].
2. **Hypermobility EDS.**
   Mutation in the *tenascin-X* gene (TNXB), which is responsible for the production of an extracellular matrix protein, has been implicated in a few percentages of cases. Most cases, however, carry no such mutation. The major diagnostic criteria include generalized joint hypermobility and hyperextensible and/or supple skin that vary in severity. A few of the minor diagnostic criteria consist of recurring joint subluxations and dislocations, chronic joint or limb pain and an autosomal dominant family history. This type is likely the most common hereditary connective tissue disorder, and patients typically possess exertional pain [20].
3. **Vascular EDS.**
   Vascular EDS (vEDS) is a syndrome inherited in an autosomal dominant manner that leads to spontaneous arterial dissection or rupture. Management of these arterial complications remains a challenge. The disorder is due to heterozygous mutations in *COL3A1*, which encodes the procollagen peptide for type III collagen. *Type III* collagen is especially abundant in the skin, blood vessels and hollow organs such as the bowel and uterus. The complications of vEDS reflect the expression pattern of the gene and include rupture and dissection of primarily medium-sized arteries (arterial aneurysm, dissection and rupture), spontaneous rupture of the intestine (*bowel rupture*) or the gravid uterus and thin, fragile skin that bruises easily and heals poorly [21, 22].

Minor diagnostic criteria include acrogeria, hypermobility of small joints, tendon and muscle rupture, talipes equinovarus (*clubfoot*), early onset varicose veins, arteriovenous and carotid-cavernous sinus fistula, pneumothorax, gingival recession, sudden death in a close relative and positive family history. Establishing the diagnosis is based on demonstrating the structurally abnormal *type III collagen* produced by fibroblasts and on demonstrating a mutation in the *COL3A1* gene. The abnormality causes defective secretion, post-translational overmodification, thermal instability and sensitivity of collagen to proteases [23]. *Vascular fragility* and the risk of rupture account for the grave prognosis associated with this type of EDS. Acute abdominal and flank pain (diffuse or localized) is a common presentation of arterial or intestinal rupture and should be investigated urgently. If possible, non-invasive diagnostic procedures are preferred to avoid future complications from poor wound closure and skin breakdown [22].

4. **Kyphoscoliosis EDS.**

   This form of EDS relates to a modified activity of the lysyl hydroxylase 1 enzyme, otherwise known as PLOD1, or procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1. More than 20 mutations of the lysyl hydroxylase 1 (*LH1*) gene, which maps to 1p36.3-p36.2, have been described [24, 25]. PLOD1 gene produces lysyl hydroxylase 1, which in turn modifies lysine, an amino acid used to make procollagen.

   The major diagnostic criteria comprise scoliosis at birth, generalized joint laxity, severe muscle hypotonia, progressive scleral fragility and rupture of the ocular globe. The presence of three major criteria in an infant is suggestive of the diagnosis. Some of the minor diagnostic criteria include atrophic scars, easy bruising, arterial rupture, marfanoid habitus, microcornea, osteopenia and family history likely in an autosomal recessive inheritance pattern.

   The recommended laboratory test is the assessment of total urinary hydroxylysyl pyridinoline and lysyl pyridinoline cross-links after hydrolysis by HPLC, which is a readily available test having a high degree of sensitivity and specificity [26]. The determination of dermal hydroxylysine in fibroblasts and mutational analysis of the *LH1* gene are performed on research basis only. Furthermore, in rare cases, patients with this type of EDS can have normal levels of lysyl hydroxylase activity [25].

5. **Arthrochalasia EDS.**

   Arthrochalasia EDS exhibits an autosomal dominant inheritance. The abnormality is usually from the loss of the substrate sequence for the N-terminal procollagen protease in one of the chains of type I procollagen.

   Severe generalized joint hypermobility with recurrent subluxations and congenital bilateral hip dislocation constitute the major diagnostic criteria. Minor diagnostic criteria include skin hyperextensibility, tissue fragility, multiple contusions, muscle hypotonia, kyphoscoliosis and mild osteopenia based on bone density imaging studies. Biochemical confirmation is based on the electrophoretic demonstration of proA1 and proA2 chains of type I collagen extracted from dermis or fibroblasts in the presence of protease inhibitors. Determination of N-proteinase activity is performed only on research basis [15, 27].

6. **Dermatosparaxis EDS.**
   Dermatosparaxis EDS carries an autosomal recessive inheritance. The molecular defect is type I collagen N-terminal peptidase deficiency [28]. The major diagnostic criteria include severe skin fragility, sagging and redundant skin, whereas minor diagnostic criteria encompass doughy skin texture, easy bruising, premature rupture of foetal membrane and large umbilical or inguinal hernias [27]. Biochemical confirmation is obtained in much the same way as for arthrochalasia EDS.

Former *subtypes* that have been removed from the current classification include EDS V (X-linked, described in a single family), EDS VIII (similar to classic EDS, except that it also presents with periodontal friability), *EDS IX* (previously known as occipital horn syndrome), EDS X (seen in one family) and *EDS XI* (familial joint hypermobility syndrome). The genetic basis of many subtypes has now been elucidated, confirming heterogeneity.

An awareness of the different conditions within this group is the starting point towards an accurate diagnosis. Keen elicitation of history and clinical signs are vital in selecting the correct confirmatory investigation. Skin biopsy with electron microscopy can be helpful in the decision process of whether and when to perform genetic testing. Correct diagnosis of the different subtypes allows targeted management, family screening and prenatal diagnosis [13, 29].

Diagnosis

The diagnosis is complicated because of the clinical variability, imprecise diagnostic criteria. A revised International Classification for the diagnosis of EDS was established in 2017 [15]. This classification was divided into *major criteria* (skin hyperextensibility and generalized joint hypermobility (GJH)) and *minor criteria* (chronic pain, recurrent joint dislocation and positive family history). GJH refers to the hypermobility of at least five or more joints, at the same time, usually at four limbs and the spine. The prevalence of GJH is estimated to be around 2%, and a twin study suggested a heritability of 70%.

Therapy

Family members of patients with *Ehlers-Danlos* syndrome should be referred for genetic counselling if one or more major criteria are present. Although a specific genetic test to diagnose EDS is not available, other types of tests may assist in identifying EDS in some families. In general, medical intervention is limited to symptomatic relief [15]. Arterial rupture requires prompt surgical assessment. Regular blood pressure control is necessary. Joint subluxation should be surgically corrected

and removal of sutures delayed for all procedures. Surgical procedures can be risky as fragile tissues can unexpectedly tear. Sunscreen should be used daily to protect against excessive sun exposure. One should avoid activities that cause the joints to lock or overextend.

Some patients have responded to ascorbic acid to decrease bruising and improve wound healing. Some symptoms may be successfully alleviated using a specific combination of nutritional supplements, comprising calcium, carnitine, coenzyme Q10, glucosamine, magnesium, methyl sulphonyl methane, vitamin C, vitamin K, pycnogenol and silica, at standard doses [30]. Also diuretics, β-adrenergic blockers, angiotensin processing blockers or receptor blockers and other antihypertensive agents could be beneficial [21]. Although there is no cure, knowledge of the diagnosis may influence surgical strategies and approaches to avoid serious complications.

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Chapter 37
Ichthyosis-Trichothiodystrophy Syndrome

Christos P. Panteliadis

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Introduction

Ichthyoses

The word ichthyosis comes from the Greek root "Ιχθύς/Ichthys", meaning fish. Ichthyosis is an umbrella term for various skin manifestations. The most frequent type is ichthyosis vulgaris with a prevalence of 1:100, caused by loss-of-function mutations in the filaggrin gene (predisposing factors, R501X mutation). It is characterized by xerosis, scaling, keratosis pilaris, palmoplantar hyperlinearity and atopic eczema [1–4]. Ichthyosis may also coexist with other rare diseases such as Sjögren-Larsson syndrome, Conradi-Hünermann-Happle syndrome, Dorfman-Chanarin syndrome, ichthyosis follicularis and Refsum syndrome [2].

Herlitz junctional epidermolysis bullosa (JEB-H) is the severe form, and non-Herlitz JEB is the milder form. The more severe JEB-H is autosomal recessive, exhibiting mechanobullous genodermatoses as its clinical manifestation, and is

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characterized by generalized mucocutaneous blistering at birth and early lethality (Fig. 37.1a). This devastating condition is most often caused by homozygous null mutations in the genes *LAMA3*, *LAMB3* or *LAMC2*, each encoding for 1 of the 3 chains of the heterotrimer laminin-332 [5].

Some of the ichthyoses that affect the central nervous system (*neuroichthyosis*) include the syndromes of *Rud*, *HID*, *KID*, *Dorfman-Chanarin* and *Tay*, which will be described briefly below. Significant morbidity and mortality occur during the neonatal period, with the majority of complications arising as a result of impaired barrier function [6]. Another type of epidermolysis bullosa other than JEB-H is Kobner-type epidermolysis bullosa simplex (Fig. 37.1b).

Neuroichthyoses collectively are rare diseases, and their classification is difficult because of their heterogeneous genetic transmission and their varying clinical picture. They are monogenically inherited skin diseases with keratosis as their primary feature whereby the entire integument can be covered with scales, versus focal keratosis that predominates in specific areas such as the palm of the hands and the sole of the feet.

Harlequin ichthyosis (HI; OMIM 242500) is a rare autosomal recessive disorder of defective lipid transport resulting in severe epidermal hyperkeratosis and large plate-like scales. Historically, Oliver Hart reported the first case in 1750 [7]. It is characterized by diffuse epidermal hyperkeratinization and defective desquamation [8]. In newborns, the hyperkeratotic covering is shed, revealing a diffusely erythematous scaly epidermis that persists for the remainder of the patient's life. The facial symptoms are distorted by severe ectropion, eclabium, flattened nose and rudimentary ears [8]. The hands and feet are oedematous and often covered by a glove-like layer. They may have finger contractures [9]. In the newborn, dehydration, thermoregulation, increased metabolic demands and risk of respiratory dysfunction, infection and sepsis may arise.

The genetic mutations underlying HI result in the dysfunction of adenosine triphosphate-binding cassette A12 (ABCA12), a keratinocyte transmembrane lipid transporter protein associated with the transport of lipids via lamellar granules in the stratum corneum of the epidermis. *ABCA12* gene mutations are known to

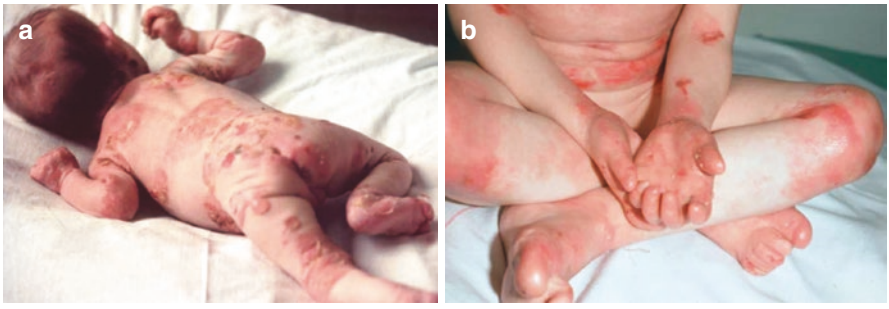

Fig. 37.1 (**a**) Junctional epidermolysis bullosa, called Herlitz type (**b**) Kobner-type epidermolysis bullosa simplex (http://www.firstskinfoundation.org)

underlie the three major types of autosomal recessive congenital ichthyoses: harlequin ichthyosis, lamellar ichthyosis and congenital ichthyosiform erythroderma [10–12]. Prenatal diagnosis using DNA analysis and ultrasound methodology is feasible. Intensive care in a tertiary centre is desirable.

Therapy

Symptom management will require involvement by a multidisciplinary team. In patients with HI, parenteral nutrition, respiratory assistance, skin care and sepsis prevention are essential. The use of retinoids is warranted, even in newborns [4]. Surgical consultation, risks of surgery, indications for and timing of surgical intervention must be well planned [13]. Gene therapy remains the most promising prospect.

Trichothiodystrophy

Trichothiodystrophy (TTD; OMIM 601675) is a rare autosomal recessive, heterogeneous, multisystem neurocutaneous disease characterized by specific hair dysplasia and numerous system involvement, e.g. brittle hair, nail dysplasia, ichthyotic skin, physical and intellectual delay and gonadal failure [14–18].

An abnormal amino acid composition (low sulphur) within the hair is the sine qua non of the disease. The term trichothiodystrophy (Greek for τρίχο (hair), θείον (sulphur), δυς (faulty) and τροφία (nourishment)) was coined by *Vera Price* in 1980 based on a series of cases, including the early report by *Pollitt*, *Jenner* and *Davies* in 1968 of a family with cognitive and physical delay and "trichorrhexis nodosa" [19, 20]. Two years later, *Brown* et al. described a case of trichoschisis with alternating *birefringence* of light-dark banding along the hair shaft visualized by polarizing microscopy, *tiger tail* anomaly and low sulphur content in the hair [21].

This was followed by *Tay* (1971) who studied three patients in Singapore with ichthyosiform erythroderma, hair shaft abnormalities and mental and somatic growth dysfunction [22]. In 1974, Jackson et al. [23] described 25 patients with a syndrome of brittle hair, short stature and intellectual impairment in one large kindred. A classification scheme was ultimately created by after an extensive review of the literature and clinical characteristics of TTD [17, 24].

Approximately half of TTD patients exhibit photosensitivity as a result of defect in the nucleotide excision repair in autosomal recessive trait, with mutations occurring in *iXPB*, *XPD*, *TTDA*, *TFIIH* and *TTDN1* genes [25]. Spliceosomes (ribonucleoprotein complexes required for pre-mRNA splicing) have been identified in X-linked trichothiodystrophy-causing gene *RNF113A* [26], but its precise incidence for TTD is unknown.

Clinical Characteristics

Trichothiodystrophy describes a group of recessively inherited multisystem neuroectodermal disorders that takes its name from the characteristic feature of brittle, sulphur-deficient hair [27]. Patients with *TTD* have sparse, short, dry, fragile hair associated with a constellation of neuroectodermal symptoms [14, 28].

Trichoschisis is characterized by a sharp fracture transversely through the entire hair shaft that is detected by a polarizing microscope [29]. Skin cancer is very rare in sun-sensitive TTD. Important laboratory tests of the hair for the diagnosis of *TTD* comprise electron microscopy and amino acid analysis of hydrolysed hair with emphasis on cysteine amino acid concentration [30–31].

Additionally, tiger tail banding is seen in all hairs with polarizing light microscopy, in conjunction with trichoschisis and low sulphur content within the hair shaft [32]. Mental and physical slowing (in 85%), microcephaly, peculiar facies, ichthyosis, osteosclerosis, short stature, gonadal failure and photosensitivity are commonly observed. Skin and nails are also affected, showing diffuse follicular keratosis (*xerosis cutis*) and ichthyosiform dermatitis [17, 33]. Cranial magnetic imaging studies in female patients may reveal almost total lack of myelination in the supratentorial white matter and progressive cerebellar and cerebral atrophy [34].

Many eponyms and acronyms have been used to describe the associated anomalies: (**a**) *BIDS* syndrome (brittle hair, impairment of intelligence, decreased fertility, short stature) (*Pollitt* syndrome refers to patients without skin involvement [35]); (**b**) *IBIDS* syndrome (Ichthyosis+) or *Tay* syndrome refers to patients with congenital ichthyosis; (**c**) *PIBIDS* (Photosensitivity+); the acronym IBIDS (extended to PIBIDS) was recommended in 1983 by Crovato [36]; (**d**) *SIBIDS* as proposed by *Chapman* who referred to osteosclerotic abnormalities in a patient with TTD [14, 36]; (**e**) *ONMR* (onychotrichodysplasia, chronic neutropenia and mild mental retardation [37]); and (**f**) *Sabinas* syndrome, which refers to patients with TTD and mental delay, but with normal stature [38–41].

The Amish brittle hair syndrome is characterized by trichothiodystrophy, intellectual delay, EEG disturbances, ataxia, intention tremor, low birth weight and hypogonadism in the absence of ichthyosis, resembling *Rud* and *BIDS* syndrome in many ways.

Patients with *TTD* often display a deficiency in excision repair of ultraviolet damage, in the same complementation group as xeroderma pigmentosum (XP; OMIM 278730). XP is a rare autosomal recessive disorder defined by extreme sensitivity to sunlight, resulting in sunburn, pigment changes (*lentiginosis*) and a higher incidence of skin cancers [42–44].

There may exist an overlap between trichothiodystrophy, Cockayne and other progeroid syndromes [33]. This may suggest an involvement of repair proteins in hair shaft development. Hair examination is a vital and useful tool. The most important finding is low sulphur content of hair shafts [28]. Amino acid analysis of hair shows a reduction in cysteine levels [45].

Approximately half of patients with TTD have photosensitivity, which correlates with a nucleotide excision repair defect (NER), which is a multi-step process via two alternative pathways [46]. The first pathway is a transcription-coupled DNA repair, which removes lesions only in the actively transcribed DNA strand, and the other is global genome repair, which removes lesions in any sequence of the genome. A novel pathogenic mutation in *ERCC2* has been described in two siblings with trichothiodystrophy and confirms the severe phenotype associated with the *p.Arg722Trp* mutation [27]. The growing knowledge of various genetic mutations has helped to prognosticate the severity of TTD.

Tay Syndrome

Tay syndrome or IBIDS is an autosomal recessive disorder characterized by congenital ichthyosis and abnormal brittle hair (*trichothiodystrophy*). Other symptoms include photosensitivity, abnormal nails and multiple developmental defects affecting organs derived from neuroectoderm lineage. The exact prevalence remains elusive given the worldwide rarity of the condition [47].

Among the various types of neuroichthyosis, Chong Hai Tay distinguished in 1971 an autosomal recessive ectodermal disorder in three siblings from an intermarried Chinese family in Singapore [22]. At times, it may be referred to as *IBIDS* (ichthyosis, brittle hair, impairment of intelligence, decreased fertility, short stature).

The general characteristics of the syndrome are ichthyatic erythrodermia (congenital ichthyosis), sulphur-deficient brittle hair (*trichothiodystrophy*), dysplastic nails, progeria-like facies and hypoplasia of subcutaneous tissue. Trichothiodystrophy is an obligatory diagnostic finding [47].

The neurologic features include microcephaly, intracerebral calcifications, EEG abnormalities, mild hearing loss, intention tremor, ataxia and mental and growth impairment. Other rare anomalies are low birth weight, short stature and cataracts. Hair may show typical changes reminiscent of a *lion's tail* with alternating dark and light stripes due to varying pigmentation [48]. Amino acid analysis of hair and nails by chromatography shows a decrease of 50–60% in the levels of cysteine. Cysteine is a sulphonic amino acid that allows for the formation of disulphide bonds and stabilization of keratin filaments in hair and nails, sparing the rest of the body. The monilethrix trichoscopy method could be used in lieu of electron microscopy, enabling analysis of the structure and size of growing hair shafts in children and adults [49].

Management

Appropriated treatment is based on the genetic markers and clinical features. Prenatal and postpartum genetic counselling is highly encouraged.

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Chapter 38
Rud Syndrome

Christos P. Panteliadis

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Introduction

Rud syndrome is characterized by congenital ichthyosis, dwarfism, hypogonadism, small stature, epilepsy, mental retardation and infrequent retinitis pigmentosa. Sensorineuronal hearing loss, edentulous, alopecia and pseudoacanthosis nigricans can occur. Sexual infantilism can be diagnosed only after puberty [1–3]. The aetiology still remains unexplained. It is presumed to be a contiguous deletion syndrome. An X-linked transmission (as well as an autosomal recessive inheritance pattern) has been observed.

Rud syndrome is a genodermatosis without male predilection as one would expect for an X-linked recessive disorder, which attests to its heterogeneity [4–6]. Skin lesions (ichthyosiform), typically in the extensor extremities, are noticed during the first few months of life (Fig. 38.1). Mild psychomotor delay appears late in children, whereas generalized seizures usually manifest in infancy, but it may occur well into the first decade.

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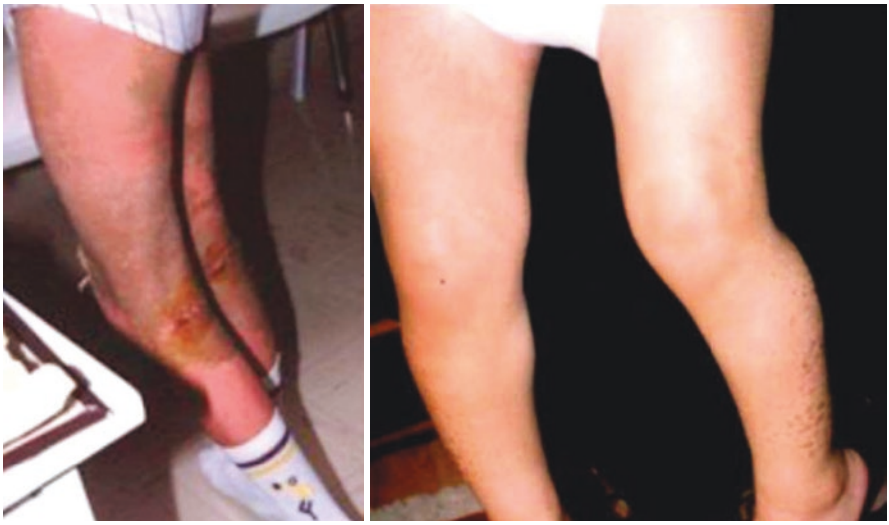

Fig. 38.1 Typical findings of neuroichthyosis

Clinical Characteristics

The principal characteristics of ichthyosis include intense rhomboid defoliculation and a yellow-brown skin colour affecting the flexor areas of the body. In one-third of the patients, hair follicles are also discoloured. Acanthosis nigricans and alopecia may coexist [7]. Other findings include horizontal nystagmus, ptosis, strabismus, retinitis pigmentosa, hypertrophic polyneuropathy, cranial dysmorphisms, unilateral renal atrophy, hypergonadotropic hypogonadism, cranial dysmorphism (*focal cortical dysplasia*) and anosmia [8–10].

Hypogonadism is seen consistently in patients with Rud syndrome, whereas cryptorchidism could be present without any other findings in those with steroid sulfatase deficiency [11–13]. In 1999, four children from three different families were documented to display the same genetic defect responsible for steroid sulfatase. Rud syndrome and other steroid sulfatase genomes are mapped to Kallman loci Xp22.2–3 on the X chromosome [12]. The deletion of steroid sulfatase gene (and adjacent genes) yields an imperfect recombination of chromosomal material between the X and Y chromosomes during meiosis.

The condition of *absent multiple sulfatase* enzymes has many common characteristics with the combined steroid sulfatase deficiency. The former is a severe neurodegenerative disease that leads to death during early childhood. The neurologic findings for both deficient and absent sulfatase are similar to those of metachromatic leukodystrophy (deficiency of arylsulfatase-A). Skin lesions in metachromatic leukodystrophy, however, are much milder than in neuroichthyoses. On the other hand, severe cases have been seen in Sjögren-Larsson syndrome, which harbours the triad of congenital ichthyosis, mental retardation and spastic diplegia/tetraplegia due to

deficient activity of fatty alcohol, NAD oxidoreductase [14]. A similar syndrome of ichthyosis follicularis, alopecia (or atrichia/ατριχία) and photophobia (*IFAP syndrome*; OMIM 308205) has been identified related to *MBTPS2* gene that regulates cholesterol homeostasis [15].

Therapy

Life expectancy ranges from death in infancy to normal adulthood. The management of patients with Rud syndrome must draw from the specialties in epileptology, dermatology, endocrinology, ophthalmology, gynaecology and audiology. For any neuroichthyosis, application of topical alpha-hydroxy acids (*lactic acid-based*), soft paraffin/urea-based moisturizing ointments (up to 10%) and other keratolytics might be beneficial. Vitamin D3 and antiepileptic medications to control seizures are generally needed. Systemic retinoids, e.g. acitretin (*Soriatane*), are frequently administered to patients over the age of 16 years [3, 16].

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Chapter 39
KID/HID Syndrome

Christos P. Panteliadis

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Introduction

The American dermatologist Frederick Burns in 1915 first published a case of generalized congenital erythroderma [1]. In 1981, Skinner et al., by reviewing 18 similar cases, coined the acronym KID (keratitis, ichthyosis and sensorineural hearing loss) [2, 3]. Heiko Traupe proposed in 1989 the term "HID syndrome" for a phenotype characterized by **H**ystrix-like **I**chthyosis associated with bilateral neurosensory **D**eafness [4].

KID syndrome is a rare congenital disorder of ectoderm that affects not only the epidermis but also other ectodermal tissues such as the corneal epithelium and the inner ear. It is named for its clinical triad of erythrokeratoderma, vascularizing keratitis and bilateral sensorineural hearing loss. Ocular findings typically commence within the first year of life and progress with time [3]. To date, approximately 100 cases of KID syndrome have been reported. It is important to emphasize that

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ichthyosis is not the major cutaneous feature and not all patients have keratitis early in the course. The disease may involve the ocular adnexa and surface with variable severity independent of the patient's age [5]. One-half of the affected patients also display frequent, severe cutaneous infections.

Clinical Characteristics

The most common clinical characteristic for KID syndrome is congenital bilateral neurosensory hearing loss (90%), followed by keratitis and erythrokeratoderma. Other clinical symptoms include lid abnormalities, corneal surface instability, dry eyes, blepharitis, conjunctivitis, alopecia, anonychia of the thumbs (great toes and the second toes), seizures, benign neoplasms, namely trichilemmal tumours and squamous cell carcinoma of the skin or of the tongue and buccal mucosa [3, 6, 7]. Patients with KID syndrome have also been identified to show photophobia, impaired visual acuity and severe meibomian dysfunction associated with hyperkeratotic lid borders [8], which may play an important role in the pathogenesis of ocular lesions.

KID and HID syndromes are identical at the molecular level in spite of the different cutaneous features [9], but distinguishable mainly on electron microscopy [10]. Germline missense mutations in *GJB2* encoding connexin 26 have been found in KID syndrome [11, 12]. The connexin 26 protein is important for intercellular communication. Connexin 26 is the most common cause of hereditary, sensorineural hearing loss [13–15]. Changes in connexin 26 are also linked to Vohwinkel syndrome (honeycomb-like calluses in palmoplantar regions beginning in infancy, causing autoamputation of digits with sensorineural hearing loss) and deafness with Clouston-like phenotype [13].

Therapy

Because of frequent cutaneous infections, therapeutic strategies utilize antibiotics, antifungals and systemic retinoids, but with variable responses [3, 15]. Patients treated with oral minocycline, topical steroids and artificial tears gain significant reduction in ocular discomfort and pathology. Chronic mucocutaneous candidiasis and superinfection of skin lesions are common. Cochlear implantation with thin receiver/stimulator has been recommended for the hearing loss [14]. Routine screening of the skin and oral mucosa for the development of malignancy is essential.

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Chapter 40
Hutchinson-Gilford Progeria Syndrome

Christos P. Panteliadis

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Introduction

Hutchinson-Gilford progeria syndrome (HGPS; OMIM 176670) is a sporadic, autosomal dominant progeroid syndrome [1–3]. In 1886, *Jonathan Hutchinson* described a 3.5-year-old boy with a peculiar old appearance. Later, *Hastings Gilford* in 1904 described a similar syndrome. The *Greek* word progeria is derived from "γήρας", meaning "premature old age".

HGPS induces premature ageing followed by death from cardiovascular complications, such as myocardial infarction, stroke, atherosclerosis or heart failure [4]. HGPS comprises several rare inherited diseases, linked to mutations in the *LMNA* gene that encodes the nuclear scaffold proteins lamins A and C on chromosome 1 [5–7]. The other autosomal dominant diseases are Hallermann-Streiff syndrome (oculomandibulodyscephaly with hypotrichosis due to a novel genetic mutation) and Gottron's syndrome (non-progressive acrogeria in distal limbs) that is both autosomal dominant and recessive. Other *autosomal recessive* progeroid conditions include Werner's syndrome on *WRN* gene that encodes for helicase protein (its

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clinical manifestations are first recognized in the third or fourth decades of life), Wiedemann-Rautenstrauch syndrome (WRS) and de Barsy syndrome. More extremely rare conditions of progeria can be referenced: Rothmund-Thomson syndrome, Storm syndrome, combined defect of growth factors, Mulvihill-Smith syndrome, Cockayne syndrome (see Chap. 30) and Berardinelli-Seip congenital lipodystrophy (lack of adipose tissue in the body). As of December 2020, only 131 children and young adults living with progeria worldwide have been identified [8].

Type-A lamins are structural components of the nuclear lamina, a polymeric proteinaceous network that covers the inner surface of the nuclear membrane that extends as a fibrous matrix into the interior of the nucleus [9], which helps maintain the normal infrastructure of a cell's nucleus (Fig. 40.1).

Progeria (προγηρία) is called a *segmental* premature ageing syndrome by inducing early cellular senescence that is associated with increased DNA-damage signalling. The LMNA alleles in HGPS are postulated to function in a heterozygous, autosomal dominant fashion [7]. The mutated lamin A on the nuclear membrane is to some degree a cellular pleiotropy, which in turn could provide selective pressure for loss of the affected allele, both during cell culture and in vivo [10]. Ninety percent of the patients with HGPS are said to have de novo point mutations in the *LMNA* gene that substitute cytosine with thymine. Investigators have concluded that the HGPS gene must lie within a 4.82 Mb region of chromosome 1q. This region contains approximately 80 known genes, including *LMNA* [11, 12]. The most common HGPS mutation is found at position G608G within exon 11 of the *LMNA* gene [13]. This mutation results in the deletion of 50 amino acids at the carboxyl-terminal tail of prelamin A, a precursor protein to lamin A by the metalloprotease ZMPSTE24 or FACE1. The truncated protein is called progerin [7, 13, 14].

Clinical Characteristics

HGPS is a rare disease characterized by extreme short stature, low body weight, early alopecia, scleroderma-like skin, decreased joint mobility, osteolysis, cardiovascular problems and facial features that resemble senility (Fig. 40.2).

Infants afflicted with the disease are generally healthy at birth, but between the first and the second year of life, the development of *sclerodermatous* skin changes commonly arises in the buttocks, lower abdomen and bilateral thighs. There is concurrent midfacial cyanosis and sculptured beak nose. Hypo- and hyperpigmentation are observed over areas of sclerodermoid changes. Hair greys prematurely (canities) and recedes over the scalp and other parts of the body. Cardiovascular and neurovascular involvement ensues, showing progressive atherosclerosis and arteriopathy, leading to myocardial infarctions and strokes (Fig. 40.3). Death occurs at an average age of 13–14 years [15–18]. Arterial ischaemic stroke in HGPS is common and often clinically silent [19].

The most frequent pathological observations are proliferative collateral vessel formation within the suprasellar, subfrontal and perisplenial regions. There is

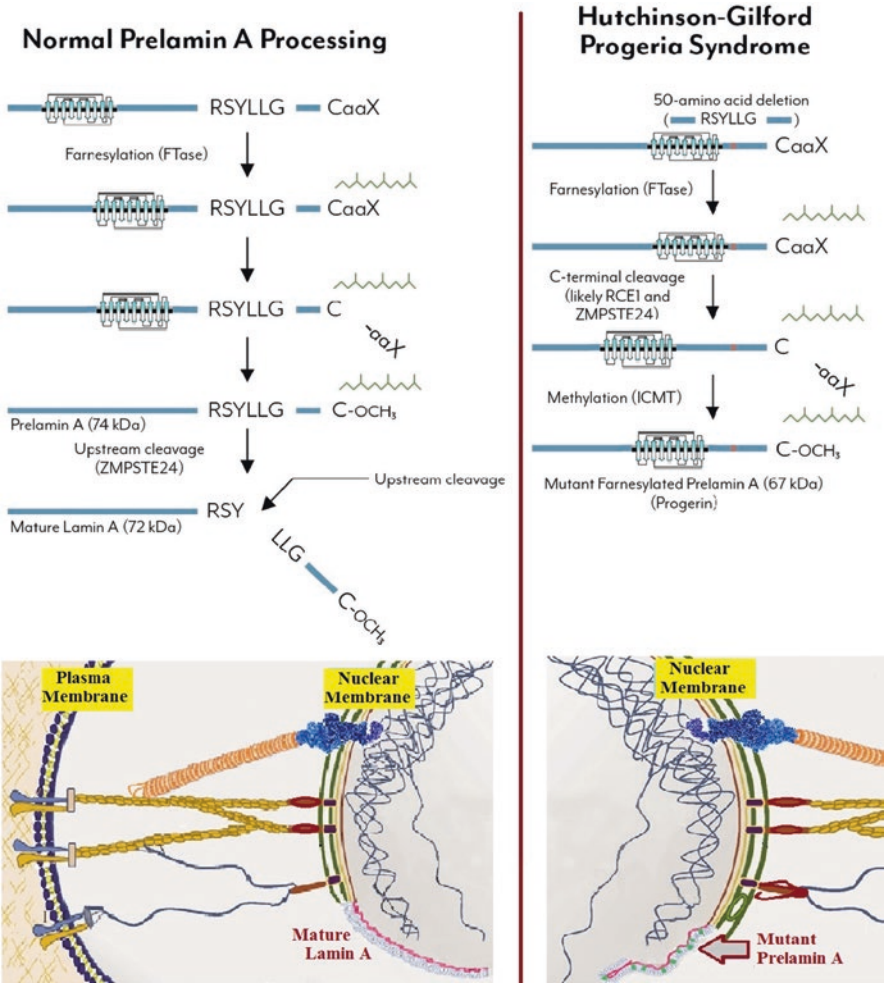

Fig. 40.1 Normal type-A lamins (to the left) and ZMPSTE24 mutation (right half) involving the farnesyltransferase. (Illustration by ©Talia Glass and R Benjamin, 2021)

enlargement of the internal maxillary and middle meningeal arteries, and slow compensatory collateral convexity flow [20]. Arterial ischaemic stroke, distal carotid artery and/or vertebral artery occlusion, stenosis and calcification, with or without clinical symptoms, are seen in 60% of the patients [21]. https://www.google.com/url?sa=i&url=http%3A%2F%2Fwww.ajnr.org%2Fcontent%2F33%2F8%2F1512&psig=AOvVaw0mO2KGPldT0wcv1DLD9ru8&ust=1610489771699000&source=images&cd=vfe&ved=2ahUKEwj7nKmH9JTuAhWYh54KHamGCCMQjRx6BAgAEAc Lipodystrophy (20% of the cases) involves primarily the face with typical senile look and a vertical nasal groove.

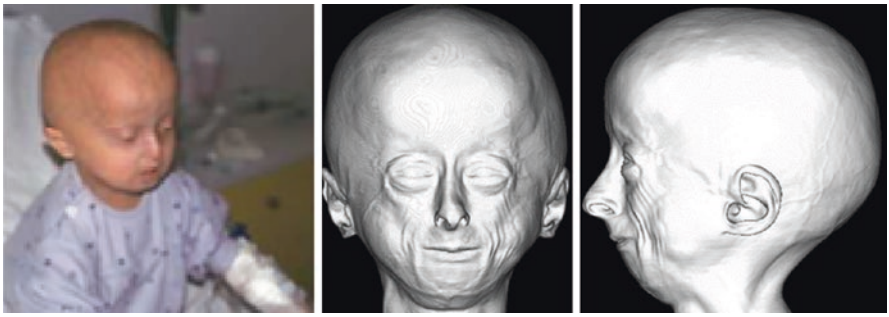

Fig. 40.2 Typical features of a child with progeria with correlative imaging studies of another patient. (With permission, Nicole Ullrich; AJNR, 2012)

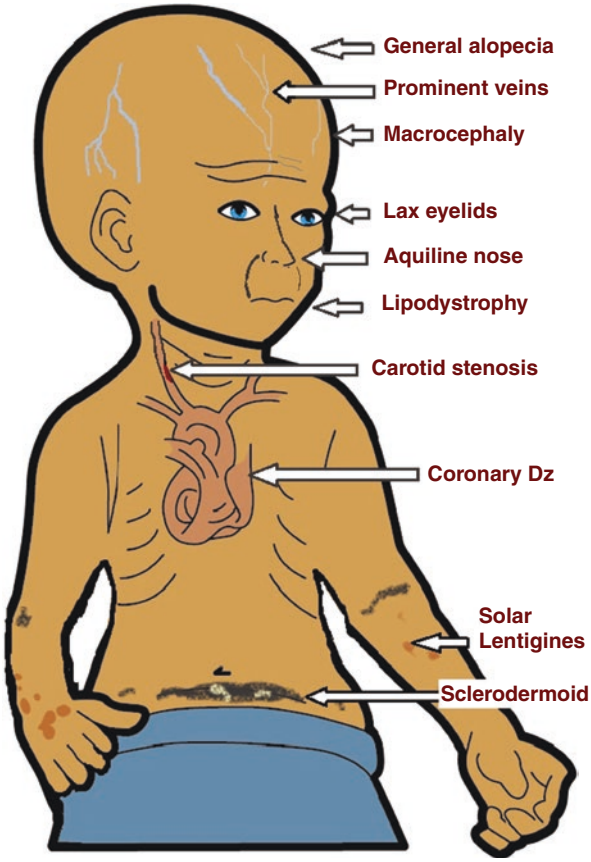

Fig. 40.3 Systemic findings in children with HGPS. (Illustration by ©Talia Glass, 2021, adapted from primumn0nn0cere)

Other clinical characteristics include micrognathia, dysmorphic craniofacial features, generalized alopecia, prominent eyes and scalp veins, short stature (<third percentile), low weight-to-height ratio and a small face relative to head

circumference [18, 22, 23]. Additional features of dystrophic nails, joint stiffness, short limbs, short clavicles, pyriform thorax, high-pitched voice, diabetes mellitus, delayed abnormal dentition and elevated levels of hyaluronic acid in urine may coexist [24].

Lax eyelid syndrome can be considered as a sign of progeria [25]. Delayed dentition, discoloration, crowding, rotation and displacement of anterior teeth also develop over time. Microscopic examination of the dentition reveals irregularity in odontoblast size and shape, reticular pulp atrophy, delay in calcification and pulpal nerves and vascular calcification [26]. Later in life, loss of subcutaneous tissue, baldness, diffuse osteoporosis, atrioventricular block and early-onset arthritic changes take precedence [22, 26, 27]. The intelligence quotient typically lies within the physiologic range. Radiographic changes such as osteopenia, acroosteolysis of the phalanges and distal clavicles manifest within the second year of life.

Another premature ageing disease is *Werner's syndrome*. In the majority of patients (83%), *Werner is* inherited as an autosomal recessive disease due to mutation in *WRN*, a 3′–5' RecQ DNA helicase-exonuclease that unwinds DNA and cleaves nucleotides from DNA termini. Patients with the disease show a high incidence of early-onset cataracts, arthrosclerosis, diabetes, premature greying and early death, usually in their 30s and 40s. Unlike HGPS, *Werner's syndrome* is associated with an increased risk of neoplasms, although the mean age of death in Werner's is much older than HGPS, which possibly allows for the accumulation of mutations that promote the risk of unchecked cell growth [28].

Diagnosis

The diagnosis of classic HGPS is based on recognition of common clinical characteristics, imaging studies and detection of classic c.1224C > T (p.Gly608.Gly) heterozygous LMNA mutation [22]. Persons with non-classic HGPS have the characteristic clinical features of HGPS and are heterozygous for another *LMNA* pathogenic variant in exon 11 or intron 11 that results in the production of progerin [21]. Most infarcts identified on the first available imaging are in patients between 5 and 10 years of age [20]. Prenatal diagnosis is possible by DNA analysis via amniocentesis at 15–18-week gestation.

Therapy and Prognosis

In November 2020, the US Food and Drug Administration approved lonafarnib (Zokinvy®), a farnesyltransferase inhibitor, as the first treatment for HGPS [29]. A regular diet with frequent small meals, routine physical and occupational therapy, nutritional assessment, active stretching and hydrotherapy are still vital in the overall care of these children. Medication dosages, such as antiseizure agents, are based

on body weight or body surface area, not age. Clinical trials using statins or isoprenylcysteine carboxyl methyltransferase inhibitors, drugs that block prelamin A maturation in mouse models of progeria, are ongoing [21, 22, 30, 31].

The average life expectancy is early teens [32], as mentioned due to cardiovascular complications. Anaesthesia is potentially problematic. Hip dislocation is best managed by physical therapy and body bracing. The need for orthodontist, especially any individual requiring general anaesthesia, should be balanced against the risks associated with the procedure and the medical necessity [33]. Extreme caution should be exercised during oral surgery due to the inelasticity of tissues and dermal atrophy. Healing appears to be normal [26]. Low-dose aspirin (2–3 mg/kg body weight) for cardiovascular prophylaxis is suggested. Annual or semiannual electrocardiogram, echocardiogram, carotid duplex ultrasound, neurologic and ophthalmologic examinations are necessary.

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Chapter 41
Lipoid Proteinosis (Urbach-Wiethe Syndrome)

Christian Hagel and Christos P. Panteliadis

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Introduction

In 1929, Erich *Urbach* and Camillo *Wiethe* provided the initial description of the disorder.

Lipoid proteinosis (OMIM 247100) has the eponym Urbach-Wiethe syndrome as the two dermatologists were the first to coin the term hyalinosis cutis et mucosae (glass-like, Greek: ὑάλινος) [1]. Approximately 300 cases have been reported in an autosomal recessive trait. It is more common in consanguineous families, and mostly found in South Africa, suggesting a probable founder effect. The disease usually starts in infancy or early childhood and presents with cutaneous lesions on the face (*called waxy papules*), eyes (cornea, conjunctiva, sclera) and fingers. Neurological problems include a barely audible hoarse cry as an infant or hoarse voice in a teenager or adult. There are also neuropsychiatric impairment,

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predisposition to epilepsy in 25% of the cases (involving the temporal lobe), calcification within the basal ganglia, hippocampus and amygdala and rarely spontaneous intracerebral haemorrhages [2–4].

Mutations have been detected in all 10 exons of the extracellular matrix protein 1 (*ECM1*) gene, located on chromosome 1q21 [5–8]. Nonsense and missense mutations predominate, especially in exons 6 and 7, and approximately 50 recessive mutations have been identified [9, 10]. Seven splice site mutations have also been discovered, the last involving mutation in intron 8 [8, 11].

Clinical Characteristics

The first clinical manifestation in early childhood is a hoarse cry or a screech as the squamous tissue of the vocal cords becomes inflamed and impregnated with the lipoid material. This is followed by varicella-like papules and acneiform scars affecting the pharynx, tongue, soft palate, tonsils and upper eyelids. The skin and mucous membrane (*hyaline*) later becomes thickened from the infiltration [2–4, 12, 13]. Enlargement of the lips and tongue may cause speech difficulties and aphonia [14]. Yellowish papules and lichenification over the scrotum and multiple discrete, round-to-oval pock-like scars over the trunk have also been observed in non-consanguineous family members (Fig. 41.1a) [15].

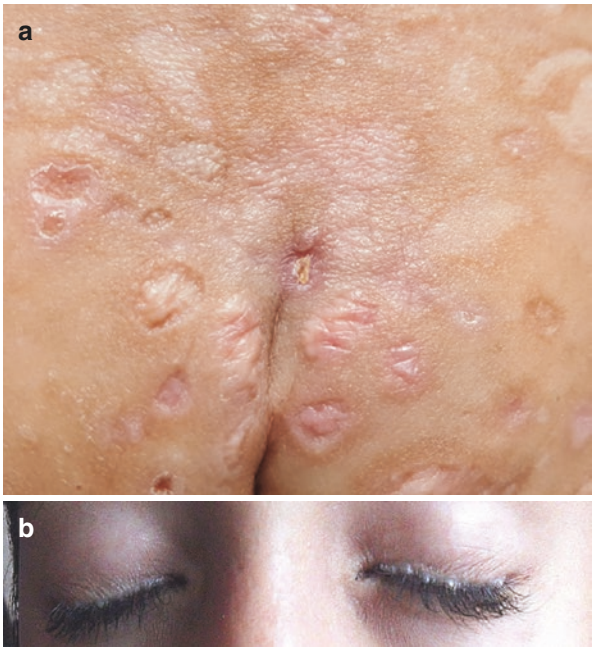

Fig. 41.1 **(a)** Hyaline sclerosis and thickening in the buttocks (with kind permission, 2021, Agarwal et al. EJPD [15]) **(b)** Yellowish beaded papules in eyelids (moniliform blepharosis) in a patient with lipoid proteinosis (with permission, 2021, Nayak et al. Indian Dermatol Online J [16])

Bilateral intracerebral calcifications in both hippocampi and mesial temporal regions give rise to neurological and psychiatric conditions like seizures in 25% of the patients, headache, delay of mental development, mutism, severe generalized dystonia, emotional fluctuations and memory deficit [17–19]. The symptoms vary from individual to individual. Another frequent finding is focal degeneration of the macula and drusen formation in *Bruch's* membrane in about 30–50% of patients. Other less common ocular manifestations include cataract, retinitis pigmentosa, keratoconus (deposition of hyaline on the cornea), unilateral or bilateral uveitis and sicca syndrome.

LiP is caused by mutations in the gene *ECM1* coding for extracellular matrix protein 1 [5–8]. The 85-kDa protein is considered as the "biologic glue" in skin physiology [8]. *ECM1* maps to 1q21 and encodes an 85-kDa glycoprotein that is expressed in several tissues. The majority of mutations are found in exons 6 and 7, and approximately 50 recessive mutations have been described [9, 10]. Alternative splicing gives rise to three distinct isoforms (ECM1a–c). Histologically, widespread deposition of hyaline material disrupts the basement membrane around blood vessels and dermal-epidermal junction (*epidermal hyperkeratosis*). The hyaline material stains positive with periodic acid-Schiff and is readily demonstrable on biopsy of the affected skin [20] (see Chap. 4.17). The diagnosis depends on the constellation of hoarse voice and the pathognomonic lesions of sallow bead-like nodules in the outer eyelids known as moniliform blepharosis [16, 21] (Fig. 41.1b).

Therapy and Prognosis

Patients should be cared by a multidisciplinary team of specialists. The overall prognosis of LiP is good; however, the permanent hoarseness and the disfigurement impair quality of life. Cutaneous lesions may be reduced by oral administration of dimethyl sulfoxide, oral retinoids, steroids, D-penicillamine and/or dermabrasion [13, 22]. Thickness of the vocal cords could be made pliable by CO_2 laser treatment [23, 24]. Patients generally succumb to acute or chronic respiratory demise.

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Chapter 42
McCune-Albright Disease

Ramsis Benjamin

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Introduction

The exact incidence of this extremely rare disease is unknown, but estimated to be in 1 in 100 000 to 1 in a million [1]. Less than 20 cases have been reported in the literature. It appears to exist equally in all races and is not inherited. The first girl with sexual precocity (a 9-year-old with her first menarche at 18 months of age), marked skeletal changes (coined as "osteopsathyrosis") and hyperpigmentation was described by Dr. A. Weil in 1922 [2]. Other cases were discovered subsequently, but considered as a variant of von Recklinghausen's disease. In 1937, Dr. Donovan McCune, an American paediatrician, and Dr. Fuller Albright, an American endocrinologist, presented a handful of cases almost simultaneously [3, 4]. The condition thus may be referred to as McCune-Albright (McAD) in the USA or Weil-Albright in Europe.

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Clinical Characteristics

At least two of the triad of endocrine hyperfunction, poly- or monostotic fibrous dysplasia and café-au-lait spots must exist to establish the diagnosis of McCune-Albright disease (*McAD*). In addition, children afflicted with this condition may present with painful skeletal deformities, skin pigmentation covering a large area of the body and varying degrees of cognitive impairment and endocrinopathies.

Pathogenesis

McCune-Albright disease occurs as a result of sporadic and somatic (*post-fertilization*) missense mutation in the *GNAS* gene encoding the α-subunit of the stimulatory heterotrimeric G-protein complex [5, 6]. This gene is located on chromosome 20q13.2, and the post-zygotic missense mutation is either at ARG201 or Gln227 during embryogenesis.

The gain-of-function mutation produces elevated intracellular cyclic adenosine monophosphate (*cAMP*) levels (Fig. 42.1) and downstream protein kinase A (*PKA*). The ubiquitous cAMP response element-binding protein (*CREB*) triggers transcription after its phosphorylation on Ser(133) by PKA. The mutation promotes mitogenesis and cell-cycle activation in melanocytes, ovarian follicular cells, thyroid nodules and in somatotroph adenomas, which causes increased skin pigmentation,

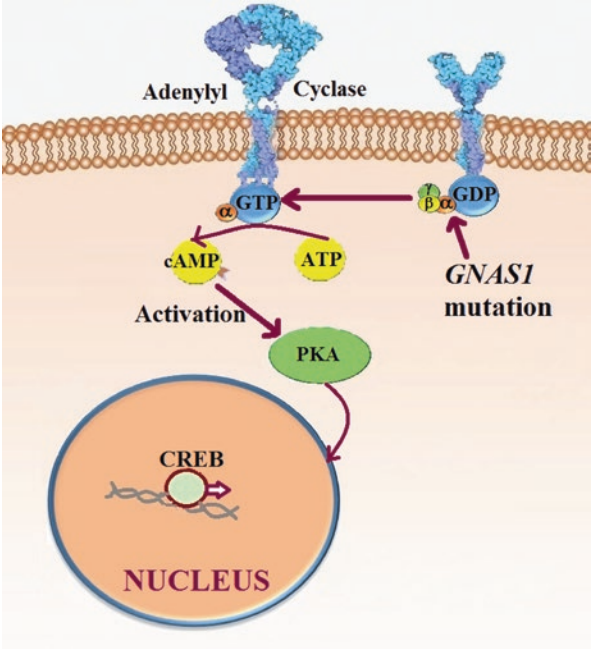

Fig. 42.1 Missense mutation in the *GNAS* gene induces the α-subunit in G_s-protein complex (GDP), which promotes ongoing activation of cAMP (cyclic adenosine monophosphate) and downstream protein kinase A (PKA). The phosphorylation of CREB (cAMP response element-binding protein) at Ser(133) in the nucleus ultimately promotes transcription of genes responsible for cell proliferation, survival and differentiation. (Illustration by ©Talia Glass and R. Benjamin, 2021)

oestrogen production and secretion, thyrotoxicosis and gigantism. Specific to the formation of fibrous dysplasia, aberrant function of fibroblast growth factor-23 due to mutated G_s-α leads to hyperphosphaturia and impaired phosphate absorption [7]. The lack of autosomal dominant transmission in McAD suggests lethality associated with activating G_s-α mutation early in embryogenesis.

Endocrinopathy

Autonomous endocrine hyperfunction is the most common endocrine anomaly, typically due to oestradiol-secreting ovarian cysts that alter in size irrespective of the hypothalamic feedback loop. It is more common in females than in males. Gonadotropin-independent precocious puberty manifests in boys with maturation of sex organs before the age of 9.5 years. The development of breast tissue and menarche in *McCune-Albright* girls can be observed as young as mid-infancy, and up to 85% of the cases the symptoms first manifest before the second year of life.

Children with McAD sprout and plateau early in height, causing them to be short as they advance in age. They may also possess goitre and thyroid nodules (in half of the cases), and rarely hypercortisolism due to adrenocorticotropic hormone (*ACTH*)-independent Cushing syndrome, and acromegaly (pituitary somatotroph adenomas), leading to coarse facial features, obesity, hypertension in infancy and growth retardation.

Polyostotic Fibrous Dysplasia

Increased levels of cAMP in bones differentiate osteoblasts into stromal cells, resulting in fibrous dysplasia and greater irregular trabeculae. The long bones, ribs and skull are commonly affected in McCune-Albright disease and vary in severity that ranges from small asymptomatic areas detectable only by bone scan to misalignment of teeth, proptosis, kyphoscoliosis and marked disfigurement that can result in pathologic fractures [8]. Hypophosphatemia occurs secondary to the excess production of fibroblast growth factor-23 (FGF-23) and the inability of the kidneys to metabolize phosphate, which in turn leads to osteomalacia and rickets in the long bones [7, 9, 10]. In many children, disparity in the length of the arms and legs has been detected, without previous fractures. The most severe forms of fibrous dysplasia cause facial disfigurement but without actual visual and auditory impairment.

Café-au-lait Spots

Café-au-lait macules may be seen during the neonatal period or more typically as the disease advances with age due to ongoing signalling transduction of alpha-melanocyte-stimulating hormone (*α-MSH*). The pigmented lesion tends to be large,

sometimes involving the entire shoulder and chest. The melanin-rich macules are characterized by an irregular border described as *coast of Norway* or *coast of Maine* (Fig. 42.2), as opposed to the smoother *coast of California* seen in neurofibromatosis 1. The pigmentation generally respects the midline and adheres to the lines of Blaschko.

Diagnosis

McCune-Albright disease resembles neurofibromatosis, Ollier's disease (*dyschondroplasia*), *Jaffe-Lichtenstein* syndrome, but with the added features of jagged café-au-lait pigmentation and precocious puberty. Diagnosis rests on finding at least two of the three phenotypic features: endocrine hyperfunction, fibrous dysplasia and café-au-lait spots. In girls afflicted with McAD, menarche typically occurs at a much younger age before the development of mammillary tissue and pubic hair. The menstrual bleeding may also be unpredictable and isolated, whereas it is more regular or continuous with other disorders.

Breast diameter and Tanner staging should be recorded at each visit. Thyroid and ovarian cysts can be visualized by ultrasonography. Regular X-rays or

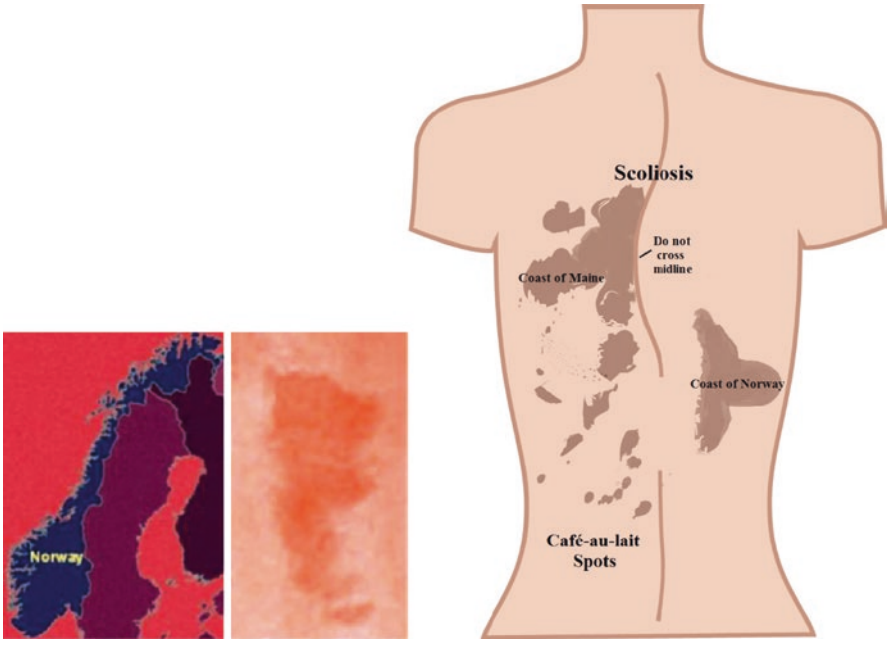

Fig. 42.2 Irregular borders of café-au-lait pigmentation in a patient with McCune-Albright disease (on the left), resembling the coast of Norway. The lesions tend to encompass a large territory, respecting the midline. (Illustration by ©Talia Glass, 2021)

radionucleotide bone scans easily identify the polyostotic fibrous dysplasia, displaying hazy, radiolucent marrow secondary to defective mineralization.

The *differential diagnosis* includes central precocious puberty, cherubism (an autosomal dominant trait with similar features that presents after the age of 3 years), Proteus syndrome, Russell-Silver syndrome and hypothalamic tumours. A specific peptide nucleic acid primer for *GNAS* exon 8 by polymerase chain reaction (PCR) technique and next generation sequencing have permitted detection of genomic mutation from the peripheral blood cells in patients with McCune-Albright disease [11, 12].

Therapy

Treating precocious puberty in McAD is challenging. The ovarian cysts usually recur after gross surgical resection. Medroxyprogesterone can be administered to suppress the menstrual bleeding, but it does not appear to halt the abnormal growth rate and bone deformity. The synthetic forms of gonadotropin-releasing hormones that suppress LH and FSH are also ineffective. Aromatase inhibitors and the oestrogen receptor modulators tamoxifen and raloxifene have demonstrated partial efficacy [13]. Fulvestrant, a pure oestrogen receptor antagonist, has been shown to decrease vaginal bleeding and rates of skeletal maturation [14–16].

Therapeutic agents that inhibit thyroid hormone synthesis such as propylthiouracil can be utilized, if thyroid hormone levels remain exceedingly elevated. Radioiodine ablation or thyroidectomy confers successful treatment option for hyperthyroidism.

There is no known hormonal or medical treatment effective in controlling progressive polyostotic fibrous dysplasia, which is the most complicated facet of caring for these children. Orthopaedic procedures such as pinning and casting of limbs may be necessary for pathologic fractures and bony overgrowth. Skull and jaw changes are often corrected surgically, with great improvement in appearance. Oral phosphorous supplementation and calcitriol could be administered in those with hypophosphatemia and rickets.

For acromegaly, surgical removal of the acidophilic region that contains the growth hormone in the pituitary gland is considered if somatostatin analog fails to suppress growth hormone secretion, which occurs in 70% of the cases [17]. Caution must be taken when irradiating the adenoma, because it increases the risk of malignant transformation of the fibrous dysplasia that falls within the radiation dosimetry.

Finally, small molecule inhibitors specific for the mutant G_s-protein, the so-called gsp oncogene, are being currently identified by novel assays [18]. Tocilizumab (an IL-6 inhibitor) and denosumab are under investigation for the treatment of fibrous dysplasia.

Prognosis

Prognosis depends on the length and magnitude of exposure to oestrogen and on adequate replacement of thyroid hormone, mineralocorticoids and glucocorticoids. Individuals remain at risk of developing diabetes, obesity and adrenal insufficiency during times of severe metabolic stress.

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Chapter 43
Menkes Syndrome (Kinky Hair Disease; Trichothiodystrophy)

Christos P. Panteliadis and Christian Hagel

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Introduction

Menkes disease (MD) is a fatal multisystem neurodegenerative disorder of copper metabolism. MD patients present with peculiar kinky hair [1, 2]. Menkes et al. first described the disease in 1962, followed by *Danks'* keen observation in 1973 of the similarity between the kinky hair seen in children and the brittle wool of Australian sheep raised in areas with copper-deficient soil. He demonstrated abnormal levels of copper and ceruloplasmin in MD patients. A girl with MD phenotype and an X-chromosome translocation was described in 1987, which led to the identification of the locus on the X-chromosome in 1993. Copper is an essential trace element in human nutrition (micronutrient) required for numerous critical enzymes, such as

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metalloenzymes, including metabolic reactions, e.g., cytochrome C oxidase of the adenosine 5′-triphosphate (ATP) in mitochondria, catecholamine, ferrum, cholesterol, and peptide hormone metabolism. The clinical symptoms include abnormal catecholamine, kinky hair, hypopigmentation, connective tissue defects, and severe neurodegeneration [2–4].

The **incidence** of the disease is estimated at 1 in 300,000 in Europe and 1 in 40,000 live births in Australia [3]. One-third of cases result from new mutations. Menkes follows an X-linked recessive inheritance and affects invariably boys via carrier mothers [5]. A few affected females with X:translocations, X0/XX mosaicism, or unfavorable lyonization have been reported.

Menkes disease is caused by mutations in the Xq13.3 gene ATP7A [3, 6–8]. The mutations are heterogeneous and show no hotspots. Splicing defects generally cause the mild variant of the disease. The mutation in each identified family has been unique, and all result in decreased ATP7A mRNA production [9] which encodes a 1500-amino-acid P-type adenosine triphosphatase (ATPase). The protein has 17 domains – 6 copper binding, 8 transmembrane, a phosphatase, a phosphorylation, and an ATP binding [4, 10].

Clinical Characteristics

Children with the classic form usually present at 2–3 months of age with loss of developmental milestones, profound truncal hypotonia, seizures, and failure to thrive. Recurrent respiratory and urinary tract infections are common. *Some* may have minimal neurological symptoms with normal intelligence or only mild mental retardation and autonomic dysfunction [11, 12].

Findings usually include [13, 14] (1) abnormal coarse, twisted, shorter, and sparser hair on the sides and back, abnormal eyebrows and eyelashes, and often lightly or abnormally pigmented (white, silver, or gray) (the scalp hair is fragile and fractures easily, resulting in apparent generalized alopecia); (2) abnormal facial features, such as sagging cheeks and ears, depressed nasal bridge, high-arched palate, and delayed tooth eruption; (3) progressive cerebral degeneration, such as loss of developmental milestones, seizures (myoclonic and myoclonic-tonic), profound truncal hypotonia with appendicular hypertonia, and temperature instability; (4) ocular manifestations, such as ptosis, visual inattention, optic disc pallor with decreased pupillary responses to light, iris hypoplasia, and hypopigmentation [15, 16]; (5) connective tissue abnormalities, e.g., umbilical and inguinal hernias, bladder diverticula, loose skin at the nape of the neck and over the trunk, joint hypermobility, vascular defects, arterial rupture, and thrombosis; (6) skeletal changes, e.g., multiple congenital fractures, deformities, osteoporosis, metaphyseal spurring and widening, diaphyseal periosteal reaction, scalloping of the posterior portion of the vertebral bodies, pectus excavatum, profound scoliosis, and Wormian bones; and (7) bleeding diathesis [17, 18] (Fig. 43.1).

Fig. 43.1 Features of an 8-month-old boy with Menkes disease (from Cremer HJ 2004 with permission)

Epilepsy in patients with *Menkes* disease falls into three distinct phases: early focal status, infantile spasms, and myoclonic and multifocal epilepsy after the age of 2 years [17, 18]. Ictal EEG may detect runs of slow spike-waves and slow waves in the posterior regions, and interictal EEG usually reveals multifocal and polymorphic slow waves or mixed slow spike-waves and slow waves.

Patients with occipital horn syndrome are affected predominantly by connective tissue anomalies, including hyperelastic and bruisable skin, hyperextensible joints, hernias, bladder diverticula, and multiple skeletal abnormalities, including occipital exostoses (*horns*), which are **wedge-shaped calcifications within the occipital tendinous insertion of the trapezius and sternocleidomastoid muscles. The** *horns* **may not be present in early childhood. These patients also suffer from mild mental retardation and autonomic dysfunction. Serum copper and ceruloplasmin levels are low but not to the degree of** *Menkes* **disease. Other clinical variants referred to as mild Menkes disease are characterized by ataxia and mild mental delay.**

Urological problems occur frequently in MD, with bladder diverticula being the most common. Therefore, imaging studies and appropriate management of urological complications, which may prevent or reduce the development of urinary tract infections and renal parenchymal damage, are required in all patients with MD [19].

Pathophysiology

Copper is essential for many enzymes, including cytochrome C oxidase, superoxide dismutase, lysyl oxidase, tyrosinase, ascorbic acid oxidase, ceruloplasmin, and dopamine β-hydroxylase [20]. Copper acts as a modulator of neuronal transmission, and its release may regulate N-methyl-D-aspartate (*NMDA*) receptor activity [21]. The deficiency or impaired function of these enzyme systems is thought to be responsible for the clinical findings in *Menkes* disease.

The genes for Menkes disease have 55% amino acid homology with Wilson disease. The ATPase in *Menkes* and *Wilson* disease utilizes common biochemical mechanisms, but the tissue-specific expression differs. The *Wilson* disease gene *(WND) located on chromosome 13q14.3 (ATP7B)* is expressed exclusively in the liver, whereas the gene for *Menkes* disease predominates in the placenta, GI tract, and blood-brain barrier [22]. All copper-transporting ATPases have a histidine residue in the large cytoplasmic loop adjacent to the ATP-binding domain [23, 24]. The histidine residue is the most common mutation site in *Wilson* disease and is essential for the function of the *Menkes* ATPase. A new defect of cellular copper trafficking has been identified, called MEDNIK syndrome, which combines the clinical and biochemical signs of both Menkes and Wilson diseases. MEDNIK syndrome (mental delay, enteropathy, deafness, neuropathy, ichthyosis, keratodermia) is caused by defect in the *AP1S1* gene that encodes σ1A, a small subunit of the adaptor protein 1 complex. MEDNIK syndrome was first reported in a few French-Canadian families sharing common genealogy [25]. The pathogenesis underlying MEDNIK syndrome has not been completely elucidated.

The *Menkes* protein is synthesized as a single-chain polypeptide localized to the trans-Golgi network of cells [26]. Under normal circumstances, ATPase transports copper into the secretory pathway of the cell for incorporation into the cuproenzymes. An increase in intracellular copper causes the ATPase to move to the plasma membrane. As the copper-filled vesicles prepare for excretion from the cell, the cytosolic copper concentration decreases and the ATPase returns to the trans-Golgi network. The migration of ATPase appears to involve amino acid sequences in the carboxyl terminus of the ATPase. In *Menkes* disease, transport of dietary copper from the intestinal cells is impaired, leading to low serum copper levels, but paradoxical copper accumulation occurs in duodenal cells, kidneys, pancreas, skeletal muscles, and placenta.

The *Menkes* gene product protein exists in truncated and long forms. The truncated form, which is located in the endoplasmic reticulum, is also present in the occipital horn syndrome [15, 27]. The partial preservation of the copper transport ATPase activity may account for the milder phenotype. The bridled mouse, viable bridled mouse, and blotchy mouse are animal models of the classic form, the mild form, and the occipital horn syndrome, respectively. *Exon skipping* is common in *Menkes* disease. Normal splicing of mRNA depends on a highly conserved, 9-nucleotide splice donor sequence [28]. Slight variations from the splice donor sequence are common, except for the invariant GT (*guanine-thiamine*) dinucleotide at the +1 and + 2 intronic positions. Splice acceptor sites have an invariant AG (adenine-guanine) dinucleotide at intronic positions −1 and − 2. Splice junction mutations of the invariant bases severely reduce correct splicing [19, 29, 30]. Patients with the milder *Menkes* phenotypes have mutations at other sites so that proper splicing of some protein still occurs [11].

A deficient cytochrome C oxidase (*COX*) *activity* leading to mitochondrial damage and apoptotic cell death probably accounts for most of the neurological

symptoms, similar to patients with *Leigh* disease (subacute necrotizing encephalomyelopathy) who have reduced or absent *COX* activity and similar neuropathologic changes [12, 31]. *COX* deficiency also leads to hypothermia, whereas decreased lysyl oxidase (LO) activity may be responsible for the connective tissue fragility and vascular abnormalities in Menkes disease, since LO deaminates lysine and hydroxylysine in the first step of collagen cross-linkage. LO also localizes to the trans-Golgi network. *Tyrosinase deficiency* (involved in melanin biosynthesis) most likely produces the hypopigmentation of the hair and skin seen in *Menkes*.

Purkinje cells have an increased amount of manganese-dependent superoxide dismutase, but the cytosolic copper-zinc binding form is inactive, which may contribute to the profound *Purkinje* cell loss of about 50% seen in Menkes disease [32] (see also ch. 4.13). Peptidylglycine α-amidating monooxygenase (*PAM*) is necessary for the removal of the glycine residue from neuroendocrine precursors, such as corticotropin-releasing factor, thyrotropin-releasing hormone, calcitonin, and vasopressin (Fig. 43.2). **Deficiency** of dopamine β-hydroxylase leads to reduced catecholamine levels. Decreased ascorbic acid oxidase activity leads to bone changes similar to those seen in scurvy. Even a low level (2–5%) of normally spliced Menkes protein is sufficient to produce the milder occipital horn syndrome [35].

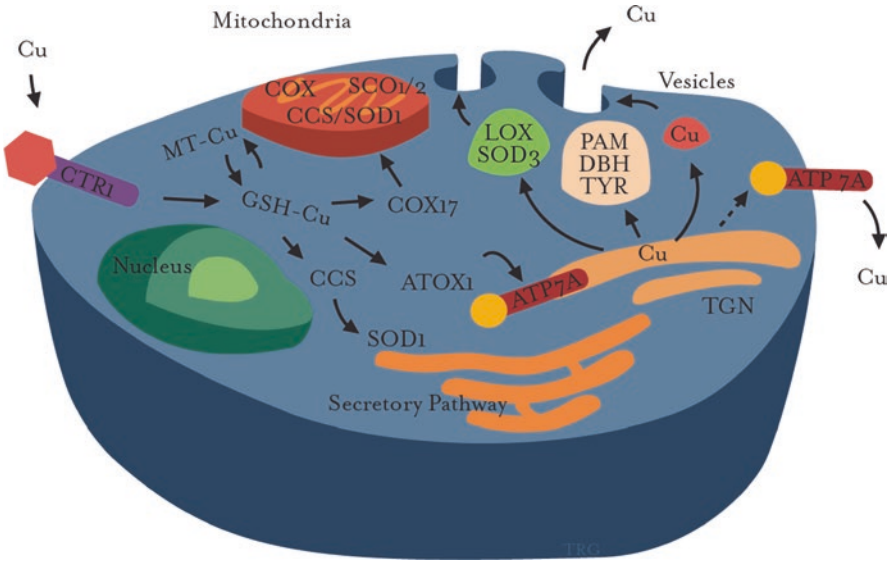

Fig. 43.2 Copper metabolism in neuronal cells. ATP7A is needed for maturation of PAM, DBH, and TYR. (ATOX1, Cu transport protein ATOX1; ATP7A, Cu-transporting ATPase1; CCS, Cu chaperone for SOD1; COX, cytochrome C oxidase; DBH, dopamine β-hydroxylase; PAM, peptidylglycine α-amidating monooxygenase; SCO, SCO1 homologue; SOD, superoxidase dismutase. Illustration ©**Talia R Glass, 2021**) [2, 33, 34]

Diagnosis

Laboratory studies reveal serum copper < 70 μg/dL (reference 80–160), serum ceruloplasmin < 20 mg/dL, decreased norepinephrine level, elevated hydroxyphenylalanine (DOPA), and dihydroxyphenylglycol (*DHPG*) ratios due to decreased activity of dopamine **β**-hydroxylase (higher values may reflect a more severe disease), increased intestinal and renal copper, decreased hepatic copper, and hypoglycemia. The urinary deoxypyridinoline level is significantly low in patients with *Menkes* disease, indicating that it is a good marker of lysyl oxidase activity, which is related to the connective tissue abnormalities [33]. *Copper* and *ceruloplasmin* levels could be normal in the milder variants and in the neonatal period. The total body copper content can be normal in infants until 2 weeks after birth or later. Ceruloplasmin levels are 6–12 mg/dL initially and only later become pathologically low. Normal term newborns also have lower serum copper (32 μg +/− 21 μg/dL) with even lower levels in preterm infants. In regard to skin alterations, the fetal hair may be normal, but later microscopic hair examination reveals a variety of abnormalities, most often pili torti (twisted hair), varying diameter of hair shafts, and trichorrhexis nodosa; fractures of the hair shaft at regular intervals [34, 36, 37].

The diagnosis of *Menkes disease* is based on clinical characteristics, especially typical hair changes, in association with reduced blood levels of copper and ceruloplasmin [3]. In neonatal period, plasma catecholamine analysis (ratio of DOPA to dihydroxyphenylglycol) indicative of dopamine *β*-hydroxylase deficiency (see Fig. 43.2) may be the choice as a rapid diagnostic test [3, 27, 34]. The possibility of prenatal as well as neonatal period diagnosis is currently under review, pending recommendations [2, 3].

CT and/or MRI and sonography could reveal white matter dysmyelination, diffuse symmetrical cerebral and cerebellar atrophy, bilateral diffuse white matter changes, subdural hematomas and effusions, and strokes [38, 39]. Conventional and magnetic resonance angiography show elongated and tortuous vessels, both intracranially and extracranially [40]. Urological problems with bladder diverticula (urinary stasis, infections) are frequent in Menkes disease. Therefore, urological imaging (kidneys) and appropriate management of urological complications are necessary [19, 39].

Therapy

The classic form is usually lethal by the age of 3 years; however, survival to the late 20s also has been reported. In families with an affected child, genetic counseling with prenatal testing can be done for future pregnancies. The child may have skeletal deformities, malformed connective tissues, and at a high risk of fractures; thus, the importance of physical therapy and rehabilitation should not be neglected. Early therapy, possibly in the first weeks of life and before the development of

neurological symptoms, is important. Initiating copper histidine is safe and effective, with treatment outcomes influenced by the timing of intervention and ATP7A mutation [3, 41].

Oral treatment with copper salts, such as copper sulfate, acetate, or chloride, does not alter serum copper and ceruloplasmin levels [3, 19, 26]. *Parenteral* copper induces the WND gene and synthesis of apoceruloplasmin, resulting in increased serum copper and ceruloplasmin concentrations; however, the cerebral copper levels are not altered significantly and no clinical improvement ensues [39, 42, 43]. The effect of early treatment with parenteral copper is unknown [11, 33, 44]. Some authors recommend copper-histidine subcutaneously 250 μg/day after the first year of life, under regular monitoring of serum copper/ceruloplasmin levels and neurological examination [3, 44]. Copper chloride and L-histidine are currently only investigational treatment modalities. In an animal model, intraventricular injection of copper-histidine resulted in significant replenishment of cerebral copper stocks [3, 21, 43]. Intracerebroventricular injection in healthy adult rats has potential a novel treatment approach [43]. An optimal management for patients with Menkes disease does not exist.

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Chapter 44
Refsum Disease (Heredopathia Atactica Polyneuritiformis)

Christos P. Panteliadis and Christian Hagel

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Introduction

The incidence of Refsum disease (OMIM 266500) is estimated at 1 in one million, affecting both sexes equally. Between the time the disease was first introduced in 1945 and the first review of the condition in 1970, less than 50 cases had been published [1]. In the latter 50 years, 10 more cases were added. Dr. Sigvald Bernhard Refsum, a Norwegian neurologist, was the first to describe the condition in 1945 in two unrelated families with central and peripheral nervous system impairment [2]. The original labelling of 'heredoataxia hemeralopica polyneuritiformis' was superseded by heredopathia atactica polyneuritiformis the following year when Dr. Refsum received his doctorate from the University of Oslo [3].

The typical clinical features of this autosomal recessive disease may vary but generally include retinitis pigmentosa (concentric visual fields), chronic or

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recurrent polyneuropathy with symmetrical distal-gradient weakness, cerebellar more than sensory ataxia, nystagmus, dermato-skeletal abnormalities and elevated protein concentration in the cerebrospinal fluid.

Phytanic acid is almost exclusively of exogenous origin from the dietary polyprenyl plant alcohol phytol, which is present as an ester in chlorophyll, and to a lesser extent from animal sources. It is a 20-carbon branched-chain fatty acid moiety with 2 oxygen molecules and 15 hydrogens (3,7,11,15-tetramethyl-hexadecanoic acid) degraded via α-oxidation pathway strictly within the peroxisomes (Fig. 44.1).

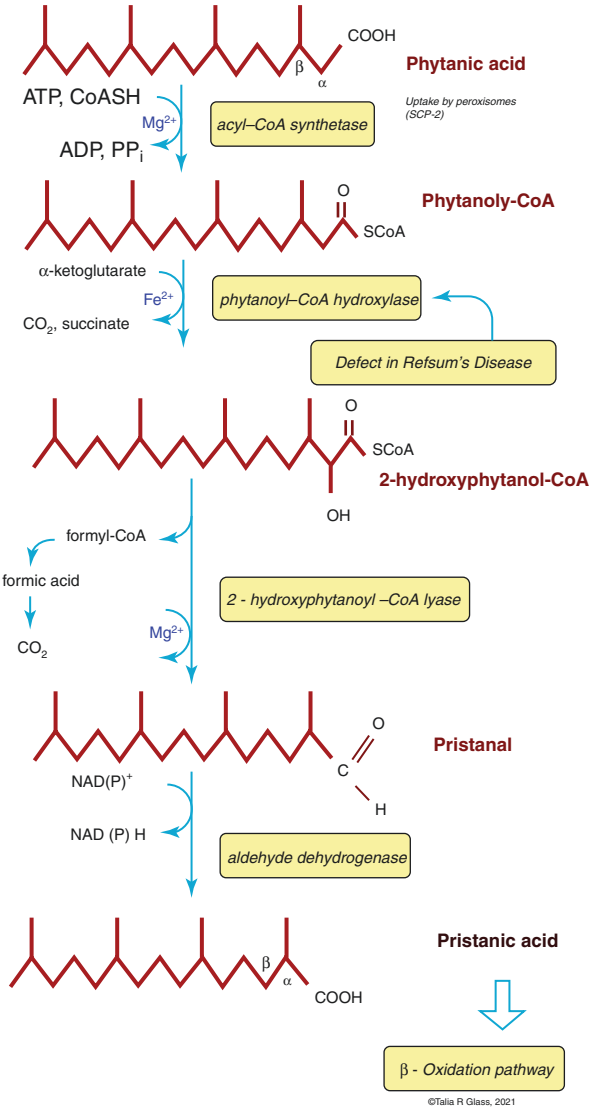

Fig. 44.1 The chemical structure of phytanic acid and its α-oxidation after transformation of chlorophyll into dihydrophylol. Illustration by ©Talia Glass, 2021

The heterogeneous *PHYH* gene of phytanoyl-CoA hydroxylase has been localized in up to 90% of cases to band 10p13 between the markers D10S226 and D10S223 [4–7]. Less frequently, RD disease has also been linked to the *PEX7* gene (peroxin-7 on chromosome 6q21-q22.2), which helps transport PHYH protein into the peroxisomes [8]. Refsum disease (RD), like other peroxisomal diseases, is a heterogeneous syndrome [9]. Because of the rarity of the disease, the diagnosis of RD delayed for years [10].

Clinical Characteristics

Refsum disease is an exceptionally uncommon autosomal recessive disorder. No racial predominance exists, and neither sex predominates. The tetrad of retinitis pigmentosa, chronic or recurrent polyneuropathy, cerebellar ataxia and elevated protein in the CSF best characterizes the disease. The symptoms evolve slowly and insidiously from childhood through adolescence and early adulthood. Neurological and ophthalmic manifestations predominate: autism spectrum disorder, partial and intermittent sensorimotor polyneuropathy, gait instability, progressive motor weakness, foot drop, cataract, nystagmus, constriction of the visual fields, night blindness as a result of progressive retinitis pigmentosa, anosmia, tinnitus and sensorineural deafness. Excess phytanic acid causes cell death in astroglia due to calcium dysregulation [11]. In a mouse model, histological loss of Purkinje cells was found to be the reason for ataxia [12].

Other symptoms consist of cardiomyopathy and arrhythmias [13]. Hepatic and renal symptoms remain clinically silent despite fatty degeneration. An ichthyosiform desquamation appears similar to an acquired form of ichthyosis vulgaris that features fine white scales over the lower trunk, but may also extend into distal extremities. Ichthyosis may range from mild hyperkeratosis in palmoplantar distribution to severe scaling of lamellar type observed on the trunk [14], which generally coincides with the occurrence of neurological symptoms [15].

Skeletal defects are not related directly to phytanic acid levels [16]. These defects occur in 35–75% of the cases and could manifest in newborns. The knees, elbows and short tubular bones of the hands and feet are affected, particularly the terminal phalanx of the thumb.

Blood levels of phytanic acid are increased in patients with RD and account for 5–30% of serum lipids. These levels are 10–50 mg/dL (normal values <0.2 mg/dL). When the levels increase, phytanic acid replaces other fatty acids, including the essential fatty acids linoleic acid (the parent fatty acid of the omega (ω)-6 series), α-linolenic acid (an ω-3 fatty acid) and arachidonic acids in plasma membranes of various tissues. This situation leads to an essential fatty acid deficiency, which correlates with the development of ichthyosis.

An infantile form but different from RD (Zellweger spectrum disorder) also exists. Similar to the adult version, the infantile form is an autosomal recessive disorder of peroxisomal biogenesis, leading to many biochemical abnormalities,

including raised plasma concentration of phytanic acid, pristanic acid, very-long-chain fatty acids and C27 bile acids [17]. The disease presents in the first year of life and manifests by developmental delay, visual and hearing disturbances and dysmorphic features. Ichthyosis is an unusual symptom in this age group.

The differential diagnosis of Refsum disease includes citrin deficiency, Zellweger spectrum disorder, multiple acyl-CoA dehydrogenase deficiency, Alström syndrome, type 1–3 Usher syndrome, Kearns-Sayre mitochondriopathy and *Sjögren-Larsson* syndrome (see section "Menkes Disease").

Diagnosis

Serum phytanic acid level usually exceeds 200 mmol/L. The normal range is less than or equal to 0.2 mg/dL; however, phytanic acid levels are higher than 10–50 mg/dL in patients with RD. Cerebrospinal fluid (CSF) shows an albumino cytologic dissociation with a protein level of 100–600 mg/dL. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels are diminished. Routine laboratory investigations of blood and urine do not reveal any consistent diagnostic abnormality.

Skeletal X-ray is required to qualify bone changes. Phytanic oxidase analysis in skin fibroblast cultures is important. Electrocardiogram (ECG) is helpful to rule out cardiac conduction defect.

Histological analysis of skin biopsy shows features of ichthyosis vulgaris, such as moderate hyperkeratosis and acanthosis with thin granular layer. Variably sized vacuoles are visible in basal and suprabasal keratinocytes. The lipid stains performed on cryostat cut sections reveal the presence of lipid accumulation in vacuoles. Nerve biopsy reveals demyelination with marked Schwann cell proliferation and onion bulb formation – hence its categorization as hereditary motor and sensory neuropathy (HMSN), type IV [15].

Ultrastructural skin examination discloses many intracellular nonmembrane-bound vacuoles in the basal layer and less numerous in keratinocytes of the suprabasal epidermis. Transmission electron microscopy fails to show changes in keratohyalin as observed in dominant ichthyosis vulgaris. Theoretically, prenatal diagnosis supported by testing of cultured amniocytes is possible. Screening all members of the family is helpful to reveal other presymptomatic cases.

Molecular genetic testing of either *PHYH* or *PEX7* gene is available to establish the diagnosis.

Therapy and Prognosis

If diagnosed and corrected quickly, phytanic acid decreases slowly, followed by improvement of the skin scaling and, to a variable degree, reversal of early neurological signs. Retention of vision and hearing is reported. The recommended diet

should be maintained strictly throughout life. Children with neurological and ophthalmologic disturbances should be screened for phytanic acid in plasma in order not to miss RD. Attenuation of neurological, ophthalmologic and cardiac symptoms requires constant adherence to a suitable diet and plasmapheresis [18, 19].

By limiting dietary intake, the drop in plasma phytanic acid levels yields improvement in the neurological signs and symptoms, but the treatment has no effect on the function of cranial nerves I and II or on retinitis pigmentosa [20]. The major dietary exclusions are green vegetables (source of phytanic acid) and animal fat (phytol). High content of phytanic acid exists in beef, milk, butter, cream and cheese. The aim of dietary restriction is to reduce the daily intake of phytanic acid from the usual level of 50 mg/dL to less than 5 mg/dL.

LDL and VLDL bound phytanic acid/pristanic acid can be effectively eliminated from plasma with extracorporeal LDL apheresis using membrane differential filtration [21]. Increased nerve conduction velocities, return of reflexes and improvement in sensation and objective coordination accompany this change.

The main indication for plasmapheresis or lipapheresis in patients with RD is severe or rapidly worsening clinical condition and very high serum levels of phytanic acid. It could also be utilized if dietary restriction fails to reduce high plasma phytanic acid levels [16, 19, 22]. Cascade filtration may be an alternative to plasmapheresis. It is as efficient as plasmapheresis and eliminates the need for albumin replacement. Dermatologic emollients and keratolytics to soften the skin can be applied as long-term treatment of hyperkeratosis. Ichthyosis typically clears with these measures; its recurrence may be a marker of rising phytanic acid blood levels. Improvement in clinical status as a result of dietary restrictions is due to the presence of alternative pathway oxidation (omega-oxidation rather than alpha-oxidation) of phytanic acid. A high carbohydrate intake should be provided to avoid rapid weight loss.

A decrease in speech perception could indicate retrocochlear degeneration. Cochlear implantation in severe hearing loss improves speech and especially when the hearing loss is combined with a severe loss of vision [23]. Bilateral cochlear implantation is an important strategy in the improvement of hearing and quality of life in cases with RD [24].

The prognosis in untreated patients is generally poor. Dysfunction of myelinated nerve fibres and the cardiac conduction system leads to central and peripheral neuropathic symptoms, wasting, depression, impaired vision and cardiac arrhythmias. Longitudinal follow-up in a multispecialty centre is necessary.

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Chapter 45
Sjögren-Larsson Syndrome

Christos P. Panteliadis

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Introduction

In 1956, the Swedish psychiatrist Torsten Sjögren reported five children with intellectual disability, congenital ichthyosis and spastic diplegia [1]. The subsequent year, in collaboration with Tage Larsson, they presented a cohort of 28 patients in Vasterbotten County in northern Sweden [2]. *Sjögren-Larsson* syndrome (OMIM 270200) is an autosomal recessive neurocutaneous disorder caused by mutations in the *ALDH3A2* gene (17p11.2) that encodes fatty aldehyde dehydrogenase (FALDH) [3], which oxidizes fatty aldehydes to fatty acids. About 90 mutations in the *ALDH3A2* gene have been identified. This condition should not be mistaken for Sjögren disease, which is an autoimmune disease causing sensory ganglionopathy and sicca syndrome.

The first symptoms of SLS include spastic diplegia or tetraplegia, intellectual delay in about 50% of patients and congenital ichthyosiform exanthema. Bilateral spastic paresis typically involves the legs more than the arms. The crystalline oculopathy (glistening white dots on the retina) together with neurological and

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cutaneous symptoms allows the ophthalmologist to reliably diagnose SLS [4]. Preterm delivery is common, with the infant demonstrating erythematous and hyperkeratotic skin at birth [5].

SLS is characterized by deficiency in FALDH, located in human microsomes. It catalyses oxidation of medium- to long-chain fatty aldehydes. Fatty acid aldehyde dehydrogenase (*FALDH*) causes an accumulation of long-chain aliphatic aldehydes and alcohols [3]. An increase in biologically active lipids primary affects the skin, the eyes and the central nervous system, giving rise to the clinical triad of congenital ichthyosis, spastic diplegia or tetraplegia and cognitive disability [6, 7]. Glistening yellow-white crystalline inclusions in the fovea and parafovea are almost pathognomonic for the disease. About 50% have pigmentary degeneration of the retina (ciliopathy), with decreased visual acuity and marked photophobia [8].

Pathogenesis

Histological examination of the skin lesions using light microscopy reveals epidermal acanthosis, papillomatosis and hyperkeratosis. The horny cells have a basket-weave appearance, and the granular cell layer is slightly thickened [9]. Both ichthyosiform and uninvolved skin examined by electron microscopy reveal abnormal lamellar or membranous inclusions in the cytoplasm of the epidermal horny cells. This finding suggests that whether the skin is involved or not the epidermis may have a genetically predetermined structural abnormality. Local environmental factors may contribute in inducing the acanthosis and papillomatosis of the epidermis [9].

The disease harbours an autosomal recessive trait. It equally affects both genders, and in approximately 50% of the cases, consanguinity between the parents is noted. *SLS* is caused by mutations in the *ALDH3A2* gene, mapped to chromosome 17p11.2. It consists of 11 exons and spans about 31 kb. The mutations in SLS are scattered throughout the *ALDH3A2* gene and are generally private mutations, occurring in single cases [10]. Seventy to 90 different homozygous or compound heterozygous mutations in the *ALDH3A2* gene have been identified originating from about 120 different families [11–13]. The gene codes for fatty aldehyde dehydrogenase (FALDH), an enzyme that catalyses the oxidation of medium- and long-chain aliphatic aldehydes to fatty acids [14, 15]. Seven novel mutations (including deletions, insertions, splicing defects and missense mutations) in the *FALDH* gene associated with four different *ALDH3A2* haplotypes have been detected [14–17]. Aldehyde substrates for FALDH are generated by metabolism of several lipids including fatty alcohol, ether glycerolipids, sphingolipids, leukotriene B4 and phytanic acid [18, 19].

Abnormal activity in the fatty alcohol nicotinamide adenine dinucleotide oxidoreductase complex activity has been noted to contribute to the pathogenesis of Sjögren-Larsson syndrome. This enzyme plays a central role in fatty alcohol synthesis. Interruption leads to accumulation of fatty alcohols such as hexadecanol

(cetyl alcohol, $C_{16}H_{34}O$). Lipids that are thus necessary for the normal function of neuronal cell membrane accumulate instead in keratinocytes. The dysfunctional fatty alcohol cycle results in the disturbance of the construction of stratum corneum and neuronal capsids [20].

Clinical Characteristics

The prevalence of SLS in Sweden is estimated at 1 in 250,000 to one million. There are about 40 cases who currently reside in Sweden. In the majority of the cases, ichthyosis is congenital and generalized in its distribution. Keratotic skin changes have a characteristic appearance and are present at birth or develop very early in life (Fig. 45.1). The yellow to dark-brown colour primarily affects the trunk and less the face, palms and soles (*palmoplantar keratoderma*), whilst hairs and nails are normal [21]. Dysarthria and delayed speech ranges from mild to profound. Other ectodermal structures are not affected, but kyphoscoliosis, hip dislocation and short stature have been observed, requiring wheelchair assistance by adolescence [22]. Neurological dysfunctions stabilize in teenage years, and the clinical picture behaves more like static cerebral palsy than the progressive deterioration often seen

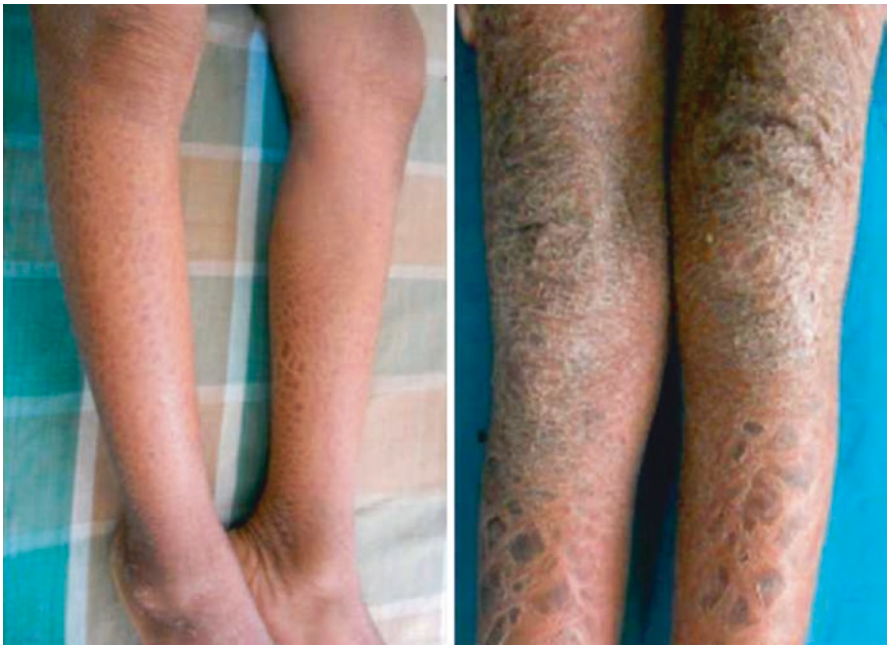

Fig. 45.1 Generalized ichthyosis demonstrating as fines scales over lower extremities in a 2.5-year-old boy (left) and lamellar type of scales in a boy aged 5 years (right) (with kind permission of Srinivas et al. 2014)

in other neurometabolic disorders such as *Dorfman-Chanarin* syndrome and *Refsum* disease [22, 23].

Neuro-Ocular Involvement

Pyramidal signs frequently display a rapidly progressive deterioration, whereas in some cases progression is insidious, reaching as far as adulthood. Bilateral spastic paresis typically involves the legs more than the arms, and contractures are common. Epileptic crises are observed in 30% of the patients and usually appear in the first months of life [12]. On electroencephalogram, generalized hypersynchronous activities or spikes, disorganized background rhythm and asymmetry between the two hemispheres are seen.

Funduscopic changes can be discovered in half of the patients and consist of macular degeneration, glistening white dots in the retina, microcysts in the fovea, optical atrophy, punctate keratitis, myopia and scleral anomaly. Glistening yellow-white crystalline inclusions in the fovea during the toddler years are almost pathognomonic [8].

Intellectual delay (oligophrenia) ranges from mild impairment to severe that includes dysarthria and delayed speech [15, 24]. Other possible symptoms include photophobia, pseudobulbar signs and dysphagia [15].

In 30% of adolescent patients, bone delay, fractures, kyphosis of the thoracic spine and short stature are observed.

Diagnosis

Clinical characteristics and reduction of FALDH levels or fatty alcohol oxidoreductase (FAO) activity in fibroblast culture or direct sequencing of *ALDH3A2* gene are the mainstay of the diagnosis. Making use of the fact that FALDH is also involved in the degradation of phytol to phytanic acid, van den Brink et al. established an enzymatic assay for the prenatal diagnosis of SLS in cultured chorionic villus fibroblasts [25].

Brain MRI may show periventricular demyelination and leukoaraiosis, characterized as hyperintense T2-weighted and isointense or slightly hypointense T1-weighted lesions. In some patients, the corpus callosum is involved. The subcortical white matter is unaffected. The brainstem and cerebellum are always spared [26]. Electroencephalogram, retinal photographs and optical coherence tomography ought to be performed when indicated.

The *differential diagnosis* should entertain trichothiodystrophy and other *neuroichthyoses* such as *Rud* syndrome (characterized by hypogonadism, epilepsy and

cognitive delay), *Refsum disease* (triad of cognitive delay, ichthyosis and spasticity), ELOVL4 deficiency (elongation of very-long-chain fatty acids-4, a new form of ichthyosis discovered by next-generation DNA sequencing), Dorfman-Chanarin syndrome, *Conradi-Hünermann-Happle* syndrome characterized as oculo-skeleto-cutaneous abnormalities (Blaschko line ichthyosis), *Tay* syndrome and *Huppke-Brendel* syndrome associated with bilateral congenital cataracts, sensorineural hearing loss and severe developmental delay.

Therapy

The management for SLS is symptomatic. Several potential therapeutic options are being investigated in correcting the metabolic and genetic defects. A multidisciplinary approach is necessary for the effective management of *SLS* patients.

Keratolytic measures can be employed to treat the ichthyotic skin. Diet rich in polyunsaturated fatty acids has been recommended, but its efficacy remains questionable. The use of antioxidants to decrease aldehyde load may curb the caloric fat intake by 30%. Skin-softening drugs, keratolytic drugs and topical vitamin D_3 preparations should be applied. Systemic retinoid acid or topical calcipotriol may improve skin symptoms, whereas both retinoids and zileuton, an orally active inhibitor of 5-lipoxygenase and leukotriene B4, C4, D4 and E4 formation, have been shown to diminish the disturbing pruritus [12]. Oral retinoid treatment resulted in marked improvement in the cutaneous symptoms. Whether dietary habits or other genetic factors that modulate endogenous lipogenesis govern the clinical severity remains to be established [3, 26, 27].

Other potential dietary management includes restriction of phytanic acid and its alcohol precursor phytol, which are metabolic precursors to the fatty aldehyde pristine. However, neither the phytanic acid nor phytol is elevated in patients with SLS and is not implicated in the causation of neurological disease. Administration of medium-chain fatty acids could reduce intestinal symptoms and exanthema [28, 29]. An effective treatment does not exist for the ocular symptoms [4].

Early and *aggressive physiotherapy*, followed by appropriate surgical intervention when walking is compromised, improves mobility in children with *SLS* [7]. Physical therapy, logotherapy and ergonomic support are important [12]. Corrective surgical interventions are warranted for skeletal deformities, muscular atrophy and contracture.

Human *FALDH* delivered into keratinocytes of *SLS* patients via recombinant adeno-associated virus-2 vector has shown to produce amelioration of *FALDH* expression, speaking in favour of future gene therapy in treating *SLS* children. Gene therapy, such as defects associated with FALDH deficiency or to correct the genetic defect by gene transfer, is in the pipeline [17, 27, 28]. In patients with residual FALDH expression, bezafibrates may be beneficial.

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Chapter 46
Fabry Disease

Dominique P. Germain

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Introduction

Fabry disease (OMIM #301500) is a rare, progressive, X-linked inherited, chronic multisystemic, lysosomal disorder caused by pathogenic variants in *GLA* which encodes the lysosomal enzyme α-galactosidase [1]. Lack of activity of the enzyme leads to failure of the breakdown of the glycolipid globotriaosylceramide (Gb_3) and its deacylated derivative lyso-Gb_3 [2]. Molecular studies have identified a remarkable variety of *GLA* variants underlying the phenotypic heterogeneity of this genetic disorder. More than 1000 *GLA* variants have been reported; most of them are 'private' and confined to individual pedigrees with variability in phenotypic expression further modulated by gene modifiers, epigenetics, and environmental factors [3]. Fabry disease is a devastating condition in which chronic damage to tissues beginning as early as childhood with neuropathic pain and cutaneous symptoms leads to renal failure, heart disease and strokes in adults.

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Clinical Characteristics

Early manifestations of classic Fabry disease in children include dysesthesia, skin angiokeratoma, reduced or absent sweating, corneal deposits and gastrointestinal (GI) discomfort [4]. Neuropathic pain represents the most striking symptom in children [1, 5, 6], but overall quality of life is often impacted and characterized by fatigue, depression and school absences (Table 46.1).

The most visible early clinical feature is angiokeratoma: clusters of small reddish purple, raised skin lesions are typically found on the buttocks, groin, umbilicus and upper thighs (Fig. 46.1). Histologically, the skin lesions are small superficial angiomas of the skin with vessel dilatation in the dermis that increase in number and size with age and can occur singly or in groups [1, 7].

Ischaemic strokes and transient ischaemic attacks are the most prevalent types of overt cerebrovascular events in Fabry disease. An analysis of a large cohort (n = 2446) reported that stroke occurs in 6.9% of men and 4.3% of women. Of these, 87% of first strokes were ischaemic, with haemorrhagic stroke accounting for 13% of cases. The analysis indicated that the incidence of stroke among patients with Fabry disease is higher across all age categories [8]. In the cohort, a majority of patients experienced a first stroke between the ages of 20 and 50 years, with 22% of patients having a first stroke at <30 years. For the *majority* of patients (>70%), stroke was the first serious complication and a high proportion (50% of men and 38% of women) had, therefore, not yet been diagnosed with Fabry disease [8]. Strokes continue to occur in patients on enzyme replacement therapy (*ERT*) [9].

Occult kidney injury may occur at a young age since Gb_3 accumulation leads to podocyte injury with foot process effacement that precedes pathologic albuminuria, a defining feature of chronic kidney disease (*CKD*). Symptomatic renal complications typically emerge in young adult patients with decreased glomerular filtration rate (*GFR*) progression to renal failure at a mean age of 40 in male patients [10].

Cardiac symptoms affect 60% of patients, including exertional dyspnoea and heart failure (23%) and palpitations or arrhythmias (27%), particularly atrial fibrillation (17%) and non-sustained ventricular tachycardia (8%). Left ventricular hypertrophy is the most frequent cardiac sign, reported in 50% of males and in over one-third of females [11, 12]. Other common abnormalities include chronotropic incompetence and/or sinus node dysfunction or severe atrioventricular block [11]. Hypertension is infrequent in the absence of renal disease, while mild-to-moderate valvular regurgitation, moderate and asymptomatic dilatation of the aortic root [11, 12] and lung manifestations (e.g. dyspnoea, dry cough) have been reported [13].

A *cardiac*, later-onset, form of Fabry disease can also cause concentric left ventricular hypertrophy or asymmetrical septal hypertrophy mimicking sarcomeric hypertrophic cardiomyopathy. In the later-onset form, left ventricular hypertrophy is usually absent in males under 30 years of age and females under 40 years. Cardiac damage may become as severe as in classic Fabry disease especially in males, but 15 years later [14]. Strokes are usually absent as well as other classic manifestations of Fabry disease such as angiokeratoma and acroparaesthesia [14, 15].

Table 46.1 Neurocutaneous signs and other symptoms of classic Fabry disease (adapted from [10])

Organ system/ specialty	Age at onset: characteristics	Pathophysiology
Nervous system		
Peripheral	First decade: Neuropathic pain, pain crises, atypical chronic or episodic pain; heat intolerance; hypohidrosis	Small fibre neuropathy, Gb_3 accumulation in dorsal root ganglia, ectopic discharges possibly due to upregulation of Na + channels (*Nav1.8*) and TRPV1; Gb_3 deposition in the sweat glands
Cerebrovascular	Third and fourth decades: Transient ischaemic attacks; ischaemic stroke and (*less frequently*) haemorrhagic stroke	Small vessel occlusion, dolichoectasia of the basilar artery, white matter hyperintensities, TIAs and stroke due to cardiac arrhythmias
Ears	Begins in second decade and increases with age: Hearing loss, tinnitus; dizziness, vertigo	Potentially due to narrowing of cochlear and vestibular vessels, Gb_3 deposition in spiral ganglia
Neuropsychological	Third and fourth decades: Depression; anxiety; rarely cognitive decline and dementia	Potentially related to living with chronic disease, plus neuropathic pain, reduced hippocampal volume, multiple infarcts and small vessel occlusions; white matter lesions
Dermatology		
Skin	First and second decades: Angiokeratomas	Capillary walls ectasia in dermis
Lymphatic	Between second and fourth decades: Lymphedema in all or part of a limb	Accumulation of glycolipids in the lymph vessels
Others		
Renal	First and second decades: pathologic albuminuria Second to fifth decades: Decreased glomerular filtration rate progressing to chronic kidney disease	Gb_3 accumulation in kidney cells; podocyte foot process effacement Glomerular sclerosis secondary to Gb_3 accumulation, podocyte loss, tubular atrophy, arteriolar injury with interstitial fibrosis
Cardiac	Third to fifth decades: Hypertrophic cardiomyopathy; syncope; cardiac fibrosis; bradycardia – Chronotropic incompetence; atrial fibrillation, ventricular tachycardia (heart failure)	ECG abnormalities, hypertrophic cardiomyopathy and myocardial fibrosis (late enhancement on cardiac MR); decreased relaxation time (*T1 mapping*)

The clinical phenotype in heterozygous females is highly variable because of X chromosome inactivation (XCI). Heterozygous females are mosaics of cells expressing different *GLA* alleles (*wild-type* or *variant*) and resulting α-galactosidase A levels. Both random and skewed patterns of XCI have been reported in females

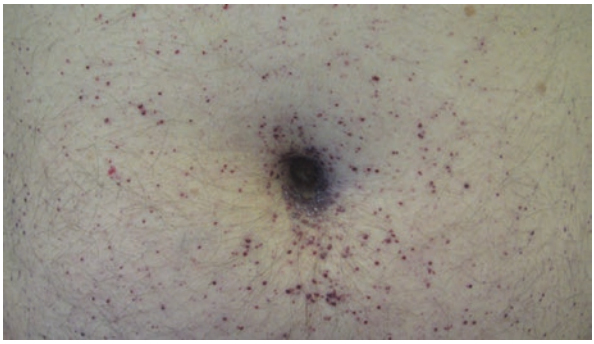

Fig. 46.1 Angiokeratoma. Clusters of small reddish purple, raised skin lesions on the umbilicus and abdomen

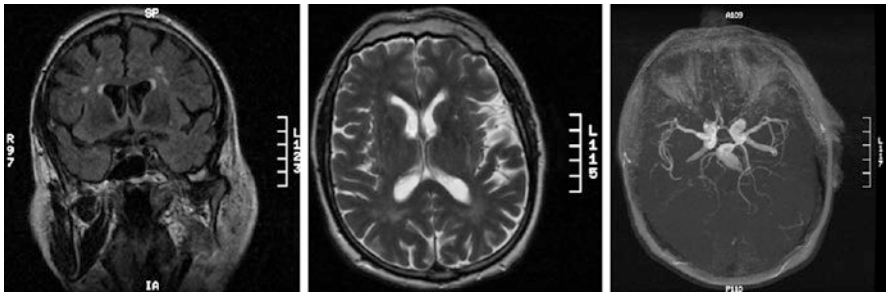

Fig. 46.2 Brain MRI in a 50-year-old male patient with Fabry disease (*GLA* p.R227* pathogenic variant). Periventricular and subcortical white matter vascular-like hyperintensities with dolichoectatic changes in the basilar artery

heterozygous for Fabry disease. Female patients with random XCI patterns exhibit age worsening of symptoms [16]. In contrast, heterozygous females with skewed XCI leading to the predominant expression of the mutant *GLA* gene experience a more severe clinical phenotype and may reach end-stage renal disease. These data suggest that XCI is a significant prognostic factor in heterozygous female patients [16].

Pathogenesis

The brain might present white matter vascular-like abnormalities, transient ischaemic attacks and ischaemic stroke at a young age, suggesting that micro- and macroangiopathy might have a pivotal role in the pathogenesis of brain lesions (see Chap. 4) [17] (Fig. 46.2). Increased vessel tortuosity has been found in the retina [18] and in the skin, and intracranial artery dolichoectatic changes have been repeatedly observed in FD patients, both at pathologic and neuroimaging evaluation [19] (Fig. 46.2).

Diagnosis

The diagnosis of Fabry disease is confirmed by demonstration of markedly deficient or absent α-galactosidase A activity in leukocytes [20]. In males, the result will be conclusive; however, females may have enzyme activity falling within the (low) normal range [20] and should therefore have their status determined by analysis of the *GLA* gene [3].

Fabry disease can be diagnosed prenatally in male foetuses (after non-invasive sex determination in maternal plasma) by molecular studies in *chorionic villi* or *cultured amniotic cells* [1]. Preimplantation diagnosis is available.

In high-risk adult populations, screening efforts have been shown to be effective in diagnosing Fabry patients among individuals with end-stage renal disease, unexplained cardiac hypertrophy or early stroke [21]. Effective *screening* of the family of a diagnosed patient is likely to result in the identification of previously unrecognized affected family members [22].

Therapy

Currently, two therapeutic modalities are approved for the treatment of FD. These are ERT and pharmacological chaperone therapy. Emerging treatment strategies include substrate reduction therapy, mRNA-based therapy and gene therapy [23]. In 2001, two forms of ERT were approved by the European Medicines Agency (*EMA*). Both forms of ERT are lifelong treatments and are administered by biweekly intravenous infusion. Agalsidase alfa is approved for children and adolescents aged 7 years and older at a dose of 0.2 mg/kg [24]. Agalsidase beta is approved for children and adolescents aged 8 years and older at a dose of 1.0 mg/kg [25].

ERT aims to restore a level of α-GalA activity that is enough to clear the cytotoxic Gb_3 accumulation in tissues, thereby preventing, stabilizing or reversing the progressive decline in the function of affected organs before irreversible damage occurs [26]. A number of *randomized* controlled trials and observational cohort studies have demonstrated beneficial effects of ERT in different organ systems, including the kidney, heart and peripheral nervous system. However, the clinical manifestations of Fabry disease are highly heterogeneous and are influenced by age, gender and genetics so that the effect of ERT varies depending on individual patient characteristics and disease severity [28].

Some missense *GLA* variants can lead to the expression of abnormal α-GalA that is not effectively delivered into the lysosomes. Those *variants* α-galactosidase forms retaining residual catalytic activity may be clinically amenable to salvage therapy with pharmacological chaperones, such as migalastat [27], which is an orally absorbed galactose analog iminosugar. By binding to its active site, pharmacological chaperone therapy can partially restore α-GalA trafficking to the lysosomes and thereby its enzymatic activity [28].

Despite the availability of ERT and pharmacological chaperone therapy, there is still a high unmet medical need. Biweekly infusion of ERT can be cumbersome and/or associated with tolerability issues and potentially induces neutralizing antibodies, jeopardizing its effectiveness [29]. Pharmacological chaperone therapy with migalastat is limited to patients with missense 'amenable' pathogenic variants.

Symptom management in patients may consist of prophylactic medications and lifestyle modifications. For example, patients with neuropathic pain may benefit from painkillers and avoidance of circumstances triggering acute pain attacks, e.g. significant physical exertion and temperature changes [5, 6].

Conclusion

Fabry disease is a genetic disease with aggravating symptoms greatly impacting on the physical performance and well-being in children and adolescents and progressing to life-threatening vital organ complications in adulthood. Given the availability of specific therapies, the benefits of early diagnosis are particularly compelling. *ERT* is most effective if treatment is started prior to the development of organ damage. Long-term outcome of chaperone therapy warrants further investigation. Organ-specific adjunctive therapies are often necessary in addition to *ERT* or chaperon therapy. Management should include appropriate, individualized patient therapeutic goals based on a comprehensive assessment of affected organs and regular monitoring.

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Part V
Specific Aspects in the Management of Neurocutaneous Disorders

Chapter 47
Ocular Manifestations of Neurocutaneous Syndromes

Trisha Kandiah, Deeksha Kundapur, and Michael D. O'Connor

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Neurofibromatosis 1 (NF1)

NF1, the most common neurocutaneous syndrome, includes a diverse range of ophthalmologic manifestations that include the anterior segment, posterior segment, orbit and afferent visual pathways (Table 47.1) For historical documents (see section "Introduction"). The most important anterior segment finding is the *Lisch nodule* (Fig. 47.1) (see Chap. 26). These benign lesions (*iris hamartomas*) are derived from melanocytes. They become progressively more common through childhood, such that they are eventually observed in 90–100% of adults with NF1 [1–3].

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Table 47.1 Common ocular features of neurofibromatosis type 1

Clinical feature	Age of onset	Frequency
[a]Lisch nodule [11]	>3 years	90–100%
[a]OPG [10, 11]	2/3 present by 7 years, greatest risk under 6 years	15–20%, 5–7% symptomatic
Infantile glaucoma [11]	Birth/infancy	0.7%
[a]Plexiform neurofibroma [6]	Birth to 18 years	25–50%
[a]Sphenoid dysplasia [7]	Congenital	4–11% of diagnosed patients
Choroidal abnormalities [17]	>2 years	33–50%

[a]Part of diagnostic criteria

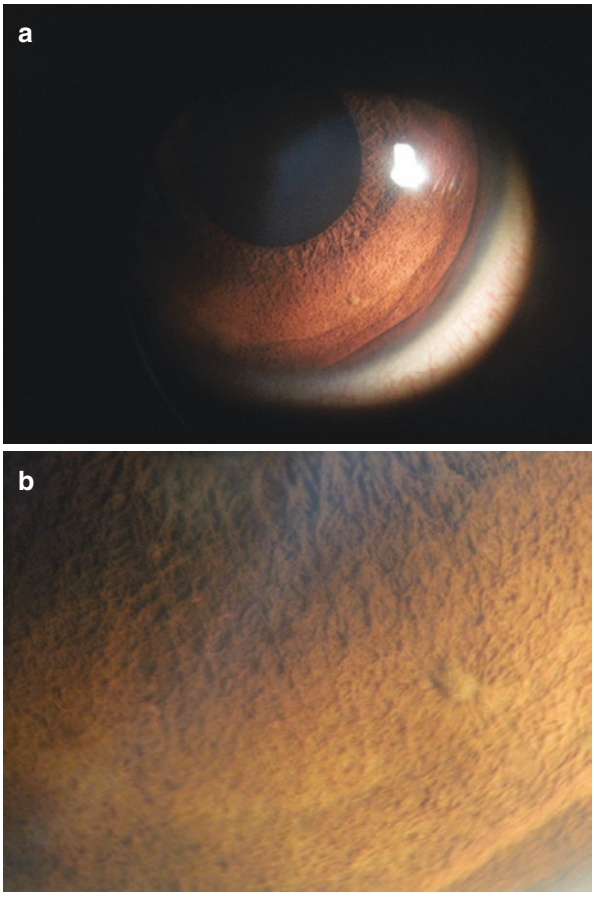

Fig. 47.1 Low (**a**) and high (**b**) magnification views of Lisch nodule in NF1

Clinically, these lesions appear as 1–2 mm raised yellow-brown dome-like lesions on the surface of the iris [3]. Diagnosis is straightforward but requires a slit lamp for adequate magnification and illumination (Fig. 47.1). They are typically asymptomatic [1, 4]. Hamartomas may also involve the choroid, presenting as indistinct yellow-white to light-brown lesions that are difficult to visualize directly [4, 5]. The number and size of these nodules increase over time, but as these lesions do not cause morbidity or impaired vision, treatment is not required [3]. *Other nonspecific* anterior segment findings may be encountered infrequently, including conjunctival neurofibromas at the limbus, malignant melanoma of the conjunctiva and thickened corneal nerves [2].

The classic orbital finding in NF1 is a *plexiform neurofibroma* of the upper eyelid, presenting as a unilateral S-shaped deformity of the lid margin with a consistency similar to a "bag of worms" on palpation [6]. Neurofibromas may present more posteriorly as well, with orbital-temporal neurofibromas often occurring in association with *sphenoid bone dysplasia* [6]. Such bony defects can result in communication between the orbit and the middle cranial fossa, with potential herniation of intracranial or orbital contents [1, 7] (Fig. 47.2). The neurofibromas also have the potential to cause vision-threatening growth and facial deformity.

Overall, clinical findings are common with orbital-periorbital plexiform neurofibromas (*OPPNs*); they are frequently associated with blepharoptosis (*incidence of* ~ 100%), as well as proptosis, eyelid oedema and strabismus [8]. However, as most do not produce visual loss, they are typically managed conservatively. Comprehensive ophthalmologic exams every 6 months have been recommended until ~8 years of age, the period of time during which amblyopia may develop [6]. *OPPN*s often do not progress or cause significant morbidity, but debulking surgery may be considered in cases of significant disfigurement or visual compromise [6]. *Sphenoid dysplasias* are typically managed with reconstructive surgery to maintain facial contour and lid function [7, 9].

Another ocular manifestation in NF1 is the optic pathway glioma (OPG), a low-grade pilocytic astrocytoma most commonly involving the optic nerve [10].

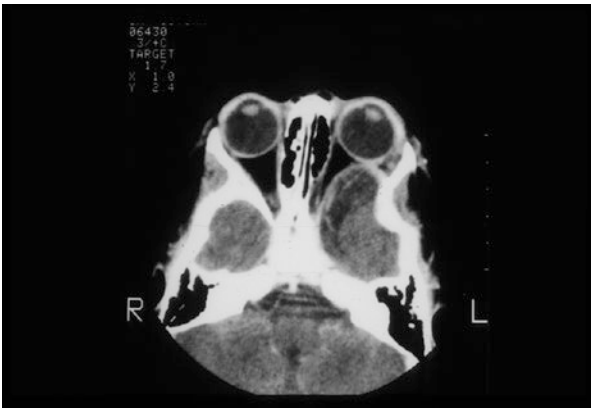

Fig. 47.2 MRI demonstrating the absence of greater wing of sphenoid

Presenting signs include those secondary to mass effect (*unilateral proptosis*, *limited ocular motility* and *strabismus*) and optic nerve compression (afferent pupillary defect, decreased visual acuity, visual field defect, decreased colour vision, optic nerve oedema or atrophy and sensory strabismus) [10]. Large *posterior tumours*, particularly those at the optic chiasm, may compromise pituitary and hypothalamic regions, thus causing endocrinopathy. Precocious puberty occurs as the presenting symptom in some cases [10]. However, OPGs can affect any component of the visual pathway, ranging from the optic nerve, chiasm and optic tract to the hypothalamus [5]. MRI is the imaging modality of choice and is usually sufficient to confirm the diagnosis in suspected cases. Many *OPGs* in patients with NF1 have a benign clinical course, such that asymptomatic or non-progressing tumours may simply be observed. However, gliomas that progress can be treated with chemotherapy with surgical debulking or radiation treatment considered in rare cases [10].

Clinical correlation: Screening practices for OPGs remain controversial. MRI is not able to predict the clinical course of NF1-related OPGs [11]. Given that these lesions are rarely progressive and that screening seldom impacts disease management, systematic MRI screening is not well supported in those under 6 years of age [12]. Instead, many experts recommend that children with NF1 undergo annual visual assessments (including visual acuity, colour vision, visual field testing, extraocular movements, pupillary response, slit-lamp examination and fundoscopy) until the age of ~7–8 to identify compromised visual function secondary to OPGs [13, 14]. In cases of non-refractive visual disturbance, neuroimaging with MRI is warranted [11]. Unfortunately, thorough and reliable clinical assessment of the afferent visual system in young children is extremely challenging (*especially with preverbal children*), and as such visual compromise may go undetected until it is severe.

An increased incidence of glaucoma has also been reported in NF1. The glaucoma is typically unilateral and ipsilateral to the side with a plexiform neurofibroma [15]. Patients with an upper eyelid neurofibroma require particularly close follow-up, as glaucoma may be diagnosed in the ipsilateral eye in up to 50% of such cases [15]. The main mechanisms for glaucomagenesis include direct neurofibroma infiltration into the anterior chamber, secondary angle closure from ciliary body thickening, neovascular glaucoma secondary to fibrovascularization and developmental abnormalities of the angle [16]. Treatments for NF1-associated glaucoma include intraocular pressure-lowering topical eye drops or goniotomy, trabeculotomy and filtering surgery for definitive management [16].

While they are not associated with visual morbidity, choroidal abnormalities have also been frequently noted. In one study, 82% of NF1 patients were found to have choroidal nodules using near-infrared reflectance (NIR) [17]. Choroidal nodules are typically located in the posterior pole, and choroidal anomalies can also be observed in the arcade regions [4]. While not detectable with fundoscopy or fluorescein angiography, these abnormalities are seen as bright, patchy nodules with NIR, often increasing with age [4, 17].

Other rare ophthalmologic associations of NF1 include astrocytic hamartomas, capillary haemangiomas, combined retinal hamartomas, corkscrew vessels overlying choroidal nodules and mild myopia, all of which are nonspecific findings [5].

Neurofibromatosis 2 (NF2)

NF2 is characterized by tumours of the central and peripheral nervous system, with little cutaneous involvement [18] (see Chap. 26). The primary tumour type in NF2 is the schwannoma (as compared to the neurofibroma seen in NF1) [18]. The majority of ocular manifestations occur at an early age, offering diagnostic clues often before the appearance of vestibular schwannomas [19, 20]. In contrast to NF1, *Lisch* nodules and optic nerve gliomas are rare findings in NF2 [20, 21].

Instead, juvenile cataracts are found in 60–80% of patients, with almost half of these identified in childhood [4, 22]. Posterior subcapsular and peripheral cortical cataracts are the most common lens opacities, with 10–20% of cataracts significantly impacting vision and therefore requiring extraction [4, 19].

Retinal hamartomas are benign lesions that may adversely affect vision when they involve the macula [19]. They are an uncommon cause of painless visual loss. Combined pigment epithelial and retinal hamartomas are often found in association with epiretinal membranes [19]. Epiretinal membranes in NF2 have characteristic findings on optical coherence tomography (OCT), with unusually thick membranes and rolled edges extending onto the vitreoretinal interface [23]. In addition to being associated with a more severe phenotype of NF 2, they may be associated with vision loss due to macular impairment and retinal detachment [19]. *Surgical* intervention, in the form of vitrectomy with membranectomy, may be offered to patients with vision-threatening pathology in select cases.

Optic nerve sheath meningioma (ONSM) is a benign tumour arising from meningothelial cells of the arachnoid villi [24]. Although 95% of ONSMs are unilateral, bilateral ONSMs are typically associated with NF2 [24]. As with optic pathway gliomas in NF1, presenting signs due to optic pathway compression include afferent findings such as relative afferent pupil defect, reduced visual acuity and visual field defects. Fundoscopy may reveal optic atrophy, optociliary shunt vessels and, in advanced stages, proptosis and strabismus [25]. ONSM does not metastasize, but although there is no associated mortality, untreated lesions will invariably lead to permanent vision loss [25]. Because of their slow growth, observation is appropriate in cases with good visual function [24]. Alternatively, radiotherapy and surgery can be offered to patients with progressive disease, severe vision impairment, severe proptosis or significant intracranial extension [19, 24].

Less common ocular findings can include nystagmus secondary to peripheral vestibular disruption and exposure keratopathy secondary to facial nerve weakness [19].

Tuberous Sclerosis

Tuberous sclerosis is a genetically heterogeneous neurocutaneous syndrome characterized by hamartomas of the eye, brain and skin. Retinal phakomas (*astrocytic hamartomas* of the retina and optic disc) are characteristic findings present in

around half of individuals [26] (see Chap. 27). They can be classified morphologically as (1) flat, ill defined, white-grey and translucent; (2) multinodular, elevated, opaque and calcified (*mulberry* like); or (3) mixed with translucent base and elevated calcified centre [27]. The noncalcified lesions often involve the posterior pole, while the calcified lesions are often found near the margin of the optic disc [28] (Fig. 47.3). These lesions can mimic retinoblastoma, toxoplasmosis and toxocariasis [29]. Calcified optic nerve hamartomas resemble optic disc drusen; however, OCT reveals that retinal hamartomas are hyperreflective with disorganized retinal layers, "moth-eaten" spaces and posterior shadowing [29]. Fluorescein angiography highlights the vascularity of retinal hamartomas, demonstrating abnormal blood vessels on the tumour surface in the arterial phase, leakage from vessels in the venous phase and intense late staining. Although the majority of these hamartomas are asymptomatic and do not progress over time [30], some exhibit aggressive growth resulting in subretinal haemorrhage, exudative retinal detachment from tumour vessels, vitreous haemorrhage, choroidal neovascularization and neovascular glaucoma [27]. In most cases, treatment is not required, as exudates and vitreous haemorrhages often spontaneously resolve [31]; however, pars plana vitrectomy is an option for recurrent or non-resolving vitreous haemorrhages [31]. Subretinal exudates from persistent vascular leakage may be managed with argon laser photocoagulation, photodynamic therapy or anti-VEGF therapy [31].

Retinal pigmentary abnormalities include *punched out* lesions of retinal pigment epithelium (RPE) hypopigmentation which may be seen in the mid-peripheral retina (retinal achromic patch) and iris, but do not impact vision [30]. These lesions are analogous to the hypopigmented skin lesions of tuberous sclerosis, representing areas of decreased melanin production [32]. Hyperpigmentation has also been noted in the retina, likely related to congenital retinal pigment epithelium hypertrophy [33]. However, these pigment changes are not specific to tuberous sclerosis.

Non-retinal findings are less common and include eyelid angiofibromas, cataracts, strabismus, coloboma, iris depigmentation, poliosis of eyelashes and papilledema [27, 29]. Of these, angiofibromas of the eyelid are the most common, reported in as many as 39% of patients [27].

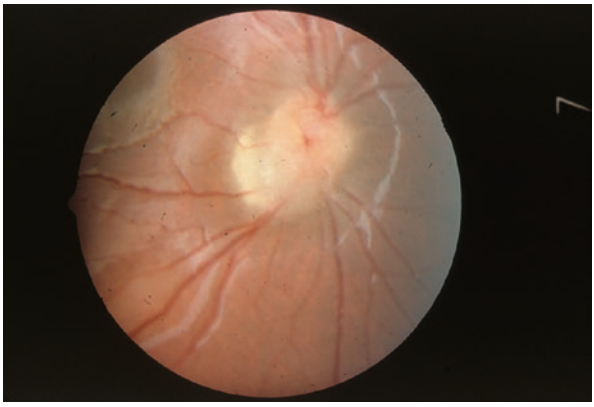

Fig. 47.3 Retinal phakoma of optic disc

Clinical correlation: A comprehensive ophthalmologic examination should be performed annually or when new visual symptoms or ophthalmologic lesions arise in patients diagnosed with tuberous sclerosis [34].

Sturge-Weber Syndrome

In contrast to other neurocutaneous disorders, *Sturge-Weber* syndrome is not a heritable disorder, resulting instead from sporadic mutations early in embryonic development (see Chap. 5). It is characterized by a port wine mark of the skin and vascular malformations involving the brain (*leptomeningeal vascular malformation*) and/or the eye [35] (for more, see chapter "Sturge-Weber Syndrome"). A port wine mark involving the entire V1 distribution suggests a high likelihood of underlying ocular and neurologic disorders [36].

The most common ocular manifestation is **glaucoma**, reported in 30–70% of patients with *Sturge-Weber* syndrome [36]. Sixty percent of cases are present at birth, but it can present at any age [35]. Glaucoma affects the eye ipsilateral to the port wine mark and is more common when the mark involves the upper eyelid [29]. The proposed aetiology is multifactorial, including a pre-existing anomaly of the anterior chamber angle and elevated venous pressure from an episcleral haemangioma [35]. Unfortunately, the elevated episcleral venous pressure mechanism appears to predominate in many cases, making long-term intraocular pressure control extremely challenging. *Sturge-Weber* syndrome glaucoma appears to become refractory to medical management [35]. Angle procedures (such as *goniotomy* and *trabeculotomy*) have thus been proposed as initial surgical options due to their relatively low adverse events [35].

Vascular anomalies and malformations may involve any part of the orbital circulation, such as the conjunctival, episcleral and retinal vessels. *Choroidal haemangiomas* can be clinically divided into localized and diffuse forms, but it is the diffuse form that typically occurs in 50–70% of patients with *Sturge-Weber* syndrome [36]. They are typically present at birth, unilateral and ipsilateral to the port wine mark [27]. Clinical exam reveals a bright red pupillary reflex related to the increase of well-formed choroidal vessels, and diffuse orange choroidal thickening of the fundus with a "tomato-ketchup" appearance, representing haemangiomas [37]. Patients are often asymptomatic in early childhood, but may present with refractive error, amblyopia and visual field defects [37]. *Subretinal haemorrhage*, retinal degeneration, retinal serous detachment, photoreceptor degeneration, cystoid macular oedema, macular serous detachment, tortuous retinal vessels and optic disc coloboma have also been described in *Sturge-Weber* syndrome patients [37]. Treatment is based on vision impairment and extent of retinal detachment. Low-dose radiation, plaque brachytherapy, proton beam radiotherapy, Gamma Knife surgery and anti-VEGF therapy have all been used to effectively induce tumour regression [38]. *Photodynamic* therapy avoids the risks of radiation and has been successful in treating exudative retinal detachments [38].

Leptomeningeal vascular malformation often affects the parietal and occipital lobes, leading to atrophy and calcifications in the vessels [36]. This may lead to homonymous hemianopsia or other visual field defects, depending on the precise cortical lesion. Impaired cerebrospinal fluid absorption from the malformation can also lead to papilledema [29]. Additional ocular findings include iris heterochromia, increased/prominent conjunctival vascularization and episcleral haemangiomas [35, 36, 38].

Von Hippel-Lindau Disease

Von Hippel-Lindau (*VHL*) disease, also known as familial cerebello-retinal angiomatosis, is commonly characterized by the development of haemangioblastomas within the retina and central nervous system [39] (see Chap. 28).

Retinal capillary haemangioblastomas (Fig. 47.4) are the most frequent and often earliest manifestation of *VHL*, with a mean age of diagnosis of 25 years [39–42]. These lesions are typically multiple and bilateral in nature [41] and are usually located in the supero-temporal aspect of the peripheral retina [42]. On *fundoscopy*, they may initially present as a small, red or grey "dot", or may appear as more advanced globular, vascular lesions featuring tortuous feeder vessels alongside subretinal fluid and hard exudates [39, 41] (Fig. 47.5). Notably, on fluorescein angiography, feeder vessels will hyperfluoresce during the arterial phase [41].

Haemangiomas can also involve the optic nerve head, known as juxtapapillary capillary haemangioblastomas. These *lesions* initially appear in the peripapillary area or on the optic disc and grow over several years, eventually resulting in increased capillary leakage, retinal oedema, hard exudates, macular oedema and possible exudative retinal detachment [43]. In the case of a single juxtapapillary angioma, patients should be screened for *VHL* disease [40].

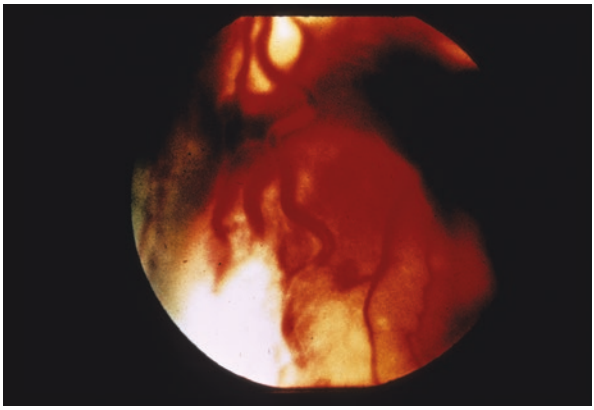

Fig. 47.4 Retinal capillary haemangioma in VHL near the optic disc, demonstrating dilated vessels

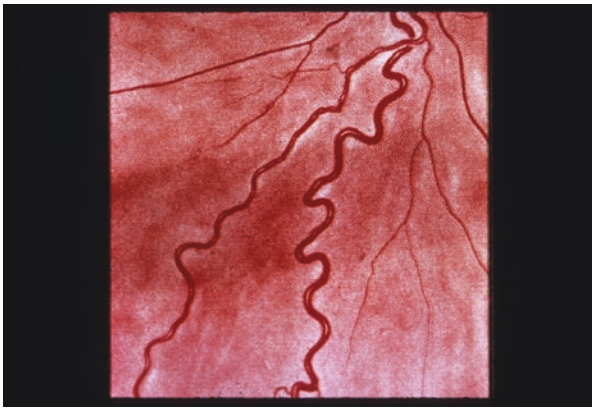

Fig. 47.5 Feeding arteriole and draining venule extending towards a peripheral retinal capillary haemangioma

The vision-threatening complications of retinal oedema, exudates, retinal traction and potential haemorrhage grow more threatening with increasing angioma size [41]. Therefore, the goals of management are focused on detecting and treating small, asymptomatic haemangioblastomas before they advance [41]. The *treatments* for retinal capillary haemangioblastomas and juxtapapillary capillary haemangioblastomas understandably differ from one another. Retinal angiomas are typically treated with laser photocoagulation, cryotherapy, radiation, photodynamic therapy, combined modalities and, in rare cases, surgical excision [41, 42]. In contrast, due to the need to avoid collateral damage to the optic nerve during treatment, juxtapapillary capillary haemangioblastomas are more difficult to manage. In cases of disease progression, management may include anti-VEGF agents, photodynamic therapy or corticosteroids [41, 43, 44].

Rarely, non-angiomatous ocular findings have been described in *VHL* disease, presenting as "twin vessels", "vascular hamartomas" and "vascularized glial veils" which may represent capillary variations [43, 45]. Furthermore, in addition to the retinal manifestations of *VHL* disease, other ocular associations include rubeosis iridis, or iris neovascularization, which can secondarily lead to neovascular glaucoma and has been associated with exudative or tractional retinal detachment [40, 43].

Ataxia-Telangiectasia

Ocular manifestations include conjunctival telangiectasia and ocular motor abnormalities (see Chap. 6). Bulbar conjunctival telangiectasia is found in almost all affected individuals and typically presents around 3–5 years of age. They are usually bilateral and located within the palpebral fissure and have aneurysmal dilatations with sharp turns [29]. They have no effect on vision, and individuals have normal fundus and intraocular pressure [46].

Ocular motor abnormalities are an important component of the spectrum of progressive neurologic dysfunction in ataxia-telangiectasia. The *abnormalities* typically present around 4 years of age. They include abnormal saccades, pursuits and optokinetic responses, along with nystagmus, strabismus and poor convergence ability [46]. Patients first demonstrate an inability to initiate saccades, which may be associated with head thrusting and abnormalities of the fast phase optokinetic nystagmus. Pursuit becomes impaired and eventually the disease can lead to total ophthalmoplegia [47]. Prisms, lenses for accommodation and surgical correction of ocular misalignment may assist in quality of life [48]. Medical treatments targeted towards neurologic symptoms may also improve ocular motor function [49] (Table 47.2).

A non-exhaustive list of common ocular manifestations in neurocutaneous disorders.

Table 47.2 Ocular manifestations of neurocutaneous disorders

Syndrome	Ocular features	References
Neurofibromatosis I	Lisch nodules; optic pathway glioma; plexiform neurofibroma; sphenoidal dysplasia; choroidal nodules/abnormalities; glaucoma; astrocytic hamartoma; capillary haemangioma; combined retinal/RPE hamartoma; corkscrew vessels overlying choroidal nodules; myopia	[2, 14]
Neurofibromatosis II	Early onset cataract; epiretinal membrane; retinal hamartoma; optic nerve sheath meningioma; strabismus; amblyopia	[24]
Tuberous sclerosis	Retinal phakomas; RPE hypopigmentation; retinal hyperpigmentation; eyelid angiofibromas; cataract; strabismus; coloboma; iris depigmentation; poliosis; papilledema	[27, 29]
Sturge-weber syndrome	Glaucoma; choroidal haemangioma; homonymous hemianopsia; papilledema; episcleral haemangioma; iris heterochromia; conjunctival vascularization	[27, 31, 35]
Von Hippel-Lindau disease	Retinal capillary haemangioblastoma; juxtapapillary capillary haemangioblastoma	[14, 40]
Ataxia-telangiectasia	Bulbar conjunctival telangiectasia; abnormal saccades, pursuits and optokinetic responses; strabismus; nystagmus; poor convergence	[24, 45]
Wyburn-Mason syndrome	Retinal/orbital arteriovenous malformation; proptosis; cranial nerve palsy; conjunctival vessel dilation; ptosis; optic nerve atrophy; visual field defect; impaired ocular motility; pupillary defect	[27]
Incontinentia pigmenti	Peripheral and macular vasculopathy; arteriovenous anastomoses; microvascular anomalies; strabismus; nystagmus; optic atrophy; microphthalmos; conjunctival pigmentation; cataract; uveitis; corneal epithelial and stromal keratitis; iris hypoplasia	[27]

Table 47.2 (continued)

Syndrome	Ocular features	References
Cutis marmorata telangiectatica congenita	Retinal vascular abnormalities; congenital glaucoma and cataract; optic disc drusen; slate grey or blue pigmentation of the sclera, cornea and conjunctiva; persistent hyaloid artery; retinoblastoma	[27]
Dyskeratosis congenita	RPE change; vascular sheathing; incomplete retinal vascularization; cotton wool spots; retinal and vitreous haemorrhage; vascular malformation; nasolacrimal duct obstruction; keratoconjunctivitis; lid abnormalities; corneal limbal stem cell deficiency; entropion; trichiasis; congenital cataract; glaucoma, strabismus; optic atrophy	[14, 27]
Phakomatosis pigmentovascularis	Retinal vascular and pigmentary abnormalities; choroidal melanoma; glaucoma; abnormal episcleral and conjunctival vasculature; iris hamartomas; scleral, iris and optic disc melanocytosis	[27]
Hereditary haemorrhagic telangiectasia	Bloody tears; conjunctival post-haemorrhagic granulomatous lesions; telangiectasias at the level of the conjunctiva and posterior pole; retinal vascular malformation	[50]
Noonan syndrome	Hypertelorism; epicanthal folds; ptosis; strabismus; refractive error; blue-green irides	[14]
Nevoid basal cell carcinoma	Hypertelorism; subconjunctival epithelial cysts; strabismus; cataract, coloboma	[14]
Blue rubber bleb nevus syndrome	Decreased visual acuity; proptosis or enophthalmos	[51]
Congenital melanotic nevi/neurocutaneous melanosis	Papilledema; uveal coloboma-like lesions; RPE alterations; limbal dermoid	[14]
Hypomelanosis of Ito	Retinal hypopigmentation	[52]
PTEN hamartoma-tumour syndrome	Corneal nerve hypertrophy; prominent Schwalbe's lines; pseudopapilledema; downward-slanting palpebral fissures; amblyopia; strabismus; myopia; angioid streaks; cataracts	[14]
Xeroderma pigmentosum	Xerophthalmia: Conjunctivitis, keratitis; blepharitis; ectropion	[14]
Chediak-Higashi syndrome	Ocular albinism (uveal hypopigmentation); photophobia; nystagmus; strabismus	[14]

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Chapter 48
Neurosurgical Management of Neurocutaneous Disorders

Michael Vassilyadi and Diana-Cristina Ghinda

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Neurofibromatosis (NF1, NF2)

Clinical Characteristics

Neurofibromatosis type 1 is the most common neurocutaneous disorder. Patients with neurofibromatosis types 1 and 2 are referred to neurology and neurosurgery for the management of epilepsy, chronic pain syndromes including headache, increased intracranial pressure including obstructive hydrocephalus, myelopathies, peripheral mononeuropathies, plexopathies, and involuntary movement disorders [1–3].

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Management

The management of patients with neurofibromatosis must be tailored to the specific presentation and often requires multidisciplinary collaboration with teams such as medical genetics, ophthalmology, and audiology [4]. Genetic counseling should be provided to all of the patients and their families. As such, evaluation should include neuroimaging of the brain and spine with and without contrast, along with ophthalmological and audiology examinations. Given the evolving nature of this disease, longitudinal monitoring is necessary.

The most common lesions on brain MRI in patients with *NF1* are unidentified bright objects (*UBOs*), which have increased signal on T2-weighted images that are nonenhancing and do not cause mass effect or deficits. Although their clinical relevance remains unknown, *UBOs* are considered benign with a significant proportion that may resolve until the adult age [5]. Those lesions are thought to represent areas of myelin edema and should not be confused with brain tumors [6]. The second most common imaging finding in *NF1* is the optic pathway glioma, which can affect one or both optic nerves, the optic chiasm, and the hypothalamus. Symptoms can include vision loss, visual field defects, endocrinopathies, diencephalic syndrome, and hydrocephalus. Less commonly, patients with *NF1* may have a hemispheric or cerebellar glioma that can present with mass effect and increased intracranial pressure. Treatment of obstructive hydrocephalus caused by aqueductal webs, chiasmatic-hypothalamic tumors, and thalamic mass effect includes tumor resection, insertion of ventriculoperitoneal or ventriculoatrial shunts, and endoscopic septostomy with or without endoscopic third ventriculostomy [2, 7].

Subcutaneous neurofibromas may be painful or disfiguring, and surgery may be used to remove these tumors [8]. Neurosurgical resection of *schwannomas* and *meningiomas* is indicated to relieve compression of adjacent structures and represents the most effective management. In general, surgical intervention is indicated for symptomatic tumors or evidence of rapid growth. Aggressive forms present with a rapid progression and can cause severe disability, and giant tumors of the craniofacial region present particular difficulty due to proximity to critical neurovascular structures [9].

Neurofibromas of small nerves can be approached with a direct linear incision along the affected nerve, followed by careful dissection along the nerve sheet and intracapsular removal. For *plexiform* tumors that invade large nerves, the dissection must proceed along the plane of the nerve with an attempt for maximal debulking while preserving function. neurophysiological monitoring with nerve stimulation is thus critical. In the case of schwannomas involving spinal nerve roots, after adequate bony decompression, the tumor should be removed as it is followed into the neural foramen. For primarily extradural lesions, employing an intracapsular approach minimizes the risk of causing new motor or sensory dysfunction [10].

In *NF1*, optic pathway *gliomas* are more indolent and slower growing than in non-*NF1* patients, and as such visual deficiencies may not be identified, especially in young children. Surgical involvement is usually limited to a biopsy performed primarily for diagnosis; in cases when there is unilateral severe vision loss, the

surgery can be more complete. Adjuvant therapy includes chemotherapy in children [11]. In cases of progressive disease, chemotherapy is the first-line treatment with the goal of treatment being visual preservation [12].

Hemispheric and *cerebellar* gliomas are more amenable to a safe gross total surgical resection. Depending on factors such as patient age, lesion location, and lesion residual/extension, there could be consideration for subsequent radiation or chemotherapy. Molecular-targeted therapy has become an option for patients with *NF1*-associated gliomas and neuroglial tumors who have progressed after receiving chemotherapy [13]. Postoperatively, all patients are followed with scheduled brain MRIs to assess for tumor stability, regrowth, or recurrence.

NF2 is characterized by bilateral *vestibular schwannomas* (formerly known as acoustic neurolemomas) that usually present with symptoms of tinnitus, unilateral sensorineural hearing loss, and imbalance (Fig. 48.1). Patients may also present with facial weakness, visual impairment, or symptoms from painful peripheral nerve lesion or spinal cord compression as a result of the neurofibromas. Other cranial lesions include non-vestibular cranial nerve schwannomas (oculomotor and trigeminal nerves), meningiomas, meningioangiomatosis, and gliomas (see Chap. 26) [14]. While spinal tumors do not represent a regular feature of *NF1*, they occur in approximately 70% of *NF2* cases predominantly with spinal schwannomas and extramedullary meningiomas. Intramedullary ependymomas occur in one-third of *NF2* patients and occur mostly in the cervical spine [14, 15].

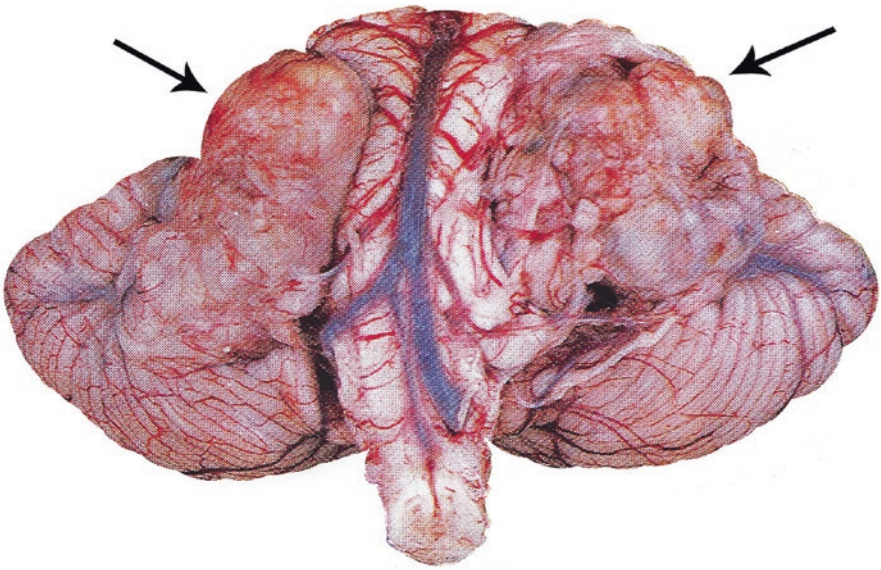


Fig. 48.1 Bilateral vestibular schwannomas lodged between the brainstem and cerebellum in a patient with NF2 (black arrows). With permission from the book Atlas of Neuropathology by Haruo Okazaki and Bernd W. Scheithauer, 1988, page 204 (Fig. 3.490)

The natural history of *vestibular schwannomas* in *NF2* is difficult to predict, and the decision between observation and neurosurgical intervention, as well as the choice of surgical procedure, depends on patient factors and on the experience of the treating center [16]. Depending on the hearing status, the tumor size, and the presence or absence of compressive symptoms, these tumors can be managed by observation, stereotactic radiosurgery, or surgical resection. Surgery may attempt to preserve hearing or aim for complete tumor resection with preservation of facial nerve function. The goal of treatment is to maximize the years of useful hearing [17]. Small intracanalicular vestibular tumors (<1.5 cm) can often be completely resected with preservation of both hearing and facial nerve function. When a microsurgical approach is proposed, the goals of surgery and potential complications, especially the potential for facial nerve injury, should be discussed extensively with the patients and their families. The suboccipital retrosigmoid approach or a middle cranial fossa approach should be used when serviceable hearing is present.

When serviceable hearing is not present, either the middle cranial fossa or the translabyrinthine approaches can be utilized for gross total resection. Tumors can be managed expectantly with decompression surgery only when there is deterioration of hearing or other symptoms of mass effect [18]; however, early management is considered favorable for good outcome [19]. As the *vestibular schwannomas* can remain stable for prolonged periods of time, when significant motor dysfunction secondary to brainstem compression occurs, decompressive resection can provide prolonged symptomatic relief while preserving facial nerve function.

Radiation therapy of *NF2*-associated tumors should be carefully considered because radiation exposure may induce, accelerate, or transform tumors in an individual (especially in childhood) with an inactive tumor suppressor gene [15, 18, 20]. Furthermore, only approximately 60% long-term tumor control is achieved for individuals with sporadic unilateral vestibular schwannoma [15].

Although *ependymomas* in individuals without *NF2* are optimally treated with complete tumor resection, *NF2*-related *ependymomas* exhibit an indolent growth pattern with tumor progression limited to a minority of patients, and therefore surveillance is reasonable for asymptomatic lesions (see Chap. 26). When the surgical approach is considered for the removal of the intramedullary tumor, after a standard exposure, a midline myelotomy is performed, followed by pial retraction and careful dissection under the microscope to remove the tumor. The use of adjunctive intraoperative techniques such as neurophysiological monitoring can decrease the risk of causing new neurological deficits.

Tuberous Sclerosis Complex (TSC)

Clinical Characteristics

CNS lesions such as cortical tubers, periventricular hamartomas (*subependymal nodules*), and subependymal giant cell astrocytomas (*SEGAs*) are the leading cause of morbidity and mortality in patients with tuberous sclerosis complex (Fig. 48.2).

Epilepsy, intellectual disability, developmental delay, and learning disabilities are common in *TSC*, and up to 40% of patients have an autism spectrum disorder. Epilepsy occurs in approximately 80% of individuals with *TSC*, with up to 60% of patients developing refractory epilepsy with infantile spasms and Lennox-Gastaut syndrome being a risk factor for refractory epilepsy [21]. The neurological complications of *TSC* are the most common and impairing aspect of *TSC*. There can also be signs of increased intracranial pressure requiring urgent management by neurosurgery.

Management

Treatment of the *CNS* lesions is directed at complications of the disease, particularly epilepsy. The pharmacologic treatment with specific antiepileptic medications is the mainstay of therapy for patients with *TSC* (see Chap. 27). Asymptomatic patients with *SEGAs* could be monitored as per the published guidelines with serial neuroimaging every 1–3 years [22]. Neurosurgical intervention is indicated for patients with medically refractory epilepsy and includes focal cortical

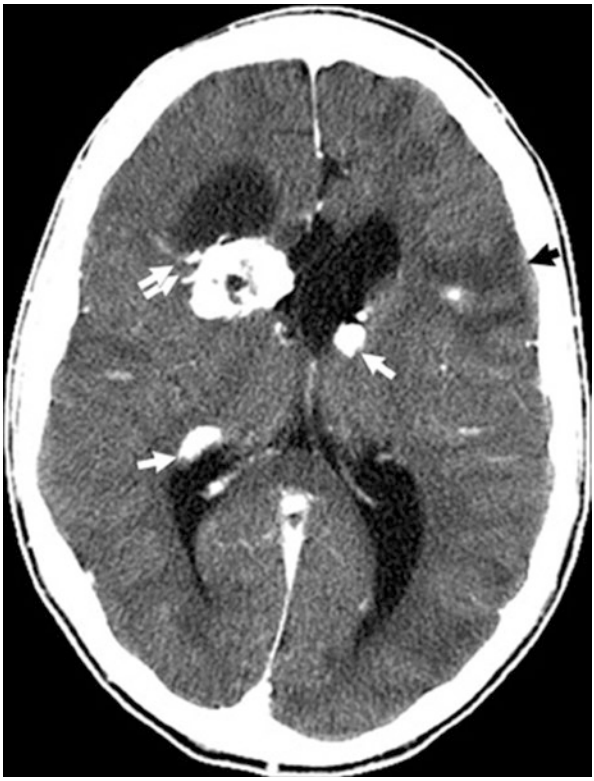


Fig. 48.2 Brain CT showing calcified subependymal nodule (*white arrow*) and right giant cell astrocytoma (double arrow) in a patient with tuberous sclerosis. Calcified left subcortical hamartoma and subcortical hypodensity (black arrow). Reprinted with permission of Anderson Publishing Ltd. from Bardo DME. Pediatric Neuroradiology, part 2: Embryologic basis for inherited neurological disease and congenital neoplasm. Applied Radiology, 2009; 38 (10): page 26 (Fig. 4A) ©Anderson Publishing Ltd.

resection, corpus callosotomy, or vagus nerve stimulation. When a discrete cortical epileptogenic lesion is present, surgery may be beneficial. Lesionectomies rarely result in seizure freedom. Corpus callosotomy is effective in the reduction of atonic seizures and drop attacks [23]. *SEGAs* do not respond to traditional chemotherapy, and radiotherapy may be associated with an increased risk of secondary malignancy.

Cortical tubers, which are the most commonly identified lesions in *TSC*, are the cause of intractable epilepsy in most patients, especially if the tubers are large [24]. They are formed from aberrant neuronal migration and are primarily in the frontal and parietal lobes. Resection of the *cortical tubers* is not always effective for seizure control; however, surgery is performed for large lesions with mass effect [22, 25]. Neurosurgical treatment of patients with *SEGAs* is indicated to relieve associated hydrocephalus or significant mass effect, and early intervention can lessen the morbidity and mortality [26]. When a gross total resection can be achieved, recurrence is unlikely [27]; this is not always possible because the tumor can arise from areas such as the caudate nucleus. Furthermore, the presence of cardiac intraventricular rhabdomyomas should be investigated before proceeding with any surgical intervention because life-threatening arrhythmias can occur in their presence.

Subependymal nodules can be calcified or non-calcified and may range from 1 to 20 (see Chap. 27). On brain CT, they resemble candle wax drippings. They are composed of abnormal, swollen glial cells and bizarre multinucleated cells with no interposed brain tissue. There is a possibility of transformation to a *SEGA* if on follow-up imaging the nodules develop contrast enhancement and enlarge in size. Nonetheless, subependymal nodules are usually stable nonenhancing lesions, while *SEGAs* display contrast enhancement and usually grow 2–5 mm per year [28]. Although *SEGAs* are benign tumors and develop in 5–15% of patients with *TSC*, they are clinically significant as their enlargement may obstruct the foramen of Monro, resulting in obstructive hydrocephalus that may be fatal if untreated [29, 30].

Among the different surgical approaches used for removal of *SEGA*, the *two traditional* ones are a transcortical frontal approach to the lateral ventricle or an interhemispheric transcallosal approach [31]. In the transcallosal procedure, the patient is positioned supine, and after a bifrontal or parasagittal incision, an interhemispheric approach is performed while preserving the bridging veins. For *SEGAs* that are amenable to surgery, resection may lessen the morbidity and mortality rates [32, 33]. Successful endoscopic removal of a *SEGA* obstructing the foramen of Monro has also been described [34–36]. While a gross total resection can be curative, biologically targeted pharmacotherapy with *mTOR* inhibitors could stabilize and decrease the size of *SEGAs* [21].

Gamma Knife therapy has been reported to produce a sustained reduction in the *SEGA* size in small case series [37]. As the patients already have a mutation of the tumor suppressor gene, there is the potential increased risk of a radiation-induced secondary tumor; glioblastoma multiforme has been reported 8 years after *SEGA* radiation [38].

Recently, laser interstitial thermal therapy (*LITT*), a newly emerging treatment modality for a variety of pathologies, with endoscopic stereotactic septostomy, has been used as a primary or adjunct treatment modality for *SEGAs* that are rapidly enlarging or encroaching on the foramen of Monro. *LITT* is a stereotactic, percutaneous procedure employed for thermal ablation of lesions. It produces light energy via a fiber-optic catheter with the recent incorporation of MRI thermometry in real time to visualize the thermal energy delivered to surrounding tissue. This modality is particularly effective when surgical excision is not a viable option secondary to deep-seated, inaccessible lesions or in patients who cannot tolerate general anesthesia for an extended time due to comorbidities [39].

Biologically targeted pharmacotherapy with *mTOR* inhibitors such as rapamycin (*sirolimus*) and everolimus has also shown promise in early investigations for the treatment of *SEGAs* (see Chap. 27). When gross total resection is impossible, rapamycin and everolimus should be considered, although they may not offer a durable response (see Chap. 27). Rapamycin has also been reported to be an effective agent for controlling epilepsy without any significant side effect in children with *TSC* [40, 41].

Sturge-Weber Syndrome

Clinical Characteristics

Sturge-Weber syndrome, also called encephalotrigeminal angiomatosis, is a rare and sporadic neurocutaneous disorder affecting the brain microvascular tissue, as well as the tegmentum. The characteristic CNS feature is capillary angiomatosis of the pia mater that disrupts the normal cerebral blood flow leading to secondary gliosis and development of calcifications. Cerebral cortical calcifications can be seen in a pericapillary distribution (radiologic picture of *tram track* or *railroad track* calcifications) in about 60% of cases (see Chap. 5).

Management

Neurological complications that occur with *Sturge-Weber* syndrome may include epilepsy, hemiparesis, changes in vision, stroke-like symptoms, and intellectual disability. Unlike the other phacomatosis, *Sturge-Weber* syndrome does not affect other organs of the body. Regular ophthalmological examination is warranted because of the risk for glaucoma, usually ipsilateral to the facial port-wine stain that is present in 30–50% of affected patients [42]. Hemangiomas of the choroid, conjunctiva, and episclera may also be present. Also, approximately 20% of patients have a diffuse choroidal hemangioma [43].

Epilepsy occurs in more than 75% of affected individuals with a median age of onset of 6 months (see Chap. 5). Aggressive seizure management is required, as it has been postulated that seizures may have a role in the development of subsequent neurological deficits [44]. Children with intractable epilepsy due to extensive lesions can present with drug-resistant epilepsy for which early epilepsy surgery may be beneficial. For the neurosurgical candidates, the degree of resection or disconnection of diseased tissue, rather than patient age at the time of surgery, is an important factor in achieving epilepsy control [45].

Treatment is usually aimed at the associated epilepsy, which can be medically intractable (see Chap. 5). In patients with intractable epilepsy and infantile-onset hemiplegia, hemispherectomy can improve the seizures and the neurodevelopmental outcome [46]. The input of both neurosurgeons and neurologists is required for adequate surgical planning. This includes evaluation of epilepsy associated with other rare neurocutaneous disorders, such as *hypomelanosis of Ito*, which clinically may mimic *Sturge-Weber syndrome* or *NF1* [47].

Focal resection and lesionectomy are effective techniques, and seizure freedom rates can be as high as 60–80% following these procedures [48]. Nonetheless, since the affected patients often have widespread CNS involvement, resection of an epileptic focus is not always possible. In patients in whom the epileptogenic zone overlaps with unresectable eloquent cortex, with no localized focus, or with widespread involvement, disconnection procedures such as a corpus callosotomy or multiple subpial transections may be appropriate [6, 49]. When disconnection procedures are performed, the concept is that interrupting the epileptic discharge–spreading pathway or isolating the primary epileptogenic zone would have the same effect as removing the epileptic focus. As such, intraoperative neurophysiological mapping and monitoring are essential [50]. Temporoparietooccipital disconnection has also been described as a safe and effective motor-sparing epilepsy surgery in selected cases [51]. As disconnection procedures can achieve reduction in seizure severity but rarely seizure freedom, it is important that the patient and family expectations with respect to outcome be adequately addressed preoperatively.

If uncontrolled, severe partial motor seizures may lead to deterioration of cognitive and psychosocial status (see Chap. 5). In these cases, surgery may be associated with seizure relief and good cognitive outcome [48]. Hence, surgery should not be delayed if there are uncontrollable episodes of status epilepticus with regression during the first year of life [52]. Although 40–50% of seizures can be medically controlled, the timing and candidacy for surgery remains controversial [45]. Aside from focal resection, hemispherectomy has been shown to result in seizure freedom in 72–81% [53, 54] of selected patients. This option is considered most appropriate for patients with unilateral involvement and the presence of hemiparesis and a visual field cut. Another less invasive palliative procedure represents the placement of a vagus nerve stimulator (Fig. 48.3), or the use of the ketogenic or Atkins diets [55, 56]. Other neurosurgical options such as the insertion of programmable pumps for intrathecal administration of baclofen (Fig. 48.4) have been used in other conditions such as *Sjögren-Larsson* syndrome [57].

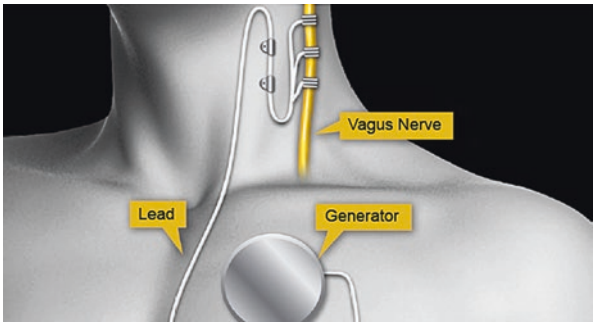
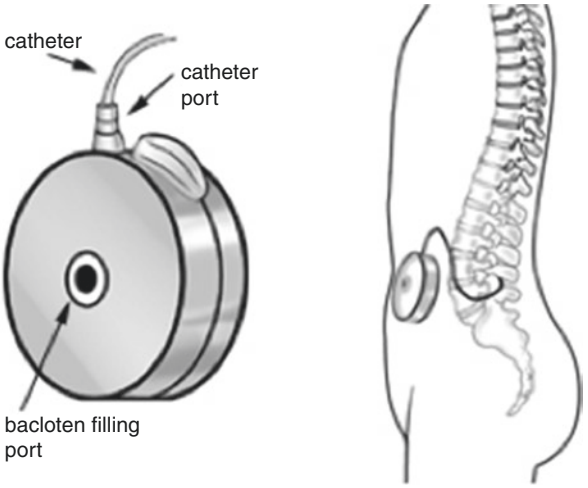


Fig. 48.3 Illustration of an implantable vagus nerve stimulation system with the generator in the left pectoral region and a flexible lead attached to the left vagus nerve. The generator is programmed to provide continuous electrical impulses of different amplitude, frequency, and periods of activity to the left vagus nerve. These impulses are transmitted to the brain where synaptic activity may be altered and seizures either dampened or eliminated

Fig. 48.4 Illustration of an implantable intrathecal baclofen system with the programmable pump in the subcostal space attached to a silicone catheter that is inserted via a lumbar puncture. The pump has a filling port for the baclofen that is delivered accurately and safely after programming into the spinal cerebrospinal fluid; this can result in effective and long-term control of spasticity of cerebral origin in children and young adults



Angiomatosis of the Retina and Cerebellum (Von Hippel-Lindau Disease)

Clinical Characteristics

Von Hippel-Lindau disease (*VHL*), also known as retinocerebellar angiomatosis, is characterized by the presence of multiple or bilateral tumors such as retinal angiomas, cerebellar and spinal cord hemangioblastomas (Fig. 48.5), renal cell carcinomas, endolymphatic sac tumors, pheochromocytomas, papillary cystadenomas of the epididymis, angiomas of the liver and kidney, and cysts of the pancreas, kidney,

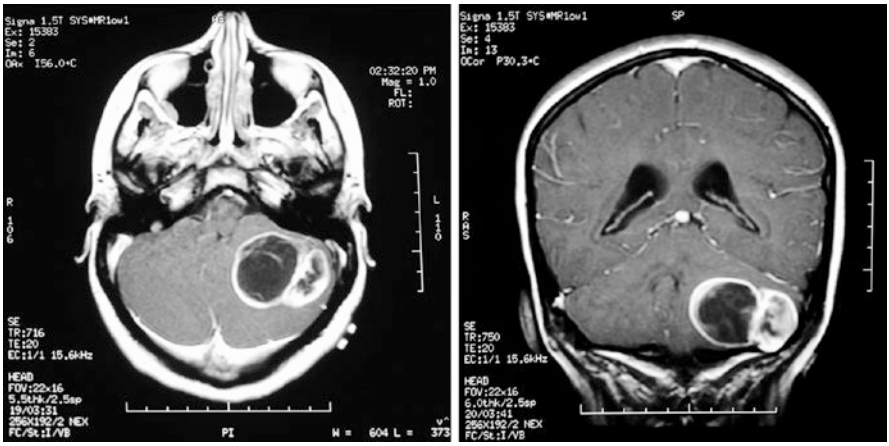


Fig. 48.5 Brain MRI (axial and coronal sections) of a patient with a left cerebellar hemangioblastoma. The contrast-enhancing nodule is lateral and the cyst medial creating left to right mass effect

liver, and epididymis. Ocular findings usually precede the cerebellar symptoms and signs. This disease, unlike most phacomatoses, has no skin involvement.

Management

Surgical treatment represents the core of *VHL* management, and complete surgical resection is usually curative. Small asymptomatic lesions may be monitored with serial brain MRIs because the growth pattern can be irregular and unpredictable (see Chap. 28). Modern neurosurgical techniques encompass microsurgery, neuronavigation, intraoperative neuromonitoring, fluorescein dye-based intraoperative angiography, intraoperative ultrasound, and minimally invasive approaches [58].

Hemangioblastomas are rare, histologically benign, highly vascularized, and well-circumscribed tumors of the brain, spinal cord, and retina that occur sporadically or in association with *VHL* disease. *VHL*-associated hemangioblastomas are more likely to be multiple and present at an earlier age than non-*VHL* lesions (see Chap. 28). They may occur anywhere along the craniospinal axis, with only 1% appearing in the supratentorial region. The symptoms are determined by the site of the tumor. The posterior fossa is the most common site for hemangioblastomas in *VHL*, and patients can present with headaches, vomiting, lethargy, dysmetria, ataxia,

papilledema, polycythemia from tumor production of erythropoietin, and enlarging cysts that may cause brainstem compression. Spinal hemangioblastomas present with neck, chest, and back pain, sensory losses, and various signs and symptoms of cord compression depending upon tumor location.

Hemangioblastomas of the CNS are the most common tumor in *VHL* disease, affecting 60–80% of all patients [59]. Annual brain and spine MRIs are recommended to look for changes or development of new lesions along the craniospinal axis, along with yearly screening for retinal angiomas [60]. The characteristic imaging features are a contrast-enhancing nodule associated with a peritumoral cyst located in the cerebellum, or a homogenously enhancing lesion with an associated syrinx for a spinal cord hemangioblastoma (see Chap. 28). These features are not pathognomonic, and the definitive diagnosis is made on histopathological examination.

The *neurosurgical* involvement is extremely important in the management of hemangioblastomas, as these lesions are a major cause of morbidity in *VHL* patients. Symptoms occur as a result of local compression of neural structures, surrounding edema, bleeding, and peritumoral cyst formation or propagation. Cysts in symptomatic patients grow more rapidly than those in asymptomatic patients compared with the size of the associated hemangioblastoma nodule (see Chap. 28).

For lateral or anteromedial lesions, a posterior subtemporal approach or far lateral infratentorial approach can provide an adequate visualization and direct access to the hemangioblastomas [61, 62]. Cerebellar hemangioblastomas located in the posterior and medial portions of the cerebellum are often approached via a midline suboccipital craniectomy, and excision of the posterior arch of C1 is used to better expose the cervicomedullary junction [63]. After opening of the dura, vessels supplying the tumors are identified, cauterized, and sharply transected, and an en bloc resection is performed to minimize intraoperative bleeding [64].

Tumor recurrence can be markedly reduced by meticulous extracapsular resection with circumferential dissection at the capsule-cerebellar interface. The cyst wall should be left intact to facilitate the identification of the resection plane. Consistent with the primarily obstructive origin of hydrocephalus, preoperative ventriculomegaly usually resolves after tumor removal, and cerebrospinal fluid diversion may not be required. If there is increased intracranial pressure, several intraoperative maneuvers can be used to reduce increased posterior fossa pressure and avoid the need for ventricular drainage such as intravenous mannitol, CSF drainage from the cisterna magna after arachnoid opening, and ultrasound-guided drainage of peritumoral or intratumoral cysts with a spinal needle [65].

Preoperative endovascular embolization has been described in literature as an effective way to reduce operative morbidity and should be contemplated when considering a neurosurgical intervention for a cerebellar hemangioblastoma [66]. Smaller hemangioblastomas may be treated by stereotactic radiosurgery, which would not be effective for the hemangioblastoma cysts [67, 68].

Neurocutaneous Melanocytosis (NCM)

Clinical Characteristics

Neurocutaneous melanocytosis (*NCM*) represents a rare nonheritable congenital phakomatosis. The diagnosis should be considered when an infant or child presents with hydrocephalus and has either large or multiple (three or more) congenital melanocytic nevi (see Chap. 11). Patients with large congenital melanocytic nevi are at increased risk for developing melanomas, with approximately half of *NCM* patients developing CNS melanoma [69].

Management

Neurological manifestations generally occur within the first 2 years of life and are often related to increased intracranial pressure [70]. According to the extent of leptomeningeal and parenchymal infiltration, the presentation ranges from focal neurological symptoms to a progressive comatose state. Once the individual is symptomatic, surgical and medical measures remain palliative as death can occur within 3 years [71]. Useful diagnostic procedures include cerebrospinal fluid cytology and magnetic resonance imaging (MRI) with gadolinium contrast [72]. MRI of the neuroaxis represents the imaging study of choice, but it is not pathognomonic; the definite diagnosis is based on tissue biopsy.

The *Dandy-Walker* complex (small cerebellar vermis, large fourth ventricle, and enlarged posterior fossa) and hydrocephalus are the main anomalies that have been reported in *NCM* [73]. Taking in account that *NCM* is believed to arise from a neurulation disorder, this could explain the occurrence of developmental malformations such as the *Dandy-Walker* complex [74]. Case reports of this association have been reported in literature where patients with biopsy confirmed leptomeningeal

melanosis also had posterior fossa malformation such as the *Dandy-Walker* complex [75, 76]. Cases of severe communicating hydrocephalus have also been described [72, 77, 78].

Shunt placement, steroids, and chemotherapy are management options that could be considered for symptomatic patients [71, 79]. Although CSF diversion usually provides relief of the symptoms associated with increased intracranial pressure from hydrocephalus, potential fatal complications such as progressive brainstem compression in patients with associated *Dandy-Walker* complex following ventriculoperitoneal shunt placement have been described [80]. Children with epilepsy should be treated with anticonvulsant medication. In refractory epilepsy with amygdala infiltration, anterior temporal lobectomy with hippocampectomy can be considered [81].

When the patients develop progressive intracranial hypertension due to leptomeningeal melanosis, the prognosis of symptomatic patients remains poor despite maximal treatment. Although the neurological status can be transiently improved following treatment for hydrocephalus, there is no definitive therapy for *NCM*. The long-term clinical significance of characteristic MRI findings in neurologically asymptomatic patients is unclear. Prognosis of *NCM* depends on its malignant transformation to leptomeningeal melanoma [72, 78].

Conclusion

Neurocutaneous disorders (*phakomatosis*) encompass a spectrum of syndromes with distinctive neural, dermatologic, ocular, and visceral manifestations, and their management should involve a multidisciplinary team given the multiple organs affected by these complex disorders. Genetic counseling represents an important part of management and should be provided to the affected individuals and their families. Ongoing clinical and radiologic monitoring is necessary to assess for potential progression of the disease. This is imperative for young *NF1* and *NF2* patients to assess for new lesions or progression of existing ones. After the management of any hydrocephalus, the various medical, endovascular, radiation, and neurosurgical options should be discussed in a multidisciplinary fashion with the patient and their family in order to offer the best evidence-based management. For conditions associated with medically intractable epilepsy such *TSC* and *Sturge-Weber* syndrome, a thorough evaluation by an epilepsy team may identify patients that could benefit from surgery (Table 48.1).

Table 48.1 Neurosurgical management options for neurocutaneous disorders

	NF1	NF2	TSC	SWS	VHL	NCM
Hydrocephalus	Lesion resection, shunt insertion, endoscopic third ventriculostomy with or without septostomy	Lesion resection, shunt insertion or temporization with external ventricular drainage	Lesion resection, shunt insertion or temporization with external ventricular drainage	Hydrocephalus may occur after epilepsy surgery with patient requiring temporary external ventricular drainage or shunt insertion	Lesion resection, shunt insertion or temporization with external ventricular drainage	Shunt insertion into the lateral ventricular system and/or into the enlarged fourth ventricle; possible endoscopic fenestration procedures
Epilepsy	Possible surgery after epilepsy work-up	Epilepsy is not a common feature of NF2; possible surgery after epilepsy work-up	Focal cortical resection, corpus callosotomy, or vagus nerve stimulation for medically refractory epilepsy	Aggressive seizure management for drug-resistant epilepsy including focal resection, lesionectomy, callosotomy, multiple subpial transections, or hemispherectomy; intraoperative neurophysiological mapping and monitoring are essential; placement of a vagus nerve stimulator can be considered	Epilepsy unlikely	Possible surgery after epilepsy work-up

Brain tumor	Possible biopsy of optic pathway gliomas; resection of hemispheric and cerebellar gliomas	Resection or observation of vestibular schwannomas, non-vestibular cranial nerve schwannomas, meningiomas, and gliomas; stereotactic radiosurgery may be considered	Resection of cortical tubers with large mass effect and subependymal giant cell astrocytomas that create obstruction at the foramen of Monro; consideration for gamma knife or laser interstitial thermal therapy with endoscopic stereotactic septostomy	No brain tumor	Resection of cerebral or cerebellar hemangioblastomas with possible preoperative endovascular embolization; consideration of stereotactic radiosurgery for smaller lesions	No brain tumor; possible biopsy of suspicious cortical lesion
Spinal tumor	Resection of neurofibromas, plexiform tumors, schwannomas, and meningiomas; may use neurophysiological monitoring	Resection of schwannomas, meningiomas, and ependymomas; may use neurophysiological monitoring	No spinal tumor	No spinal tumor	Resection of spinal hemangioblastomas	No spinal tumor

NF1 neurofibromatosis type 1; *NF2* neurofibromatosis type 2; *TSC*, tuberous sclerosis complex; *SWS* Sturge-Weber syndrome; *VHL* von Hippel-Lindau disease; *NCM* neurocutaneous melanocytosis

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Chapter 49
Presurgical Evaluation of Children with Tuberous Sclerosis Complex and Epilepsy

Georg Dorfmüller and Martine Fohlen

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Introduction

Tuberous sclerosis complex (*TSC*) is a multisystem disorder with autosomal dominant inheritance and a high rate of de novo pathogenic variants (60%; see Chaps. 27, 48, 50). The incidence of this illness is 1 in 7000–8000 people. Diagnostic criteria were defined at the first International TSC Consensus Conference in 1998 [1] and updated at the second consensus conference in 2012 [2]. Neurological symptoms are common in TSC as epilepsy occurs in 80–90%, cognitive impairment in 50%, and autism spectrum disorders (*ASD*) in up to 40%. These *manifestations* are attributable to the neuroanatomic abnormalities, such as cortical tubers, white matter abnormalities, subependymal nodules, and subependymal giant cell tumors. Furthermore, the elements of neuropsychiatric disorders in TSC may be directly

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attributable to dysregulation of mTOR signaling [3] (see Chap. 27). Cortical tubers are the lesions underlying epilepsy, and the epileptogenicity is located either within the tuber [4], in the perituberal cortex [5], or in both [6]. In those with TSC who develop epilepsy, almost two-thirds have seizure onset within their first year of life. One-third of them will develop infantile spasms, and in about two-thirds, the seizures will be refractory to drug treatment [7]. The presence of *refractory* epilepsy and infantile spasms in TSC has been shown to be significantly associated with cognitive impairment, ASD, and psychiatric disorders [3, 8–10]. Moreover, any type of poorly controlled seizures is an important predictor of ASD and plays an aggravating role in the so-called tuberous sclerosis-associated neuropsychiatric disorders (*TAND*) [3]. Surgery should be considered early in TSC patients with drug-resistant epilepsy, according to a European panel of experts in 2012 [11], and has proved to be effective in some patients with drug-resistant epilepsies in several retrospective series [12–18], with a cessation of seizures in up to 50–60%. A good outcome after surgery has been shown to be associated with improvement in quality of life and neurodevelopmental disorders.

Epilepsy surgery requires a careful patient selection. As for any type of epilepsy surgery, eligibility is based upon clinical, neuroimaging, and electrophysiological data including scalp and, if needed, invasive EEG recordings in order to accurately identify the epileptogenic zone(s) before proposing surgery. Nevertheless, children with *TSC* carry many specificities that render decision-making somewhat difficult. These consist of non-localizing infantile spasms, early onset of seizures, and the presence of multiple, potentially epileptogenic tubers in the brain. The diagnostic modalities and the decision to propose or reject surgery are decided by a multidisciplinary team of experts in childhood epilepsy surgery (see Chaps. 48 and 50).

Infantile Spasms

Of the patients with TSC who develop epilepsy, roughly one-third will present with infantile spasms (IS). Previous retrospective data alluded to poor prognostic factor with regard to postoperative seizure control in TSC patients with IS [12]. However, according to a recent series on preschool children [18] and to two meta-analyses [13, 19], the presence of IS did not correlate with a worse seizure outcome after surgery. In fact, surgical intervention for *refractory spasms* of focal onset with various pathologies has been shown to have similar outcome to that of other seizure types [20].

The *presence* of IS with focal onset should not exclude TSC patients from surgery. On the contrary, drug-resistant infantile spasms could be an indication for prompt referral to an epilepsy surgery center, considering the increased risk of neurodevelopmental sequelae associated with ongoing IS and the potential improved cognitive outcome from early surgery [21].

Age at Epilepsy Onset and Age at Surgery

Of the patients with TSC who develop epilepsy, almost two-thirds have seizure onset in the first year of life [7]. The International TSC Consensus Conference in 2012 concluded that the prevalence of medically refractory epilepsy is high in TSC even with adequate trials of currently available anticonvulsant medications. Therefore, early presurgical evaluation should be the next immediate step after failure of two antiepileptic drugs [2, 22–24]. This recommendation is in line with the definition of ILAE drug-resistant epilepsies, which is the prerequisite for starting presurgical investigations.

Seizure onset before the age of 12 months is a poor prognostic factor [12, 16, 19]. However, this may be too simplistic of a view. In a series of children having all developed epilepsy before the age of 1 year, the main factor of poor prognosis was not the age at seizure onset, rather the age at surgery, with the best results in infants as compared to older children [18].

Regarding postoperative cognitive outcome, as for the other series reporting epilepsy surgery in infants and young children with catastrophic epilepsies, the young age at surgery, seizure freedom, and drug discontinuation are good prognostic factors for cognitive improvement [25]; moreover, it has been shown that the cessation of the seizures at an early age is a major factor in preventing the development of autism [18].

Early surgery might positively affect neurodevelopmental trajectory in some patients, even though data on cognitive outcome are still to be confirmed with longitudinal studies. Considering the strong correlation between epilepsy duration and neurocognitive outcome, all patients with TSC ought to be referred early to a dedicated epilepsy center for individually tailored presurgical evaluation by a multidisciplinary epilepsy surgery team [26].

Structural Imaging

MRI may show multiple cortical hamartomatous malformations known as “tubers” and subependymal nodules. The pathology of the cortical tubers is similar to type 2b cortical dysplasia (see Chap. 4). They are cortical glioneuronal hamartomas that alter the cellular morphology. The tubers are generally triangular, vary in size, and point to the ventricles, the majority involving the frontal lobes. The number of tubers may range from a solitary lesion to over a 100 within both cerebral hemispheres, one of the main challenges in determining which tubers are epileptogenic or quiescent. Several investigators have attempted to predict the epileptogenicity of certain tubers. Cystic tubers on magnetic imaging studies, for example, are associated with TSC2 gene mutation and intractable seizures [27]. Tubers with *subcortical hypointensity* on volumetric T1, hyperintense signal on T2-weighted images, and heterogeneous signal on fluid-attenuated inversion recovery (FLAIR) images

with characteristic hypointense central region surrounded by a hyperintense rim are associated with more severe neurological forms [28]. These "cyst like" tubers frequently are calcified and CT scan can be helpful to enhance the visibility of such calcifications, mainly in infants and young children. However, any type of tubers, whatever the MRI characteristics, may be responsible for epilepsy and be part of an epileptic network.

When one or several seizure types are identified in a patient, it is important to identify the "candidate tuber" for each seizure type by assessing the *anatomo-electro-clinical* profile. In some patients with multifocal epilepsies or *Lennox-Gastaut* syndrome in whom the epileptic network fails to identify any candidate tuber, a palliative procedure such as corpus callosotomy or vagal nerve stimulation must be considered (see Chap. 3).

Functional Imaging

Several studies over the last three decades have shown that FDG-PET may be helpful for the presurgical localization of the seizure origin in adults and children with refractory focal epilepsy [29–31]. Its localization value has been enhanced with co-registration to the structural MRI [32].

In children with TSC, presenting with multiple tubers over one or both cerebral hemispheres and failure of the interictal/ictal *video-EEG* telemetry to sufficiently capture the seizure foci, interictal *FDG-PET* may show several hypometabolic areas that correspond to the different tubers. It has a high degree of sensitivity but low specificity concerning the epileptogenic lesion in TSC patients [33]. Therefore, FDG-PET as a single investigation tool cannot sufficiently differentiate the epileptic from non-epileptic tubers. It may, however, contribute in a multimodal diagnostic approach.

Interictal magnetoencephalography/magnetic source imaging seems to be a promising newer presurgical investigation in focal epilepsy and particularly in children with TSC, when compared to the gold standard video-EEG recording [34]. This method can provide complementary neurophysiological information and should be considered as part of a noninvasive tool, if available [35].

Wu et al. [36] retrospectively studied 28 children with TSC, multiple cortical tubers, and intractable epilepsy by noninvasive means. Whereas they considered that their standard presurgical evaluation with *video-EEG*, *MRI*, and *FDG-PET* was insufficient to identify the epileptogenic tubers, an expanded protocol with *FDG-PET*/*MRI* co-registration and magnetic source imaging (MSI) was helpful to localize the epileptogenic zone. Eighteen of the 28 children thus explored underwent resective surgery with a seizure-free outcome of 67%.

Compared to FDG-PET, a higher specificity for detecting the epileptogenic lesion in patients with TSC and multiple cortical tubers seems to be obtained with the PET tracer alpha-methyl-L-tryptophan (*AMT*), which demonstrates an increased uptake in the epileptic tubers as compared to a decreased uptake in

non-epileptogenic tubers [37]. Being restricted to only few centers, the lack of availability has prevented this tracer to become more widely used in the presurgical evaluation of TSC patients.

Ictal HMPAO-SPECT (*single photon emission tomography*) is another noninvasive functional imaging evaluation that can successfully identify epileptogenic tubers in TSC patients [38]. The tracer should be intravenously injected once the seizure onset is identified. The localization value indicating the seizure focus is superior if the injection is rapidly performed after the beginning of the seizure. Subtracting ictal from interictal *SPECT* and co-registered with MRI (*SISCOM*) is a further development that has considerably enhanced the sensitivity and specificity of ictal SPECT in temporal and extratemporal neocortical focal epilepsies in adults and children [39]. The only inconveniences with this diagnostic tool are the necessity of continuous monitoring in a video-EEG unit and the reactivity of the medical personnel to rapidly inject the radioactive tracer within seconds from the seizure onset, the need of trained personnel handling radioactive material, and its availability by a nearby nuclear medicine department.

Electrophysiological Data

The presurgical assessment of patients with TSC and intractable epilepsy begins with a careful review of the long-term video-EEG monitoring. As for focal epilepsies of other etiologies, interictal abnormalities, all types of ictal patterns, and its corresponding clinical semiology should be scrutinized. All the previous EEGs must be carefully reviewed. One must bear in mind that connectivity might be altered in TSC patients with multiple cortical and subcortical lesions and that semiology may not follow the same patterns as observed in patients with a single focus. *Moreover*, the semiology of the seizures may be poor when compared to adult patients, due to the frequently younger age of seizure onset in TSC patients and lack of cooperation in case of mental retardation.

Indication and Methods of Invasive Exploration

Intracranial EEG monitoring is indicated when all prior noninvasive investigations have failed to identify the target tuber and its epileptogenic boundaries, or when eloquent cortex concerning mostly language or sensorimotor function is suspected to be within or neighboring the epileptogenic zone. In older children and cooperate patients, noninvasive techniques, such as functional *MRI* or functional mapping with *MEG*, can be used to establish hemispheric dominance and to provide an approximate map of eloquent brain areas. In contrast, cortical stimulation through intracranial electrodes has the advantage of identifying the precise anatomical relationship between the identified eloquent cortex with the seizure onset zone and its

spread patterns. *Furthermore*, it can be used in younger children and mentally delayed patients, particularly for language mapping where simplified test paradigms can obtain reliable results [40].

There are basically two surgical techniques for chronic intracranial EEG recording, the *subdural electrodes*, i.e., arrays of disk electrodes arranged in the form of rectangular multiple row grids or single row strips that are placed during craniotomy under visual control over the cerebral surface, and the *stereotactically implanted* multiple depth electrodes (*stereo-EEG*, or *SEEG*) [41]. Following the electrode implantation surgery, the patient is monitored over a period of several days in order to record at least one spontaneous seizure. If the patient has presented more than one type of seizures, each type should be ideally recorded at least once during the monitoring period.

Both methods have their advantages and disadvantages. Subdural grids will allow a dense and continuous coverage of large cortical areas over the brain convexity [41]. This density together with the relatively large diameter of each electrode disk will also provide more reliable results when electrical stimulation is required for functional mapping, in particular concerning the language-related areas. Depth electrodes with their thin diameter of roughly 1 mm can only allow a limited spatial sampling of brain volume, which can miss EEG activity "in between" the electrodes concerning the seizure localization. They are less suited for mapping cortical functions that are more dispersed, such as over the language areas.

On the flip side, each depth electrode can contain between 5 and 20 contacts, depending on the length of the selected electrode *trajectory* that allows simultaneous recordings of the brain convexity, intermediate and deep cortical structures, such as the depth of a sulcus, the insular cortex, the mesiotemporal region, or the deep mesial hemispheric surface.

The SEEG method facilitates the electrode placement within several distant and even bilateral anatomical targets with stereotactic precision. The analysis of the SEEG recordings will thus give a three-dimensional view of the seizure origin and its propagation, if the anatomical position of each depth electrode had been carefully chosen according to a pertinent working hypothesis.

See illustrative case – Figs. 49.1, 49.2, 49.3, 49.4, 49.5.

The SEEG technique is certainly less invasive when compared to an exploration with subdural grids, and it is particularly well tolerated in children and infants. Its feasibility, however, depends on a minimum thickness of the skull bone for fixing all depth electrode-guiding anchor bolts. It can thus only be performed in children older than 2 years of age, whereas subdural grids can be proposed in even very young infants [41].

A *third technique* for performing intracranial EEG, historically the oldest, is the direct cortical recording during the epilepsy surgery, also called *intraoperative electrocorticography* (ECoG), which was pioneered by Penfield and Jaspers in the early 1950s [42]. This recording is limited to the interictal EEG, since it is performed under general anesthesia and during a short time window between opening of the

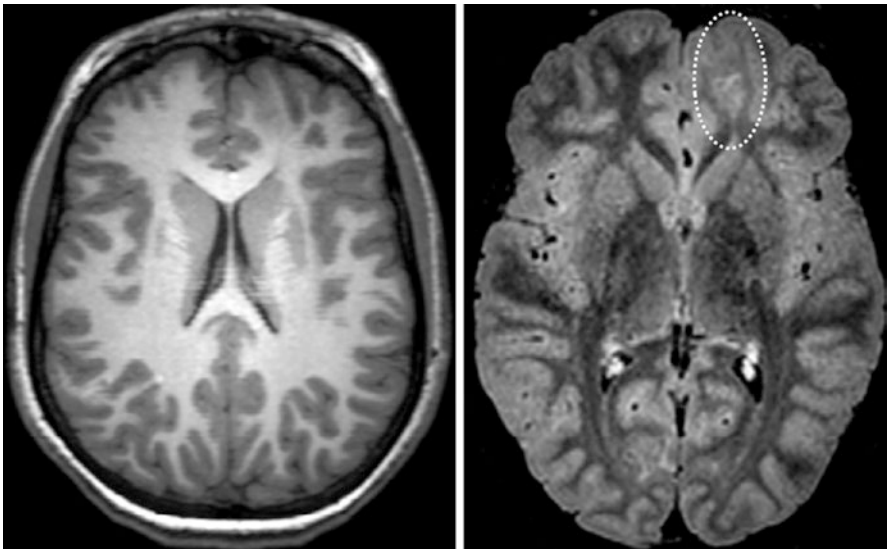
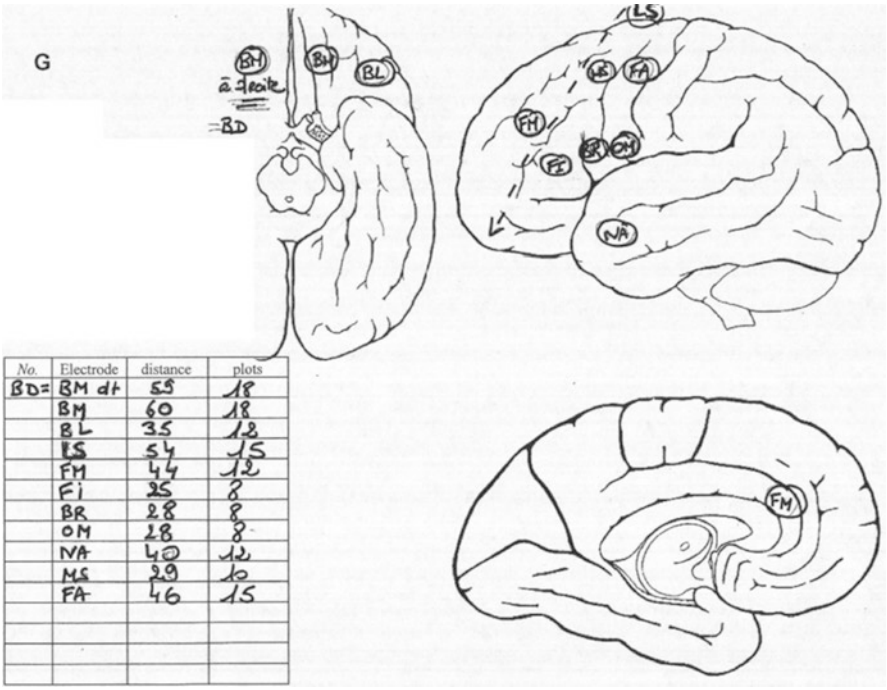


Fig. 49.1 MRI of an 8-year-old girl with TSC and drug-resistant focal epilepsy. She presented with frequent seizures since the age of 19 months, including asymmetric infantile spasms, with a progressive developmental and language regression. The wide interictal epileptic focus on scalp EEG was anterior bifrontal and temporal, mainly left-sided. The EEG recording of the seizures oriented towards the left anterior frontal lobe but the corresponding clinical semiology was not consistent. This high-resolution MRI, including axial T1-weighted (*left*) and fluid-attenuated inversion recovery (FLAIR) (*right*) sequences, reveals a left anterior frontal lesion (*white dotted oval*), suspected to be mainly responsible for her seizures. The radiological aspect, including the transmantle sign, evokes a focal cortical dysplasia type 2

dura and the surgical removal of the epileptic brain area. It can be of considerable value if the patient's EEG demonstrates focal and frequent interictal epileptiform activity, such as repetitive and rhythmic spikes, polyspikes, or waves. This is characteristically observed in patients with focal type 2 cortical dysplasia [42], but also in EEG recordings over epileptogenic tubers and the surrounding perituberal cortex in TSC patients [5], thus delineating the boundaries of resectable cortical area.

Conclusion

Recent publications report on an increasing number of operated patients with TSC and epilepsy. Case series and meta-analyses all agree that a 50–60% long-term seizure freedom can be achieved after curative surgery. A *presurgical* workup should be started as early as possible once two appropriate antiepileptic drug trials have failed. This could, in the future, lead to an increased percentage of TSC patients



No.	Electrode	distance	plots
BD=	BM dt	55	18
	BM	60	18
	BL	35	12
	LS	54	15
	FM	44	12
	Fi	25	8
	BR	28	8
	OM	28	8
	NA	40	12
	MS	29	10
	FA	46	15

Fig. 49.2 Scheme of the intracranial multiple stereo-EEG electrode placements, as decided after case presentation and discussion in the presurgical multidisciplinary epilepsy staff round. This is basically an extensive left frontal lobe exploration. An additional electrode in the left anterior temporal lobe targeting the amygdala (*NA*) and a contralateral right anterior and mesial frontal electrode (*BD*) complete the areas to be explored. The suspected cortical dysplasia in the left anterior and inferior frontal region is explored with the electrodes LS, BM, BL, FI and FM being located in the closer proximity

undergoing surgery. Direct surgery is feasible when there exists a clear electroclinical and MRI correlation concerning a suspected lesion. *Further* noninvasive investigations as well as invasive EEG recording are often mandatory in more complex cases with discordant results. The *goal* of *curative* epilepsy surgery is to achieve seizure freedom through removal or complete isolation of the epileptogenic zone. In some TSC patients with multifocal seizure onset or generalized epilepsy, partial resections and palliative procedures can be considered in order to reduce the seizure burden and ameliorate quality of life.

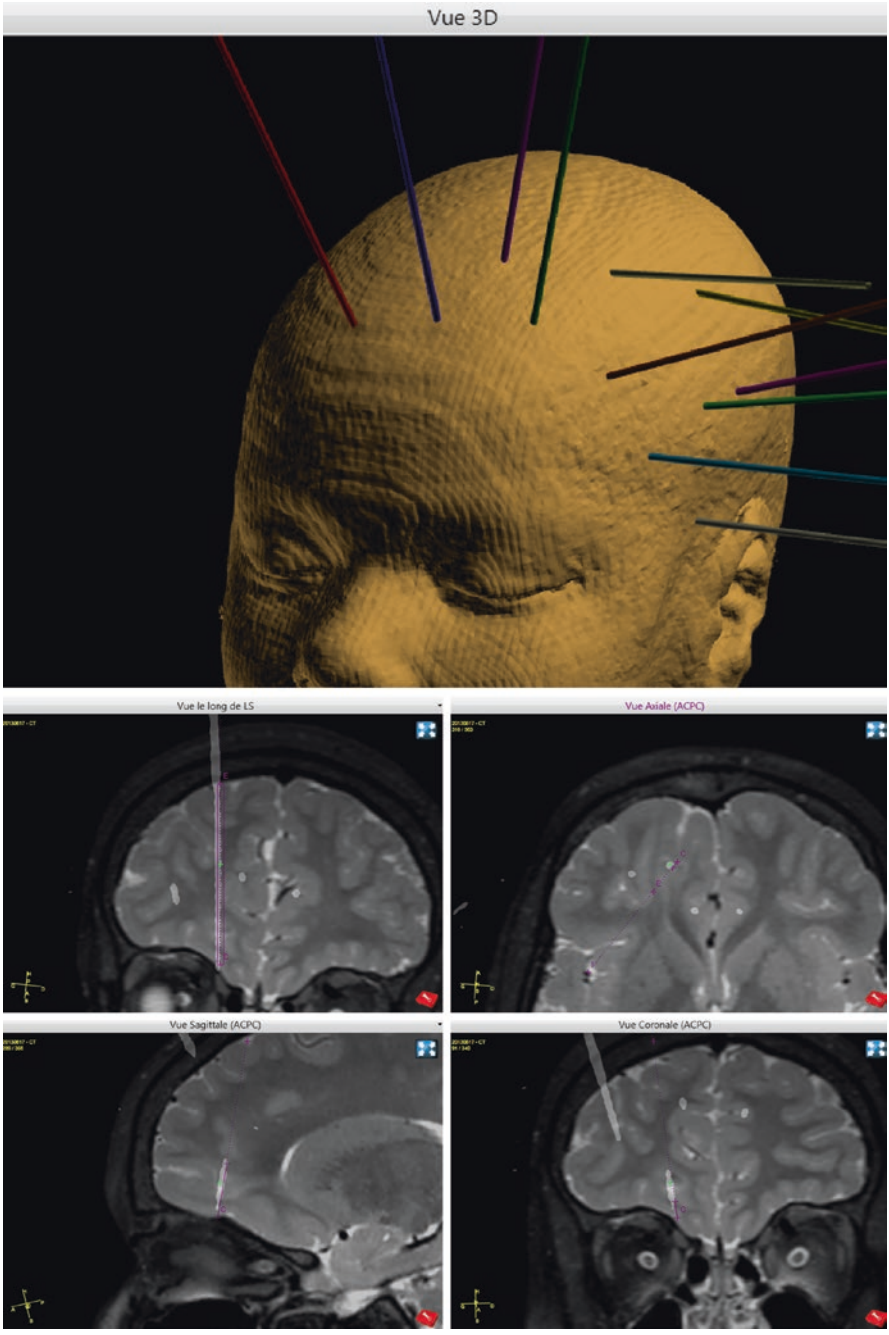


Fig. 49.3 3D aspect of the orientation and skin entry point of all SEEG electrode trajectories. Below: Fusion of the MRI with a postoperative CT showing the implanted SEEG electrodes. The trajectory (purple line) of the electrode LS which traverses the lesion has a vertical orientation. Several smaller white spots correspond to contacts of nearby placed electrodes

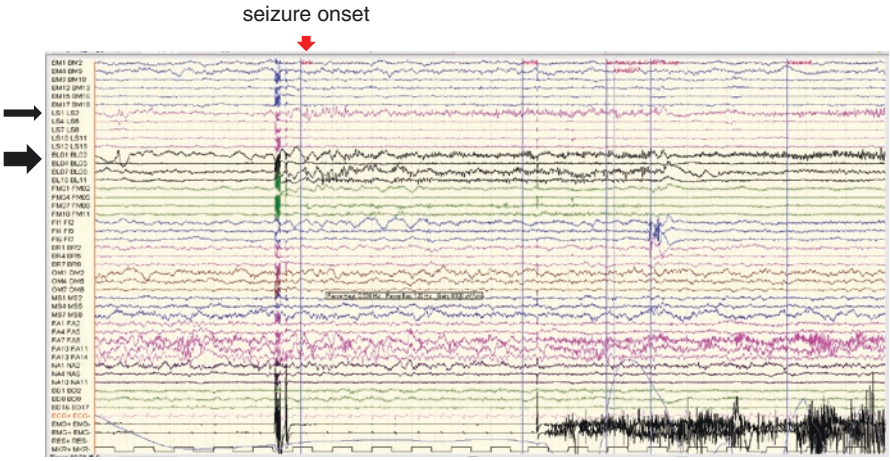


Fig. 49.4 SEEG recording with seizure onset, implying initially the deepest contacts of the electrodes LS and BL (black arrows)

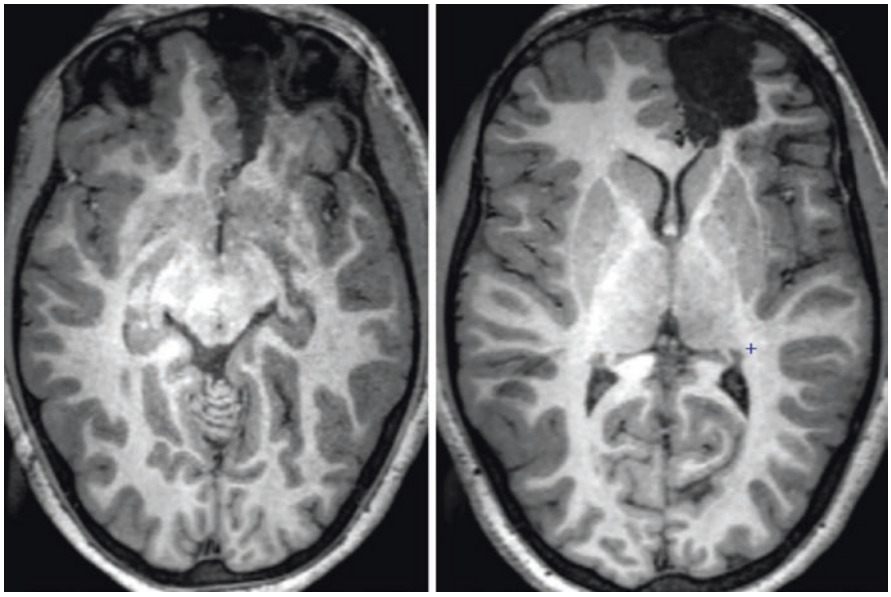


Fig. 49.5 Postoperative axial T1-weighted MRI performed 3 months after a tailored anterior frontal resection of the epileptogenic zone as indicated by the electrode contacts implied in the seizure onset and immediate propagation. This epileptogenic zone went beyond the MRI-visible lesion and included also the fronto-basal and fronto-mesial cortex. Histology confirmed focal cortical dysplasia, type 2b. The young girl is since seizure-free and off medication for over 6 years

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Chapter 50
Managing Epilepsy in Neurocutaneous Disorders

Cliff Hampton and Ramsis Benjamin

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Introduction

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures [1]. In neurocutaneous disorders, seizures may precede the clinical diagnosis in 40% of cases, and about a third will show psychomotor delay, particularly in the three most common disorders: tuberous sclerosis complex, neurofibromatosis, and Sturge-Weber syndrome [2]. The age of onset ranges between 3 months and 5 years. Seizures in younger life are linked to a poor neurological outcome, and early aggressive control may prevent the detrimental neurodevelopmental effects of epilepsy.

In some neurocutaneous disorders, the mechanisms responsible for generating epilepsy have been elucidated, such as over-activation of the mTOR or Ras pathways, cortical dysgenesis or malformation, channelopathies, cerebral calcifications, and astrogliosis [3]. As with epilepsy syndromes resulting from other causes, the goal is prevention of seizures and reduction of developmental delay due to epileptic

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encephalopathy. Antiseizure medications act as first-line treatment, and surgical resection of epileptogenic foci is reserved for pharmacologically refractory, localization-related cases. Neuromodulation with vagus nerve stimulation, responsive neurostimulation, or deep brain stimulation of the anterior thalamic nucleus can also be used to reduce seizure frequency in instances where the risks of surgical resection exceed potential benefits, such as poor outcomes from the resection of eloquent cortex or in multifocal epilepsy [4–6].

Epilepsy in Tuberous Sclerosis Complex

The prevalence of epilepsy in individuals with tuberous sclerosis complex (TSC) is very high, above 85% in studied cohorts, and is a significant source of morbidity and mortality (see Chap. 27) [7–10]. It is unclear how cortical "tubers" cause seizures, though abnormalities in glutaminergic and γ-aminobutyric acid receptor subunits, as well as abnormal glutaminergic transport in astrocytes, have been observed in mouse models with tuberous sclerosis [11]. In a large tuberous sclerosis registry, 38.9% of patients presented with infantile spasms, and 67.5% with focal seizures [12]. Older children and adults with TSC can develop multiple seizure types including both generalized and focal seizures. Managing epilepsy in the setting of tuberous sclerosis has a few important nuances when compared to the treatment of epilepsy in general.

First generation antiseizure drugs are poorly tolerated, pose significant drug-drug interaction, and are typically ineffective in patients with TSC. Vigabatrin (γ-vinyl-GABA), a second generation agent, is an irreversible inhibitor of γ-aminobutyric acid transaminase with proven efficacy in reducing infantile spasms, possibly by increasing the concentration of γ-aminobutyric acid [13]. Marked reduction in infantile spasms has been shown with vigabatrin administration, and it is recommended as the primary treatment for infantile spasms [14]. However, it is important to note that most prior studies have evaluated clinical cessation of infantile spasms rather than the resolution of hypsarrhythmia on EEG, which is a severely disorganized interictal brainwave pattern (Fig. 50.1).

Additionally, long-term exposure to vigabatrin may produce a relatively common and serious adverse effect of irreversible visual field loss due to retinal toxicity [15]. Vigabatrin can also cause T2-weighted hyperintense signal changes in the basal ganglia and brainstem on magnetic imaging studies. These appear to be asymptomatic and reversible, unlike the retinal toxicity, but awareness of this phenomenon is important when monitoring patients who are taking vigabatrin [16]. Despite these limitations, there is emerging evidence that in cases of tuberous sclerosis, aggressive treatment of seizures with vigabatrin may reduce not only infantile spasms, but other clinical seizures and even the incidence of drug-resistant epilepsy, thus improving the natural course of the disease process [17].

Everolimus and sirolimus inhibit the mammalian target of rapamycin (mTOR) (see Chap. 27), a serine-threonine kinase in the downstream pathway of the PI3K/AKT (Fig. 50.2). In tuberous sclerosis, there is inactivation of the *hamartin* or

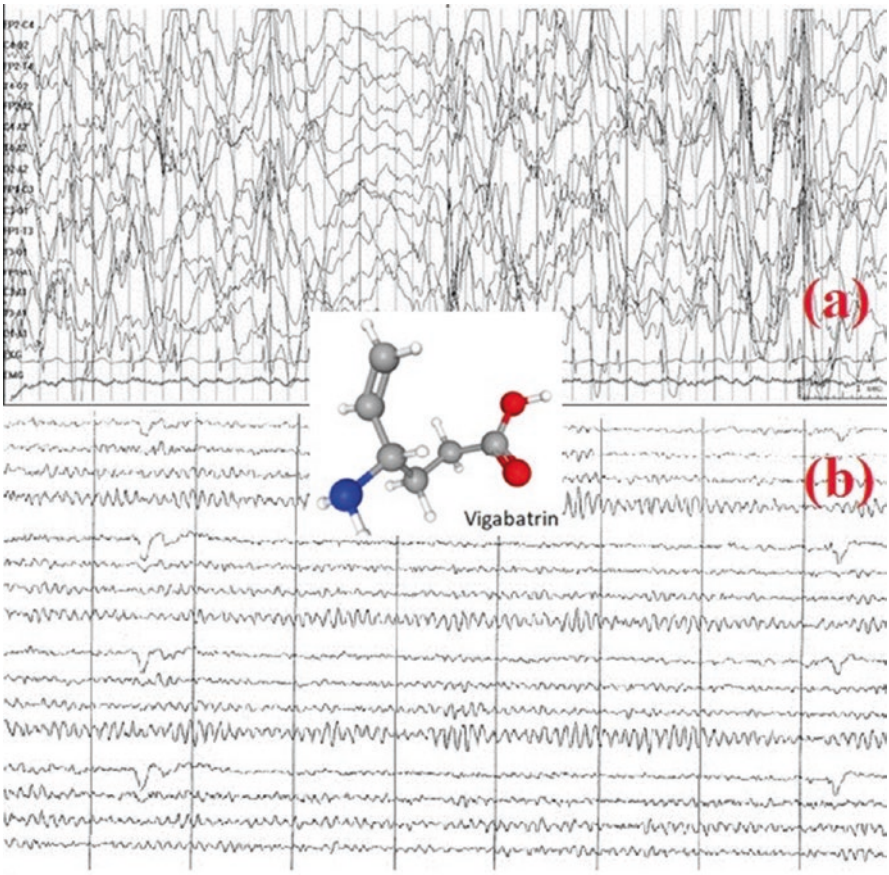

Fig. 50.1 Hypsarrhythmia in a child with infantile spasms (**a**) displaying a variable, chaotic, and dynamic electroencephalogram compared to a normal background rhythm (**b**). The insert is the molecular structure of vigabatrin (C6H11NO2), a 4-aminobutyrate-2-oxoglutarate transaminase inhibitor, the first-line treatment for infantile spasms

tuberin oncogene suppressors *TSC1* and *TSC2*, which normally provides a negative feedback loop to mTORC1.

Loss of *TSC1* and *TSC2* leads to activation of downstream signaling, which in turn produces hamartoma, subependymal giant cell astrocytoma, neuronal dysplasia, increased excitatory synaptic currents, and disruption of cortical laminar matrix. Inhibition of the mTOR pathway has a negative impact on tumor volume and growth and thus may indirectly improve seizure control and epileptogenesis [18]. Adjunctive everolimus administration, approved for the ages 2 years and older, has been associated with a 50% reduction in the rate of partial-onset seizures [19]. The recommended starting dose is 5 mg/m^2/24 hours, increased to achieve blood trough levels of 5–15 ng/mL. Pneumonitis and stomatitis are potential untoward effects and need to be monitored closely.

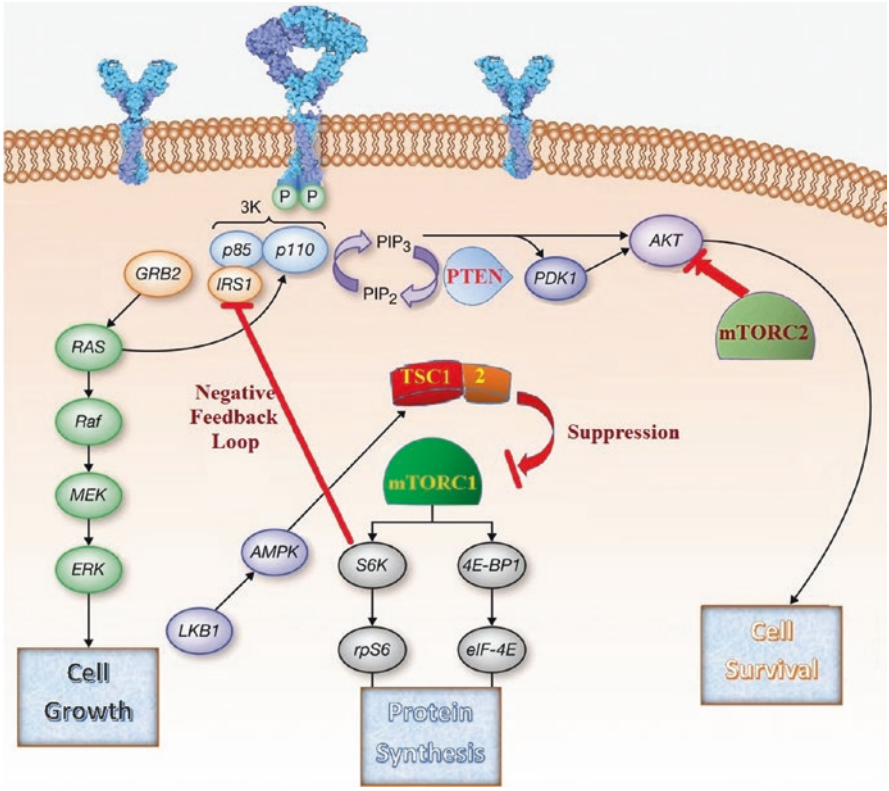

Fig. 50.2 Intracellular signaling pathway of mTOR and its relation to TSC1/2 in maintaining cellular homeostasis in response to growth factors

Medically refractory epilepsy is common in patients with tuberous sclerosis, necessitating surgical consideration (see Chaps. 48 and 49). Because an individual may have multiple types of seizures arising from disparate brain lesions, careful correlation of the seizure type with the epileptogenic locus and weighing risks of surgical resection against potential benefit is essential [20]. Long-term video EEG monitoring combined with conventional MRI remains the standard means of correlating clinical events with anatomic lesions, but often advanced imaging and neurophysiological studies with SPECT, PET, electrocorticography, or stereo-EEG are also utilized to identify surgical resection targets. It is important to recognize that the epileptogenic zone can extend beyond the borders of the known lesion and to plan any proposed resection accordingly. Despite all these challenges, appropriately chosen surgical candidates with thoughtfully selected surgical targets can lead to good outcomes, with seizure freedom in possibly 55% of cases, as well as significant improvement in quality of life [21–23].

The use of strict ketogenic diet has been studied particularly in patients with TSC and demonstrates good efficacy in seizure reduction, but it is difficult to sustain long-term adherence [24].

Vagus nerve stimulation has also been investigated in this setting and found to be safe and effective for medically refractory cases deemed not ideal for surgical resection, showing improved outcomes in seizure frequency, cognitive and neuropsychological functioning, and overall quality of life [25]. While responsive neurostimulation and deep brain stimulation (DBS) have not been systematically studied specifically in tuberous sclerosis, their general usefulness in focal onset epilepsy syndromes warrants their consideration in medically refractory epilepsy related to tuberous sclerosis [26].

Infantile Spasms

Infantile spams (IS) are synonymous with West syndrome, after Dr. William James West, an English surgeon and apothecary, who first described them in 1841 in his own son, James Edwin West [27]. The spasms are characterized by a sudden epileptic stiffening of the body and 1–2 seconds of internal-external rotation of the arms ("Jackknife" or "Flexor" seizures), invariably during awake phase and not when asleep. Developmental delay coexists. The spells first manifest within the first 12 months of life.

Electroencephalogram recordings often include the characteristic finding of hypsarrhythmia, although in cases of tuberous sclerosis with infantile spasms, there is a significant percentage of children that do not exhibit this finding on the EEG (see Chap. 27). Infantile spasms are associated with a number of underlying neurologic disorders, but are particularly common in tuberous sclerosis complex [28]. However, infantile spasms are also seen less commonly in other neurocutaneous disorders including neurofibromatosis type 1 and Sturge-Weber syndrome [29, 30].

In cases of early refractory epilepsy, especially in those presenting with infantile spasms, neurodevelopmental delay is to be expected [31]. Whether cognitive impairment is due to uncontrolled seizures themselves or to other independent causes is not known, but early treatment of infantile spasms does appear to ameliorate neurodevelopmental markers [32].

Hormonal therapy with high-dose steroids, either prednisolone or adrenocorticotropic hormone (*ACTH*), has been studied and found effective for early treatment of IS. A notable exception, however, is in the specific case of tuberous sclerosis, where response to vigabatrin has been shown to be superior to hormonal therapy. Vigabatrin should be used as a first-line treatment for IS in the setting of tuberous sclerosis, hormonal therapies being reserved for cases where vigabatrin is not an option [14].

Epilepsy in Sturge-Weber Syndrome

Sturge-Weber syndrome (SWS) is associated with vascular malformation and neurologic demise due to somatic mutations in *GNAQ* which may cause hyperactivation of mTORC1 pathway. (The vascular proliferation is via the AKT-mTORC2 pathway in response to VEGF; see Fig. 50.2.) The prevalence of epilepsy is 75–90% in SWS. Risk for epilepsy can be predicted based on clinical examination as approximately 70% of individuals with unilateral facial leptomeningeal capillary malformations and 90% of those with bilateral facial involvement will develop epilepsy (see Chap. 5). Most presentations occur within the first 2 years of life, and focal motor seizures are often the presenting symptom [33]. Infantile spasms, tonic, atonic, or myoclonic seizure types can be less commonly seen [34].

Sturge-Weber-associated epilepsy has a characteristic pattern of sporadic "seizure clusters" wherein multiple seizures occur in a 24-hour period, followed by variable lengths of time with relative seizure freedom [35]. These "seizure clusters" are thought to possibly contribute to the epileptic encephalopathy that can occur in patients with SWS-related epilepsy. Brain atrophy due to cerebrovascular insufficiency and calcifications that develop over time, as well as cortical malformations due to ischemia early in life, may ultimately underlie epileptogenesis in SWS, and conversely frequent clusters of seizures may also contribute to brain injury [36]. As in other epilepsy syndromes, seizure freedom is the goal and is achievable in the majority of cases [37].

Pharmacologic treatment with antiseizure medications is used as first-line therapy. Treatment should be initiated early, and there is evidence that presymptomatic treatment may improve long-term outcomes including cognitive delay [38]. Higher rates of seizure freedom were observed with oxcarbazepine and carbamazepine when compared to levetiracetam in one study [39]. Oxcarbazepine could be used as adjunctive therapy in children >2 years, and as monotherapy in >4 years, at weight-dependent dosing, but generally 8–10 mg/kg in divided doses, not to exceed 600 mg/day. It can be titrated weekly and adjusted with concomitant use of strong inducers of CYP3A4 enzyme or uridine glucuronosyltransferase (UGT). Thyroid function should be monitored routinely as hypothalamic/pituitary irregularity is naturally present in SWS and can independently occur with the use of oxcarbazepine.

Initial studies have found the popular home remedy cannabidiol well tolerated and effective as adjunctive treatment in SWS-related epilepsy [40].

Because disease progression in Sturge-Weber probably involves recurrent thrombosis and venous stasis, the use of low-dose aspirin (3–5 mg/kg/day) has been studied and appears not only to improve neurodevelopmental outcomes but also to reduce the frequency of seizures [41]. The reason for this phenomenon is not entirely clear, but it is believed that aspirin blocks NR2A-containing NMDA receptors which prevents pilocarpine-induced limbic seizures, as well as facilitating the calcium-dependent release of glutamate [42, 43].

Surgical options include complete or incomplete focal resection/lobectomy or hemispherectomy for patients with extensive hemispheric disease (see Chap. 48)

[35]. In appropriately selected patients, surgery can be effective for seizure reduction at any age, but early intervention may have further benefit of preventing developmental decline due to epileptic encephalopathy [44, 45].

Epilepsy in Neurofibromatosis Type 1

In published review series, the prevalence of seizures varies from 7% to 14% in neurofibromatosis type 1, probably owing to the differences in studied populations [30, 46]. While not as high as in tuberous sclerosis or Sturge-Weber, seizures remain a source of morbidity and mortality for a significant percentage of individuals with neurofibromatosis type 1. Epilepsy in this population often presents initially as febrile seizures in young children and can develop either into localization-related epilepsy or generalized onset epilepsy later in childhood. Focal cortical dysplasia, gliomas, or other malformations of cortical development, as well as mesial temporal sclerosis, can be seen in cases of neurofibromatosis type 1 with localization-related epilepsy [30]. Epilepsy surgery in medically refractory cases should be considered, albeit in cases of NF1 with drug-resistant epilepsy, there are often multiple epileptogenic foci which complicate decisions regarding surgical resection (see Chaps. 26 and 48) [47, 48].

Other Neurocutaneous Disorders

The less well-known neurocutaneous disorders also have a higher predilection for developing epilepsy, generally as a result of structural anomalies such as malformations within the parenchyma, or when associated with psychomotor insult. These conditions are discussed below and are referenced in various chapters of this textbook. Table 50.1 outlines the semiology of seizures most commonly observed in some of these disorders and the potential treatment options.

Ataxia-telangiectasia presents with hyperkinetic movement disorders that include dystonia, chorea, and tremors. Patients with A-T may startle easily and exhibit stimulus-sensitive "dystonic jerks" and myoclonus, occasionally as presenting symptoms, and partially responsive to levodopa and not antiseizure agents [49, 50].

Neurological abnormalities and seizures occur late but in half of the patients with Chédiak-Higashi syndrome. Generalized seizures predominate, requiring multiple agents for control. The exact etiology of epileptogenesis is unclear, but infusion of cytoplasmatic granules into the leptomeninges and anti-NMDA receptor antibodies have been detected in the CSF [51].

Children with the classic form of Menkes disease, related to copper derangement, present at 2–3 months of age with truncal hypotonia and generalized seizures [52].

Central nervous system involvement in hypomelanosis of Ito occurs in 70% of cases. Seizures are believed to be related to tumor burden, such as choroid plexus

Table 50.1 Types of seizure disorder seen in various neurocutaneous disorders

Neurocutaneous disorders	Semiology of seizures	Treatment	Chapter
Tuberous sclerosis complex	IS, F/C, T/C	Vig, Oxc, CBZ, everolimus	27
Sturge-weber disease	F/C, IS, T, MC, aT	Lam, lev, lac, Vig, Oxc, CBZ	5
Neurofibromatosis	Febrile, F/C, T/C, IS	Lam, lev, Oxc, Vig, CBZ	26
Ataxia-telangiectasia	Stimulus-sensitive MC, "dystonic jerks"	Levodopa	6
Atypical form, Chédiak-Higashi	T/C	Lam, lev, lac, Oxc, CBZ	33
Menkes disease	T/C, hypotonia	Lev, lac, Oxc, CBZ	43
Hypomelanosis of Ito	T/C, MC, IS	Lam, lev, lac	7
Xeroderma pigmentosa	CPS	Lev, lam, lac	31
Cerebrotendinous xanthomatosis	T/C, IS	Lev, lam, lac	32
Neurocutaneous melanosis	IS, MC, T/C	Vig, VPA, lev, lam, lac	11
Sjögren-Larsson syndrome	T/C	Lev, lam, lac	45
Incontinentia pigmenti	F/C, IS	Lev, lam, lac, Vig	8
Xeroderma pigmentosum	T/C	Lev, lam, lac	31

aT atonic; *CBZ* carbamazepine; *CPS* complex partial seizures; *F/C* focal clonic; *IS* infantile spasms; *Lac* lacosamide; *Lam* lamotrigine; *Lev* levetiracetam; *MC* myoclonus; *Oxc* oxcarbazepine; *T* tonic; *T/C* tonic-clonic; *Vig* vigabatrin.

papilloma and hemimegalencephaly, autism, hypoplasia of the corpus callosum, and cortical malformation (neural heterotopia). Seizures are frequently generalized tonic-clonic or myoclonic, and afflict 30% of the cases, often resistant to therapy. Rarely infantile spasms occur [53, 54].

Neurocutaneous melanosis may present with intractable daily infantile spasms and myoclonic seizures starting at the age of 2 months, due to melanocytic proliferation in the brain and hydrocephalus [55].

The autosomal recessive *Sjögren-Larsson* **syndrome** is characterized by congenital ichthyosis, spasticity, intellectual disability, and seizures [56].

Incontinentia pigmenti, an X-linked dominant disease pertaining to *NEMO* gene, an essential component of the nuclear factor-kappa B (NF-kB) signaling pathway, present with focal motor-clonic rhythmic seizures and rarely with infantile spasms. Neonates have the characteristic skin lesions distributed on Blaschko lines [57]. For all other syndromes, please refer to Chaps. 6, 7, 8, 11, 33, 43, and 45.

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Chapter 51
Orthopaedic Problems in Neurocutaneous Disease

Michèle Kläusler and Erich Rutz

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Introduction

Neurocutaneous disorders or syndromes are conditions that affect the brain, spinal cord, organs, skin and bones. These diseases are lifelong conditions that can cause tumours to grow in these areas. Due to skin manifestations, they are often called neurocutaneous disorders. Most of them are rare, and as there is no cure at this timepoint, the focus of the treatment should include the management of the symptoms, therefore. Based on our experience, a patient is best treated by an interdisciplinary team approach.

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Orthopaedic problems might include spinal deformities, growth disturbances and joint instabilities or contractures. Due to accompanying skin problems, conservative treatment options including orthoses or braces might be difficult for such neurocutaneous conditions, in particular.

Neurofibromatosis Type 1

Orthopaedic Problems

Neurofibromatosis type 1 (NF-1), also known as von *Recklinghausen* disease, is an autosomal dominant disease (see Chap. 26). Management of the orthopaedic problems is often difficult [1].

Spinal Deformity: In 49% of patients with NF-1, spinal deformity has been reported. Spinal deformities may develop from osteomalacia, intraspinal neurofibromas that erode and infiltrate bone, endocrine disturbance, but often the definitive aetiology remains unknown [2]. There have been reports of several dystrophic changes, which include rib pencilling, vertebral scalloping, dumbbell lesions and dural ectasia.

The definition of rib pencilling is a rib whose width is narrower than the narrowest portion of the second rib. It is the most prevalent dystrophic osseous change. These ribs show more often dislocations, and there have been reports of it entering the spinal canal, which might cause paralysis [3].

Vertebral scalloping, or marginal erosion, can be seen in radiographs, and posterior scalloping is the most common in NF-1. There is an association between posterior scalloping and the presence of intraspinal pathologies [4].

The presence of neurofibromas can cause dumbbell lesions. The name originates from the dumbbell-like shapes caused by the expansion outwards through the neural foramina.

Dural ectasia is the circumferential dilatation of the thecal sac. It erodes the surrounding osseous structures and is meant to be caused by elevated pressure in the dural sac. Because it is thinning the surrounding osseous elements, it can end in significant instability and deformity, even leading to vertebral destabilization.

Less common dystrophic changes are spindling of the transverse process, vertebral wedging and rotation, foraminal enlargement, widened interpedicular distance and dysplasia of the pedicles [1].

Scoliosis: Patients with NF-1 can develop dystrophic and nondystrophic scoliosis. Although dystrophic scoliosis presents less common, it is more severe than nondystrophic scoliosis [2].

Nondystrophic scoliosis progresses at a similar rate as adolescent idiopathic scoliosis and shows a similar clinical appearance, even though it has an earlier onset and poorer prognosis than adolescent idiopathic scoliosis. It requires a careful follow-up, because a modulation in which dystrophic characteristics develop over time can occur [3].

It is necessary to perform an early scoliosis screening and regular follow-up for patients with NF-1. When there is a diagnosis of scoliosis, all patients with NF-1 should receive a further investigation with an MRI to rule out dystrophic changes (Fig. 51.1).

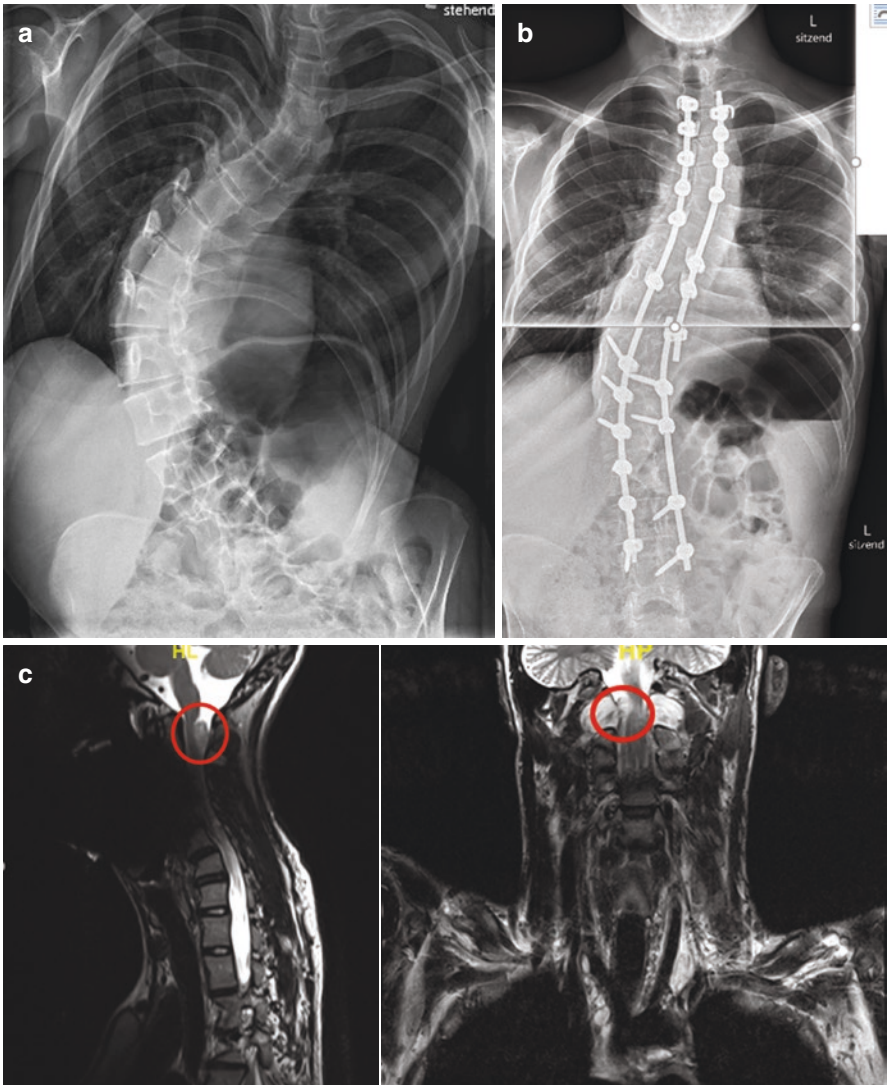

Fig. 51.1 Pre- (**a**) and post-operative (**b**) radiographs of a 17 year old patient with NF. The routine preoperative MRI scan (**c**) showed a neurofibroma compressing the myelon on level C1/C2, which had to be removed by the neurosurgeon before scheduling the patient for operative treatment with posterior spondylodesis for his scoliosis

A characteristic of *dystrophic scoliosis* is rapid progression, which despite treatment leads to severe deformity. The curves are sharply angulated segments of four up to six vertebrae in combination with one or more osseous abnormalities, which were mentioned previously [5].

A classification of dystrophic curves has been established, where curves according to their pattern are divided into two groups: type I, scoliosis in the coronal plane and a kyphosis in the sagittal plane measuring less than 50°, and type II, additional significant kyphosis (>50°) [5]. Dystrophic curves with their complex and severe nature and the risk of neurological injury are a great challenge to orthopaedic surgeons.

Other Spinal Abnormalities: Abnormalities of the cervical spine in patients with NF-1 are common (up to 30%) [6]. They might present with neck pain or neurological symptoms, but many are asymptomatic. Therefore, screening of the cervical spine is important. There have been reports of an association of spondylolisthesis with NF-1, although it is unclear whether the incidence is higher for these patients than in general population. Usually it is found in combination with foraminal neurofibroma or dural ectasia [1].

Congenital Pseudarthrosis of the Tibia: Congenital pseudoarthrosis of the tibia (*CPT)* is commonly found in NF-1 patients. Only 5% with NF-1 are diagnosed with *CPT*, but 75% of all patients with *CPT* have NF-1.

When in conjunction with NF-1, CPT is found as an anterolateral bowing of the tibia and typically presents in the first year of life, rarely at birth. The anterolateral bowing might be coupled with spontaneous fracture, which is followed by pseudoarthrosis, which is a common complication in patients with NF-1 [1].

Bony Dysplasias: In less frequent patterns, pseudoarthrosis has also been found in other long bones like humerus, radius, ulna and clavicle [3]. Furthermore, pelvic dysplasias have been observed.

Metabolic Bone Disorders: Multiple studies have shown decreased bone mass in the NF-1 population (including children). The lowest bone mass was found in the lumbar spine [1].

Growth Patterns: One of the most recognized characteristics of NF-1, which can lead to a distorted appearance, is the overgrowth of some or all tissues in one region of the body. This has been described as unilateral segmental hypertrophy or giantism. Furthermore, subperiosteal bone growth has been found in NF-1 which results in irregular bone elongation [4]. Another trend is short stature, which affects 13–40% of children with NF-1 [5].

Orthopaedic Management

Nondystrophic Scoliosis: As in adolescent idiopathic scoliosis, nondystrophic scoliosis is treated based on the degree of curvature. Curves <20° will be observed. Curves measuring 20° to 40° in skeletally immature patients should be braced. For

curves greater than 40°, fusion is recommended. Whereas posterior instrumentation can be successful in treating less severe nondystrophic curves, anterior fusion is recommended for curves greater than 90° [6].

Dystrophic Scoliosis: In general, bracing is not effective in preventing progression. Curves <20° can be observed with a follow-up usually every 6 months to monitor progression. For curves greater than 20° to 40°, surgery is recommended [7]. For type I dystrophic scoliosis, posterior fusion alone might be sufficient [8], although it is associated with high rates of pseudoarthrosis [9]. For type II dystrophic curves, a more aggressive surgical management is indicated with a more extensive anterior-posterior approach [8, 9].

Congenital Pseudarthrosis of the Tibia: The management of CPT is difficult. Nonsurgical management includes bracing with a knee-ankle-foot orthosis or an ankle-foot orthosis, although casting rarely results in union in patients with CPT. It can be used to prevent fracture in a dysplastic bone and can be used to delay surgical intervention if the dysplastic bone is fractured.

Common surgical interventions are bone grafting with intramedullary fixation, external fixation and free-vascularized fibular grafting. All methods have the objective to maximize union through resection of the pseudoarthrosis. Stable fixation and correction of angular deformity are important for healing. When multiple surgical attempts have failed, amputation might be the best solution [1].

Growth Patterns: To achieve both cosmetic and functional improvement, surgical equalization of limb length may be indicated.

Ataxia-Telangiectasia

Orthopaedic Problems

Ataxia-telangiectasia (AT) is an autosomal recessive neurodegenerative and immunological disease. Growth retardation can be found in a subset of patients (see Chap. 6). For a majority of patients, initial signs of the disease are truncal ataxia as well as ataxia of stance and gait starting at the age of 1–2 years.

The initial improvement of gait and stance delays the diagnosis of AT a crucial period of time. The cerebellar tremor occurs inconstantly in variant around the age of 12–34 years. Usually patients become wheelchair-bound around the end of the first decade or beginning of second decade of life due to progression of ataxia and hypotonia. Choreoathetosis and dystonia are the most frequent extrapyramidal problem in older children [10]. Myoclonic jerks of limbs may also be present in addition to dystonic posturing of fingers. Clinical signs of peripheral neuropathy and subsequent progressive spinal muscular atrophy have also been described. Muscular atrophy and incipient areflexia are noted in most patients at the end of the first decade of life.

Orthopaedic Management

Peripheral neuropathy presents with consecutive muscle atrophy and malpositioning of extremities. Besides targeted injections of botulinum toxin in well-selected muscles mainly at the neck or lower legs, the treatment with ankle-foot orthoses (AFO) (Fig. 51.2) might be a solid treatment option for gait disorders due to ataxia [11]. Furthermore, intensive physiotherapy and a well-adjusted wheelchair as well as motor aids can be of help [12]. Rarely surgical lengthening of contracted muscles might be indicated.

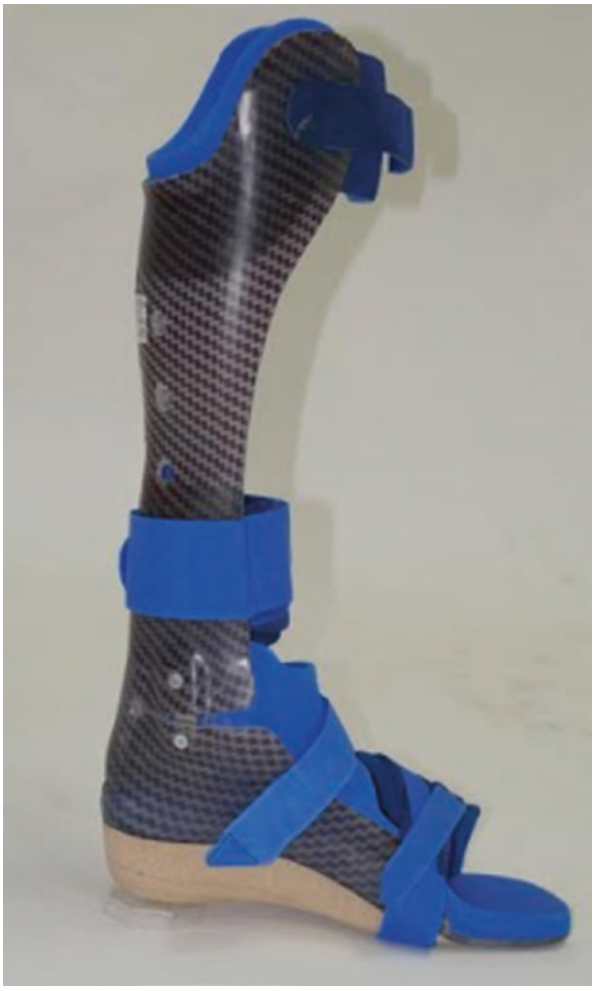

Fig. 51.2 Flexible Ankle-Foot orthosis (AFO) (Approved for publication by Basler Orthopädie René Ruepp AG)

Hypomelanosis of Ito

Orthopaedic Problems

Although hypomelanosis was first described as a purely cutaneous disease, later reports have included a 33–94% association with extracutaneous manifestations such as problems of the central nervous, musculoskeletal and ocular system [13].

Looking at specific orthopaedic problems, asymmetry of length or size of limbs and body parts along with joint contractures, particularly talipes, can be found. Around 20% of patients are at or below the third percentile of height. Another 20% of patients have a delayed skeletal maturation. Furthermore, kyphoscoliosis and scoliosis which is not requiring surgery as well as pectus excavatum and carinatum are frequently found. Other findings are small hands and feet, pes valgus or varus, genu valgus or congenital hip dislocations (see Chap. 7). Sometimes patients have polydactyly, ectrodactyly or syndactyly. It has to be said that craniofacial, limb and skeletal abnormalities are particularly common in patients who have chromosomal mosaicism [13].

Orthopaedic Management

All the neuroorthopaedic efforts should aim to maintain the ambulatory function. Therefore, in case of the presence of seizures or changed muscular tone, the orthopaedic treatment must address for optimal foot position including treatment with ankle-foot orthoses. Kyphoscoliosis and scoliosis might need a corset treatment, but rarely need surgery.

Incontinentia Pigmenti (Bloch-Sulzberger Syndrome)

Orthopaedic Problems

Incontinentia pigmenti (IP) (see Chap. 8) (Fig. 51.3).

The neurological involvement lies at around 20–30%, but there are only a few published series [14]. The main clinical expression of the CNS involvement consists of seizures, mental retardation, hemiparesis, spasticity, microcephaly, cerebellar ataxia and coma.

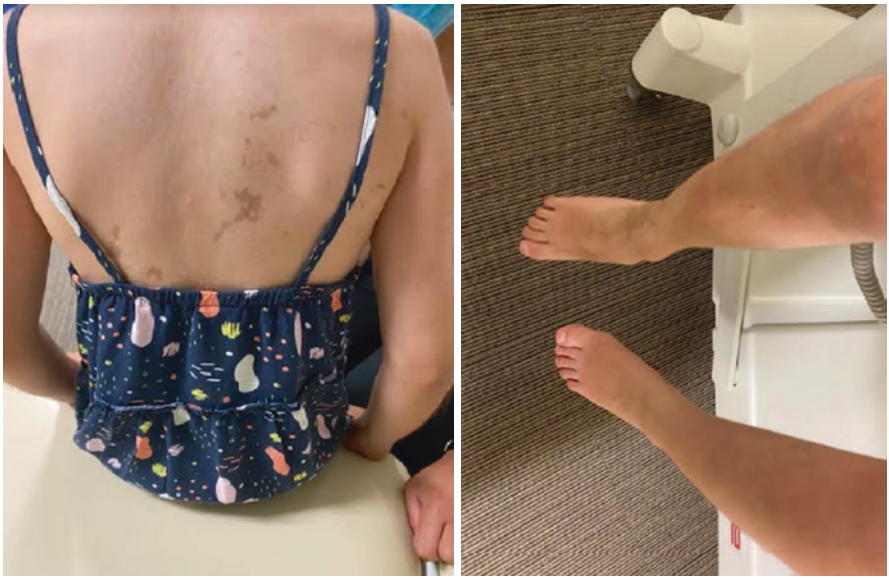

Fig. 51.3 7 year old patient with incontinentia pigmenti. She presented with increased tripping due to her excessive internal tibial torsion on the left side. A external derotational supramalleolar tibia osteotomy was planned

Orthopaedic Management

The neuroorthopaedic treatment is similar as the one for hypomelanosis of Ito and should aim to maintain the ambulatory function. Developmental milestones should be closely monitored.

Klippel-Trenaunay Syndrome

Orthopaedic Problems.

Klippel-Trenaunay syndrome (see Chap. 9).

Skeletal and soft tissue hypertrophy is one of the important characteristics of the syndrome. Usually a single lower extremity is involved. The increased length of the limb is due to bone hypertrophy, while the increased girth is a result of the soft tissue hypertrophy. There have been reports of limb discrepancies of up to 12 cm [15]. In about 29% of patients, syndactylies, macrodactylies, polydactylies and hip dysplasia have been reported [16].

Orthopaedic Management

Non-operative treatments include compression therapy. Minor leg length discrepancies can be managed by insertion of a lift in the contralateral shoe. In some cases of recurrent cellulitis, prophylactic antibiotics might be necessary. An indication for surgery is a projected leg length discrepancy of more than 2 cm. In this case, *epiphysiodesis* is often recommended to stop the growth of the abnormally long extremity. The timing therefore is crucial, and a careful assessment of the bone age is mandatory.

Sometimes digits with severe deformity, poor skin coverage or chronic infection may need to be amputated. Sometimes ray resection of a foot with or without debulking is indicated to improve gait characteristics. Amputation of a limb may rarely be necessary to improve function. The excision of venous or lymphatic malformations is technically challenging. Debulking procedures have limited usefulness and should only be considered when the excess bulk limits the function severely [17].

Epidermal Naevus Syndrome

Orthopaedic Problems

The major manifestations in patients with epidermal naevus syndrome (ENS) are epilepsy, development delay, intellectual disability and focal motor deficits (see Chap. 10). The presence of various forms of skeletal involvement has been reported in 68% of patients with ENS [18]. They include alterations of the cranium consistent with fibrous dysplasia as well as primary or secondary bony defects. There may be the presence of scoliosis in early infancy. Kyphoscoliosis is a common complication but might only become evident in late childhood. Any skeletal structure (calvarium, mandible scapula, ribs, vertebrae, pelvis and long bones of the extremities) can show a unilateral hypoplasia.

Some case reports have shown association between ENS and vitamin D-resistant rickets. There is a suggestion that the cause is the production of phosphaturic substances by the epidermal naevi. Clinical symptoms include body abnormalities, muscle weakness and bone pain. There have been reports of multiple bone fractures in the neonatal period. In some cases, hemicorporeal hypertrophy has been found [19].

Orthopaedic Management

A therapy plan needs to be adjusted individually to each patient. Also here it is important to maintain ambulatory function. Because scoliosis might be present in early childhood, the screening of the spine is important. For hemicorporeal

hypertrophy or unilateral hypoplasia of a skeletal structure, it might be necessary to use epiphysiodesis to stop growth or use lengthening procedures to lengthen short extremities.

LEOPARD Syndrome

Orthopaedic Problems

LEOPARD syndrome (LS) is a rare condition with multiple congenital anomalies, which are mainly skin, facial and cardiac anomalies (see Chap. 17). Skeletal anomalies include thorax anomalies including a broad chest, pectus carinatum or excavatum and are found in up to 75% of newborns [20]. Furthermore, we can see mandibular prognathism, scapular winging, scoliosis and joint hyperflexibility.

Orthopaedic Management

Growth parameters and musculoskeletal/neurological monitoring should be considered during follow-up. There are benefits for patients with hypotonia from physical and occupational therapy [21].

Orthopaedic Management in General

Gait disturbances in children with neuroorthopaedic conditions such as neurocutaneous disorders initially contribute to functional deformities which later become structural. Such findings might include bony deformities, joint contractures or joint instabilities. The main problem is increased energy consumption during gait and limited function in daily tasks. However, under normal conditions, energy consumption is optimal.

Therefore, correction of biomechanics towards normality improves energy consumption, and for this reason, any correction of deformities aims at normality [22].

As, in principle, normal function rather than normal anatomy is the treatment goal, biomechanics and muscle function need to be understood in normal and pathological situations.

Common problems might be listed as pathological situations:

– Restrictions on ranges of motion (ROM). Limited ROM of joints and muscle shortness and contractures affect either flexion or extension of a joint. Both conditions provide functionally problems concerning the leg length: the leg is (too) long in swing phase or (too) short in stance phase. Both situations might be compensated.

– Leg length discrepancies (LLD). LLD lead to a short leg in stance phase and a long leg in swing phase contralaterally. Possible compensations for LLD might include the fact that in stance phase the short leg shows increased plantar flexion (equinus) and knee and hip extension in order to lengthen the functional short leg, whereas the contralateral functional long leg shows the opposite by more flexion of the knee and hip joints.
– Muscle weakness of any cause affects active joint control. Either muscle synergists can be activated (e.g. the flexor hallucis for weak triceps surae) or the centre of mass is positioned (e.g. Duchenne lateral trunk lean) in such a way to avoid working the weak muscle.
– The situation in cases with spasticity is even more difficult and complex. This may require an interdisciplinary team approach.

This list of pathological situations and compensation mechanism is incomplete; it may be that not all of the possibilities are known yet [22]. However, understanding of the biomechanics of normal gait and muscle function provides the necessary basis for detecting and understanding complex pathological problems.

Treatment options might include conservative treatment such as orthotics or surgical corrections including corrective complex osteotomies and joint stabilizations or lengthening of contracted muscles.

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Chapter 52
Improving Quality of Life in the Neurocutaneous Syndromes

Alasdair P. J. Parker, Frederick J. Wilkinson, Finbar J. O'Callaghan, and Sam Amin

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Introduction

Quality of life (*QOL*) has become an essential measure of a patient's welfare but continues to be challenging in terms of definition. The World Health Organization defines QOL as "*an individual's* perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns" [1]. Conversely, the *Encyclopaedia Britannica* quotes that it is the degree to which an individual is healthy, comfortable and able to participate in or enjoy life events [2]. The *Britannica* definition encapsulates the challenges within the neurocutaneous syndrome to both assess and improve quality of life. They are a heterogeneous group of disorders affecting health, comfort and ability to participate in/enjoy life.

We outline what is known about this subject with a comprehensive *literature* review, leading onto a series of pragmatic conclusions focussing on areas that the clinician should address if they want to optimise the patient's *QOL*. We outline the optimal multidisciplinary nature, key principles and management of families affected by NCS, in a pragmatic way that is likely to optimise *QOL*, within efficient and rewarding clinical services.

How Quality of Life Is Affected in Neurocutaneous Syndromes

We undertook a comprehensive literature review searching for all the diseases outlined within this book on *PubMed*. We identified *over 70,000* papers. We further searched under the relevant syndrome/disease name and health-related quality of life or quality of life. We identified a further *796* papers. Within these, we concluded that key information was held within papers regarding *incontinentia pigmenti*, *Klippel-Trenaunay* syndrome, *hereditary haemorrhagic telangiectasia*, *angiomatosis of the retina and cerebellum/von Hippel-Lindau*, *naevoid basal cell carcinomatosis*, *Xeroderma pigmentosum*, *McCune-Albright* syndrome and *Sjögren-Larsson* syndrome. There was more information available for *tuberous sclerosis complex* (*TSC*) and *neurofibromatosis* type 1 (*NF1*). We reviewed the comprehensive study and references on QOL in TSC published by *Amin* et al. [3] as well as the systematic review of seven studies on NF1 published by Vranceanu et al. [4].

Patients and families affected by NCS have a significantly increased incidence of ill health compared to the unaffected population. This can be reflected in a global scale as seen in *Klippel-Trenaunay* syndrome [5] where affected patients had lower scores compared to the general population (except for the mental health and emotional domains). Wider issues around health affecting QOL seen in the general population will also be reflected in NCS, e.g. age. In Klippel-Trenaunay, the lower QOL scores further deteriorated when comparing older to younger patients.

Each NCS may have specific areas of disease burden which can impact QOL. In *Naevoid basal cell carcinoma – Gorlin's* syndrome – the quality of life deteriorated

with increasing numbers of basal cell carcinoma in particular comparing those with more or less than 100 [6].

Site of involvement can negatively affect QOL. Within *McCune-Albright* syndrome, the impact on physical functioning negatively correlated with quality of life, but there was further impact with extracranial involvement [7]. There are themes that run almost universally through the NCS. Pain is a particular problem and is likely to impact negatively, as shown in *Klippel-Trenaunay* syndrome [8] and *hereditary haemorrhagic telangiectasia* [9].

Psychological impact correlates with the poorer QOL. This is well demonstrated in studies of many of the conditions including *Klippel-Trenaunay* and HHT, both of which have over-representation of anxiety and in the latter condition-depression [10, 11]. The psychosocial domain is particularly affected. *Amin* et al. noted impact within the this domain in a comprehensive overview of quality of life in both adults and children affected by TSC in a large cohort of adults and children [3]. This is one of the few studies comparing NCS to controlled populations of other common disorders, including asthma, diabetes and oncological disorders. The findings were striking with a statistically significant reduction in quality of life in TSC, even compared to patients with oncological disorders.

The cutaneous manifestations are particularly relevant for NCS. Both the complex medical manifestation such as the basal cell carcinomas in *naevoid basal cell carcinoma* [6], but also body image and the cosmetic appearance such as the facial port wine stain that correlates poorer quality of life in Klippel-Trenaunay syndrome [12] and facial angiofibromatosis in TSC [3].

With the advent of modern genomics, disease surveillance and *QOL* can be further sub-classified into genotype-specific recommendations (see Chap. 1). In TSC, affected patients tend to have many more stigmata and complications with variants in *TSC2* versus *TSC1* [13]. In *hereditary haemorrhagic telangiectasia*, patients with the *ALK1* nonsense variant demonstrated higher health-related quality of scores than patients with the *ENG* (*HHT1-ENG*) missense variant [14]. The impact of the disease can both vary over a longer time period as patients age, but also in a shorter time frame should they have a specific complication. This was demonstrated in the negative correlation between epistaxis and QOL in HHT [15].

One person's assessment of their own quality of life may not match another person with an identical series of underlying disorders and complications. For many, *the assessment of QOL may be delivered by carers whose perspective on* QOL may differ from patients [3]. The patients rate their QOL higher than the scores given by parents or carers. Although the *NCS* can negatively affect QOL, sometimes patients with very significant issues rate their *QOL* relatively highly. For example, in *Sjögren-Larsson* syndrome, the median QOL scores – although slightly reduced – were generally acceptable, and mood problems were rarely mentioned, despite the itchy skin, reduced mobility and dependency prevalent in the condition [16].

Key Areas to Consider

- The *general* health of the patient.
- Likely physical complications of that neurocutaneous syndrome.
- Age-related worsening in health and complications.
- Rare but severely impacting complications.
- Sub-types of the neurocutaneous syndrome, e.g. *TSC1* vs. *TSC2*.
- Psychological well-being with particular reference to anxiety, pain and depression.
- Intellectual disability.
- Patients with similar disease burden can consider themselves to have strikingly different quality of life.
- Many patients will be unable to report their quality of life due to their coincident disability and use a proxy, e.g. parental carer. *Proxies* may not accurately reflect the patients' feeling.
- Quality of life assessments can be very helpful, but may not be specific to the condition and not cover all domains of a patient's life.

How Does One Improve the Quality of Life Affecting Both Patients and Their Families Affected by Neurocutaneous Syndromes?

Surveillance: Most patients affected by a neurocutaneous syndrome will require review on a regular basis.

We recommend a clear evidence-based and structured plan for surveillance as illustrated in guidelines on NF1 and TSC [17–20]. As an example, we outline the natural history of NF1 that can be used to base a rational programme for surveillance (Fig. 52.1).

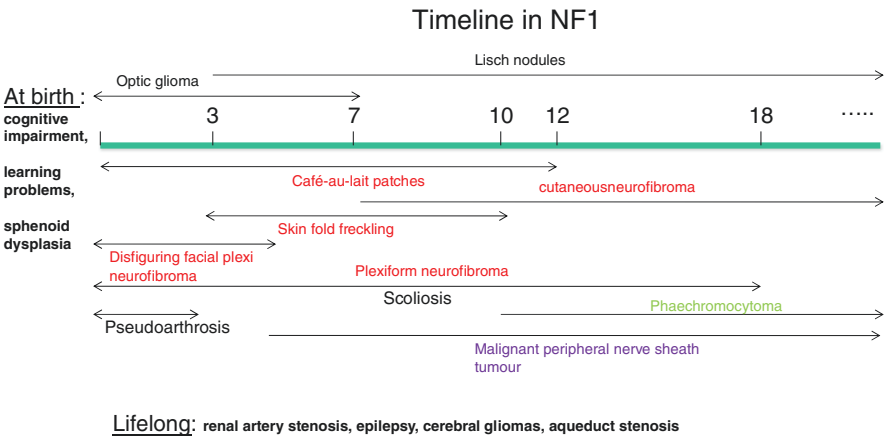

Fig. 52.1 Illustative timeline of disease manifestation in NF1

For this common *NCS*, we recommend at least yearly surveillance for disease-specific complications and QOL. In the UK, this may be done at either secondary or tertiary levels, *as long as the team performing the assessments have access to appropriate recommendations* in terms of what, when and how it is performed. There should be a structured approach to the age- and genotype-specific complications that are affecting that patient/family.

Genomics (See Chap. 1)

In all patients affected by NCS, the genomic basis should be investigated with a clinical genetic opinion assisted by appropriate molecular genetic analysis (see Chap. 1 and "Introduction"). Families will require referral through to an expert in clinical genomics to interpret both positive and negative genomic findings, e.g. parental mosaicism can mean a substantial recurrence risk with "negative" results. The genomic variant(s) needs to be correlated with that patient's disease, e.g. TSC2/PKD1 contiguous deletions are strongly associated with polycystic kidney disease. Subsequent support can be correlated to a certain extent with likely complications. There is a considerable recurrence risk for many of the disorders, and appropriate genomic analysis/counselling for family members should be undertaken.

The investigation and interpretation of genomic variants in families can be extremely challenging. Therefore, careful documentation of who and how families have been consented, the technology undertaken and results, with particular reference to when the genomic pathway has been completed, should be recorded. As families are likely to require specialist services that may be geographically disparate, good practice empowers families to be able to report and recall this information, ideally with easily accessible copies of the relevant diagnostic tests.

Disease-Specific Complications

Where the *NCS* has a high chance of a complication – as an example the renal angiomyolipomata that will occur in the majority of patients with *TSC*, but may not require intervention, or the pial angiomatosis in Sturge-Weber syndrome, this should be assessed carefully with documentation of the results and plan for both reassessment/management.

As an *example*, a 6-year-old child with neurofibromatosis has a significant chance of scoliosis, an annual review should document the spine is straight and when reassessment should be performed (in this case, UK practice would be yearly until 18). Many patients will both have a manifestation of the disease such as the angiomatosis seen in *Sturge-Weber* syndrome, but also complications of this manifestations, e.g. the epilepsy caused by the angiomatosis. These will require a separate pathway for investigation, management and surveillance, in addition to that assumed for all patients affected by the relevant condition.

General Health

Most NCS affect the general health of the patient in a broader sense than just the disease-specific manifestations/complications, e.g. the increased chance of failure to reach appropriate height/weight in children with NF1 [18]. In addition, independent problems seen within the general population such as obesity-dependent type 2 diabetes mellitus are likely to have a greater impact in patients with coincident other health disorders such as the NCS.

We recommend that both adults and children require surveillance for their general health and in children this includes height, weight and body stature. For adults, proxies for general health include BMI, blood pressure, pulse and an enquiry as to their general health during assessments.

Where patients are referred for expert management of either disease-specific manifestations such as renal involvement or independent abnormalities such as oncological disorders that would not be part of the disease spectrum, close liaison with other specialists is essential. The NCS are a very challenging group of disorders in terms of their multi-system involvement. For many of the rarer conditions, most specialists will not have an understanding of the key management issues, and in particular whether any particular signs or symptoms can be explained by the underlying disorder. Clear communication with standardised summary of investigation results, treatment and surveillance appointments can be very helpful.

Psychological Well-Being

Although many patients enjoy both good quality of life and excellent cognitive functioning, the incidence of problems in these areas is over-represented in the NCS. The specialist should enquire as to the patient's well-being. Direct questioning could be misleading, and structured quality of life questionnaires can be very helpful. These can be completed prior to clinical assessments and compared between appointments to see if there is a significant change.

In view of the increased incidence of pain and anxiety in NCS, specific questioning around these two domains is important.

Intellectual Disability

Impairments of intellect and/or social communication (causing *autistic spectrum disorders*) have a significantly increased incidence in many of the NCS, in particular *TSC* and *NF1*. For both adults and children, it is important to have a clear understanding on their cognitive ability and whether they require greater support from

services for daily living and management of their medical care. For children, it is likely if they are in a structured education system that this will have been identified, but it would be important to compare their learning age with their chronological age. For adults, if this is unclear, more structured psychological assessment of key domains including intellectual quotient is likely to inform subsequent surveillance/support plans. Even where patients are assessed to have a grossly "normal intellect", there may be specific isolated learning disabilities that can have a significant impact on QOL.

Missing the presence of a social communication disorder can be frustrating for both children and adults. Their diagnosis and classification can be very challenging, and we recommend consideration for them in all NCS, with appropriate onward referral for expert opinion as needed. Checklists of complications can aid the clinician, as used within the TSC-associated neuropsychiatric disorders (*TAND*) [21].

Transition

Active planning needs to be undertaken from the mental age of 13 years or chronological age of 15 years for transition through to adult services aged 16–18 years (dependent on maturity and mental age). The young adult should have access to a specialist dealing in neurogenetic disorders. Where this is not possible, the young adult and family/general practitioner should be empowered to take ownership for subsequent surveillance. The paediatrician should summarise the above issues including disease manifestations, complications and longer-term surveillance requirements, e.g. in the UK young adults with TSC, an MRI head is needed between the ages of 18 and 25 at least three yearly, but if there is no nodule above 10 mm after the age of 25 years, routine surveillance scanning can cease [19]. This would be beyond the scope of knowledge for both general practitioners and many hospital specialists.

The Psychosocial Domain

The impact of the NCS is broad, and in adults, consideration for employment, housing and family life are examples of important areas that would need surveillance and support. Children require greater care around education, housing and independence.

As adults and children are likely to have complex physical complications, as well as neurodisabilities, the incidence of safeguarding issues requiring expert opinion within this area will also increase. A clear understanding of the disease process will help the clinician decide as to whether further action should be taken and in particular what action.

Clinical Vignette 1

A 17-year-old girl with tuberous sclerosis moves into your region and is asked to attend your specialist clinic. Her general practitioner has written to you requesting your advice on optimal management.

How can you optimise her quality of life?

First, a comprehensive history and clinical assessment on areas that might negatively affect her quality of life should be undertaken.

You note that she has a confirmed de novo variant in the *TSC2* gene and the family have previously received comprehensive genetic counselling. Although she previously had an epilepsy diagnosis, she has been stable and seizure-free for 18 months on a low dose of carbamazepine therapy.

You note that she has had an MRI scan 18 months previously and although this shows the typical cortical tubers of *TSC2*, she does not have a subependymal nodule larger than 10 mm. She has not had a renal ultrasound or MRI scan, chest X-ray/CT chest within the previous 2 years, but you note that she has seen an ophthalmologist/cardiologist, both of whom have noted no abnormality.

You enquire as to her learning and her parents feel that she has a significant intellectual disability. She is in a specialist educational unit, and although she has not had a structured assessment for a social communication disorder, her parents feel she may lie on the autistic spectrum. Recently, they have found her behaviour very challenging.

To direct questioning, they do not feel she is in pain, but she can become very anxious around social situations. She feels the absence of a friendship group has made her depressed.

Action

You reassure her parents that the picture is something that you recognise, and you can make some structured recommendations to support and help. You reassure them that a number of important investigations have been undertaken and would not need to be repeated *including* cardiology, ophthalmology and genomic assessments.

On *examination*, you noted that she has the typical skin changes including *shagreen patches*, but also facial angiofibromatosis.

You *recommend* there are some key areas that do need ongoing surveillance, and these would include a further MRI scan of her head in 18 months and then 3 yearly until she is 25 when it should be able to stop. She requires bi-annual renal ultrasound and advice as to whether renal MRI is also needed. You reassure them that lung involvement does not occur in all young people, but she does require a CT of her chest and expert interpretation/advice from a respiratory physician.

Her parents are reassured by this, but you explain to them that there are a number of other factors which could be reducing her quality of life. You recommend that

together you complete a TSC associated neuropsychiatric disorders (*TAND*) checklist and *QOL* questionnaire: the *latter* will be useful when repeated after 6 months, to give an objective assessment of the outcome of interventions.

First, you note that the facial angiofibromatosis is quite significant and on asking the young girl she explains to you that she finds it embarrassing and is reluctant to socialise. You recommend an assessment from a dermatologist for *sirolimus* ointment which is likely to improve the disfigurement, her *social* confidence and *QOL*. In view of the intellectual disability, you recommend that transition through to adult services involves referral through to adult intellectual disability and social care services. They are likely to be able to both help produce an appropriate care plan and to support her mental health.

Although she does not seem to have any pain, both the girl and her parents have expressed concern over anxiety, and you arrange expert assessment from an adult psychiatrist specialising in the mental health of young people with *intellectual* disability. They have a specialist interest in social communication disorders.

Six *months later*, you are glad to note that she remains seizure-free on a low dose of carbamazepine. Chest radiography was unremarkable and on starting sirolimus ointment under the supervision of a dermatologist, her facial *angiofibromatosis* is significantly less visible. The young adult and her parents tell you that she is much more confident in social situations.

Support from the adult psychiatrist has involved cognitive and social communication assessments. She has been diagnosed with a moderate intellectual disability and a social communication disorder. She has undertaken a programme of behavioural therapy and support. She has re-entered education and is attaining an increased level of independence, with support of transitional social care workers. She was recently assessed for anxiety/depression. Objective analysis showed that she was much less anxious.

Structured assessment of her *QOL* using the *PedsQl* teenage version [22] showed significant improvement over the previous 6 months.

Clinical Vignette 2

This 6-year-old boy was referred through to your specialist clinic with a confirmed diagnosis of NF1 and concern over rapid increase in his height.

You *note* the confirmed diagnosis of NF1 both on clinical grounds and a disease-causing variant in the *NF1* gene inherited from his father. You note that they have received extensive genetic counselling, but he has not been under an active programme of surveillance.

You *look* at the age-related disease demographics and undertake a formal examination. On his skin that he has the typical *stigmata* with axillary and flexure freckling, café au lait patches as well as a few small skin *neurofibromata* less than 1 cm across.

On *neurological* assessment you identify no abnormality, he has normal learning, good social communication and eye examination including fundoscopy is unremarkable.

Wider *examination* demonstrates a normal blood pressure, but his height velocity has dramatically increased in the previous year, with stage 3 *pubertal changes* on genital examination. You ask his mother whether she is comfortable with his learning ability and social communication. She reassures you that he is above average in school with a strong friendship group. You specifically enquire as to whether there are any lumps or areas of concern, and in particular whether he is expressing pain anywhere, for example, around his spine. She explained she cannot find anything different compared to her other children, but has noted his advanced pubertal stage.

Although the normal *fundoscopy* and eye examination would normally mean that following your national guidelines on surveillance for NF1 that MRI head would not be needed, in view of the advanced pubertal stage, you arrange an urgent MRI scan of the brain including the pituitary/hypothalamus. You ask for copies of school reports to confirm that his attainment is within normal limits and arrange for his genomic analysis to be transferred from his previous centre to be placed in his notes. You encourage his mother to carry copies of all medical correspondence and results, e.g. the disease-causing variant in the *NF1* gene. You encourage his father to check with his specialist whether he needs specific surveillance/intervention.

One *year later*, he attends for an annual appointment to survey his health/NF1. You noted that previous MRI scan was unremarkable except for typical *hamartomatous* changes that may be seen in NF1 which would not warrant any further imaging/intervention. There was no abnormality of pituitary/hypothalamus or optic nerves. He had been assessed by a paediatric endocrinologist who had introduced therapy to halt puberty. Although his final height may have been reduced, it was likely he would be within normal limits. His school report noted that he was attaining adequately, with a good friendship group.

To direct *questioning*, there were no other areas of pain or deformity, and he was not anxious. Blood pressure was unremarkable, and there was no bony abnormality including scoliosis. You recommended ongoing support from the paediatric endocrinologist and that he would continue to attend your specialist clinic for a yearly assessment. *Within* this, you would follow national guidelines for appropriate age and disease-related surveillance which would evolve through his teenage years. In *particular*, it would involve further assessment to check that his academic and social attainment was within normal limits, and there were no further concerns over his mental health with particular reference to anxiety/depression. You recommend annual QOL assessment via a simple questionnaire, e.g. *PedsQL* [22].

Conclusion

The NCS are a disparate group of disorders affecting *QOL* in many different ways. Management cannot be generalised either between the disorders, families affected by the same disorder or even between members of the same family. There are a

number of key areas that can deleteriously affect *QOL* in the *NCS* including general health, disease manifestations/complications, pain, anxiety, intellectual disability, social communication and wider psychosocial well-being.

It is important to consider the quality of life in all contact with patients and families affected by *NCS*. Structured assessment, repeated as needed, can be very informative. Appropriate surveillance for the specific syndrome, disease manifestations, complications and age can be challenging. *However*, with a structured and evidence-based approach, supported with liaison from appropriate experts, management can be optimised with significant implications for quality of life.

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