3 Syndromes Associated with Vascular Anomalies

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Vascular anomalies encompass a spectrum of disorders that unfortunately continues to be plagued by incorrect nomenclature and misdiagnosis. Recent advances in clinical and basic research have led to better understanding of these lesions and their more appropriate categorisation. The international society for the study of vascular anomalies (ISSVA) has recently updated the classification that provides a sound framework and clarification of terminology, which can be used across the various clinical specialities [1].

Vascular anomalies are often sporadic, though in a small proportion of patients they can be associated with underlying diseases or systemic conditions. Some of the associated syndromes are well recognised, but other associations are not as well known [1–4]. Vascular lesions associated with syndromes can be difficult to treat and require long-term management plans and perspectives. In this chapter, the associated syndromes are discussed according to the presenting vascular lesion, as either vascular tumours or malformations, in accordance with the recently updated ISSVA classification.

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3.1 Syndromes Associated with Vascular Tumours

3.1.1 PHACE Syndrome (Fig. 3.1)

Pascual-Castroveijo in 1978, described a series of seven patients with vascular and non-vascular intracranial malformations associated with external capillary haemangiomas [5]. Freiden et al. in

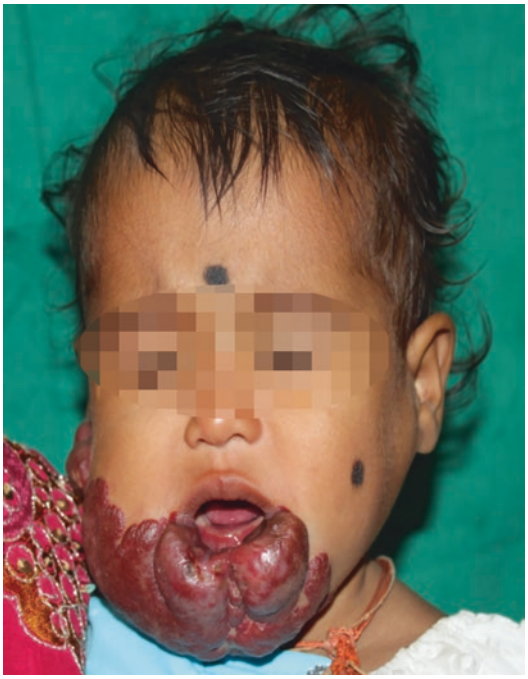

Fig. 3.1 Phace syndrome - Large segmental facial haemangioma

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1996 reported PHACE syndrome, an acronym that encompassed posterior fossa malformations, haemangiomas, arterial anomalies, cardiovascular anomalies, eye anomalies, and sternal defects [6]. The haemangiomas are infantile haemangiomas, often occurring in the face and neck, segmental in distribution and over 5 cm in diameter. Posterior fossa anomalies include Dandy-Walker malformations and ventricular dilatation. Cardiac anomalies include coarctation of the aorta, atrial septal defect, and ventricular septal defects. Eye anomalies include cataract, glaucoma, microphthalmos, and optic nerve hypoplasia. A recent multi-specialty consensus document (Table 3.1) provides updated diagnostic criteria and care recommendations [7]. In patients with a large head and neck/face haemangiomas more than 5 cm should be evaluated for PHACE. Patients with smaller haemangiomas with characteristic/major criteria and those without haemangiomas, but with major cri-

Table 3.1 PHACE syndrome—Revised diagnostic criteria [7]

Organ system	Major criteria	Minor criteria
Arterial anomalies	Anomaly of major cerebral or cervical arteries* Dysplasia of the large cerebral arteries# Arterial stenosis or occlusion with or without moyamoya collaterals Absence or moderate–severe hypoplasia of the large cerebral and cervical arteries Aberrant origin or course of the large cerebral or cervical arteries except common variants such as bovine arch Persistent carotid–vertebrobasilar anastomosis (proatlantal segmental, hypoglossal, otic and/or trigeminal arteries)	Aneurysm of any of the cerebral arteries
Structural brain	Posterior fossa brain anomalies Dandy-Walker complex Other hypoplasia/dysplasia of the mid and/or hindbrain	Midline brain anomalies Malformation of cortical development
Cardiovascular	Aortic arch anomalies Coarctation of the aorta Dysplasia Aneurysm Aberrant origin of the subclavian artery with or without a vascular ring	Ventricular septal defect Right aortic arch/double aortic arch Systemic venous anomalies
Ocular	Posterior segment abnormalities Persistent hyperplastic primary vitreous Persistent foetal vasculature Retinal vascular anomalies Morning glory disc anomaly Optic nerve hypoplasia Peripapillary staphyloma	Anterior segment abnormalities Microphthalmia Sclerocornea Coloboma Cataracts
Ventral/midline	Anomaly of the midline chest and abdomen Sternal defect Sternal pit Sternal cleft Supraumbilical raphe	
Definite PHACE		
Haemangioma >5 cm in diameter of the head including scalp PLUS 1 major criteria or 2 minor criteria Haemangioma of the neck, upper trunk or trunk and proximal upper extremity PLUS 2 major criteria		
Possible PHACE		
Haemangioma >5 cm in diameter of the head including the scalp PLUS 1 minor criteria Haemangioma of the neck, upper trunk or trunk and proximal upper extremity PLUS 1 major or 2 minor criteria No haemangioma PLUS 2 major criteria		

*Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery or vertebrobasilar system

#Includes kinking, looping, tortuosity and/or dolichoectasia

teria, should also be evaluated. Screening tests include a thorough physical examination, echocardiogram, MRI/MRA of the brain, neck and aortic arch and ophthalmological examination.

3.1.2 Kasabach–Merritt Syndrome/ Phenomenon

Kasabach and Merritt in 1940 reported a case of capillary haemangioma with extensive purpura [8]. It was associated with coagulation abnormalities, reduced platelets and anaemia, causing haemorrhage, infection and multi-organ failure, leading to death in 12–24% of patients. It is now recognised that patients with Kaposiform hemangioendothelioma or tufted angiomas, but not infantile haemangiomas or malformations develop Kasabach–Merritt phenomenon (KMP) [9]. Abnormal platelet activation and aggregation may occur secondary to interaction with the abnormal tumour endothelium resulting in localised trapping of the platelets and consumption of clotting factors [10]. Kaposiform hemangioendothelioma involving more than one anatomic site, invading underlying muscle, bone, retroperitoneum and thoracic cavity are more often associated with increased incidence of KMP [11]. Outcomes have significantly improved and current management includes excision of the lesion, steroids, interferon, vincristine and radiotherapy.

3.2 Syndromes Associated with Capillary Malformations

3.2.1 Sturge–Weber Syndrome (Fig. 3.2a, b)

Sturge–Weber Syndrome (SWS) is characterised by a dermal capillary malformation occurring in association with vascular malformations of the

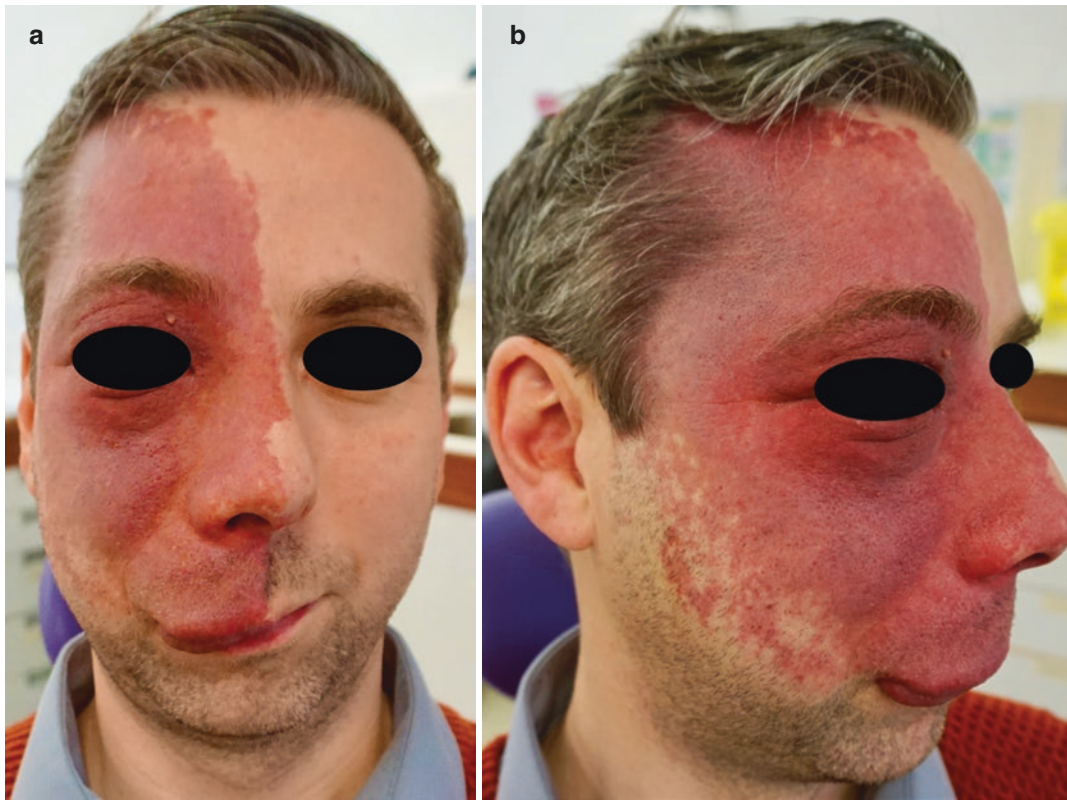

Fig. 3.2 (**a, b**) Sturge Weber Syndrome Frontal and lateral view- Capillary malformation affecting dermatomes supplied by the first and second divisions of the trigeminal nerve. Tissue hypertrophy in long standing lesions

leptomeninges and the eye. It was initially described by Sturge in 1879 and further characterised by Weber in 1922 [12, 13]. It typically includes a triad of facial dermal capillary malformation, ipsilateral central nervous syndrome vascular malformations (leptomeningeal angiomatosis), and vascular malformations of the choroid of the eye associated with glaucoma. Partial forms with eye and meningeal lesions without skin lesions and skin and eye lesions without meningeal lesions have been described, but all three features are required to be considered as having SWS [14].

The risk of SWS is determined by the distribution of the capillary malformations. SWS occurs exclusively in patients whose capillary malformations are located in the distribution of the first division (ophthalmic) of the trigeminal nerve. Talman et al. [15] found ocular and CNS abnormalities occurred exclusively in patients with capillary malformations involving the upper and lower eyelids (91%) or lower eyelids (9%). Though this study suggests an increased incidence of SWS with second division involvement, this discrepancy could be attributed to the anatomic variability of the "watershed" area of the upper and lower eyelids that can be innervated by the first or second division of the trigeminal nerve. The overall incidence of ocular or CNS involvement in patients with capillary malformation located in the first or second division is around 8%, but higher when multiple dermatomes (V1, V2, V3) or bilateral involvement (24%).

Leptomeningeal vascular malformations are most often present over the occipital lobes, followed by the temporal and parietal lobes [16]. Seizures are the most common neurologic abnormality associated with SWS and occur in 55–90% of patients. They are frequently focal but can become generalised and often occur within the first year of life. Most patients achieve normal developmental milestones in the first year of life and about 50% continue to develop normally. Those with extensive leptomeningeal involvement and seizures refractory to treatment are at a higher risk of developmental delay.

Glaucoma is the most common ophthalmologic abnormality seen in patients with SWS. It is associated with ipsilateral vascular malformation of the choroidal vasculature of the eye, though it can present on the contralateral side. Glaucoma is often present at birth in about two-thirds of patients, though it can arise at a later date. All patients with capillary malformations of the eyelids should be evaluated periodically for glaucoma, as early identification and management may prevent blindness.

SWS should be suspected in all patients with capillary malformations affecting the first division of the trigeminal nerve. Regular ophthalmological examination should be carried out to evaluate and manage glaucoma. Neurological development should also be monitored and seizures managed appropriately. Cutaneous capillary malformations can be managed by pulsed dye laser.

3.2.2 Klippel–Trenaunay Syndrome

Klippel–Trenaunay Syndrome (KTS) was initially reported by Klippel and Trenaunay in 1900 [17]. It is characterised by (1) capillary malformation of the lower limbs, (2) congenital varicose veins or venous malformations associated with abnormal, dilated "lateral megaveins" that develop in the lateral aspect of the affected limbs and (3) bone and soft tissue hypertrophy resulting from overgrowth. Just one limb is affected in over 75% of patients, though in a few the upper limb or both lower limbs can be affected. Lymphatic anomalies can also occur in the affected limbs [18–20].

The capillary malformation may be distributed in a confluent geographic pattern or randomly on the affected limb and adjacent trunk. Geographic patterns are often located in the lateral aspect of the thigh, knee and lower leg and can be a predictor of associated lymphatic malformation and complications of KTS. Life-threatening complications include deep vein thrombosis, pulmonary embolism, sepsis and coagulopathy [18–20].

KTS should be suspected in all infants with capillary malformations involving the limbs. If KTS is diagnosed, regular monitoring of the leg length is mandatory. It is important to look out for a high-flow arteriovenous malformation, to

rule out Parkes Weber syndrome. The venous anomalies are often managed conservatively with elastic support garments. Surgery may be required in selected patients.

3.2.3 Rubinstein–Taybi Syndrome (Fig. 3.3a, b)

Rubinstein and Taybi in 1963 reported a condition characterised by mental retardation, growth retardation, broad thumbs, large toes and a typical facial appearance [21]. Though no specific diagnostic criteria have been established, a variety of additional features have been reported [22]. Skin manifestations included capillary malformations, hirsutism, keloid and excessive scar formation, and café au lait macules. Oral manifestations include thin upper lip, small oral opening, retro/micrognathia and high arched narrow palate. Cleft uvula and palate can be part of the syndrome. Dental anomalies include hypodontia, hyperdontia and natal teeth. Talon cusps were present in 73% of patients and 92% of permanent teeth. Two or more talon cusps are rarely found in the normal population and this finding supports the diagnosis of Rubinstein–Taybi syndrome, when this is suspected [23].

3.2.4 Beckwith–Wiedemann Syndrome (Fig. 3.4a, b, c)

Beckwith–Wiedemann syndrome is characterised by gigantism, omphalocele (exomphalos) and macroglossia [24, 25]. Predisposition to tumours in childhood (Wilms', rhabdomyosarcoma, hepatoblastoma, adrenal tumours) posterior helical pits, hypoglycaemia / hyperinsulinism and facial capillary malformations also occur as a part of the syndrome. Many of the cases are sporadic, though a familial autosomal dominant inheritance has been associated with this syndrome. A recent international consensus document has set out recommendations (Table 3.2) for clinical and molecular diagnoses, screening and management [26]. It is the most common (epi)genetic overgrowth-cancer predisposition disorder. An understanding of the genetic inheritance and specific mechanisms for tumorigenesis will assist in genetic counselling, early tumour detection and prognostic determination.

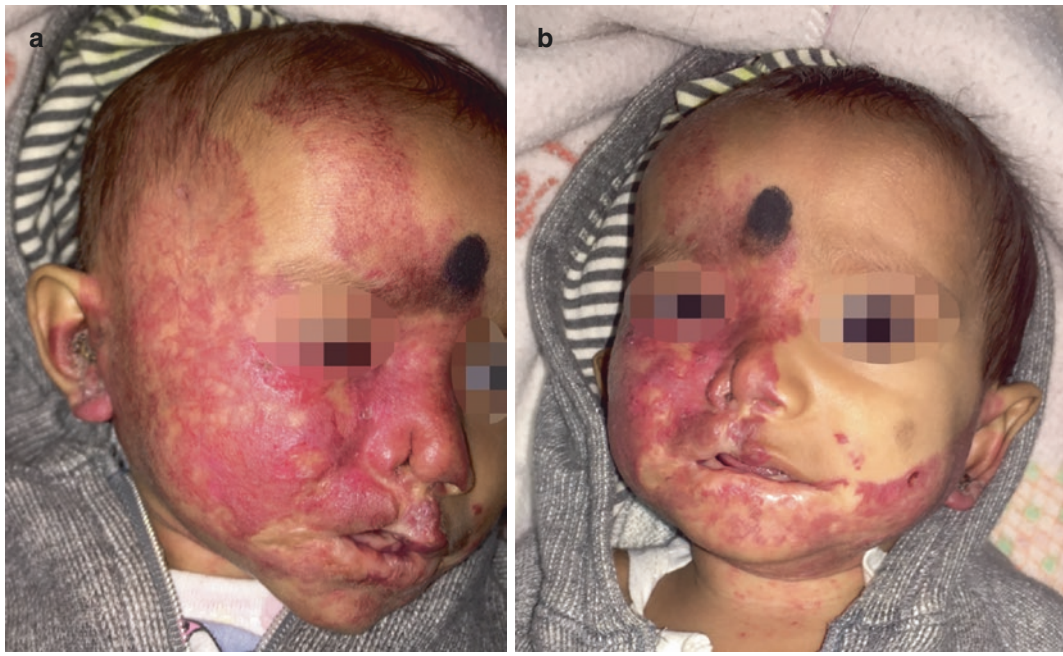

Fig. 3.3 (**a, b**) Rubinstein-Taybi syndrome - Infantile hemangioma involving V1, V2, V3 divisions of trigeminal nerve with cleft lip and nose

Fig. 3.4 Beckwith - Wiedmann Syndrome - Capillary malformation with tissue hypertrophy and macroglossia

3.3 Syndromes Associated with Low-flow Venous Malformations, Lymphatic Malformations or Mixed Malformations

3.3.1 Blue Rubber Bleb Nevus Syndrome (Fig. 3.5)

Gascoyne in 1860 reported a vascular malformation in the parotid region complicated by haemorrhage of the gastrointestinal (GI) tract [27]. Bean in 1958 reported additional cases and reviewed the literature and coined the term "blue rubber bleb nevus syndrome" to describe the classical skin and gastrointestinal tract findings [28].

The typical findings are compressible blue subcutaneous venous malformations ranging in size from 0.1 cm to 5.0 cm. They are often present at birth or early childhood and become more obvious and numerous as the patients become older. They can be present in any part of the skin

Table 3.2 Beckwith–Wiedemann syndrome—diagnostic criteria [26]

Cardinal features (2 points per feature)
Macroglossia
Exomplalos
Lateralised overgrowth
Multifocal and /or bilateral Wilms' tumour or nephroblastomatosis
Hyperinsulinism (lasting >1 week and requiring escalated treatment)
Pathology findings: Adrenal cortex cytomegaly, placental mesenchymal dysplasia or pancreatic adenomatosis
Suggestive features (1 point per feature)
Birth weight > 2 SDS above mean
Facial naevus simplex
Polyhydramnios and /or placentomegaly
Ear creases and/or pits
Transient hypogylcaemia (lasting <1 week)
Typical BWSp tumours (neuroblastoma, rhabdomyosarcoma, unilateral Wilms' tumour, hepatoblastoma, adrenocortical carcinoma or phaeochromocytoma)
Nephromegaly and/or hepatomegaly
Umbilical hernia and / or diastasis recti

For clinical diagnosis of classical Beckwith–Wiedemann syndrome (BWS), a patient requires a score of ≥4 (this clinical diagnosis does not require the molecular confirmation of an 11p15 anomaly). Patients with a score of ≥2 (including those with classical BWS with a score of ≥4) merit genetic testing for investigation and diagnosis of BWS. Patients with a score of <2 do not meet the criteria for genetic testing. Patients with a score of ≥2 with negative testing should be considered for an alternative diagnosis and/or referral to a BWS expert for further evaluation

BWSp Beckwith–Wiedemann spectrum, *SDS* standard deviation scores

and mucosa, including the scalp, but are more commonly located in the trunk and extremities.

Gastrointestinal venous malformations most commonly affect the small intestine and colon, though the entire bowel may be affected. Lesions may also be found in the orbit, genitourinary tract and central nervous system. GI lesions may present as chronic anaemia, abdominal pain, rectal bleeding and intussusception.

Blue rubber bleb syndrome should be considered in patients who present with multiple cutaneous venous malformations and patients should undergo evaluation for GI tract involvement and anaemia. Cutaneous lesions can be managed by carbon dioxide lasers, sclerotherapy and surgical excisions. GI lesions may be treated by endoscopic Argon or Nd:YAG lasers or surgical excision.

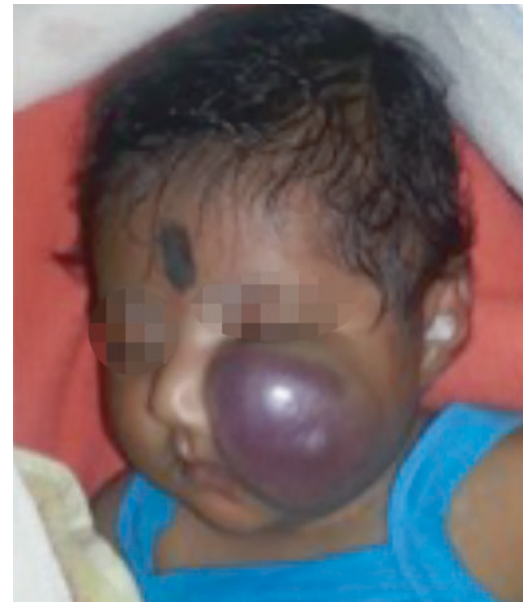

Fig. 3.5 Blue Rubber Bleb Nevus Syndrome (Compressible blue subcutaneous venous malformation from birth)

3.3.2 Parkes Weber Syndrome

Parkes Weber in 1907 described a vascular lesion with hemihypertrophy. It is characterised by overgrowth of the limb (usually lower) with diffuse arteriovenous fistulas and shunts. The arteriovenous fistulas often develop around puberty and can be complicated by high-output congestive cardiac failure. Lymphatic anomalies and lymphoedema may be present. It should be differentiated from Klippel–Trenaunay syndrome, the latter being associated with low-flow vascular malformations.

3.3.3 Proteus Syndrome (Figs. 3.6, 3.7)

Wiedemann et al. in 1983 described a disorder characterised by hypertrophy of the hands and feet, pigmented nevi, hemihypertrophy, skull and visceral abnormalities [29]. They named it Proteus syndrome after the Greek god, who could change his shape. Patients subsequently reported in the literature had very variable features, raising concerns about misdiagnosis. In 2004, specific

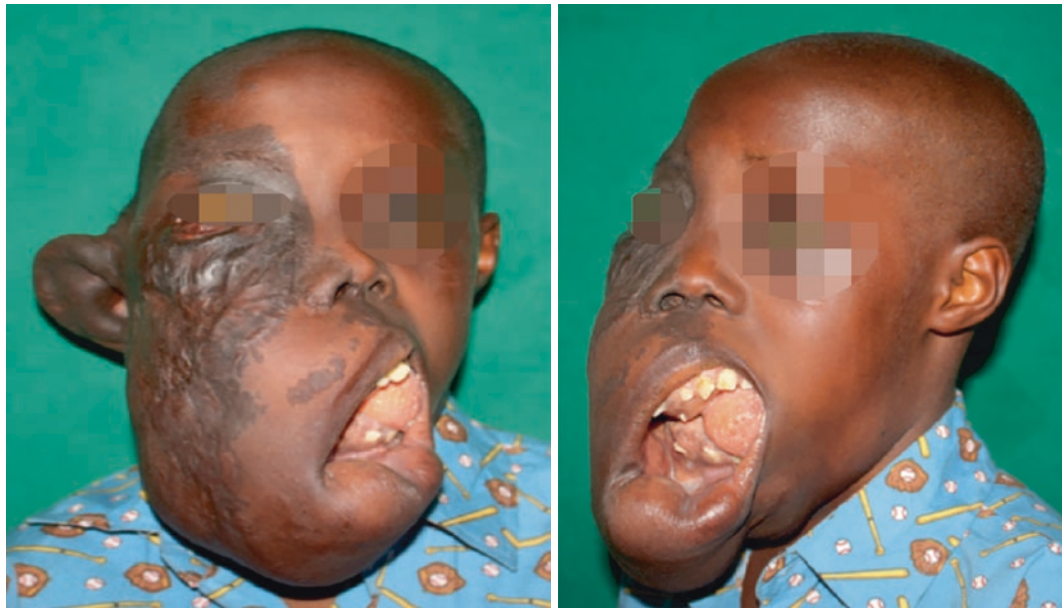

Fig. 3.6 Proteus syndrome - Typical facies - Hemihypertrophy of the face, lymhovenous malformations

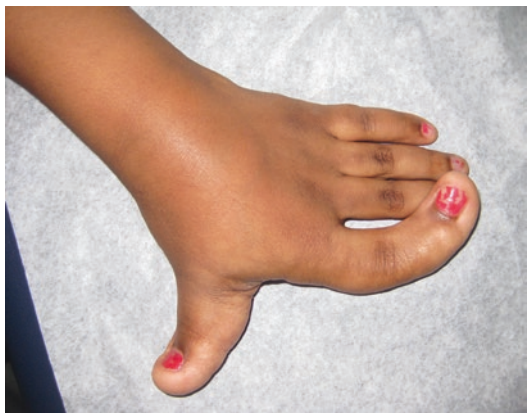

Fig. 3.7 Proteus syndrome - Asymmetric disproportionate growth of the digits. Adapted from

criteria (Table 3.3) were established for diagnosing Proteus syndrome [30]. The general characteristics of a sporadic occurrence, mosaic distribution of lesion, and a progressive clinical course are mandatory. Clinical features include connective tissue nevus of the palms and soles, epidermal nevus, disproportionate overgrowth, parotid monomorphic adenomas or ovarian cystadenomas before the second decade of life, lipomas or localised absence of fat and vascular malformations (venous, capillary, lymphatic). The characteristic facial features of dolichocephaly, long face, down slanting palpebral fissures, low nasal bridge and open bite have also been reported.

Joseph Merrick, who exhibited himself as the "elephant man" and whose story subsequently led to many medical articles, books and a movie by David Lynch, is now considered to have been affected by Proteus syndrome, rather than neurofibromatosis.

The diagnosis is currently based on satisfying the revised diagnostic criteria.

3.3.4 Maffucci Syndrome

Initially described by Maffucci in 1881, the disorder is characterised by enchondromatosis and multiple low flow vascular (mainly venous and rarely lymphatic) malformations [31].

It often manifests in early childhood with multiple superficial and deep venous malformations

Table 3.3 Proteus syndrome—Revised diagnostic criteria [30]

General criteria	Specific criteria
All the following: Mosaic distribution of lesions Sporadic occurrence Progressive course	Either category A (or) Two from category B (or) Three from category C A. 1. Cerebriform connective tissue nevus* B. 1. Linear epidermal nevus 2. Asymmetric, disproportionate growth# One or more (a) Limbs: Arms/legs Hands/feet/digits Extremities (b) Hyperostoses of the skull (c) External auditory meatus (d) Megaspondylodysplasia (e) Viscera Spleen/thymus 3. Specific tumours before the 2nd decade One of the following: (a) Ovarian cystadenoma (b) Parotid monomorphic adenoma C. 1. Dysregulated adipose tissue Either one: (a) Lipomas (b) Regional absence of fat 2. Vascular malformations One or more (a) Capillary malformation (b) Venous malformation (c) Lymphatic malformation 3. Lung cysts 4. Facial phenotypes+ All (a) Dolichocephaly (b) Long face (c) Down slanting palpebral fissures and/or minor ptosis (d) Low nasal bridge (e) Wide or anteverted nares (f) Open mouth at rest

To make a diagnosis of Proteus syndrome (PS), one must have all the general criteria and various specific criteria

*Cerebriform connective tissue nevi are skin lesions characterised by deep grooves and gyrations as seen on the surface of the brain

#Asymmetric, disproportionate overgrowth should be carefully distinguished from asymmetric proportionate overgrowth

+The facial phenotype has been found to date only in PS in patients who have mental deficiency and in some cases seizures and/or brain malformations

in the extremities. Oral and intra-abdominal venous and lymphatic malformations have also been reported [32, 33]. Simultaneously, endochondromas present as hard nodules in the fingers and long bones. About 30%–40% of these lesions undergo malignant transformation into chondrosarcomas. Breast, ovarian, pancreatic, parathyroid and pituitary tumours have also been reported in patients with Maffucci syndrome. Spindle cell hemangioendothelioma is commonly found beside venous nodules or intermingled with the venous malformations on pathologic sections in these patients.

Diagnosis is based on the clinical features and regular follow-up is mandatory to monitor the endochondromas and detect malignant transformation. The venous malformations are managed conservatively, unless symptomatic.

3.3.5 Gorham–Stout Syndrome (Fig. 3.8a, b)

Initially reported by Jackson in 1838 [34], Gorham and Stout in 1955 reported 24 cases characterised by vascular malformations, intraosseous vascular malformations and osteolysis [35]. This syndrome has also been termed as disappearing bone disease, phantom bone disease and diffuse skeletal haemangiomatosis. Lymphatic malformations are most common, though capillary and venous malformations have been reported. Cutaneous malformations are uncommon. Truncal bone and upper extremities are most commonly affected. Patients often present in early childhood with a pathological fracture following minor trauma. The degree of bone resorption is variable and complete resorption has been reported in several cases.

The cause has not been established and pathological analysis demonstrates a proliferation of dilated lymph channels communicating with blood vessels in the bone. When osteolytic lesion of unknown is identified, Gorham–Stout syndrome should be considered. Surgery, radiotherapy and bisphosphonates have been used in its management [36].

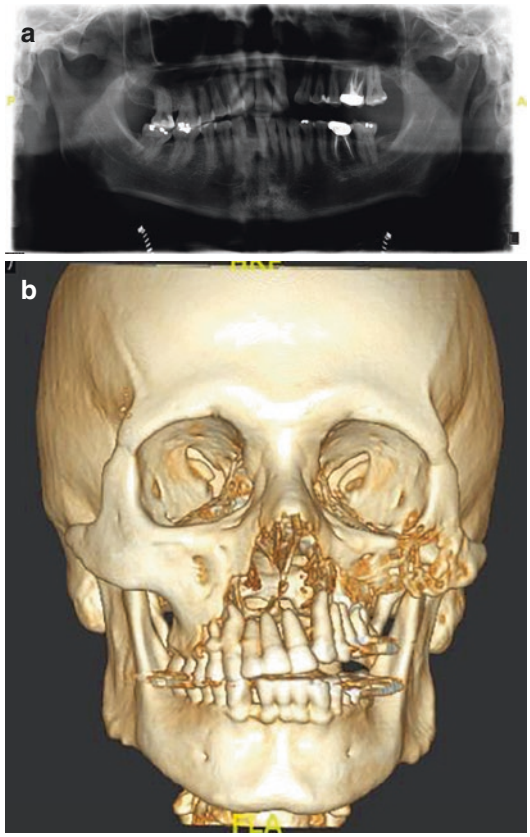

Fig. 3.8 Gorham Stout syndrome—Left facial skeleton with maxillary and zygomatic bone osteolysis. (**a**) Orthopantomograph (**b**) 3D reconstruction of the CT scan

3.4 Syndromes Associated with High-flow Vascular Malformations

3.4.1 Rendu–Osler–Weber Syndrome (Hereditary Haemorrhagic Telangiectasia)

Rendu (1896) [37], Osler 1901) [38] and Weber (1907) [39]described a hereditary disorder characterised by dilated skin and mucosal blood vessels leading to epistaxis and haemorrhage into the digestive tract (hereditary haemorrhagic telangiectasia—HHT). It is an autosomal dominant disorder affecting one to two per 100,000 people and belongs to the group of diseases with abnormal transforming growth factor-beta. Clinically it is classified into five phenotypes based on ENG, ALK or SMAD4 abnormalities: HHT1, HHT2, HHT3, HHT4 and juvenile polyposis and hereditary haemorrhagic telangiectasia (JPHT). HHT1 is the most common and is caused by the ENG mutation [40].

Telangiectasia in the nose, leading to recurrent epistaxis is often the initial presentation and occurs before the appearance of cutaneous lesions. Telangiectases are also present in the lips, oral mucosa, upper extremities, fingers and trunk. Arteriovenous malformations and fistulas in the lung, liver and central nervous system are also found in these patients. Criteria have been established for the diagnosis of HHT (Table 3.4) and people with three criteria receive a "definitive" diagnosis and those with two a "possible" diagnosis [41].

HHT should be suspected in children with multiple skin and mucosal lesions. Once established, they should be evaluated for pulmonary and other site involvement. Management of local lesions has included cautery, laser photocoagulation and sclerotherapy. Bevacizumab, when injected submucosally has also been shown to be of benefit [42].

Table 3.4 Hereditary Haemorrhagic Telangiectasia—Diagnostic criteria [41]

Criteria	Definition
Epistaxis	Spontaneous, recurrent nose bleeds
Telangiectasia	Multiple characteristic sites (lips, oral cavity, nose, fingers)
Arteriovenous malformations (AVM)	Any of the following: 1. Cerebral AVM 2. Spinal AVM 3. Pulmonary AVM 4. Hepatic AVM 5. Gastrointestinal telangiectasia (with or without bleeding)
Family history	A first-degree relative with HHT according to criteria
Definite HHT—If 3 criteria are present Possible HHT—If 2 criteria are present Unlikely HHT—If fewer than 2 criteria are present	

HHT Hereditary haemorrhagic telangiectasia

3.4.2 Bonnet–Dechume–Blanc Syndrome or Wyburn–Mason Syndrome

Bonnet et al. [43] in 1937 and Wyburn et al. [44] in 1943 reported a disorder characterised by cerebral arteriovenous malformation usually involving the midbrain, ipsilateral retinal vascular malformation and a red stain in the face, often misinterpreted as a capillary malformation. Bonnet–Dechume–Blanc syndrome and Wyburn–Mason syndrome are generally considered to be synonymous.

The cutaneous vascular malformation is not a consistent feature and when present can be unilateral and involves the skin innervated by the trigeminal nerve or central involving the midforehead, glabella, nose and upper lip. Patients can present with headaches and seizures. Fundoscopy and MRI can be helpful in delineating the extent of the lesions.

3.5 Summary

Recent advances have enabled this complex group of patients to be more accurately diagnosed, enabling tailored management plans. Some of these patients are at a greater risk of developing tumours and serious complications. Identifying the varying elements of syndrome complex, recognising the potential complications and liaising with the various specialities is essential to improve the management of these patients.

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