# Neurocutaneous Syndromes

# 13

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## 13.1 Introduction

In a time of increasing ability to perform advanced testing—radiologic, genetic, or otherwise—the concept of neurocutaneous syndromes remains relevant to the clinician. Also termed phakomatoses, these are congenital conditions that arise as the skin and brain form embryologically from the ectoderm. Distinct findings affecting the skin, hair, and eyes portend not only underlying neurologic involvement but involvement of other organ systems as well, some of which manifest at birth and others that take years to evolve. Depending on the condition, there may be a predisposition to tumors or vascular abnormalities, which can be the basis for surveillance of affected individuals and screening of at-risk family members. Over the years, an understanding of the genetics and pathophysiology for many of these conditions has been a focus for research and ultimately the basis for improved availability of treatment options not only for these entities but other conditions as well.

## 13.2 Tuberous Sclerosis Complex (TSC)

Tuberous sclerosis complex (TSC) has been a model neurocutaneous syndrome to exemplify the merging of clinical diagnosis, genetics, and molecular biology. Poorly regulated cellular proliferation and differentiation lead to hamartomas affecting the brain, skin, kidneys, heart, and other organ systems. Autosomal dominant in its inheritance, the syndrome was depicted by drawings and models of individuals with angiofibromas as early as 1835, and the hamartomatous involvement was described in more detail by von Recklinghausen later in the century [1]. Credited with first

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using the term tuberous sclerosis in 1880, Bourneville has also been associated with the condition eponymously [2]. Names such as Bournesville's disease, Pringle's disease, Vogt's triad (seizures, mental retardation, and cutaneous angiofibromas), and epiloia (*ep*ilepsy, *l*ow *i*ntelligence, *a*denoma sebaceum) were utilized through much of the twentieth century; diagnostic criteria were defined more rigorously by Gomez in 1979 and by a diagnostic criteria committee in 1992 [3]. The responsible genes were identified soon afterwards: TSC1 coding for hamartin on chromosome 9 and TSC2 coding for tuberin on chromosome 16. These proteins are subunits for an upstream modulator for the mammalian target of rapamycin (mTOR) pathway [4]. An updated diagnostic criteria committee convened in 1998, still mandating a clinical diagnosis pending further genetic updates [5]. Most recently, diagnostic criteria developed in 2012 (Table 13.1) added a mutation of TSC 1 or TSC 2 to otherwise clinical diagnostic criteria [6].

**Table 13.1** Updated diagnostic criteria for tuberous sclerosis complex 2012

| *A. Genetic diagnostic criteria* |
|---|
| The identification of a pathogenic mutation in either TSC1 or TSC2 is sufficient to make a definite diagnosis of TSC. A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation which effect on protein function has been established. Other TSC1 or TSC2 variants which effect on function is less certain do not meet these criteria and are insufficient to support a definite diagnosis of TSC. Note that 10–25% of TSC patients have no mutation identified by conventional genetic testing, so a normal result does not exclude TSC or affect the use of clinical diagnostic criteria to diagnose TSC |
| *B. Clinical diagnostic criteria* |
| Major features |
| 1. Hypomelanotic macules (≥3, at least 5 mm diameter) |
| 2. Angiofibromas (≥3) or fibrous cephalic plaque |
| 3. Ungual fibromas (≥2) |
| 4. Shagreen patch |
| 5. Multiple retinal hamartomas |
| 6. Cortical dysplasias[a] |
| 7. Subependymal nodules |
| 8. Subependymal giant-cell astrocytoma |
| 9. Cardiac rhabdomyoma |
| 10. Lymphangioleiomyomatosis (LAM)[b] |
| 11. Angiomyolipomas (≥2)[b] |
| Minor features |
| 1. "Confetti" skin lesions |
| 2. Dental enamel pits (≥3) |
| 3. Intraoral fibromas (≥2) |
| 4. Retinal achromic patch |
| 5. Multiple renal cysts |

**Table 13.1** (continued)

| |
|---|
| 6. Nonrenal hamartomas |
| Definite diagnosis: Two major features or one major feature with ≥2 minor features |
| Possible diagnosis: Either one major feature or ≥2 minor features |

Adapted from Northrup H, Krueger DA. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international tuberous sclerosis complex consensus conference. *Pediatr Neurol* 2013; 49:243–254

[a]Includes tubers and cerebral white matter radial migration lines

[b]A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet the criteria for a definite diagnosis

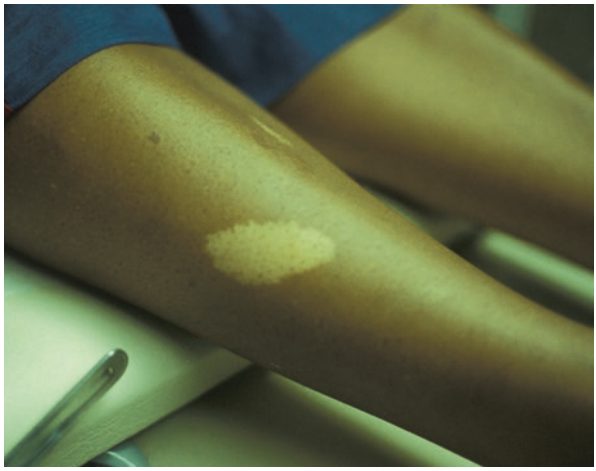

**Fig. 13.1** Hypomelanotic patch in the characteristic ash leaf configuration on the leg of an individual with tuberous sclerosis (Reprinted with permission from Weiner, D.M., Ewalt, D.H., Roach, E.S., et al., 1998. The tuberous sclerosis complex: a comprehensive review. J Am Coll Surg 187, 548–561)

Despite the identification of hamartin and tuberin, their function was not known until 2002: the formation of a complex by the two proteins was determined to impact a phosphoinositide-3-kinase (PI3K) pathway and inhibit the function of mammalian target of rapamycin (mTOR) [7]. This results in a downstream loss of tumor suppressing activities relating to cell proliferation and growth [8]. The tuberin-hamartin complex suppresses mTOR activity, an effect similar to that of rapamycin. To target the dysregulation of this pathway, rapamycin and an oral rapamycin derivative, everolimus, have been under investigation. There has been promising use in the treatment of several TSC-related complications: facial angiofibromas, subependymal giant cell astrocytomas (SEGAs), renal angiomyolipomas, and pulmonary lymphangioleiomyomatosis (LAM) [9, 10].

From a clinical perspective, skin manifestations are present in infancy but may not draw attention in the absence of other clinical features or risk factors. Present in up to 90% of affected individuals, hypomelanotic macules are apparent most reliably with the use of ultraviolet light, a Wood's lamp. As these can be seen in the general population, at least three must be present to count as a major diagnostic criterion (Fig. 13.1). Ash leaf spots has been another term for these lesions;

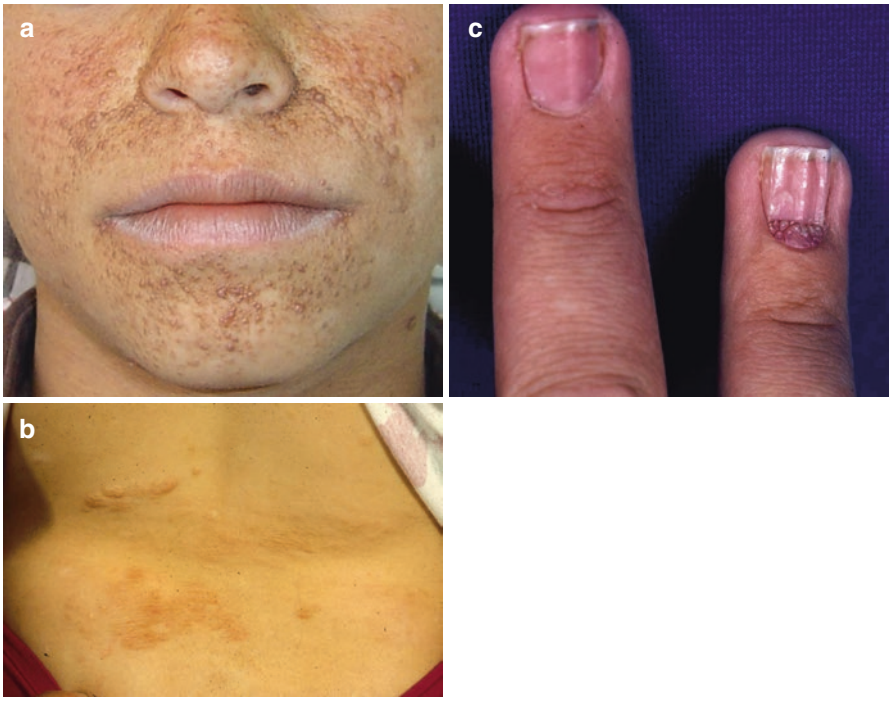


**Fig. 13.2** Typical cutaneous findings in tuberous sclerosis include (**a**) facial angiofibromas, (**b**) shagreen patch, and (**c**) ungual fibromata (Reprinted with permission from Roach, E.S., Delgado, M.R., 1995. Tuberous sclerosis. Dermatol Clin 13, 151–161)

hypomelanosis can also occur in a stippled pattern (confetti lesions) or as poliosis [11]. Facial angiofibromas, previously known as adenoma sebaceum, are more unique to individuals with TSC but are not present in all; they arise in early childhood, characteristically over the malar region (Fig. 13.2a). Composed of small vessels and connective tissue, these begin as discrete red macules that become larger, more numerous, and papular over a more extensive portion of the face; forehead fibrous plaques might also develop. Another skin finding is the shagreen patch: a raised, textured lesion of the flank or back that arises after the early childhood years [12] (Fig. 13.2b). Ungual fibromas occur adjacent to the nails or even underneath the nails (Fig. 13.2c). Shagreen patches and ungual fibromas do not occur in the majority of patients with TSC but are major features in the diagnostic criteria schema.

Facial angiofibromas and ungual fibromas are the skin lesions most likely to cause symptoms. The former can be disfiguring; laser therapy has been one treatment option, and mTOR inhibitors in oral or topical formulation have been under more recent consideration. These interventions may be most suitable in the prepubertal age range, before accelerated growth takes place. Ungual fibromas can be painful and can be resected surgically or treated via laser—though with the likelihood of recurrence [13].

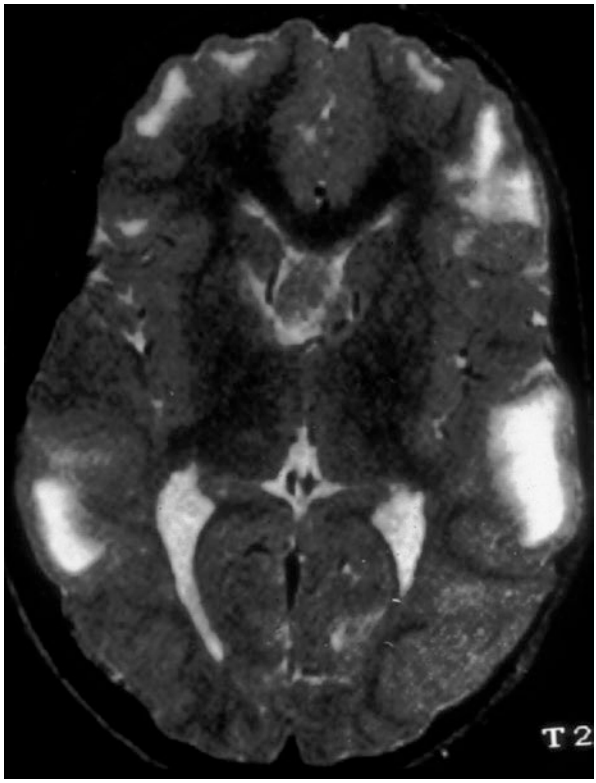


**Fig. 13.3** T2-weighted hyperintense lesions on noncontrast magnetic resonance imaging of the head demonstrate the burden of cortical tubers in a child with tuberous sclerosis (Reprinted with permission from Islam, M.P., Roach, E.S. 2016. Neurocutaneous syndromes, In: Daroff, R.B., Jankovic, J, et al., Eds., Bradley's Neurology in Clinical Practice. Elsevier, pp. 1538–1562)

Neurological involvement in TSC manifests as epilepsy, intellectual disability, and behavioral disorders. These arise related to abnormal neuronal migration that can be seen at least partially on imaging as cortical tubers, cortical dysplasia, and gray matter heterotopia (Fig. 13.3). Subependymal nodules (SEN) are also present on imaging. These may enlarge in the first few decades and ultimately calcify; given the location in proximity to the foramen of Monro, even minimal growth threatens obstructive hydrocephalus. SEN are also at risk for malignant transformation into subependymal giant cell astrocytomas (SEGAs) [14]. The burden of tubers is established by week 16 gestational age; however, immature myelination in the first 2 years of life may prevent them from being seen fully on magnetic resonance imaging (MRI). Surveillance imaging can monitor for enlargement of SEGAs; everolimus has been a recently available treatment to decrease tumor size and reduce the risks of—if not eliminate the need for—surgical resection [9]. Epilepsy surgery previously had been suspected to be unlikely to be helpful in these patients on the basis of multiple tubers or regions of cortical dysplasia that might be epileptogenic. The more current practice favors resection of a tuber or cortical dysplasia responsible for seizures at a given time; the seizure reduction or even freedom that might arise is a benefit that may outweigh the risk of future seizures arising from another region later in life [15]. Early seizure control has an additional benefit on

development and on socialization; autism and intellectual disability are more likely in those with early-onset epilepsy and intractable epilepsy. Tuberous sclerosis-associated neuropsychiatric disorders (TAND) are an important complication to consider in the surveillance and management of these individuals [16].

Mostly asymptomatic, cardiac rhabdomyomas are present in two-thirds of patients and have a propensity to involute with time. Often multiple, they can be seen on prenatal ultrasound and raise early suspicion for tuberous sclerosis; these infants should be screened more readily for other signs of tuberous sclerosis [17]. Depending on the size and location, these hamartomas may contribute to high cardiac failure; otherwise they may be associated with arrhythmia or thromboembolism. Surveillance echocardiogram and electrocardiogram are helpful to monitor cardiac rhabdomyomas until they demonstrate evidence of involution.

Renal manifestations in the form of angiomyolipoma can be identified in childhood and increase in size and number with age. These benign tumors can contribute to renal failure; they are also at risk for malignant transformation into renal cell carcinomas. TSC patients have a higher likelihood of renal cysts, which also contribute in some to renal failure. Renal complications are a leading cause of mortality and morbidity that is cumulative over the lifetime [18]. Surveillance imaging, preferably with MRI, every few years can monitor progression. Blood pressure monitoring and serum laboratory investigations can monitor renal function. Everolimus has been studied and utilized for the treatment of angiomyolipoma; surgical intervention and embolization remain additional options, especially for acute hemorrhage. Nephrectomy should be avoided [10].

Pulmonary lymphangioleiomyomatosis (LAM) is a significant source of morbidity, most often in postpubertal girls and young women but also with potential to affect men. Pulmonary symptoms related to TSC can include dyspnea, pneumothorax, and hemoptysis; once symptoms develop, they are associated highly with mortality within several years. Screening with chest CT for cystic changes, a 6-min walk test, and pulmonary function tests are recommended for all asymptomatic women older than 18 years and individuals otherwise symptomatic at any age [19]. These lesions are estrogen sensitive such that symptoms might arise or worsen with menses or pregnancy. The serious potential for pulmonary complications should guide counseling against smoking and even use of estrogen-containing treatments.

## 13.3 Neurofibromatosis Type 1 (NF1)

Also known as von Recklinghausen disease, neurofibromatosis type 1 is the most common neurocutaneous syndrome—with an estimated prevalence of 1 in 3000. Descriptions of the condition date back to the third century BC though some features were not described until the nineteenth and twentieth centuries. Defining diagnostic criteria in 1988 contributed to the identification of the NF1 gene. Neurofibromin is the gene product of the NF1 gene found in chromosome 17; a mutation disinhibits the GTPase-activated tumor suppression function to result in ras-mediated cell proliferation. NF1 exhibits autosomal dominant inheritance with

complete penetrance, but a large number of individuals have de novo mutations [20]. Some demonstrate segmental NF1, with a single region of the body manifesting the superficial and deeper features as a result of a somatic mutation in the NF1 gene during development.

Despite abnormalities on neuroimaging and advances in genetics, the diagnostic criteria continue to rely on clinical manifestations. An individual meeting two or more of the seven criteria can be diagnosed with NF1 [21]. If present, bony dysplasia with pseudoarthrosis can be one of the first signs—usually affecting a long bone and visible in the neonate. The sphenoid wing is another common location for dysplasia. Café au lait spots begin to develop in infancy (Fig. 13.4). As they are present in the general population, they must number more than six and measure greater than 5 mm in the prepubertal individual and greater than 15 mm in the postpubertal individual; usually an individual with NF1 unequivocally surpasses these numbers and measurements early in life. These macules and patches are hyperpigmented and difficult to see in darker skinned individuals; sun exposure may allow them to be seen more readily in any race. Less sun exposed, the axillary, inguinal, and intertriginous areas develop otherwise unexpected freckling (Crowe sign) by the mid-childhood years. Neurofibromas can develop in childhood and increase in number around puberty. Symptoms related to these benign peripheral

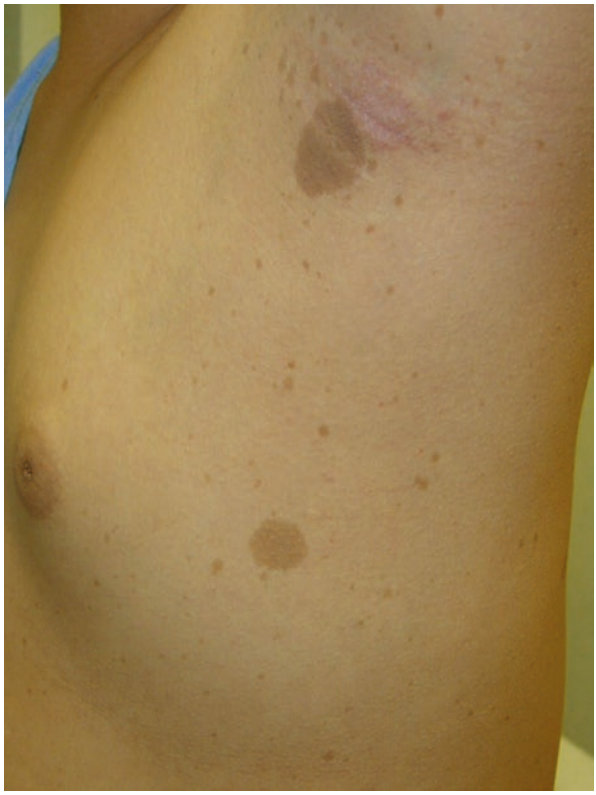

**Fig. 13.4** Characteristic café-au-lait macules and axillary freckling in an individual with neurofibromatosis type 1 (Reprinted with permission from Roach, E.S., 1988. Diagnosis and management of neurocutaneous syndromes. Semin Neurol 8, 83–96)

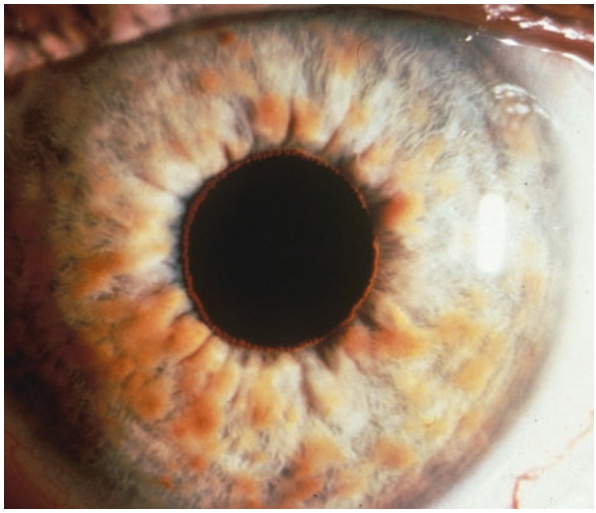

**Fig. 13.5** Lisch nodules in a patient with neurofibromatosis 1 are best seen with slit lamp examination (Reprinted with permission from Islam, M.P., Roach, E.S. 2016. Neurocutaneous syndromes, In: Daroff, R.B., Jankovic, J, et al., Eds., Bradley's Neurology in Clinical Practice. Elsevier, pp. 1538–1562)

nerve tumors relate to their size and location not only at the skin surface but also along the course of all peripheral nerves. Plexiform neurofibromas are more likely to cause symptoms on the basis of deformity and potential for transformation into malignant peripheral nerve sheath tumors (MPNST). Though they are asymptomatic, Lisch nodules are pathognomonic for NF1 and therefore important in establishing a diagnosis; these are pigmented hamartomas of the iris most easily seen by slit lamp eye examination (Fig. 13.5). Some preemptively will have at-risk individuals complete brain MRI to screen for optic glioma as the majority will develop in the first decade, a time most may not self-identify progressive changes in vision or cooperate with careful examination [22]. Otherwise, surveillance ophthalmologic evaluation is considered adequate for many [23]. Occurring in up to 15% of individuals with NF1, optic gliomas may be unilateral or bilateral and spread to involve the optic chiasm, thus with potential for homonymous bitemporal hemianopsia and precocious puberty via involvement of the pituitary axis (Fig. 13.6). Other signs and symptoms include optic nerve atrophy, proptosis, eye pain, or progressive loss of vision. NF-1 individuals account for the majority of individuals with optic gliomas. The slow-growing nature of these tumors usually accommodates close surveillance and infrequently guides intervention such as resection, radiation, or chemotherapy. An affected first-degree family member is another diagnostic criterion.

Individuals with NF1 are at higher risk for arterial dysplasia—predisposing them to aneurysmal formation, systemic hypertension, and moyamoya syndrome [24]. Short stature and macrocephaly—with or without hydrocephalus from aqueductal stenosis—can be present. White matter volume can be increased and contribute to megalencephaly [25]. MRI of the brain demonstrates T2 hyperintense signals across deep gray nuclei and cerebellum, sometimes referred to as

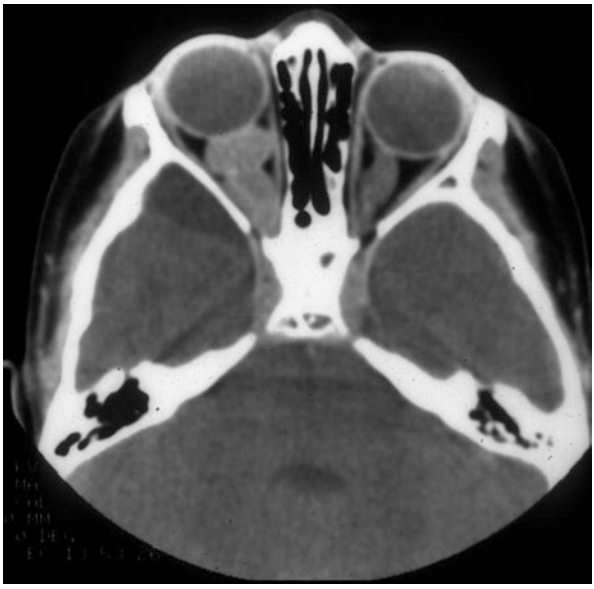

**Fig. 13.6** Bilateral optic nerve gliomas, larger on the right, demonstrated on computed cranial tomography in a child with neurofibromatosis type 1 (Reprinted with permission from Roach, E.S., 1992. Neurocutaneous syndromes. Pediatr Clin North Am 39, 591–620)

unidentified bright objects (UBOs); they are not visible on head CT—nor are they thought to contribute to the burden of neurologic symptoms. NF1 is associated with developmental delay, intellectual disability, attention disorders, and scoliosis. These individuals are subject to neuropathic pain and have a higher likelihood of epilepsy. The life expectancy is reduced, primarily on the basis of neurologic and nonneurologic malignancy. There is an increased incidence of malignant gliomas and pheochromocytoma.

The management of NF1 should include an awareness of the possible complications. Though there is controversy over whether to screen for optic glioma with brain and orbital MRI in the absence of vision concerns, once an optic glioma has been identified then the individual should be screened carefully and frequently for any progression of vision loss. For optic gliomas that warrant treatment, chemotherapy usually is first-line. Surgery may be an option only for certain intraorbital presentations. Given the risk for secondary malignancy and moyamoya syndrome, radiation is avoided [26]. Symptoms of cutaneous neurofibromas are guided by location and some may be surgically removed. Plexiform neurofibromas may cause significant complications and warrant debulking—though surgical interventions introduce risks of bleeding and neurologic injury. Given their slow growth, they do not respond to most chemotherapy. These tumors are at risk for transformation in ~10% to malignant peripheral nerve sheath tumors (MPNST) which also can arise de novo. These spindle cell carcinomas occur in younger individuals relative to those without NF1 [27]. This transformation is best detected on 18-FDG positron-emission tomography (PET) in the setting of new neurologic deficit [28]. The 5-year survival rate in these individuals with MPNST is poor.

## 13.4 Neurofibromatosis Type 2 (NF2)

Neurofibromatosis type 2 (NF2) is also autosomal dominant and occurs much less frequently than NF1: affecting an estimated 1 in 35,000. Although it was not fully separated from NF 1 until 1987, this entity differs from NF1 not only in clinical manifestation but also in pathophysiology. The responsible gene product is merlin, coded in chromosome 22; the identification of this NF2 gene separate and distinct from neurofibromin in 1987 led to the distinct classification of the two entities. Cutaneous findings are not well defined, and this condition more typically affects the central nervous system rather than peripheral nerves.

Bilateral vestibular schwannomas, possibly presenting asymmetrically with unilateral hearing loss, eventually develop in most—with symptoms of bilateral and progressive hearing loss, tinnitus, vertigo, and facial weakness referable to cranial nerves 7 and 8. These tumors previously were called acoustic neuromas. Other CNS tumors occur variably, giving rise to the term MISME syndrome: multiple inherited schwannomas, meningiomas, and ependymomas. The diagnosis often is delayed and perhaps missed given the under-recognition or lack of symptoms; a typical age of diagnosis is in the third decade. The diagnostic criteria call for a combination of unilateral or bilateral vestibular schwannomas, family history of NF2, CNS tumors, and subcapsular lenticular opacities.

Other than hearing loss or facial weakness, individuals with NF2 are at risk for a generalized polyneuropathy, which occurs in approximately 5%. This neuropathy manifests as paresthesias in a stocking-glove distribution or hyporeflexia and can even progress to atrophy. Neurophysiologic studies demonstrate mixed features of axonal loss and demyelination. Nerve biopsy demonstrates an onion bulb appearance that may relate to Schwann cell proliferation. Small tumors along the nerve can also contribute to neuropathy [29].

At the time of possible or definitive diagnosis, baseline MRI of the entire neuroaxis can be helpful to assess any tumor burden. In the cases of hearing loss and vestibular schwannomas, surveillance brain MRI and brainstem auditory evoked responses can be helpful to monitor progression. Although tumor is a significant cause of morbidity—many will go deaf despite surgery—and mortality, the majority of tumors detected on neuroimaging will not progress or produce symptoms. Compared to schwannomas, meningiomas are faster growing and can generate symptoms reflective of location. Treatment of tumors with radiation markedly increases the potential for malignant transformation.

Although autosomal dominant in inheritance, there also is a high spontaneous mutation rate. Tumors arise when one copy of the NF2 gene carries a mutation and the second normal copy is inactivated—common to other tumor suppressor mechanisms. Some individuals with a milder phenotype demonstrate mosaicism; mutation in these individuals may not be identified in blood. Identifying a mutation specific to an individual or family, even via tumor analysis rather than blood analysis, and utilizing an age-at-onset curve can help guide genetic counseling for at-risk family members. For an at-risk individual with the relevant mutation identified in family members, negative blood testing for the specific mutation could obviate the need for

other surveillance testing. For those who do not yet meet diagnostic criteria, testing in the form of neurologic and ophthalmologic examination is recommended annually, with audiologic evaluation starting at age 10 years. In the absence of symptoms, a screening brain MRI in adolescence and again around age 30 years is informative regarding confirmation or dismissal of a diagnosis. The duration of surveillance testing can be guided by the family age-at-onset curve [30].

Merlin, also known as schwannomin, takes its name from moesin-ezrin-radixin-like protein. Its tumor suppressor function is related to Ras and Rac signaling, and it has demonstrated linkage between cell membrane and cytoskeleton [31]. Based on the expression of vascular endothelial growth factor (VEGF) in vestibular schwannomas, VEGF-neutralizing antibody bevacizumab has been examined with some promise in reducing the size of schwannomas and improving or stabilizing hearing loss; the long-term efficacy and adverse events have not been established [32].

## 13.5 Sturge-Weber Syndrome

Sturge-Weber syndrome can be easily suspected from birth given the presence of the characteristic facial capillary malformation: the port-wine nevus or stain (Fig. 13.7a, b). The cutaneous manifestation is associated with abnormal vasculature involving the ipsilateral brain and eye. The corresponding neurologic symptoms can include contralateral hemiparesis (atrophy and spasticity), homonymous hemianopia, intellectual disability, and epilepsy. There are some with minimal neurologic impairment though the isolated cutaneous finding alone does not make the diagnosis; there are also some with minimal cutaneous manifestations. Some variants have had cutaneous and eye manifestations without developing brain involvement. An isolated port-wine nevus occurs in 1 in 300 but estimates of Sturge-Weber syndrome range from 1 in 20,000 to 1 in 50,000. Unlike many neurocutaneous syndromes, the inheritance pattern is sporadic—though a somatic mutation in GNAQ recently has been identified for port-wine nevus—and there is no potential for tumor formation.

The typical distribution of the port-wine stain is along the upper face and eyelid, and some can demonstrate bilateral involvement—usually still with one side predominantly affected. With time, the cutaneous involvement can become thickened and nodular. Early evaluation by a dermatologist and laser therapy minimizes disfigurement; the treatments can be painful and frequent. The vascular involvement can extend to the airway and pharynx. The conjunctiva can also demonstrate increased vascularity. The ipsilateral eye is at risk for glaucoma, which can peak in infancy and again in late childhood. Ophthalmologic follow-up is important to identify early progression of impaired vision and increased intraocular pressure. Eye drops are a mainstay of therapy though surgical intervention is not uncommon [33].

Abnormal leptomeningeal vessels are visible on cerebral imaging; the propensity to calcification is apparent on head CT and even skull radiographs on which the appearance of “tram tracks” has been described. However, brain MRI with contrast

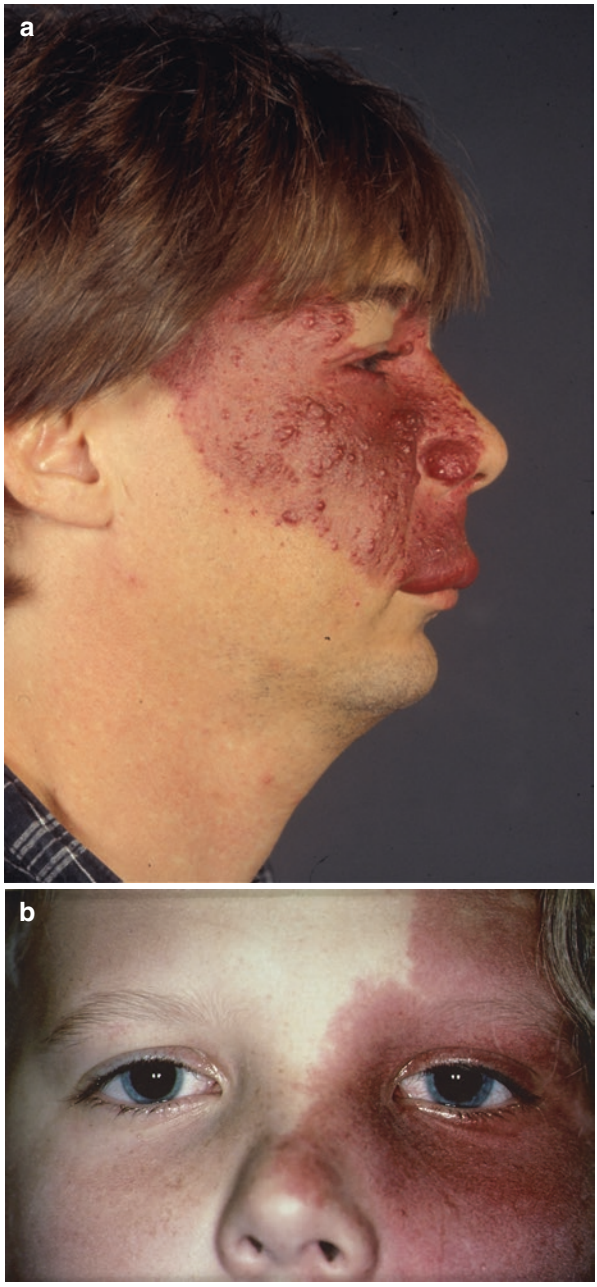


**Fig. 13.7** Examples of port-wine nevus or stain in two individuals with Sturge-Weber syndrome. (**a**) The texture can be nodular in some individuals. (**b**) Conjunctival or episcleral involvement may be present on the affected side (Reprinted with permission from Islam, M.P., Roach, E.S. 2016. Neurocutaneous syndromes, In: Daroff, R.B., Jankovic, J, et al., Eds., Bradley's Neurology in Clinical Practice. Elsevier, pp. 1538–1562)

demonstrates the earliest changes that might be sought to make a diagnosis of Sturge-Weber syndrome in an infant with a port-wine nevus. The scan can be repeated after 1 year of age to demonstrate the extent of involvement more definitively. Imaging demonstrates contrast enhancement of pial vessels, atrophy, and

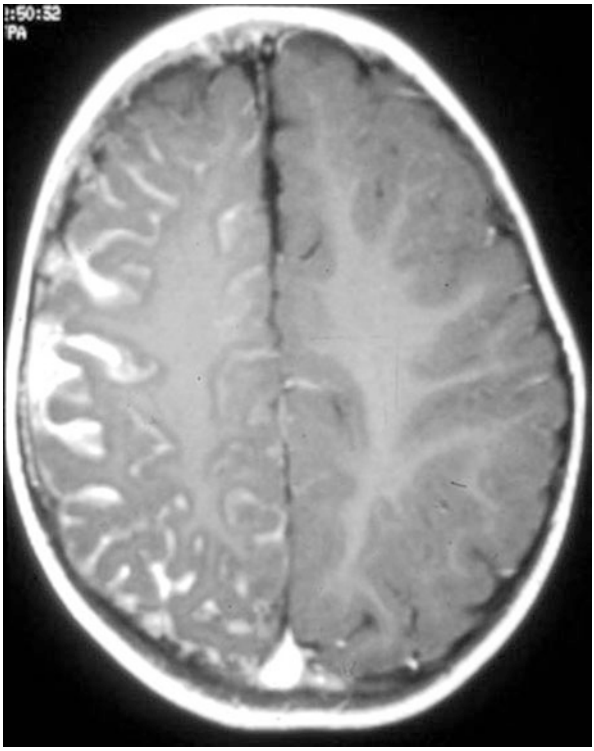

**Fig. 13.8** T1-weighted magnetic resonance imaging with gadolinium of the head demonstrates leptomeningeal and intraparenchymal angioma; this was not well seen without contrast (Reprinted with permission from Islam, M.P., Roach, E.S. 2016. Neurocutaneous syndromes, In: Daroff, R.B., Jankovic, J, et al., Eds., Bradley's Neurology in Clinical Practice. Elsevier, pp. 1538–1562)

ischemic changes depending on the timing (Fig. 13.8). Though it may not be evident radiologically, pathology has demonstrated cortical dysplasia that may not have been suspected on imaging [34]. Repeat neuroimaging may be performed on the basis of new neurologic concerns and demonstrates progressive atrophy of the affected hemisphere. At the time of diagnosis, an EEG may be a noninvasive method of screening for cerebral involvement.

As is the case for any epilepsy occurring early in life, seizures before the age of 2 years are more likely associated with intellectual disability. Approximately 80% with Sturge-Weber syndrome develop seizures and develop them early in life; for those without epilepsy or intellectual impairment early in life, it is less likely that these will develop after the first few years. Seizure types can be varied. While seizures in some can be controlled with medication, for other patients, resective epilepsy surgery or hemispherectomy are appropriate options. Aside from postictal weakness related to focal seizure, these patients are at risk for transient ischemic attacks and stroke-like episodes with progression of neurologic deficits; prolonged seizures increase the risk. Ictal single-photon emission computed tomography (SPECT) scans demonstrate decreased perfusion—rather than increased perfusion—in the hemisphere of seizure onset, further linking the association of seizure and cerebral ischemia [35]. Low-dose aspirin has been used by some to prevent strokes and improve epilepsy control. Some have considered the use of antiepileptic

medications and aspirin even before onset of epilepsy [36]. Migraine can occur early in life and worsen with poor seizure control.

The regional occurrence of Sturge-Weber syndrome—and nonhereditary pattern—had contributed to the suspicion that a somatic mosaic mutation was responsible. Study of affected tissue from port-wine stains and brain tissue in individuals with and without Sturge-Weber syndrome led to a recent discovery confirming a single-nucleotide variant (c.548G → A, p.Arg183Gln) in *GNAQ*. The population of cells affected by a mutation and timing during embryogenesis may impact the phenotype, which extends beyond Sturge-Weber syndrome and nonsyndromic port-wine stains [37].

## 13.6 Von Hippel-Lindau Syndrome

Von Hippel-Lindau syndrome is classified as a neurocutaneous syndrome though the "cutaneous" manifestation is restricted to ocular findings. Von Hippel described retinal involvement, and Lindau described characteristic CNS tumors and cysts. Retinal hemangioblastomas can manifest early in life as vision loss; a propensity to hemorrhage leads to other ocular involvement such as retinal detachment, glaucoma, uveitis, or macular edema. Demonstrating autosomal dominant inheritance, these individuals are at risk for CNS hemangioblastomas. These tend to be multiple and to affect relatively young individuals. Endolymphatic sac tumors (ELSTs) and visceral tumors, such as renal cell carcinoma, pheochromocytoma, and neuroendocrine tumors, contribute to diagnostic criteria.

CNS hemangioblastomas occur in the majority, typically in the third and fourth decades. They are slow growing but vascular; the symptoms relate to mass effect or hemorrhage at a given location. These tumors have a predilection for the cerebellum, spinal cord, and brainstem (Fig. 13.9). They tend to increase in incidence with age. The most reliable imaging includes brain and spine MRI with and without contrast. These lesions commonly demonstrate a cystic component and mural nodule. Since the pattern of growth may be stuttering, surgical excision should occur on the basis of symptoms or rate of growth; tumors that are multiple or relatively small might be amenable to stereotactic radiotherapy [38]. ESLTs occur in 10–15%.

In addition to CNS hemangioblastomas, renal cell carcinoma is a frequent occurrence; these two tumor types account for the leading causes of mortality in VHL. Renal tumors can be multiple and cysts are present as well; these malignancies can be multiple and occur at a younger age compared to sporadic renal cell carcinoma. The histology typically is clear cell. Cysts may contribute to renal failure. Resection should be performed with every attempt to preserve normal kidney function; resection at a size of 3 cm has been shown to avert potential for metastases while minimizing frequent interventions [39]. Pancreatic cysts and neuroendocrine tumors can also occur, and surgical intervention must balance metastatic potential and size with the risks of the procedure.

Up to 20% with VHL have pheochromocytoma; the presence defines 2A, 2B, and 2C phenotypes, which are further broken down by the presence of renal cell

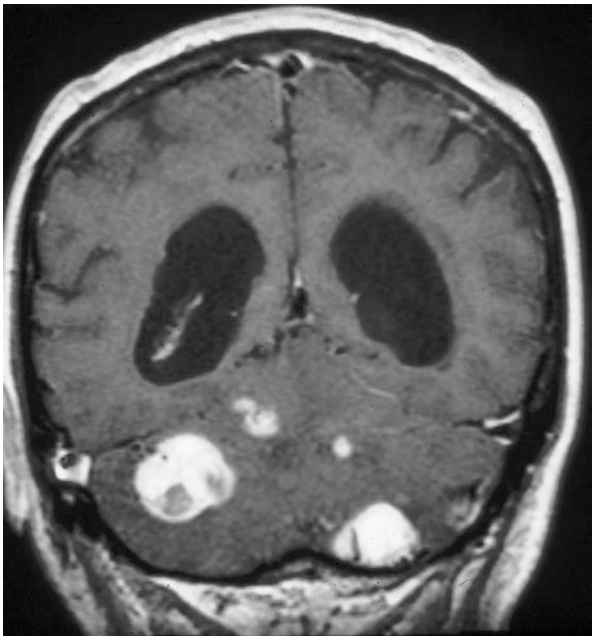

**Fig. 13.9** Multiple cerebellar hemangioblastomas demonstrated on T1-weighted magnetic resonance imaging of the head (Reprinted with permission from Islam, M.P., Roach, E.S. 2016. Neurocutaneous syndromes, In: Daroff, R.B., Jankovic, J, et al., Eds., Bradley's Neurology in Clinical Practice. Elsevier, pp. 1538–1562)

carcinoma. These tumors can be bilateral and multiple; paragangliomas may also occur. Those with pheochromocytomas demonstrate elevations in catecholamines before demonstrating symptoms such as hypertensive crisis. Surgical resection should attempt to preserve normal adrenal function.

Also known as retinal capillary hemangiomas, retinal hemangioblastomas occur in the majority and can lead to blindness in approximately 10%. These tumors occur frequently and earlier than other VHL tumors. The tumors often are symptomatic at presentation based on proximity to the optic nerve or macula, scarring, and hemorrhage. The number of tumors may not increase with age but the comorbidities do. Treatment includes laser photocoagulation and cryotherapy [40]. The presence of these tumors bilaterally or in multiple should raise suspicion for VHL in the undiagnosed individual; this predilection also applies to endolymphatic sac tumors (ELSTs), which are rare in the general population. Bilateral occurrence has been reported only with VHL. These tumors in the vestibular aqueduct can manifest hearing loss, impaired balance, tinnitus, or facial weakness. As these otherwise benign tumors enlarge, they can erode the adjacent temporal bone. Surgical resection with neurophysiologic intraoperative monitoring is recommended to prevent progression of symptoms, and they do not typically recur [41].

The responsible gene has been identified as one contributing to tumor suppression in chromosome 3. It impacts the function of hypoxia-induced factor, HIF2α, and contributes to angiogenesis and vascularization via upregulation of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor alpha (TGF-α), glucose transporter-1 (GLUT1), carbonic anhydrase IX, erythropoietin, and similar oxygen-sensitive gene products.

Among numerous mutations seen, those with missense errors are prone to pheochromocytomas while those with nonsense, frameshift, and splice-site mutations are not [42].

Testing first-degree family members for a VHL gene mutation helps guide surveillance in at-risk individuals. Affected individuals should undergo annual physical examination, urine and serum catecholamine testing, and ophthalmologic evaluation with imaging of the brain and abdomen every few years; similar recommendations are proposed for at-risk relatives [38].

## 13.7 Hereditary Hemorrhagic Telangiectasia

Also known as Osler-Weber-Rendu syndrome, hereditary hemorrhagic telangiectasia (HHT) consists of cerebral vascular malformations, cutaneous telangiectasias, and vascular dysplasia throughout varied organs. Autosomal dominant in inheritance, there are two definitively identified gene products responsible: endoglin in chromosome 9 (HHT1) and activin A receptor type II-like 1 kinase (ACVRL1) in chromosome 12 (HHT2).

Cutaneous telangiectasias are present most commonly on the face (lips, nose, oral cavity) and hands; epistaxis is recurrent and severe. These two findings are included in the Curaçao Criteria that were defined in 2000; the remaining two criteria include visceral arteriovenous malformations or telangiectasias and first-degree relative with HHT. The presence of three criteria makes a definite diagnosis; caution is advised against making a diagnosis on the basis of a single criterion [43]. The characteristic distribution of cutaneous telangiectasias and recurrent nature of epistaxis should draw suspicion; epistaxis often is the presenting symptom and occurs before age 10 years. Epistaxis often is significant enough to contribute to anemia; historically individuals with HHT died from the blood loss; in present day, many not only take iron supplements but also have been subject to blood transfusions. Telangiectasias are relatively uncommon in the first decade and then enlarge and multiply many years later.

Peaking in the sixth and seventh decades, bleeding can occur in the lungs, gastrointestinal tract, and genitourinary systems. Telangiectasias are present in the stomach and small intestine of most individuals though only 15–45% endorse bleeding. Arteriovenous malformations in the liver can cause not only portal hypertension and biliary disease but also otherwise significant shunting, which secondarily can contribute to high-output cardiac failure [44]. The threat of this complication increases during pregnancy [45]. Pulmonary arteriovenous malformations (AVMs) occur in 15–20% of affected individuals; conversely, among patients with pulmonary AVMs, the majority have HHT. When symptomatic, hemorrhage can cause hemoptysis and—more significantly—right-to-left shunting contributes to dyspnea, hypoxia, and pulmonary hypertension. Paradoxical left-to-right shunting contributes to cerebral comorbidity in the form of cerebral ischemia, embolic stroke, hemorrhage, or abscess from passage of clot, air, or infected material.

For those with cerebrovascular involvement, pulmonary AVMs account for etiology in 61% [46]. Otherwise, neurologic symptoms can arise from primary CNS involvement, which may be present radiographically in up to one-fourth as AVMs, fistulae, and telangiectasias—and less likely as cavernous malformations, venous angiomas, and vein of Galen malformations [47]. Neurologic symptoms can involve headaches, seizures, and dizziness. Headaches have been associated with pulmonary AVMs and with epistaxis [48]. High-pressure malformations are more prone to hemorrhage but most are of low flow; children may be more likely to demonstrate high-flow fistulae that might manifest catastrophic bleeding [49]. Spine AVMs are uncommon but at high risk for being symptomatic based on location.

The pathophysiology arises from impaired TGFβ signaling, particularly in relation to angiogenesis. Those with a mutation for endoglin may be more prone to pulmonary involvement. Those with a mutation in ACVRL1 may present later in life [50].

The identification of gene mutation for an affected individual can impact whether to consider relatives at risk. For the at-risk individual, counseling and screening are important in managing debilitating symptoms such as epistaxis and identifying other life-threatening involvement early. All individuals with confirmed or suspected VHL should be evaluated for pulmonary AVM. Transthoracic echocardiogram actually is the recommended screening tool to identify right-to-left shunting though many other modalities are available [49]. Embolization of a pulmonary AVM decreases the risks of stroke and abscess; migraine also improves. Antibiotic prophylaxis during dental procedures is recommended given the possibility of undiagnosed or recurrent pulmonary AVM. There is limited agreement over the role of surveillance brain MRI and angiography; symptoms referable to the spine should be investigated with dedicated spine imaging. Monitoring for anemia out of proportion to epistaxis is recommended as an indicator of gastrointestinal bleeding. Epistaxis is considered the symptom most commonly impacting the quality of life.

## 13.8 Incontinentia Pigmenti

Incontinentia pigmenti affects the skin, eyes, and central nervous system; it also carries the eponym Bloch-Sulzberger syndrome for the dermatologists who described it early. X-linked dominant inheritance, the pattern of affected female family members with skin pigment abnormalities and association with developmental delay, was noted in the first half of the twentieth century. The incidence is rare, approximately 1 in 50,000. Gene testing is available; alternatively, the diagnosis has been confirmed by skin biopsy.

The characteristic skin manifestations are present from the neonatal period and evolve through four stages over time. The abnormalities typically follow Blaschko lines, indicators of embryonic skin development pathways. Stage 1 findings appear as blisters; stage 2 appear verrucous; stage 3 appear linear and hyperpigmented; and stage 4 appear atrophic and hypopigmented (Fig. 13.10a, b). Also known as the

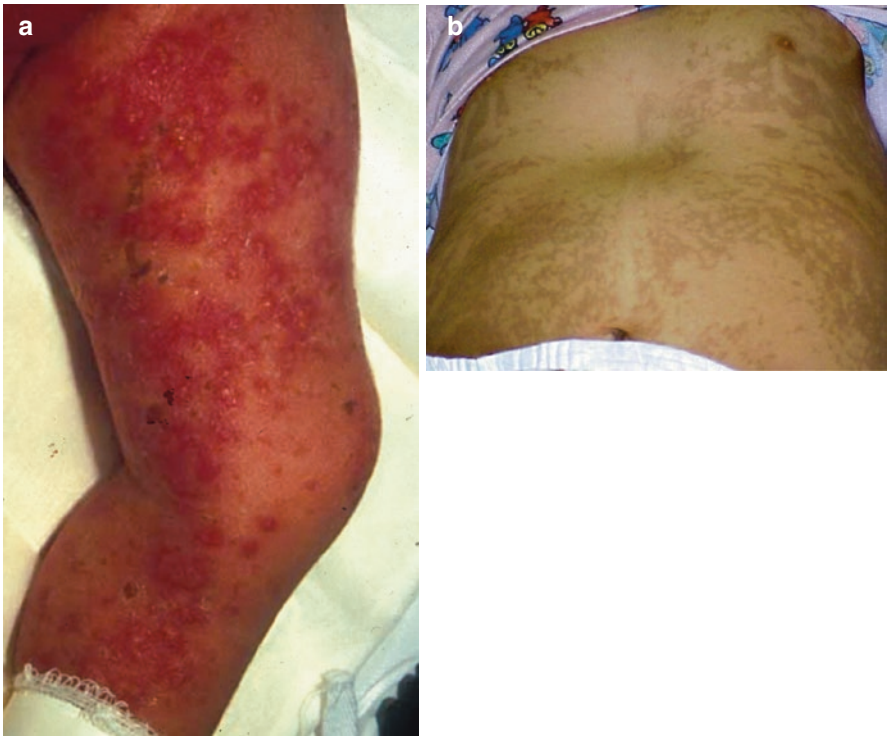


**Fig. 13.10** Skin findings in incontinentia pigmenti change over time with (**a**) blistering lesions seen in the infant and (**b**) hyperpigmented lesions in the older individual (Reprinted with permission from Islam, M.P., Roach, E.S. 2016. Neurocutaneous syndromes, In: Daroff, R.B., Jankovic, J, et al., Eds., Bradley's Neurology in Clinical Practice. Elsevier, pp. 1538–1562)

bullous stage, the blistering appearance in the newborn transitions to the appearance of warts in infancy. Hyperpigmentation evolves in childhood and remains into the second or third decade; these areas are not always in the regions previously vesicular or verrucous. The loss of subcutaneous elements may accompany hypopigmentation to give the appearance of the atretic stage; for individuals in whom not all stages occur, this may be the most likely to be skipped. The extremities and trunk can be involved with relative sparing of the face [51].

Starting in infancy, abnormalities of the hair may arise—more likely at the vertex. Alopecia may accompany skin pigment changes or may occur independently. Otherwise, scalp hair can be coarse or thin; the eyebrows may be affected also [52]. The nails manifest variable dystrophic changes throughout life. Subungual keratotic tumors can be painful and accompany underlying bony deformities. Dental abnormalities are common but often overlooked; they are considered minor diagnostic criteria [53].

Ocular abnormalities occur frequently and have the potential to impact vision, one of the more significant comorbidities in this disorder. Abnormalities such as

nystagmus, strabismus, microphthalmos, or ptosis may be mild, but detachment of a dysplastic retina in the setting of retrolental fibroplasia is a serious and not uncommon occurrence. Retinal vascular abnormalities are demonstrated on dilated funduscopic examination and retinal angiography [54].

The extent of neurologic involvement is variable, and the absence of neurologic involvement may contribute to an underestimation of the disorder. Intellectual or physical disability is estimated at around 10%. Seizures may arise in the neonatal period and accompany ischemic stroke—affecting the subcortical or cortical structures. The mechanism relates to large and small vessels—favoring a microangiopathy. Ischemia may lead to findings of perivascular leukomalacia, hemorrhage, and cerebellar atrophy. Outside of findings of stroke, brain MRI may demonstrate thinning of the corpus callosum and cerebral atrophy [55].

The female preponderance and higher rate of miscarriages in families with incontinentia pigmenti guided early suspicions for X-linked dominance. Rare males with the condition have been reported, such as in the situation of Klinefelter syndrome or suspected postzygotic mutation and mosaicism, but otherwise the condition has been lethal prenatally for males. Nuclear factor-kappa β (NF-κβ) essential modulator (NEMO)/IKKγ (Iκβ kinase-γ) is the responsible gene product; a deletion in exons 4–10 is present in 80–90%. Normal function of this signaling pathway implicates tumor necrosis factor and apoptosis, immune function, and inflammation [56]. Skewed X inactivation impacts disease expression and progression. The pathophysiology may guide future intervention, perhaps more so in regard to retinal involvement as the manifestation of seizures and stroke occurs early in life.

## 13.9 Hypomelanosis of Ito

Hypomelanosis of Ito, sometimes called incontinentia pigmenti achromians, variably affects the skin, brain, eyes, and other organs. It appears to be sporadic in inheritance; there have been varied cytogenetic abnormalities such as translocation, mosaicism, or ring chromosomes. It can occur as frequently as 1 in 8000, but there is some question as to whether it constitutes a distinct single entity or may be a set of symptoms accompanying myriad other conditions [57]. In pediatric neurology practices, the estimated prevalence may be up to 1 in 700.

Cutaneous findings are fairly consistent: whorls and streaks of decreased pigmentation that are present either from birth or in infancy and involve multiple body segments (Fig. 13.11). These mostly but do not always follow Blaschko lines. These hypopigmented areas are present in infancy and may be more easily seen with an ultraviolet light. For some, the distribution might be patchy or consist of other variations: café-au-lait spots, cutis marmorata, aplasia cutis, nevus of Ota, trichorrhexis, focal hypertrichosis, and nail dystrophy [58]. There are no preceding vesicular or verrucous stages [59]. Heterochromic iris has been reported, and the retina can demonstrate hypopigmentation. Other nonneurologic, noncutaneous involvement can affect the teeth, muscles, and bones.

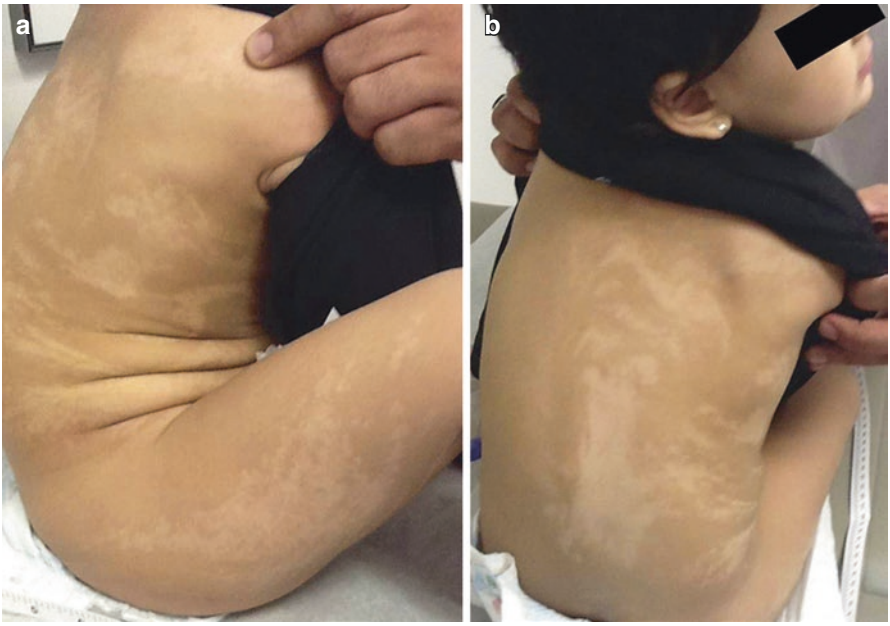


**Fig. 13.11** Hypopigmented cutaneous manifestations following Blaschko lines on (**a**) the right flank and thigh and (**b**) the midline back in hypomelanosis of Ito

The majority of individuals with typical skin findings have neurologic involvement; the estimates vary when relying on the report of neurologists versus dermatologists. For those who develop cutaneous lesions postnatally, neurologic symptoms usually appear earlier than the skin findings. This most typically manifests as intellectual disability—usually with an intelligence quotient less than 70. Epilepsy can also be common: seizure onset occurs early in life and focal seizures are more typical than generalized. Neuroimaging can be abnormal; there is no typical finding but the possibilities include white matter abnormalities, cerebellar or brainstem hypoplasia, neuronal migrational abnormalities, or hemimegalencephaly [60]. These children can demonstrate macrocephaly—more so than microcephaly. Hypotonia can also be present. For those in whom the skin findings are unilateral, the affected side may demonstrate hemihypertrophy or hemiatrophy.

Hypomelanosis of Ito remains a clinical diagnosis; major diagnostic criteria call for the presence of hypopigmented lesions in multiple body segments and at least one neurologic or musculoskeletal abnormality. Combinations of malformations in other system count as minor criteria. Although a unique inheritance pattern or genetic defect is not responsible, the pathophysiology has been attributed to chromosomal mosaicism or chimerization that may promote the differential migration of neural crest cells that are genetically different [61]. Recurrence in a family is rare but an affected individual should undergo karyotype analysis to identify abnormalities that may have been passed down from the parents. For females, there should be some suspicion for

incontinentia pigmenti in the differential diagnosis such that they should be monitored closely for developmental progress and evolution of skin findings.

## 13.10 Ataxia Telangiectasia

Ataxia telangiectasia is a neurodegenerative condition that manifests with progressive ataxia. The cutaneous telangiectasias arise later relative to the gait concerns. Among genetic causes of ataxia, it is the most common to affect young children—compared to Friedreich's ataxia, which is more common but presents in older children. Other distinctive processes include immunodeficiency and a sensitization to ionizing radiation; the clinical features were described early by Boder and Sedgwick [62]. Affecting 1 in 40,000 to 1 in 100,000, the inheritance is autosomal recessive for the gene ataxia telangiectasia mutated (ATM) in chromosome 11. Given the predisposition to immunodeficiency, testing immunoglobulins, which are low, and α-fetoprotein, which is elevated, are screening measures.

For these children, the first symptoms manifest as ataxia as they are learning to walk; they may be mistakenly diagnosed with cerebral palsy before the progressive nature of their ataxia is noted. They may learn to walk at a typical age and plateau in their unsteadiness in the early years of life. By age 10 years, they may no longer be capable of ambulating independently. The trunk is affected preferentially and early with later development of limb ataxia; choreoathetosis, dystonia, tremor, and myoclonus also develop and eventually are disabling. Dysarthria and even silent aspiration develop in the second decade [63]. Despite the presence of neurologic symptoms, brain MRI usually is normal in the first few years and then demonstrates progressive cerebellar atrophy. This atrophy initially is vermian [64]. Brain telangiectasias may be noted but these are unlikely to have clinical importance.

On examination of eye movements, oculomotor apraxia is evident early—especially related to saccadic movements. Patients will be noted to thrust the head characteristically to accommodate the impairment. The abnormal eye movements may be intermittent early and then gradually become continuous. Later there are findings of nystagmus and limited upgaze. Strabismus can also manifest. The abnormal eye movements diverge from abnormalities seen in other conditions involving cerebellar atrophy [65].

Ocular telangiectasias are present in nearly all patients, but usually not until age 6 years. These do not interfere with vision and do not accompany other ocular concerns such as retinal neovascularization or glaucoma seen in other neurocutaneous syndromes. With age, telangiectasias in other regions—notably malar—can arise (Fig. 13.12). Otherwise, abnormalities of pigment can arise and premature graying of hair [66].

With time, polyneuropathy accompanies the central nervous system signs: adults demonstrate loss of vibration and position sense, and they develop fasciculations and muscle atrophy. This sensorimotor neuropathy is axonal and length dependent. As most are nonambulatory by the time this manifests, it is unlikely to contribute to

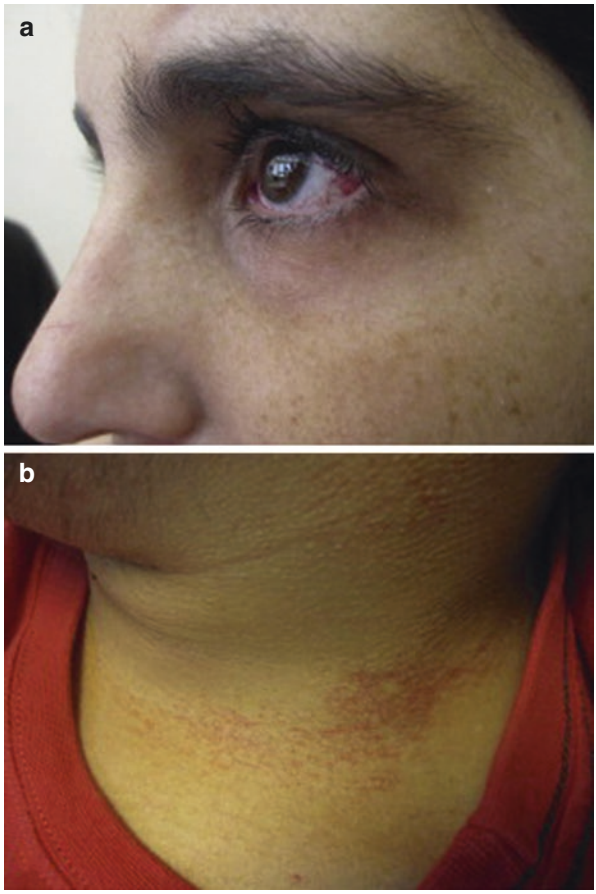


**Fig. 13.12** Telangiectasias in ataxia telangiectasia arise (**a**) on the conjunctiva and (**b**) in other regions (Reprinted with permission from Greenberger, S., Berkun Y., et al. 2013. Dermatologic manifestations of ataxia-telangiectasia syndrome. Journal of the American Academy of Dermatology 68(6): 932–936)

new neurologic deficit; it may be more meaningful in some who atypically are still walking in the second decade and beyond [63].

Immunodeficiency and a predisposition to malignancy are major sources of morbidity and even mortality. Frequent sinus and pulmonary infections can be present as many have a variable immunodeficiency; this is nonprogressive and the pathogens usually are common rather than opportunistic. Various immunoglobulin subtypes are decreased or absent. These patients frequently have lymphopenia and many will have leukopenia [67]. The thymus is small or absent on imaging. Malignancies, particularly T-cell lymphocytic leukemia and non-Hodgkin B-cell lymphoma, are present in about 20% with a mean age of 14 years [68]. Nonlymphoid malignancies arise in several organs, but brain tumors are rare.

Involved in DNA repair, ATM falls in the category of phosphatidylinositol 3-kinase-like protein kinases. Its normal function is to phosphorylate and therefore inactivate DNA breaks that occur normally and spontaneously. Unchecked, damaged DNA—including damaged tumor-suppressor genes—replicates and promotes carcinogenesis. Most affected individuals are double heterozygotes for point mutations in the ATM gene [69].

Once a diagnosis is established by clinical features and laboratory evaluation such as α-fetoprotein, immunoglobulins, and tests of cellular radiosensitivity, these patients should be monitored closely for development of leukemia and lymphoma. Treatment protocols for certain malignancies that involve radiotherapy should have lower doses of radiation administered to limit secondary malignancies. Sinopulmonary infections arise from common pathogens; the frequency is reduced with replacement of immunoglobulins. The pneumococcal polysaccharide vaccine may be poorly effective [67]. No definite neuroprotective measures are known to slow the progression, and so treatment of neurologic features is symptom based. It is noteworthy that the age of diagnosis approximates the age at which telangiectasias develop more closely that the age when ataxia develops; the diagnosis should be considered in children with progressive ataxia even in the absence of the ocular findings. Earlier diagnosis not only informs regarding the affected child's management but also allows for genetic counseling as many times at-risk siblings are born in the time before diagnosis in the older sibling who already is symptomatic [70].

## 13.11 Neurocutaneous Melanosis

Neurocutaneous melanosis is a disorder of melanocytes that affects the skin and central nervous system—primarily the leptomeninges. The condition is nonhereditary and rare. The earliest report dates back to 1861 when the autopsy of an adolescent with large nevi, intellectual disability, and hydrocephalus demonstrated leptomeningeal melanocytic deposits that were benign [71]. As melanocytic nevi occur in the absence of CNS involvement and melanin otherwise can be a normal finding in the CNS, the pathophysiology likely represents either abnormal migration or overproduction of melanin-producing cells. Among those with large congenital melanocytic nevi, up to 12% have neurocutaneous melanosis; posterior and axial location is higher risk [72]. The location of nevi over the trunk as opposed to the extremities in combination with CNS lesions suggests an early embryonal process [73].

Diagnostic criteria include large congenital melanocytic nevus and absence of melanoma in both the skin and the meninges (Fig. 13.13). The nevus in an adult should measure at least 20 cm; for an infant, the size criteria are 9 cm for a scalp lesion and 6 cm for a body lesion. Alternatively, the presence of multiple congenital nevi may suffice. Melanoma in either the skin or the meninges is allowable with the diagnosis [74]. The nevi are present at birth; they are hyperpigmented and hairy. The most typical location is over the lower trunk—swimming trunk nevus—but the upper back is another common location—cape nevus. Adjacent satellite nevi can develop in the early years. The cutaneous findings may be more prone to eczema and therefore some degree of depigmentation; an autoimmune response may arise [75].

Leptomeningeal melanosis impedes cerebrospinal fluid (CSF) flow, thus contributing to hydrocephalus and accompanying signs and symptoms of increased intracranial pressure: increasing head circumference, bulging skull fontanelles, irritability, lethargy, vomiting, papilledema, impaired eye movements, or seizures. CSF analysis

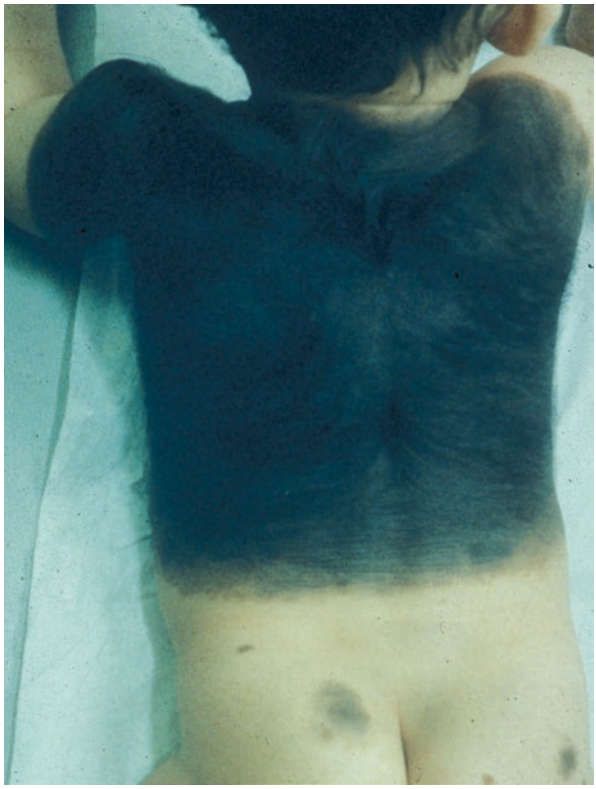

**Fig. 13.13** Large congenital melanocytic nevus along the upper back (cape nevus) (Reprinted with permission from Islam, M.P., Roach, E.S. 2016. Neurocutaneous Syndromes, In: Daroff, R.B., Jankovic, J, et al., Eds., Bradley's Neurology in Clinical Practice. Elsevier, pp. 1538–1562)

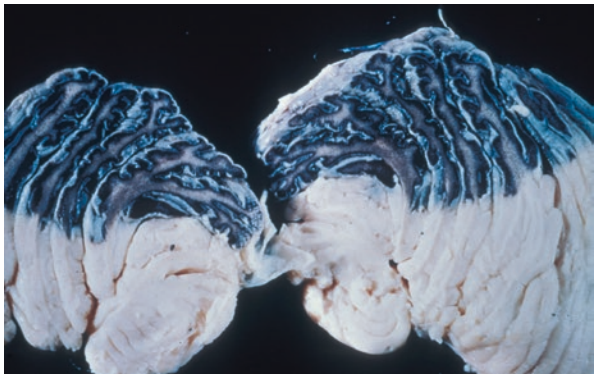

**Fig. 13.14** Autopsy brain specimen from a patient with neurocutaneous melanosis (Photo courtesy of Dr. John Bodensteiner; Reprinted with permission from Miller, V.S. 2004. Neurocutaneous melanosis, In: Roach, E.S., Miller V.S., Eds., Neurocutaneous disorders. Cambridge, pp. 71–76)

can demonstrate elevated protein and presence of melanin granules. Even prior to the development of neurologic symptoms, neuroimaging often is abnormal; the brainstem, deep gray nuclei, temporal lobes, and basal frontal lobes are common sites. Abnormal findings may be better appreciated in infant brains that have not myelinated [75]. On pathology, the degree of melanin deposits rather than the distribution is abnormal (Fig. 13.14). Necrosis, edema, enhancement, or hemorrhage are indicators of melanoma versus melanosis. For some, abnormalities such as Dandy-Walker

malformation may be present and an indicator of impaired CSF flow during development. Imaging may also demonstrate dorsal spinal arachnoid cysts; these usually are asymptomatic [71].

Individuals with neurocutaneous melanosis are at risk for malignant transformation of lesions in either the skin or the CNS. Even in the absence of proven malignancy, the neurologic complications manifest early in life—in the early childhood years or even infancy. The median age for neurologic manifestations is 2 years and most will have developed neurologic involvement by 5 years [73]. Although there are individuals who may remain asymptomatic, there is a high mortality rate and death occurs early in life—usually by age 10 years in those who develop neurologic symptoms. For those who survive the early childhood years, survival may span decades. For these individuals, the excision of cutaneous nevi may provide cosmetic benefit and lessen the future risk of malignant transformation; for children already manifesting neurologic symptoms, the risk:benefit ratio of these interventions is unlikely to be favorable. Similarly, other surgical interventions that are elective or of high risk may warrant waiting beyond the first few years of life in the case of neurologic progression. Reporting may be biased by cases that come to autopsy versus those with suspicious cutaneous lesions who undergo imaging though asymptomatic. Neurologic symptoms may be missed without early developmental screening and neurology care. Once neurologic involvement is present, the care is symptomatic—in the form of medical management of seizures and shunting for hydrocephalus. An indwelling shunt may provide a tract for metastasis of CNS melanoma to the abdominal cavity. No definitive guidelines are available regarding the frequency of imaging [72].

## 13.12 Summary

Neurocutaneous syndromes are a testament to the common embryologic origin of the nervous system and skin. Dysregulated cellular growth and differentiation result in anomalies not only of the skin and nervous system but also of other organ systems. The pathophysiology commonly predisposes these individuals to tumor, vascular abnormalities, and disruption of specialized functions. These processes pose variable risks throughout the life span such that an accurate diagnosis is important in establishing surveillance plans that may include combinations of patient education, a multidisciplinary approach to care, and imaging. The hereditary nature of many of these conditions also introduces the obligation to be cognizant of at-risk family members and the effects on family planning. Understanding the mechanisms by which cellular and vascular proliferation is regulated has contributed to exciting research advances that importantly have channeled opportunities to modify the disease course.

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