Neurocutaneous Disorders in Children

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Practice Gaps

1. Clinicians may miss early signs of neurofibromatosis (NF), tuberous sclerosis complex (TSC), and Sturge-Weber syndrome, thereby delaying diagnosis.
2. Clinicians may be unaware of the diagnostic criteria for these disorders and, therefore, be unable to establish a clear diagnosis.
3. Clinicians may be unaware of the availability, indications, and limitations of genetic testing to assist in diagnosis of NF, TSC, and Sturge-Weber syndrome.
4. Clinicians may be unfamiliar with the natural history of the disorders and, therefore, unable to provide appropriate support to families.

Objectives After completing this article, readers should be able to:

1. Recognize signs of neurofibromatosis (NF), tuberous sclerosis complex (TSC), and Sturge-Weber syndrome.
2. Use diagnostic criteria to establish the diagnosis of NF, TSC, and Sturge-Weber syndrome.
3. Order genetic testing to assist in the diagnosis of NF, TSC, and Sturge-Weber syndrome.
4. Provide support to patients and their families once the diagnosis is established.

AUTHOR DISCLOSURE Dr Korf has disclosed that he is coinvestigator on NIH grant 08-UTR001417A for the University of Alabama's Center for Clinical and Translational Science; principal investigator on Department of Defense NF Clinical Trials Consortium grant W81XWH-12-1-0155; and consultant for Astrazeneca, Novartis, Alexion, Illumina, and Accolade. He has received honoraria from 23andMe and Sequenom to attend roundtable meetings and to speak at meetings. He also serves as an advisor for Envision Genomics and Genome Medical, and has conducted a CME Course for Quantia. Dr Bebin has disclosed that she is a consultant and site principal investigator for Novartis Pharmaceuticals epilepsy clinical trials and a consultant for GW Pharma epilepsy trials. She receives NIH-NINDS grant funding for tuberous sclerosis research studies, serving as principal and coinvestigator, respectively, on NIH grants F121213001 and F120629001. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

MRI	magnetic resonance imaging
NF	neurofibromatosis
NF1	neurofibromatosis type 1
NF2	neurofibromatosis type 2
TSC	tuberous sclerosis complex

Abstract

Neurofibromatosis (NF), including type 1 (NF1), type 2 (NF2), and schwannomatosis; tuberous sclerosis complex (TSC); and Sturge-Weber syndrome are 3 neurocutaneous disorders that typically present in childhood. Early recognition by the pediatrician can be critical to surveillance for treatable complications and genetic counseling. These conditions are diagnosed clinically, but genetic testing is available to clarify an uncertain diagnosis or help with genetic counseling. Although many of the complications can only be treated symptomatically, advances in understanding of the pathogenesis are opening new approaches to molecularly targeted therapeutics, which promise to alter the natural history of the conditions in the years to come.

INTRODUCTION

The term "neurocutaneous syndrome" refers to a set of disorders that have prominent manifestations on the skin and in the nervous system. The list includes many conditions, some of which are extremely rare, but 3 of the most common are neurofibromatosis (NF), tuberous sclerosis complex (TSC), and Sturge-Weber syndrome. These lifelong disorders generally present during infancy and early childhood, so the pediatrician is likely to be the first clinician to recognize the condition, arrange for diagnosis, and participate in management. Although the presenting signs are obvious in some cases, the initial signs can be subtle and may overlap with common skin findings seen in the general population. Therefore, overlooking the condition early in its course is easy, with the risk of not quickly recognizing treatable complications. Conversely, some children have suggestive cutaneous markings but do not have a neurocutaneous disorder. Referral of a child for formal evaluation can be anxiety-provoking for the family, but confirmation of the diagnosis can help ameliorate the likelihood of severe complications. For these reasons, the pediatrician should be aware of the presenting signs, criteria for diagnosis, role of genetic testing, and approaches to surveillance and management for NF, TSC, and Sturge-Weber syndrome, which are covered in this review.

NEUROFIBROMATOSIS

NF is an umbrella term for 3 genetically distinct disorders: NF1, NF2, and schwannomatosis. They have in common a tendency toward development of tumors of the nerve sheath, but the specific manifestations are distinct and the conditions result from variants in different genes. Because NF1 is the most common and the most likely to present in childhood, this review focuses primarily on this form of NF, with some comments about NF2 and schwannomatosis.

Epidemiology of NF1

NF1 occurs in approximately 1 in 3,000 individuals around the world, with no known ethnic, racial, or geographic predilection.

Presentation in Childhood

Major clinical features of NF1 are listed in Table 1, most of which could occur in childhood and might be the presenting problem in a child. By far the most common pediatric-onset manifestations are café-au-lait macules and plexiform neurofibromas (Fig 1A, B). Recognition of the possibility of NF1 in a child with either of these early signs can help make a diagnosis and guide management to avoid delay in recognizing potentially serious complications.

Cutaneous Manifestations of NF1. Café-au-lait macules are brown macules that may be scattered anywhere on the body and range in size from 1 millimeter to several centimeters. They may be present at birth but often gradually appear in the first few postnatal months. Diagnostic criteria (Table 2) require 6 or more café-au-lait macules larger than 5 mm before puberty or 15 mm after puberty. The presence of 1 to 3 café-au-lait macules is common in the general population, and children with one dark-skinned parent and one light-skinned parent often have several café-au-lait macules. There is a differential diagnosis of café-au-lait macules (Table 3), and genetic testing (see section on diagnosis) can help to distinguish these other disorders. There is no correlation between the number, size, or location of café-au-lait macules and the severity of NF1. In addition to café-au-lait macules, patients may have larger hyperpigmented patches that often overlie plexiform neurofibromas; these are distinguished from café-au-lait macules by their larger size and irregular margins.

The other major cutaneous pigmentary feature of NF1 is freckling in the axillary and inguinal regions (Fig 1C) as well as the base of the neck and around the mouth. Such skinfold freckling usually appears between ages 3 and 5 years. A café-au-lait macule that resides in a skinfold does not constitute a skinfold freckle; the freckles are usually multiple and sometimes extend to non-skinfold regions.

Neurofibromas are benign tumors of the nerve sheath that arise from Schwann cells. Dermal neurofibromas are typically seen in adults and can be disfiguring from their sheer numbers. Dermal neurofibromas are not seen as often in prepubertal children, although sometimes small subcutaneous bumps are visible with side-lighting. In contrast, plexiform neurofibromas often are recognized in young children. These tumors also arise from Schwann cells, but unlike the dermal neurofibromas, which are focal growths, plexiform neurofibromas grow longitudinally along nerves and may involve a major nerve and its branches. Sometimes these arise from spinal nerve roots and spread along the spinal nerves. They can occur on the surface of the body, where they may be clinically recognized as a subtle soft-tissue overgrowth, or can grow internally and not be recognized until they cause a symptom by impingement on a surrounding structure. Approximately 50% of individuals with NF1 have at least one plexiform neurofibroma, (1) and about 50% of these are clinically evident. Plexiform neurofibromas can grow to cause major disfigurement and hypertrophy of skin and soft tissues, and growth tends to be most rapid during childhood. Typical sites of involvement in children are the eye, neck, and limbs.

TABLE 1. **Major Manifestations of NF1**

MANIFESTATION	AGE OF ONSET	COMMENTS
Café-au-lait macules	Birth–2 years	6 or more larger than 5 mm is diagnostic criterion
Skinfold freckles	3-5 years	Specific to NF1; axillary and inguinal regions, neck
Dermal neurofibromas	Preadolescence	Small fleshy skin growths; sometimes visible in younger children
Plexiform neurofibromas	Birth	May cause overgrowth and disfigurement; grow in childhood
Macrocephaly	Birth	Benign; no relationship with neurologic problems
Bone dysplasia	Birth	Long-bone dysplasia or orbital dysplasia; may have nonossifying bone cysts; scoliosis
Neurocognitive	Birth	Learning disabilities; attention-deficit disorder; some with severe developmental impairment and rare autism spectrum disorder
Optic glioma	Birth–6 years	Optic nerves and/or chiasm; detect by MRI, but often asymptomatic, although a subset cause visual loss
Glioma	Any age	Gliomas of other regions of brain may occur; often have indolent course
Malignant peripheral nerve sheath tumors	Any age	Arise from preexisting plexiform neurofibromas; signs of pain, sudden growth, hard texture
Other tumors	Any age	Rhabdomyosarcoma and juvenile myelomonocytic leukemia in children; glomus tumors, gastrointestinal stromal cell tumors, and pheochromocytoma in adults

NF1=neurofibromatosis 1; MRI=magnetic resonance imaging.

Noncutaneous Manifestations of NF1. Other manifestations might draw attention to the fact that a child is affected with NF1. These include tibial dysplasia, optic glioma, and neurocognitive dysfunction. Tibial dysplasia (or dysplasia of any long bone) is congenital but usually comes to clinical attention around the time that a child begins to stand. Optic glioma generally occurs between ages 2 and 6 years. It is most often asymptomatic but can cause visual loss or hypothalamic disturbance if the chiasm is involved. Neurocognitive dysfunction affects at least 50% of children who have NF1 and can include learning disability, attention-deficit disorder (with or without hyperactivity), social immaturity, poor speech articulation, lack of coordination, and hypotonia.

Diagnosis of NF1

NF1 is diagnosed based on fulfilling at least 2 clinical criteria (Table 2). (2) Many of the features are age-dependent, so the diagnosis may be unresolved for a few years in a young child who presents with multiple café-au-lait macules until another feature, such as skinfold freckling, appears. Genetic testing is available,

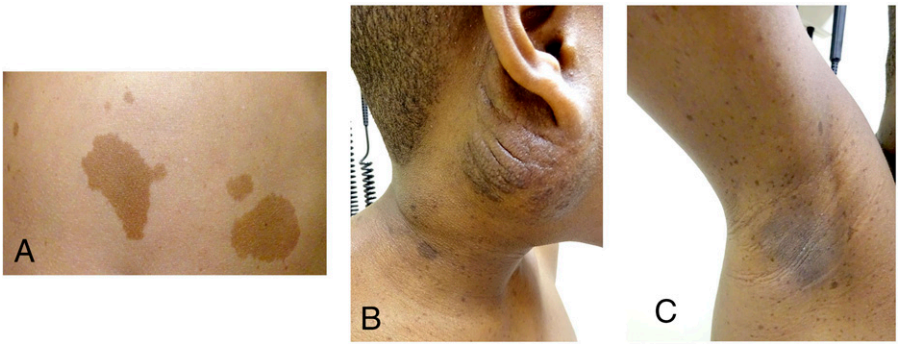


Figure 1. Characteristic skin lesions of neurofibromatosis 1. A. Multiple café-au-lait macules. B. Plexiform neurofibroma (this tumor had previously been partially resected). C. Axillary freckling.

TABLE 2. **Diagnostic Criteria for NF1***

CRITERION	COMMENTS
Six or more café-au-lait macules larger than 5 mm prepubertal or 15 mm after puberty	1-3 café-au-lait macules common in general population
Skinfold freckling	Axillary, inguinal, submammary regions; also may occur on neck and around mouth
Two or more neurofibromas or 1 plexiform neurofibroma	Plexiform neurofibromas are usually congenital, but dermal tumors are not seen at birth
Characteristic skeletal dysplasia	Long bone or sphenoid wing (orbit)
Optic glioma	
Iris Lisch nodules	Requires slitlamp to be seen; usually seen after age 6 years
Affected first-degree relative	Inherited as autosomal dominant trait
Noonan syndrome	Dark cafe-au-lait spots, pulmonic stenosis; some with multiple lentigines; mutations in various genes associated with Ras signaling

**The diagnosis of NF1 is established if 2 or more criteria are met.*
NF1=neurofibromatosis 1.

which can detect *NF1* gene mutations in about 95% of individuals who fulfill diagnostic criteria. (3) Thousands of pathogenic mutations have been described, and most lead to loss of function of the *NF1* gene product. Genetic testing can be offered to establish a diagnosis in advance of waiting for a second clinical feature to emerge and can also distinguish NF1 from Legius syndrome, which also presents with café-au-lait macules but does not lead to the other NF1 complications. Some affected individuals are somatic mosaics for the *NF1* gene mutation due to mutation during embryogenesis. They may present with segmental distribution of signs of NF1 (such as café-au-lait macules and skinfold freckles confined to one region of the body), or the signs can be widespread but perhaps ameliorated by the mosaicism.

Management of NF1

There is no medical treatment for NF1, so management involves surveillance for potentially treatable complications. (4) This includes observation of plexiform neurofibromas, both

TABLE 3. **Differential Diagnosis of Café-au-lait Macules**

CONDITION	COMMENTS
Legius syndrome	Café-au-lait macules and skinfold freckles but no risk of tumors; due to *SPRED1* mutation; gene product also a Ras protein regulator
McCune-Albright syndrome	Fibrous dysplasia; precocious puberty in females; café-au-lait macules tend to be larger and have irregular margins; due to mosaic *GNAS1* mutation
Ataxia-telangiectasia	Cerebellar ataxia; telangiectasia (easily seen on conjunctiva); due to *ATM* gene mutation
Bannayan-Riley-Ruvalcaba syndrome	Macrocephaly; freckling on glans penis in males; due to *PTEN* mutation
Tuberous sclerosis complex	Hypopigmented macules more common
Neurofibromatosis 2	May have multiple café-au-lait macules but less often than in NF1
Congenital DNA mismatch repair deficiency syndrome	Café-au-lait macules and freckling; homozygous mismatch repair gene mutation; most develop malignant tumors in childhood
Chromosomal mosaicism	Irregularly shaped hyperpigmented spots with various abnormal chromosomes found in pigmented tissue

NF1=neurofibromatosis 1; NF2=neurofibromatosis 2.

clinically and by magnetic resonance imaging (MRI). Surgical intervention is reserved for circumstances where a tumor causes major symptoms or disfigurement, such as airway or spinal cord compression. Tumor regrowth after surgery is common. Clinical trials are now underway with a variety of medications that target the aberrant cellular signaling that occurs in neurofibromas; current trials can be located through www.clinicaltrials.gov. Recently, the MEK inhibitor selumetinib was found to lead to shrinkage of plexiform neurofibromas in more than 2/3 of individuals treated, suggesting that such treatment may be an effective nonsurgical therapy for plexiform neurofibromas. (5)

Optic gliomas can be recognized from a loss of visual acuity or constriction of visual fields; if the chiasm is involved, precocious puberty and other neuroendocrine disturbances can occur. Most optic gliomas are self-limiting in their growth and do not require treatment. If progression occurs, it usually does so by age 6 years. Current guidelines suggest annual ophthalmologic examination to detect optic pathway tumors, at least until about age 6 to 7 years. Some clinicians advocate screening by MRI, but the issue remains controversial because most of the lesions detected by MRI never require treatment. Symptomatic optic gliomas are usually treated with chemotherapy (typically vincristine and carboplatin); clinical trials are underway for the small number of patients who fail to respond to this treatment.

Children with NF1 are at risk of hypertension due to renal artery stenosis, so blood pressure monitoring is important. Pheochromocytoma may also cause hypertension, which is usually an adult-onset problem, although presentation in childhood is possible. Moyamoya syndrome (occlusion of the internal carotid with consequent collateral blood flow) can occur and lead to stroke. Long-bone dysplasia should be evident by about age 1 year, and if present, should be verified by radiography and prompt referral to an orthopedist. Scoliosis occurs commonly, and some children require surgical treatment. Children should be followed for cognitive development and referred for formal neuropsychological testing if developmental concerns arise. Attention-deficit disorder often responds to stimulant medication.

Although not usually life-threatening, NF1 can shorten lifespan, most often due to complications of vascular dysplasia or malignancy. About 10% of patients develop a malignant peripheral nerve sheath tumor, usually after the first decade. They present with pain and a growing mass. Positron emission tomography with 5-flurodeoxyglucose can be helpful in distinguishing a benign neurofibroma from a malignant peripheral nerve sheath tumor.

Genetics of NF1

NF1 is transmitted as a classic autosomal dominant trait with complete penetrance but variable expression. An affected person has a 50% chance of transmitting NF1 to a child. Approximately 50% of cases occur sporadically due to a new mutation. If the parents of a child with NF1 are examined and neither has signs (eg, café-au-lait macules, neurofibromas), then the child is most likely affected due to new mutation and the parents face a low risk of recurrence, barring the rare phenomenon of germ line mosaicism. It is important, though, to be thorough in questioning and even examining the parents because some adults with mild manifestations are unaware that they are affected until a child with more obvious signs is born.

Other Forms of Neurofibromatosis

NF2 affects about 1 in 30,000 individuals in all populations. Signs can begin in childhood, and some do not experience complications until adulthood. The defining feature is bilateral vestibular schwannomas (previously referred to as "acoustic neuromas" [6]), which typically present with tinnitus, hearing loss, loss of balance, and sometimes facial nerve paralysis. Café-au-lait macules are not a reliable indicator of NF2, although some affected individuals have several café-au-lait macules and some have 6 or more, raising confusion with NF1. Those with NF2 do not have skinfold freckling or cutaneous neurofibromas, although some may have plaquelike skin growths representing schwannomas. A child known to be at risk for NF2 because of an affected parent (and perhaps diagnosed by genetic testing) should be followed in childhood by audiology and MRI to monitor abnormal findings. All children with NF2 should have a brain MRI by adolescence. Other cranial nerve schwannomas can occur as can meningiomas and ependymomas. The former can become symptomatic due to compression of brain or spinal cord; the latter are most often asymptomatic. Genetic testing is available for diagnosis of NF2 and is especially helpful in determining whether the child of an affected parent has inherited the mutation, given the paucity of signs that may be present in young children. Treatment has focused primarily on surgery for symptomatic tumors, but recently the angiogenesis inhibitor bevacizumab has been used with some success to treat progressive vestibular schwannomas, reducing tumor size and improving hearing.

Schwannomatosis is the most recently recognized form of neurofibromatosis. The major feature is multiple schwannomas, usually of adult onset. (7) These are often accompanied by pain, which may be severe and usually only relieved by surgery. The vestibular nerves are typically not involved, although some patients with vestibular schwannomas or meningiomas have been described, leading to confusion with NF2. At least 2 genes have been implicated

(*SMARCB1* and *LZTR1*), and genetic testing is available for these. Other genes may also be involved in some families.

TUBEROUS SCLEROSIS COMPLEX

TSC, like NF, is a multisystem genetic disorder that usually presents in infancy and early childhood. Pathologic variants in either of 2 distinct genes (*TSC1* and *TSC2*) underlie the disorder in different individuals.

Epidemiology of TSC

TSC affects about 1 in 6,000 individuals worldwide. It is due to mutation of either the *TSC1* or the *TSC2* genes, which, as noted previously, results in the same phenotype. The trait is transmitted as dominant with complete penetrance but variable expression. At least 50% of cases are due to new mutation, and mosaicism can occur.

Presentation in Childhood

The most common pediatric presentations of TSC are dermatologic features or the development of complications, usually cardiac or neurologic.

Cutaneous Manifestations. The hallmark dermatologic manifestations of TSC are hypopigmented macules (Fig 2A). These are congenital lesions, but they may not be obvious at birth, especially in fair-skinned infants. They may range in size from a few millimeters to several centimeters; usually they are 1 to 2 cm and classically have a lancinate, or "ash-leaf" shape. Clusters of smaller confetti-like white spots may also occur. Hypopigmented macules are best visualized with the Wood lamp in an otherwise dark room. A diagnosis of TSC should be suspected if 3 or more lancinate hypopigmented macules are seen in different regions of the body. The differential diagnosis includes nevus depigmentosus, which usually occurs singly or in clusters in a restricted region of the body and lacks the lancinate shape of the hypopigmented macules seen in TSC. Nevus anemicus may also be confused with the hypopigmented macule. This is not an area of depigmentation but rather one of constricted skin blood vessels and typically appears as an isolated irregular region of pallor that does not become red if the skin is rubbed.

Other characteristic skin lesions include angiofibroma, collagenous plaques (Fig 2B), and the shagreen patch. An angiofibroma usually appears on the face, especially the cheeks and nose, but other sites can be involved. Angiofibroma is often confused with acne, but unlike acne does not involve skin pores and lacks inflammation and comedones. The archaic term "adenoma sebaceum" is no longer used because the growths do not arise from sebaceous glands. Angiofibromas often appear in the early childhood years. Collagenous plaques are small raised areas under the skin, often seen on the face and around the eye (referred to in the diagnostic criteria as "fibrous forehead plaque"), but they can occur anywhere. Shagreen patch is a region of irregular raised skin caused by excessive deposition of collagen in subcutaneous tissue that is most often seen in the lower back. Periungual fibromas involving the finger- and toenails may arise in adolescence. Any of these findings should prompt a more thorough search for other signs of TSC.

Noncutaneous Manifestations. The typical cardiac manifestation of TSC is rhabdomyoma, a benign tumor of the myocardium. This congenital tumor, unlike other lesions associated with TSC, tends to regress spontaneously over time in childhood. Cardiac rhabdomyomas are usually diagnosed in infancy and may be identified prenatally by ultrasonography. Although often asymptomatic, they may cause obstruction of blood flow in the heart or arrhythmia such as Wolff-Parkinson-White syndrome. Approximately

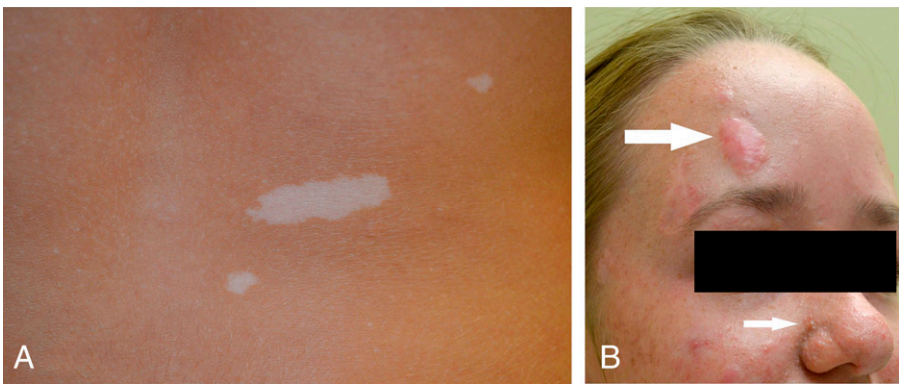


Figure 2. Characteristic skin lesions of tuberous sclerosis syndrome. A. Hypopigmented macules. B. Collagen plaque on forehead (large arrow) and angiofibroma (small arrow).

50% of children who present with cardiac rhabdomyoma have TSC; in those who do not have other signs of TSC, the tumors occur sporadically, for unknown reasons.

Neurologic complications are among the most serious aspects of TSC and often are the presenting feature. Seizures can occur at any age in individuals with TSC, but most who have seizures present in childhood, often in the first 2 years after birth. Infantile spasms or partial seizures may occur in infants younger than age 12 months and can be associated with severe intellectual disability. Infantile spasms are an ominous sign and can easily be misinterpreted initially as normal infant behaviors. The pediatrician should be vigilant for any signs of seizure activity in a child with TSC; a new diagnosis of the disorder might be part of the evaluation for a child with an unprovoked seizure. Specific brain manifestations are described later in this article.

Diagnosis of TSC

Clinical diagnostic criteria are shown in Table 4. (8) Dermatologic manifestations have already been described and should be sought in a child who presents with another TSC feature. As noted previously, such a search should include a Wood lamp examination if signs are suspected. The central nervous system lesions associated with TSC include subependymal nodules, cortical dysplasia, and subependymal giant cell astrocytoma. The subependymal nodules and cortical dysplasia are congenital lesions that should be visible by MRI. Subependymal nodules tend to calcify and can also be seen by computed tomography scan. Subependymal giant cell astrocytoma is a growing tumor usually located near the foramen of Monro, where it can obstruct ventricular outflow, leading to hydrocephalus. Management is discussed in the following section.

Renal lesions characteristic of TSC include angiomyolipoma and renal cysts. Both can occur in childhood and can be visualized by ultrasonography, but MRI provides better definition. Rare individuals with TSC have a deletion on chromosome 16 that encompasses the *TSC2* and adjacent *PKD1* genes and, hence, have both TSC and polycystic kidney disease. Cystic lesions can also be seen in bone but are not considered diagnostic criteria. Even though retinal hamartomas do not typically affect vision, their presence can be helpful in diagnosis. Ophthalmologic assessment may also reveal achromic patches. Although pulmonary lymphangioleiomyomatosis is listed among the diagnostic criteria, this complication is usually seen in adulthood and most often, though not exclusively, in females, so it is unlikely to be identified in children.

TABLE 4. **Clinical Diagnostic Criteria for Tuberous Sclerosis Complex***

Major Criteria	Hypomelanotic macules (≥3 at least 5 mm diameter) Angiofibroma (≥3) or fibrous cephalic plaque Ungual fibroma (≥2) Shagreen patch Multiple retinal hamartomas Cortical dysplasias Subependymal nodules Subependymal giant cell astrocytoma Cardiac rhabdomyoma Lymphangioleiomyomatosis Angiomyolipomas (≥2)
Minor Criteria	"Confetti" skin lesions Dental enamel pits (≥3) Intraoral fibromas (≥2) Retinal achromic patch Multiple renal cysts Nonrenal hamartomas

**The diagnosis is established with 2 major criteria or 1 major and 2 or more minor; a possible diagnosis is made if there is 1 major or 2 or more minor criteria.*

Genetic testing is available for TSC and requires analysis of both the *TSC1* and *TSC2* genes. Although there is evidence that TSC may be less severe in those with *TSC1* mutation, the natural history cannot be predicted from the mutation, and clinical features are not a reliable indicator of whether *TSC1* or *TSC2* is mutated (except in the setting of coincident polycystic kidney disease, which suggests *TSC2* deletion). A substantial number of individuals who fulfill diagnostic criteria do not have a mutation, and at least some of these are mosaics for a mutation that cannot be detected in blood.

Management of TSC

The pediatrician can play a key role in surveillance for early diagnosis of complications of TSC. As a reminder, the most important are infantile spasms and partial seizures. Prompt diagnosis with electroencephalography, neurologic consultation, and initiation of treatment can be critical to avoid intractable seizures and severe cognitive impairment. In some cases, seizures can be very difficult to control with medication, and surgery can be helpful. Recommendations for routine surveillance are shown in Table 5. (9) The pediatrician should be particularly alert to signs of cognitive impairment and facilitate access to supportive services. Renal lesions are rarely symptomatic in children but can cause hypertension, bleeding, or renal failure. In the past, larger or symptomatic lesions were treated by embolization or surgery, but medical treatment currently is the first-line therapy.

TABLE 5. **Recommendations for Surveillance of Individuals With Diagnosis of Tuberous Sclerosis Complex**

• **BRAIN**
• MRI (repeat every 1-3 years)
• EEG
• Developmental screening
• **KIDNEY**
• MRI abdomen (repeat every 1-3 years)
• Blood pressure annually
• GFR annually
• **LUNG (FEMALE >18 YEARS)**
• PFT, 6-minute walk test
• High-resolution chest CT scan (repeat every 5-10 years)
• **EYE**
• Ophthalmology examination annually
• **HEART**
• Echocardiography on children
• ECG all ages (every 3-5 years)
• **SKIN**
• Examination annually
• **TEETH**
• Examination every 6 months

CT=computed tomography; ECG=electrocardiography; EEG=electroencephalography; GFR=glomerular filtration rate; MRI=magnetic resonance imaging; PFT=pulmonary function tests.

The identification of the genes associated with TSC has led to understanding of the cellular pathway involved in formation of lesions, and this, in turn, has led to the possibility of drug treatment, specifically with inhibitors of mTOR, a protein whose function is regulated by a protein complex that is the product of the *TSC1* and *TSC2* genes. mTOR inhibitors, including rapamycin and everolimus, have been shown to shrink subependymal giant cell astrocytomas and renal angiomyolipomas. (10) Everolimus is now approved by the Food and Drug Administration for these indications, and use of topical rapamycin may be helpful in treatment of angiofibromas.

Genetics of TSC

As already noted, TSC is transmitted as a classic autosomal dominant trait with complete penetrance and variable expression. At least 50% of cases occur sporadically, with an affected child and 2 apparently unaffected parents. In some cases, the signs of TSC can be subtle and may not have been recognized clinically. Parents should undergo skin examination, ophthalmologic evaluation, and imaging of the brain and kidneys because some will have signs of the disorder that may not have been suspected clinically. Genetic testing can be used to determine if a parent carries a gene mutation, but the parent of an affected child could be a mosaic and, hence, have negative blood test results for the mutation yet still have signs of the condition. Prenatal or preimplantation diagnosis is possible if the underlying TSC mutation is known.

STURGE-WEBER SYNDROME

Sturge-Weber syndrome is defined as the occurrence of a port-wine stain on the face (Fig 3) in association with leptomeningeal angiomatosis that can lead to seizures, strokes, and glaucoma. The port-wine stain can occur without leptomeningeal involvement, and leptomeningeal angiomatosis can occur without the port-wine stain. From the perspective of the pediatrician, the concern is usually whether a child with a port-wine stain on the face is at risk for seizures and glaucoma and how to follow that child.

Port-wine stains should be distinguished from nevus simplex, which is benign. Nevus simplex is common; usually occurs at the nape of the neck, glabella, and eyelids; and blanches with pressure and darkens with crying. The

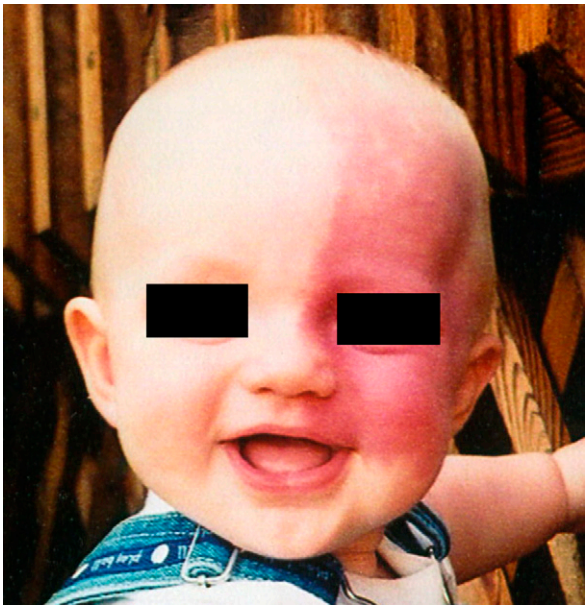


Figure 3. Port-wine stain in a child with Sturge-Weber syndrome.

port-wine stain can occur in the upper, middle, and lower regions of the face and may involve just a single region or contiguous regions. The risk of central nervous system manifestations is greatest when the upper division of the trigeminal nerve is involved; the risk of neurologic involvement in this setting is estimated to be 10% to 35% and that of glaucoma is 50%. (11) Children with port-wine stains in this distribution can be examined by MRI, preferably after age 1 year (unless seizures have occurred at an earlier age). Those found to have leptomeningeal involvement are often treated with aspirin to reduce the risk of stroke and should be closely monitored for seizures and glaucoma. Electroencephalography can be performed to look for subclinical seizure activity. The port-wine stains can be treated with laser therapy. Children with Sturge-Weber syndrome are at risk for hypopituitarism and hypothyroidism, so growth and thyroid status should be monitored. Intractable seizures occur in some individuals and may be treated surgically.

Port-wine stains, with or without leptomeningeal angiomatosis, have recently been found to be associated with mosaicism for activating mutations in the *GNAQ* gene, which encodes a subunit of the G protein. (12) All cases are sporadic; presumably nonmosaic mutations would be lethal.

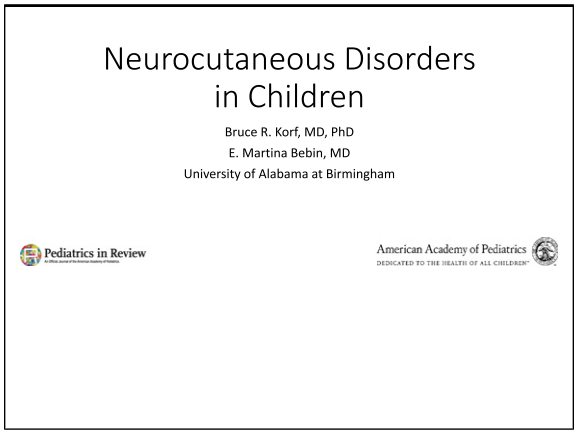
CONCLUSION

Although individually rare, the neurocutaneous syndromes collectively are sufficiently common that most pediatricians will have a least a few patients with NF, TSC, and port-wine stain, including Sturge-Weber syndrome. The pediatrician is in a position to recognize signs of these disorders in children not previously diagnosed and to be vigilant for complications in those in whom the diagnosis is established. On the other hand, many healthy children have a few café-au-lait macules, hypopigmented regions such as nevus depigmentosus, or nevus simplex, which are not indicative of an underlying neurologic syndrome. The differential diagnosis of the characteristic skin lesions has been emphasized in this review and may help guide the pediatrician as to when further testing or referral is indicated. Much has been learned about the genetics of these disorders, and treatments have begun to emerge or are in clinical trials that promise to alter the course of the disorders in the years to come.

Summary

- Diagnosis and management of the various forms of neurofibromatosis and of tuberous sclerosis complex are based on consensus criteria. (2)(8)(9)
- On the basis of strong evidence, genetic testing can be helpful in establishing a diagnosis of all 3 disorders, (3)(8)(12) although most mutations are not predictive of specific complications or severity.
- On the basis of consensus, the conditions are lifelong and management consists primarily of surveillance and symptomatic treatment.
- On the basis of strong evidence, subependymal giant cell astrocytomas and renal angiomyolipomas in tuberous sclerosis complex respond to mTOR inhibitors. (9)

To view the teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/38/3/119.supplemental.



References for this article are at http://pedsinreview.aappublications.org/content/38/3/119.

PIR Quiz

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1. A 2-year old girl is brought by her parents for a well-child visit. On skin examination, her pediatrician counts 8 café-au-lait macules on her back, trunk, arms, and legs. Her parents state that 2 of them were present at birth. There are no skinfold freckles or other skin findings, head size is normal, development is normal, and there is no known family history of neurocutaneous diseases. Which of the following is the minimum number of neurofibromatosis 1 (NF1) criteria needed to make the diagnosis of NF1?
   A. 2.
   B. 3.
   C. 4.
   D. 5.
   E. 6.
2. The girl is seen again at age 16 years. She has more café-au-lait macules but no new clinical criteria for NF1. Her father reports that he was recently diagnosed with NF2 and requests brain magnetic resonance imaging (MRI) for his daughter. For which of the following findings on brain MRI will the clinician be screening in this disorder?
   A. Leptomeningeal angiomatosis.
   B. Neurofibroma.
   C. Subependymal giant cell astrocytoma.
   D. Optic glioma.
   E. Vestibular schwannoma.
3. The physician discusses with the family that, in addition to audiology and MRI of the brain, genetic testing is warranted for their daughter. In counseling the family, which of the following is the most accurate statement about the primary goal of genetic testing?
   A. Establish a diagnosis in advance of waiting for a second clinical feature to emerge.
   B. Establish a treatment plan for confirmed cases.
   C. Satisfy 1 of the diagnostic criteria for NF1.
   D. Screen for sporadic mutations.
   E. Use the specific mutation to predict disease severity.
4. A male infant is seen in the newborn nursery. He was diagnosed with a cardiac rhabdomyoma on prenatal ultrasonography. The parents are concerned because they were told that 50% of children with this finding may have tuberous sclerosis complex. Which of the following skin findings represents the hallmark dermatologic manifestation of tuberous sclerosis that would be best seen on Wood lamp (ultraviolet light) examination?
   A. Angiofibromas.
   B. Ash-leaf spots (hypomelanotic macules).
   C. Fibrous forehead plaque.
   D. Periungual fibromas.
   E. Shagreen patch.
5. A male newborn is evaluated on rounds in the newborn nursery. The only finding of note on physical examination is a large dark red birthmark that covers half of the left side of his face. It is nonblanching and does not change when he cries. This physical finding is consistent with a port-wine stain. In counseling the family about port-wine stains, involvement of which of the following division(s) of the trigeminal nerve is associated with the highest risk of epilepsy and glaucoma?
   A. The more divisions that are involved, the higher the risk.
   B. V1 (upper division).
   C. V2 (middle division).
   D. V3 (lower division).
   E. V1 and V2 have equal risk.

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