Common Neurocutaneous Syndromes
Heather Little, DO; Deepak Kamat, MD, PhD; and Lalitha Sivaswamy, MD

Abstract

Neurocutaneous syndromes are a diverse group of neurologic disorders with concurrent skin manifestations. Most neurocutaneous syndromes have a genetic basis and are believed to arise from a defect in the differentiation of the primitive ectoderm. In this regard, the skin can be a window into the central nervous system and can aid in the diagnosis of neurologic disease in children. The cutaneous signs may be subtle, which places great importance on the physical examination skills of clinicians providing primary care to children. Early recognition can help with proper diagnosis, formulating a treatment plan, anticipating potential complications, making appropriate referrals, and offering genetic counseling to families. [Pediatr Ann. 2015;44(11):496-498,500-504.]

The skin and the central nervous system (CNS) are derived from a common embryologic origin during fetal development. Mutations affecting the formation, migration, and differentiation of these cells are responsible for a group of diseases termed neurocutaneous syndromes, with considerable overlap of neurologic and dermatologic manifestations. This review discusses the clinical spectrum, diagnostic criteria, and management of some of the most common neurocutaneous syndromes in children. It also emphasizes the role of the primary care provider in caring for these children and summarizes important areas of the annual physical examination.

NEUROFIBROMATOSIS

Neurofibromatosis (NF) was previously considered a single disorder, but is now divided into two genetically distinct forms: NF type 1 (NF1) and NF type 2 (NF2).1 Both types are transmitted by autosomal dominant inheritance with considerable variation in expression, but approximately 50% of patients represent new, spontaneous mutations.1

NF1

NF1 is the most common neurocutaneous syndrome with a prevalence of approximately 1 in 3,000 people.2 The NF1 gene is located on chromosome 17 and is responsible for encoding the protein neurofibromin, which aids in the down-regulation of cellular proto-oncogenes. Mutations in the NF1 gene result in reduced amounts of functional neurofibromin, causing the wide variety of clinical features and associated tumors.3

Clinical Features

Skin. The most common skin manifestations are café au lait spots, as all patients will have them by age 2 years. Café au
Cutaneous neurofibromas occur in 99% of patients and manifest as single or multiple firm, rubbery bumps of varying sizes on the skin.

**Eye.** Lisch nodules are small hamartomas on the iris that don’t impair vision and are seen in nearly all patients by age 21 years. Optic gliomas are benign tumors that occur in 15% to 20% of patients. Patients with optic gliomas may also have precocious puberty if there is invasion of the hypothalamus.

**Central nervous system:** Learning difficulties occur in the majority of patients with NF1, although severe cognitive impairment is rare. Gliomas may occur in all parts of the nervous system but have a preference for the optic nerves, brainstem, and cerebellum. Patients can also develop aqueductal stenosis, epilepsy, cerebral gliomas, and central nervous system (CNS) vasculopathy. NF1 vasculopathy can result in cerebrovascular disease, including carotid artery stenosis, moyamoya syndrome, hemihypertrophy, and aneurysm.

**Peripheral nervous system.** Plexiform neurofibromas are benign tumors that grow along the length of a nerve and can cause significant morbidity because of the propensity for diffuse nerve and plexus involvement. Malignant peripheral nerve sheath tumors can occasionally arise from preexisting plexiform neurofibromas and are predominately found in adults.

**Renal.** Pheochromocytoma and renal artery stenosis are rare, but must be considered in patients with hypertension.

**Orthopedics.** Sphenoid dysplasia causing orbital proptosis, scoliosis of the spine, and bowing of long bones may occur in patients with NF1.

### Diagnosis

The diagnostic criteria for NF1 (Table 1) are reliable and based on clinical assessment. An important caveat to note is that skin findings develop over time and only half of children with NF1 will meet diagnostic criteria in infancy; thus, a thorough annual examination is crucial. Magnetic resonance imaging (MRI) may provide additional diagnostic information as areas of increased T2 signal intensity (formerly called unidentified bright objects [UBOs]) are often present and are pathognomonic of NF1. DNA testing is available but rarely needed.

### Management

Once the diagnosis is considered, referral should be made to a clinician skilled in the diagnosis of NF1. A multidisciplinary team is ideal for the care of children with NF1 (Table 2). Management is primarily supportive, such as controlling seizures with antiepileptic drugs, providing educational help for children with academic challenges, orthopedic intervention when necessary, and performing surgery for symptomatic and accessible brain and nerve tumors. Baseline brain and spine MRI and routine screening investigations in asymptomatic patients are not recommended as they do not influence management. All children with NF1 younger than age 10 years should undergo yearly eye examinations. All children with uncomplicated disease should be assessed once a year, at minimum, by a physician knowledgeable in the manifestations of NF1, preferably in a multidisciplinary clinic.

### Table 1. Diagnostic Criteria for Neurofibromatosis Type 1

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of two or more of the following features is considered diagnostic</td>
<td></td>
</tr>
<tr>
<td>• Six café au lait spots &gt;5 mm in diameter in prepubertal children or &gt;15 mm in postpubertal children</td>
<td></td>
</tr>
<tr>
<td>• Two or more neurofibromas or one plexiform neurofibroma</td>
<td></td>
</tr>
<tr>
<td>• Freckling in the axillary or inguinal region</td>
<td></td>
</tr>
<tr>
<td>• Optic glioma</td>
<td></td>
</tr>
<tr>
<td>• Two or more iris hamartomas (Lisch nodules)</td>
<td></td>
</tr>
<tr>
<td>• A distinctive osseous lesion (sphenoid dysplasia or thinning of long bones)</td>
<td></td>
</tr>
<tr>
<td>• A first-degree relative with neurofibromatosis type 1</td>
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</tbody>
</table>

Adapted from the National Institutes of Health.

### Table 2. Important Areas of Annual Physical Examination in Patients with Neurofibromatosis Type 1

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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<tbody>
<tr>
<td>Development (learning disabilities and cognitive impairment)</td>
<td></td>
</tr>
<tr>
<td>Visual acuity and fundoscopy until age 7 years (optic pathway glioma, glaucoma)</td>
<td></td>
</tr>
<tr>
<td>Head circumference (rapid increase might indicate tumor or hydrocephalus)</td>
<td></td>
</tr>
<tr>
<td>Height and weight (abnormal pubertal development)</td>
<td></td>
</tr>
<tr>
<td>Pubertal development (precocious puberty due to pituitary/hypothalamic lesion)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (consider renal artery stenosis/pheochromocytoma)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular examination (congenital heart disease)</td>
<td></td>
</tr>
<tr>
<td>Evaluation of spine (scoliosis ± underlying plexiform neurofibromas)</td>
<td></td>
</tr>
<tr>
<td>Skin examination (cutaneous, subcutaneous, and plexiform neurofibromas)</td>
<td></td>
</tr>
<tr>
<td>Focal neurologic symptoms or examination findings (plexiform or cerebral neurofibroma, aqueductal stenosis)</td>
<td></td>
</tr>
</tbody>
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NF2

The defining feature of NF2 is the development of bilateral vestibular schwannomas (VS). NF2 is caused by mutations in the NF2 gene, which is located on chromosome 22 and is responsible for encoding the protein merlin. The estimated prevalence is 1 in 60,000.\(^1\)\(^,\)\(^10\)

**Clinical Features**

**Skin.** Skin manifestations in NF2 are more subtle and less common than in NF1. About 70% of patients with NF2 have skin tumors, which are usually schwannomas, but occasionally neurofibromas can occur.\(^10\)

**Eye.** Patients often suffer from reduced visual acuity due to cataracts, optic nerve meningiomas, or extensive retinal hamartomas.

**CNS.** VS typically appear in early adulthood and present with hearing loss, tinnitus, and dizziness. Other CNS tumors, such as meningiomas and ependymomas, can also occur. In childhood, patients often present with symptoms from an intracranial meningioma, spinal tumor, or cutaneous tumor.\(^10\)

**Diagnosis**

Diagnosis is made by taking a thorough clinical and family history, conducting a physical examination (including ophthalmic examination), and obtaining MRI of the brain and spinal cord. Genetic testing can be performed in the setting of a positive family history or to confirm diagnosis of NF2, although it is not a part of the diagnostic criteria (Table 3).

**Management**

Management of NF2 involves surgical removal of symptomatic cranial and spinal tumors as well as supportive care.\(^10\)

In the setting of a positive family history, screening for VS should begin at age 10 years. In asymptomatic patients without tumors, MRI of the brain should be conducted annually for those younger than age 20 years and every 3 to 5 years for those older than age 20 years. Once tumors are present, MRI screening should be performed annually. MRI of the spine should be performed every 3 years or if new symptoms arise.\(^10\)

### TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex (TSC) is a neurocutaneous disorder that results in the growth of benign tumors and can affect virtually every organ system. The two most common systems affected are the skin and the brain, and there is a wide range of phenotypic variability. TSC has an estimated prevalence of 1 in 6,000 newborns, making it the second most common neurocutaneous disorder.\(^2\)\(^,\)\(^11\)\(^,\)\(^12\)

**Clinical Features**

**Skin.** Hypomelanotic macules (ash leaf spots) are seen in 90% of patients\(^11\) (Figure 2). Facial angiofibromas (adenoma sebaceum) (Figure 3) are another common finding and are characterized by reddish spots or bumps on the face in a butterfly distribution. A Shagreen patch is an isolated raised plaque in the skin over the lower back or buttocks that is seen in 50% of affected children by adolescence.\(^2\) Ungual fibromas, small tumors under the toenails or fingernails, may also be present (Figure 4). Other cutaneous findings include skin tags, café au lait spots, and poliosis (depigmentation of the hair), although these are not unique to TSC.

**Eye.** Phakomas (retinal astrocytic hamartomas) are benign tumors of the eye appearing as white patches on the retina. Generally they do not cause vision loss or other vision problems, but they can be used to help diagnose the disease.

**CNS.** Seizures are most often the first presenting symptom of TSC, especially infantile spasms.\(^2\) Most children will also experience some degree of developmental delay. Behavioral problems can be a significant issue, including aggression, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, and/or self-harming behavior. About one-third of children with TSC meet criteria for autism spectrum disorder. Glial tumors, such as subependymal giant cell astrocytomas, are common and form in the walls of the ventricles. The growth of these tumors near the foramen of Monro can im-

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**TABLE 3.**

**Manchester Criteria for Diagnosis of Neurofibromatosis 2**

<table>
<thead>
<tr>
<th>I. Bilateral vestibular schwannomas</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>II. A first-degree relative with NF2 AND either</td>
<td>OR</td>
</tr>
<tr>
<td>• Unilateral vestibular schwannoma</td>
<td>OR</td>
</tr>
<tr>
<td>• Any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities</td>
<td>OR</td>
</tr>
<tr>
<td>III. Unilateral vestibular schwannoma AND</td>
<td>OR</td>
</tr>
<tr>
<td>• Any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities</td>
<td>OR</td>
</tr>
<tr>
<td>IV. Multiple meningiomas AND</td>
<td>OR</td>
</tr>
<tr>
<td>• Unilateral vestibular schwannoma</td>
<td>OR</td>
</tr>
<tr>
<td>• Any two of: schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities</td>
<td>OR</td>
</tr>
</tbody>
</table>

Abbreviation: NIH, National Institutes of Health.

Adapted from Evans.\(^49\)
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Renal cysts are also common. Cysts are usually small, few in number, and cause no serious problems. In rare instances, patients may develop a pattern similar to polycystic kidney disease during childhood causing impaired kidney function.

**Cardiac.** Rhabdomyomas are found in 50% of people with TSC and are often detected on prenatal ultrasound. The majority of these lesions are asymptomatic and will spontaneously regress over time. In rare circumstances, they can cause arrhythmias or block left ventricular outflow.

**Lung.** Lymphangioleiomyomatosis (LAM) exclusively affects women and is found in one-third of women with TSC in the third to fourth decade of life.\(^{16}\) LAM is a tumor-like disorder in which cells proliferate in the lungs, and there is lung destruction with cyst formation.\(^{14}\) Multinodular multifocal pneumocyte hyperplasia is a more benign tumor that occurs in men and women equally.

**Diagnosis**

The diagnosis of TSC has classically been based on a clinical examination in combination with imaging of the brain, heart, liver, and kidneys. Identification of a pathogenic mutation in TSC1 or TSC2 is now considered sufficient for the diagnosis of TSC regardless of the clinical findings.\(^{16}\) However, 10% to 25% of TSC patients do not have an identifiable mutation, and thus a normal result does not exclude TSC.\(^{16}\) The diagnostic criteria for TSC are listed in Table 4.

**Management**

Similar to NF, a multidisciplinary team approach is often helpful in the management of TSC, as outlined in Table 5. All patients suspected of having TSC should undergo MRI of the brain with and without contrast.\(^{17}\) MRI should be repeated every 1 to 3 years in asymptomatic patients and sooner if the patient is having symptoms. At the time of diagnosis, abdominal MRI should be obtained and repeated every 1 to 3 years to assess for the presence of renal lesions.\(^{17}\) Women age 18 years and older should have baseline pulmonary function testing and high-resolution chest computed tomography to evaluate for LAM.\(^{17}\) All patients should have a detailed dermatologic examination at the time of diagnosis and a dental examination performed every 6 months.\(^{17}\) In pediatric patients, an echocardiogram should be obtained at the time of diagnosis to evaluate for rhabdomyoma, and if present, the echocardiogram should be repeated every 1 to 3 years until its regression.\(^{17}\) An electrocardiogram should also be obtained to evaluate for cardiac arrhythmia and conduction defects. An initial ophthalmologic evaluation is recommended for all patients to evaluate for retinal hamartomas. An annual ophthalmologic evaluation is warranted in patients with confirmed ophthalmologic lesions or visual symptoms.

**STURGE-WEBER SYNDROME**

Sturge-Weber syndrome (SWS) is a rare neurocutaneous disorder that has classically been defined as a triad of vascular malformations involving the face, eye, and brain. The prevalence of SWS is estimated to range from 1 in 20,000 to 50,000 live births.\(^ {14}\) SWS occurs due to sporadic mutations and appears to be due to failure of the embryonal cephalic venous plexus to regress and mature, leading to tortuous and abnormal vasculature in the face and brain.\(^ {18}\)

**Clinical Features**

**Skin.** Facial angiommas (ie, port-wine stains) (Figure 5) are usually present at birth and found in the ophthalmic (V1) and maxillary (V2) distributions of the trigeminal nerve.\(^ {14}\) The size of the cutaneous angioma does not correlate with the size of the intracranial angioma. Facial angiommas are unilateral in 70% of children and when the facial nevus is bilateral, the intracranial angioma is usually unilateral.

**Eye.** Glaucoma occurs in 50% to 70% of children with SWS, usually developing...
in the first decade of life. Glaucoma develops due to vascular anomalies involving the eye, leading to increased episcleral venous pressure. Glaucoma can be unilateral or bilateral, regardless of the location of the facial angiomatous tissue.

CNS. The majority of leptomeningeal angiomatous tissue involves the parietal and occipital regions ipsilateral to the facial angiomatous tissue. Bilateral brain lesions are rare but can occur. Seizures occur in 80% to 90% of children with SWS. Onset of epilepsy is generally within the first year of life, and the seizures are usually focal in nature. The majority of children with SWS who have seizures in the first year will have some degree of cognitive impairment. Hemiplegia occurs in as many as 33% to 50% of children. Hemiplegia often appears after a focal onset seizure and progresses in severity after subsequent seizures. Transitory episodes of hemiplegia lasting days or weeks can follow a prolonged seizure. It is controversial whether the seizures cause the injury to the brain or vice versa. Hemianopia may also be present contralateral to the occipital lobe involvement.

Diagnosis

When a newborn has a facial port-wine stain, ophthalmologic examination and neuroimaging must be performed. The ideal imaging modality is an MRI of the brain with contrast to best visualize the leptomeningeal angiomatous tissue. The presence of facial and leptomeningeal angiomatous tissue suggests type I SWS. Type II SWS has facial angiomatous tissue and glaucoma without evidence of intracranial lesions, and type III presents with only leptomeningeal angiomatous tissue.

Management

The seizures are often intractable and difficult to control with anticonvulsant medications. Hemispherectomy can sometimes improve seizure control as well as development, and should be considered if seizure activity proves medically intractable. Aspirin therapy may reduce the incidence of stroke-like episodes, and is typically used in individuals with either recurrent vascular events or progressive neurologic deficits. An ophthalmologist can aid in the treatment of glaucoma, if present. Treatment of the port-wine stain by pulsed dye laser may also be considered for cosmetic reasons.

INCONTINENTIA PIGMENTI

Incontinentia pigmenti (IP) is a relatively uncommon multisystem disorder with a prevalence of 0.7 per 100,000 people. Over 70% of children with IP have mutations in the NEMO gene, located on chromosome Xq28. The condition is inherited in an X-linked dominant manner, most affected children are girls. The condition is usually fatal in boys.

Clinical Features

Skin. Unlike other neurocutaneous disorders, the skin lesions of IP tend to change over the course of the child’s life. Stage I consists of an erythematous vesicular or bullous rash that is present in the neonatal period (Figure 6). The lesions follow a linear pattern on the arms and legs with a whorled appearance on the trunk (Figure 7). Stage II lesions that follow within a few weeks are wart-like or verrucous. The lesions of stage III are hyperpigmented and may persist into adolescence. Stage IV lesions are hypopigmented and hairless and persist for the rest of the person’s life. Dermatologic stages may overlap, and not every child goes through all suc-
cessive stages. Stage I lesions occur in over 90% of children, usually appear in the first week of life, and often clear by 4 months. The lesions of IP follow the lines of Blaschko (embryologic lines of development) along the skin, and this constitutes a salient feature of this disease. Other dermatologic manifestations include wooly hair and alopecia. Nail involvement may range from nail pitting to onychogryphosis.

**Eye.** Ophthalmologic features occur in about 20% to 30% of children and include retinal detachment, retinal artery occlusion, congenital cataract, and microphthalmia.

**CNS.** Neurologic features are present in approximately 30% of children with IP and range from epilepsy to stroke and developmental delay. Seizures and strokes may occur in the first week of life, and in the vast majority of cases neurologic symptoms are most prominent in infancy and early childhood. Ischemic strokes caused by microvascular infarcts or inflammatory mechanisms are believed to account, at least partly, for the abnormalities on brain imaging, which include diffuse lesions in the white matter of the brain, cerebral hemorrhage, and generalized atrophy of the brain parenchyma.

**Diagnosis**

Histologic examination of affected tissue reveals infiltration of the epidermis with eosinophils during stage I of the disease, which is a highly characteristic feature. Other changes such as dyskeratosis, apoptosis, and increased free melanin may also be helpful toward making a definitive diagnosis. An MRI of the brain should be obtained if there are neurologic manifestations.

Diagnosis can usually be established by using clinical criteria of Landy and Donnai (Table 6). Confirmatory diagnosis can be made by demonstrating mutations in the IKBKG gene in situations in which there is ambiguity.

**Management**

Treatment is supportive, as in the case of other neurocutaneous syndromes discussed above. Patients should have regular ophthalmologic evaluations in the first year of life for retinal detachment. Referral to a neurologist should occur if seizures commence. The pediatrician should closely monitor head circumference and developmental milestones.

**HYPOMELANOSIS OF ITO**

Hypomelanosis of Ito (HI) is a disorder involving the cutaneous, central nervous, and musculoskeletal systems, akin to IP criteria already discussed. The condition was first described by Ito in 1952.

No consensus exists regarding the identity of the gene causing HI. The prevalence has not been clearly ascertained.

**Clinical Features**

**Skin:** The skin manifestations of HI include streaks or whorls of hypomelanosis on the trunk, limbs, or head, interspersed with areas of normal skin...
The skin lesions are caused by lack of melanocytes or hypomelanosis in the affected cells. The swirls of hypopigmentation follow the embryologic lines of Blaschko. The skin lesions are usually present at birth, invariably manifest within the first few years of life, and darken over time, blending into normal skin as the child reaches adulthood. Alopecia and anomalous hair pigmentation have also been observed.

Eye. Strabismus, cataracts, and retinal degeneration may constitute the ocular manifestations.

CNS. Psychomotor retardation, autism, epilepsy, language disorders, hypotonia, and macro- and microcephaly are common neurologic manifestations in children with HI. Approximately 50% to 75% of affected children have features related to the nervous system. One-third of children with HI and epilepsy are refractory to seizure medications. A wide variety of brain malformations, such as migrational disorders, hemimegalencephaly, microcephaly, and dysgenesis of the corpus callosum, have been described that can account for the clinical features.

Skeletal. The skeletal features may consist of short stature, limb asymmetry, scoliosis, chest deformities, coarse facial features, and finger anomalies.

Diagnosis
The diagnosis requires only a thorough physical examination with attention to the neurologic and dermatologic features. Multidisciplinary care with involvement of an ophthalmologist, neurologist, pediatrician, and dermatologist is optimal. No clear-cut diagnostic criteria have been set forth.

CONCLUSION
Neurocutaneous syndromes are a fascinating group of diseases that can affect several organ systems and be diagnosed at the bedside by an observant clinician. Knowledge of the common clinical features of these disorders can be helpful in providing guidance to families of affected children. Primary care health providers play a significant role in coordinating the care of these complex multisystem disorders.

REFERENCES