Tuberous Sclerosis Complex: A Review

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ABSTRACT

Tuberous sclerosis complex (TSC) is an inherited neurocutaneous disorder characterized by the potential for hamartoma formation in almost every organ. The inheritance is autosomal dominant with almost complete penetrance but variable expressivity. The two gene loci that code for TSC are \( TSC1 \), located on chromosome 9q34, and \( TSC2 \) on 16p13.3. TSC complex may affect the skin, central nervous system, kidneys, heart, eyes, blood vessels, lungs, bone, and gastrointestinal tract. The diagnosis of TSC is based on the identification of hamartomas in more than one organ system. Treatment should be symptomatic and organ specific. A multidisciplinary management approach is necessary. J Pediatr Health Care. (2007) 21, 108-114.

EPIDEMIOLOGY

TSC affects both sexes and all ethnic groups. The prevalence is estimated to be one case per 6000 to 10,000 individuals (Jozwiak, Schwartz, Janniger, & Bielicka-Cymerman, 2000; Kandt, 2003).

ETIOLOGY AND PATHOGENESIS

TSC has an autosomal dominant mode of inheritance with almost complete penetrance but variable expressivity (Henske, 2005; Sweeney, 2004). Approximately 65% of cases are caused by a spontaneous mutation (Menkes & Maria, 2000; Narayanan, 2003). Molecular genetic studies have identified two loci for TSC; \( TSC1 \) is located on the long arm of chromosome 9 (9q34) and \( TSC2 \) is located on the short arm of chromosome 16 (16p13.3). These loci encode for hamartin and tuberin, respectively (Jozwiak, 2006). Hamartin and tuberin are thought to function together as a protein complex or as adjacent steps.
within the same intracellular pathway, and this might explain why the phenotypic expression of either mutation leads to almost identical disease (Narayanan). Both TSC1 and TSC2 have tumor suppressor activity, which, when not activated, leads to uncontrolled cell cycle progression and the proliferation of hamartomas throughout the body (Jozwiak; O’Callaghan, 1999). The expressivity is not determined by the specific gene mutation, because different manifestations can develop in affected members of the same family (Sparagana & Roach, 2000).

The TSC2 gene is located only 48 base pairs of DNA away from the PKD1 gene for autosomal dominant polycystic kidney disease (ADPKD) (Franz, 2004; Laass et al., 2004). A contiguous deletion that affects both the TSC2 and PKD1 genes results in both TSC and ADPDK (Sampson et al., 1997; O’Callaghan & Osborne, 2000).

**CLINICAL MANIFESTATIONS**

**Dermatologic Manifestations**

The most common dermatologic manifestations are hypomelanotic macules or “ash leaf spots” named after the European mountain ash tree (Tsao, 2003). Typically, the macules are rounded at one end and tapered at the other (Figure 1). Hypomelanotic macules are found in more than 90% of patients with TSC (Sweeney, 2004). The macules are usually present at birth and almost all lesions are evident within the first 2 years of life (Sweeney). In newborn infants and in fair-skinned individuals, these lesions often are difficult to visualize without the aid of an ultraviolet light (Wood’s lamp). Hypomelanotic macules usually become more apparent with age.

Facial angiofibromas (adenoma sebaceum) are comprised of vascular and connective tissue elements and are found in approximately 75% of patients with TSC (Sweeney, 2004). The lesions typically appear during preschool years in the malar area as small pink to red dome-shaped papules in a “butterfly distribution.” The lesions gradually enlarge and become more numerous with age (Figure 2). Forehead plaque, a variant of angiofibroma, is seen in approximately 20% of patients with TSC (Sweeney; Tsao, 2003). These lesions appear in early childhood, grow very slowly, and present as firm, elevated plaques that are yellow-brown to flesh-colored (Sweeney).

The shagreen or “leather” patch is the result of an accumulation of collagen and typically is found in the lumbosacral region in 20% to 30% of patients with TSC (Roach & Sparagana, 2004). Characteristically the lesion presents as an irregularly shaped, grayish-green or light brown, unevenly thickened plaque with a cobblestone or or-
ange-peel appearance. The lesion might not be apparent in young children (Roach & Sparagana).

Periungual and ungual fibromas (Koenen tumors) are smooth, firm, nodular or fleshy lesions that are adjacent to or underneath the nails (Roach & Sparagana, 2004). The nails of the toes are more commonly involved than those of the fingers (Osborne, 2006; Tsao, 2003). Periungual and ungual fibromas are found in approximately 20% of unselected patients with TSC and are more common in adolescents and adults than in young children (Roach & Sparagana). These lesions occasionally develop subsequent to trauma (Roach & Sparagana).

In some patients with TSC, large, soft, pedunculated, flesh-colored papules and nodules develop that resemble skin tags (molluscum fibrosum pendulum) (Osborne, 2006). The lesions typically develop in flexural areas such as the neck and axillae.

Café au lait spots are seen in up to 30% of patients with TSC (Sweeney, 2004). Most patients have fewer than six lesions. Other dermatologic abnormalities include confetti lesions (stippled hypopigmentation), poliosis (a white patch or forelock), and thumbprint macules (Kandt, 2003; Roach & Sparagana, 2004).

**Neurologic Manifestations**

There is considerable heterogeneity in the neurologic manifestations. The spectrum includes patients with normal intellect and no seizures and extends to those with severe mental retardation and incapacitating seizures. About half of persons with TSC will have normal intellect, and a quarter will not have seizures (O’Callaghan & Osborne, 2000). However, when present, neurologic complications are the most common causes of mortality and morbidity and the most likely to affect the quality of life. Seizures are the most common neurologic complication and are reported to occur in 75% to 90% of patients (Sparagana & Roach, 2000). However, when present, neurologic complications are the most common causes of mortality and morbidity and the most likely to affect the quality of life. Seizures are the most common neurologic complication and are reported to occur in 75% to 90% of patients (Sparagana & Roach, 2000). The most common types of seizures are infantile spasms, partial motor seizures, and generalized tonic clonic seizures (Curatolo, 1996; Kandt, 2003). Infantile spasms are most common during infancy. Mental retardation occurs in approximately 50% of patients with TSC (Kandt). Almost all mentally retarded children with TSC have seizures (Kandt; Santos, Miller, & Roach, 2004). Conversely, many patients with TSC have seizures but not mental retardation (Roach & Delgado, 1995). In general, the earlier the onset of the seizures, particularly infantile spasms, the greater is the risk of mental retardation, cognitive impairment, and behavioral disorders (Prather & de Vries, 2004; Zaroff, Devinsky, Miles, & Barr, 2004). Autism, attention deficit, hyperactivity, and sleep problems are the most frequent behaviors (Curatolo, Porfirio, Manzi, & Seri, 2004; Prather & de Vries, 2004; Wiznitzer, 2004).

The intracranial abnormalities include tubers, subependymal nodules, and subependymal giant cell astrocytomas (Di Mario, 2004). No correlation has been found between the number of subependymal lesions and the clinical severity of TSC (Santos et al., 2004). However, patients with numerous cortical tubers tend to have more cognitive impairment and more difficulty with seizure control (Kandt, 2003; Santos et al.). Autism is more common in patients with frontal and parieto-temporal tubers (Curatolo, 1996; Kandt, 2003). Subependymal giant cell astrocytomas develop in about 5% of patients and might lead to obstructive hydrocephalus (O’Callaghan & Osborne, 2000; Santos et al.). Symptoms of increased intracranial pressure are fairly straightforward to discern in patients with normal intellect but might be subtle in those with mental retardation (O’Callaghan & Osborne).

**Renal Manifestations**

Renal complications are the second most common cause of mortality (O’Hagan, Ellsworth, Secic, Rothner, & Brouhard, 1996). The most common renal lesion is an angiomyolipoma, which occurs in approximately 75% to 80% of affected children older than 10 years (Roach & Sparagana, 2004). Angiomyolipomas are benign tumors composed of blood vessels with
thickened walls, immature smooth muscle cells, and adipose tissue (Henske, 2005; O’Hagan et al.). The lesions are often multiple and bilateral and increase in size and number with age (Henske; Roach & Sparagana). Females are more often affected with a female to male ratio of 3 to 4:1 (Cooper & Elder, 2004). Smaller angiomyolipomas usually do not cause symptoms, but lesions larger than 4 cm in diameter are associated with an increased risk of serious hemorrhage (Henske; Roach & Sparagana).

The second most frequent renal manifestation is a renal cyst. Single cysts are common, and multiple cysts might be present (Laass et al., 2004; Lendvay & Marshall, 2003). A combination of renal cysts and angiomyolipomas is characteristic of TSC (Roach & Sparagana, 2004; Santos et al., 2005).

The most common presentation of cardiac dysfunction is heart failure soon after birth (Roach & Delgado, 1995). The lesions often regress over the first few years of life (Roach & Sparagana).

Ophthalmic Manifestations

Retinal hamartomas occur in 40% to 50% of patients with TSC and are bilateral in a third of cases (Franz, 2004; Lendvay & Marshall, 2003). Most lesions are asymptomatic, but some patients have visual impairment as a result of a large macular lesion (Santos et al., 2004). Three types of retinal lesions have been described, including classic “mulberry” lesions adjacent to the optic disc, plaque-like hamartomas, and “punched-out” areas of retinal hypopigmentation (Roach & Sparagana, 2004; Santos et al.). Angiofibromas might develop on the eyelids (Franz).

Oral Manifestations

Almost all patients with TSC have enamel pitting in the permanent teeth (Franz, 2004). Russell, Russell, Praetorius, and Russell (1996) examined 87 shed deciduous teeth from 20 patients with TSC aged 6 to 14 years and found enamel pits in all 87 deciduous teeth but in none of the 253 deciduous teeth from 142 control subjects. Gingival fibroma occurs in 50% of adults with TSC (Franz). Other oral manifestations include fibrous hyperplasia, hemangioma, bifid uvula, cleft lip and palate, high-arched palate, macroglossia, thickening of the alveolar bone, and pseudo-cystic lesions of the mandible (Barron et al., 2002; Celenk, Alkan, Canger, & Gunhan, 2005).

Vascular Manifestations

Patients with TSC are at increased risk for arterial aneurysms (Franz, 2004; Lendvay & Marshall, 2003). Arterial aneurysms might affect the aorta as well as peripheral arteries such as the carotid, renal, and intracranial arteries, with potentially appreciable morbidity or mortal consequences (Franz; Lendvay & Marshall). Histologically, the arterial walls demonstrate a loss of elastin fibers similar to that seen in patients with Marfan syndrome (Lendvay & Marshall).
Osseous Manifestations

Osseous lesions on radiographs include bone cysts found mainly in the phalanges of the hands and feet, sclerotic lesions, and periosteal new bone formation (Bernauer et al., 2001). Symptomatic bone disease is rare.

Gastrointestinal Manifestations

Hamartomatous polyps in the gastrointestinal tract, especially in the rectum, are common and are usually asymptomatic (Tsao, 2003). Papillomas in the gastrointestinal tract also have been reported.

DIAGNOSIS

Diagnostic criteria are summarized in the Box. According to a National Institute of Health (NIH) consensus conference, a definitive diagnosis of TSC can be made when two major features or one major feature plus two minor features are demonstrated (Box) (Hyman & Whittemore, 2000; Roach, Gomez, & Northrup, 1998). Additional diagnostic categories include probable TSC when one major feature plus one minor feature is present, and possible TSC when either one major feature or two or more minor features are present (Hyman & Whittemore; Roach et al.). Hamartomas are individually rare in the non-TSC population, and the presence of hamartomas in two different organ systems is considered by some clinicians to be sufficient for the diagnosis (O’Callaghan & Osborne, 2000).

A thorough dermatologic examination is essential because many of the major features of TSC are cutaneous, and these lesions often herald the diagnosis. Pediatric nurses and nurse practitioners might be the first to notice these lesions and to suggest the need for further diagnostic evaluation. If hypopigmented macules are not obvious under ambient light, a Wood’s lamp illumination of the skin should be performed in every child with infantile spasms, cardiac rhabdomyoma, or renal angiomyolipoma.

LABORATORY EVALUATION

When either parent is affected, fetal echocardiography should be performed in subsequent pregnancies. Echocardiography should be repeated in the neonatal period because it provides a better assessment than fetal echocardiography (Osborne, 2006). An electrocardiogram should be performed to look for arrhythmias.

A magnetic resonance image (MRI) or a computed tomogram (CT) should be performed to look for confirmatory evidence of TSC such as tubers, subependymal nodules, and subependymal giant cell astrocytomas. Calcification is frequently seen in subependymal nodules and giant cell astrocytomas (Caldemeyer & Mirowski, 2001). Calcification is best detected on a CT (Roach & Delgado, 1995). Conversely, an MRI is more sensitive for the detection of cortical and subcortical tubers, areas of heteropia, and small subependymal nodules especially when not calcified (Figure 3) (Caldemeyer & Mirowski; Menkes & Maria, 2000). An electroencephalogram should be performed if seizures are present. Single-voxel proton spectroscopy and α-[11C] methyl-L-tryptophan (AMT) uptake on positron emission tomography (PET) are useful for the evaluation of epileptogenic tubers and should be considered if neurosurgical intervention is contemplated (Kagawa et al., 2005; Yapici, Dincer, & Erksoy, 2005).

Renal ultrasonography should be performed at the time of diagnosis (Tsao, 2003) and should be repeated every 1 to 2 years depending on the level of concern. Other laboratory tests such as chest and skeletal roentgenograms should be ordered when indicated. Molecular genetic studies are available to rule out TSC in clinically normal family members.

MANAGEMENT

Treatment should be symptomatic and organ specific and directed to improve the patient outcome and quality of life. Patients with TSC will benefit from a multidisciplinary approach. Early intervention is important to educate the family, organize the most appropriate educational placement, and plan specialist referral and follow-up. Consultations with a dermatologist, neurologist, nephrologist, cardiologist, and ophthalmologist should be considered. Seizures are managed with an anticonvulsant medication. Vigabatrin has been shown to be remarkably effective for treating infantile spasms (Hyman & Whittemore, 2000; Os-
Lamotrigine is effective in the treatment of generalized seizures (Curatolo, 1996). Neurosurgical intervention should be considered for intractable seizures, increased intracranial pressure, and giant cell astrocytomas (Romanelli, Verdeccchia, Rodas, Seri, & Curatolo, 2004). When mental retardation or autism is present in a child with TSC, the educational needs require special assessment. Some children will do satisfactorily in a regular class, others might need extra support to remain in a regular class, and those with more severe mental retardation or autism will require assignment to a special class. Facial angiofibromas are a potentially embarrassing cosmetic stigmata of TSC and can be treated with demabrasion or laser surgery.

Genetic counseling is important. With one affected parent, the recurrence risk is 50%. When both parents appear to be unaffected, the recurrence risk is 1 in 22 after one affected offspring and 1 in 3 after two affected offspring (Menkes & Maria, 2000).

The Tuberous Sclerosis Alliance (formerly the National Tuberous Sclerosis Association) is a helpful resource for affected families. The TSA was formed by parents and families of patients with TSC who have volunteered their time and efforts to increase awareness of tuberous sclerosis and to find the cause and cure for the problem. Their Web site offers helpful information on TSC in lay terminology, medical news updates on the condition, and new treatment approaches, and it provides a fundraising vehicle to support research on the problem. The Tuberous Sclerosis Alliance Web Site is www.tsalliance.org.

**PROGNOSIS**

Life expectancy was previously reduced mainly because of intercurrent infection, uncontrolled seizures, or other complications. Modern diagnostic imaging and treatment has improved both the quality of life and life expectancy of patients with TSC. Diagnostic imaging studies can potentially identify complications in an earlier and more remedial stage.

**CONCLUSION**

TSC is a neurocutaneous disorder that is inherited in an autosomal dominant fashion with almost complete penetrance but variable expressivity. The dermatologic manifestations of TSC often herald the diagnosis. Morbidity and quality of life are largely determined by the neurologic manifestations, which include seizures and mental retardation. Almost every organ system might be involved with hamartoma formation, especially the heart, kidneys, and eyes. Symptomatic, organ-specific treatment and a multidisciplinary approach can improve the quality of life for patients with TSC.

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**REFERENCES**


