

# Tuberous Sclerosis

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## GOAL

To understand the clinical features of tuberous sclerosis (TS)

## OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the clinical features of TS.
2. Understand the diagnostic criteria for TS.
3. Explain the management of TS.

CME Test on page 110.

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*Tuberous sclerosis (TS) is an autosomal dominant disorder with a significant range of clinical expression. Renal, pulmonary, central nervous system, and cardiac complications may result in severe morbidity. Early recognition of the syndrome is important to ensure prompt identification of systemic involvement. We review the clinical features of tuberous sclerosis and discuss recent advances in our understanding of its pathogenesis and appropriate management.*

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**T**uberous sclerosis (TS) is an autosomal dominant complex that involves multiple organs, including the brain (cortical tubers, subependymal nodules, subependymal giant cell astrocytomas, mental retardation), kidneys (cysts, angiomyolipomas, Wilms tumors), blood vessels (aortic aneurysms), bones (sclerosis, cysts), lungs (lymphangiomyomatosis), skin and appendages (angiofibromas, hypomelanotic macules, unguis fibromas, gum fibromas, shagreen patches), pancreas, and parathyroid glands.<sup>1,2</sup> In addition, 50% of TS cases involve the heart (rhabdomyoma[s], Wolff-Parkinson-White syndrome), and 50% to 75% of cases involve the eyes (retinal astrocytomas, pigmentary defects).<sup>1,3</sup>

The most common manifestations of TS, facial angiofibromas (Figures 1 and 2) and ash-leaf spots (Figure 3), occur in 75% of patients and 87% to 98% of patients, respectively.<sup>4</sup> Although multiple facial angiofibromas are common presentations of TS, they are also part of the cutaneous complex seen in multiple endocrine neoplasia syndrome, type 1, and as such are not pathognomonic.<sup>3</sup> Forehead plaques,



Figure 1. Angiofibromas on chin.



Figure 2. Nasal angiofibromas.

though histologically similar to facial angiofibromas, typically are present from birth or early infancy.<sup>5</sup>

Ash-leaf spots, the earliest skin lesions in most cases of TS,<sup>1,3</sup> also occur in roughly 4% of the general population.<sup>6</sup> These white macules are charac-

teristically found on the trunk or buttocks, are hypomelanotic, and number from 3 to 100. The macules may be oval, confettilike, or resemble a thumbprint.<sup>6</sup> Dermatomal distribution of macules has been reported, but distribution along Blaschko lines (related to chromosome mosaicism or loss of heterozygosity) is more likely. The macules are usually oriented transversely on the trunk and axially on the extremities. The size and color of these lesions do not change. Presence of 3 or more circumscribed macules is strongly suggestive of TS. For many patients with lighter skin, the lesions are visible only when examined under a Wood's lamp (the macules contain melanocytes with a reduced number of small melanosomes). The shagreen patch (Figure 4), often found on the mid to lower back, develops in 21% of patients with TS.<sup>1</sup> Characteristically, this patch is a thickened, orange peel–textured area of connective-tissue hamartoma.

Less common mucocutaneous features of TS include enamel pitting, which occurs in deciduous and permanent teeth in 48% of cases; molluscum fibrosum pendulum (large acrochordons) in 20% of cases; and periungual fibromas (Figure 5) in 15% to 20% of cases.<sup>1,3</sup>

TS affects about 1 in 10,000 persons in the general population and has an estimated incidence of 1 case per 6000 live births.<sup>1</sup> Fifty percent to 75% of cases result from new gene mutations. Two TS genes have been identified. The TS complex 1 (TSC1) gene, located on chromosome 9q34, encodes the protein hamartin<sup>3</sup>; the TSC2 gene, located on chromosome 16p13, encodes the protein tuberin.<sup>3</sup> Both proteins modulate cellular differentiation, tumor suppression, and intracellular signaling. The classic clinical triad of seizures, mental retardation, and facial angiofibromas occurs only in patients with TSC1; these patients represent less than 30% of patients with TS.<sup>7</sup>

Several authors have reported unilaterally distributed facial angiofibromas in patients with segmental forms of TS; this unilateral distribution results from chromosome mosaicism<sup>8,9</sup> or loss of heterozygosity.<sup>10</sup> Chromosome mosaicism reflects heterozygosity for a postzygotic mutation and may be associated with gonadal mosaicism. Gonadal mosaicism may result in inheritance of the nonsegmental form of TS. Loss of heterozygosity occurs when heterozygous somatic cells become hemizygous after loss of the corresponding wild-type alleles.<sup>10</sup> Loss of heterozygosity may result from a mutation such as mitotic recombination, localized gene conversion, point mutation, or point deletion. In TS, angiofibromas, renal angiomyolipomas, cardiac rhabdomyomas, and cortical tubers



**Figure 3.** Ash-leaf spots (A and B).

result from loss of heterozygosity at chromosome 9q34 or chromosome 16p13.<sup>10</sup> Thus, variability of TS in clinical expression and in penetrance might result from somatic mosaicism and germinal mosaicism, respectively.

According to a National Institutes of Health (NIH) consensus conference, diagnostic criteria are as follows: definite TS, 2 major features or 1 major feature and 2 minor features; probable TS, 1 major feature and 1 minor feature; and possible TS, 1 major feature or 2 or more minor features (Table 1).<sup>5,11</sup> Each feature is categorized as major

or minor based on its apparent degree of specificity for TS. Another method for diagnosing TS is based on the presence of 2 or more independent hamartomas.<sup>12</sup> Recommended diagnostic studies for evaluating and screening newly diagnosed individuals, parents, and first-degree relatives are listed in Table 2.<sup>11</sup>

Management of TS depends on the affected organ system. In the brain, cortical tubers along the gyri and sulci are responsible for seizures seen in TS. These tubers are most easily evaluated by magnetic resonance imaging; distinguishing them



**Figure 4.** Shagreen patch (A and B).



**Figure 5.** Periungual fibroma.

Table 1.

**Diagnostic Criteria for Tuberous Sclerosis**

Major Features	Minor Features
Facial angiofibromas or forehead plaque	Randomly distributed pits in tooth enamel
Nontraumatic unguual or periungual fibroma	Hamartomatous rectal polyps
Hypomelanotic macules, >3	Bone cysts
Shagreen patch	Radial migration lines in cerebral white matter
Retinal nodular hamartomas	Gingival fibromas
Cortical tuber	Nonrenal hamartoma
Subependymal nodule	Retinal achromic patch
Subependymal giant cell astrocytoma	Confettilike skin lesions
Cardiac rhabdomyoma(s)	Renal cysts
Lymphangiomyomatosis	
Renal angiomyolipomas	

from astrocytomas, however, is difficult.<sup>12</sup> Seizures can be controlled with antiepileptic medications. The NIH consensus conference named vigabatrin as the first-choice drug for treating infantile spasms.<sup>11</sup> A response to vigabatrin is usually evident within 2 or 3 days, and a reasonable starting dosage is 50 to 100 mg/kg per day increasing to 150 mg/kg per day if required.<sup>13</sup> Subependymal giant cell astrocytomas may obstruct the flow of cerebrospinal fluid, giving rise to signs and symptoms of raised intracranial pressure.<sup>12</sup> As a result, management should be directed toward relieving increased intracranial pressure. Astrocytomas are slow-growing tumors that can be neurosurgically removed. There is no convincing evidence that radiation treatment increases the survival rate or reduces the likelihood of tumor recurrence.<sup>13</sup>

Although the cutaneous lesions of TS are usually asymptomatic, facial angiofibromas and unguual fibromas can cause complications such as bleeding after minor trauma. Laser therapy seems to provide the best treatment results; dermabrasion, shave excision, and cautery also can be effective.<sup>13</sup> The argon laser, tunable dye laser, pulsed dye laser, and 532-nm Nd:YAG laser are all helpful in treating angiomatous lesions, whereas the carbon dioxide laser may be best for more fibrous lesions.<sup>13</sup>

In TS, angiomyolipomas are the main hamartomas affecting the kidney. Large symptomatic

lesions should be evaluated with angiography and, if possible, selectively embolized.<sup>13</sup> Renal arterial embolization or renal-sparing surgery is the mainstay of treatment for renal angiomyolipomas. Often, this renal disease eventually becomes bilateral; partial nephrectomy or enucleation of a peripheral lesion may be appropriate in some cases, but complete nephrectomy should be avoided if possible.<sup>13</sup>

Lymphangiomyomatosis affects women in their early reproductive years almost exclusively, occurs in 5% of young women with TS,<sup>14</sup> and may respond to progesterone and/or oophorectomy.<sup>13</sup> Because lung transplantation may be required in end-stage disease, clinical progression should be monitored with pulmonary function tests.<sup>1</sup> Spontaneous resolution of cardiac rhabdomyomas often occurs with time, and the mainstay of treatment for heart failure and arrhythmias is medical.<sup>13,15</sup> Cardiac rhabdomyomas can be resected, and this procedure should be considered in neonates with obstructive heart failure that is unresponsive to medical treatment. In Wolff-Parkinson-White syndrome, the arrhythmias may become less troublesome, even if the electrocardiographic evidence of pre-excitation remains.<sup>12,15</sup>

At the Mayo Clinic, Webb and Osborne<sup>13</sup> recorded the causes of death among patients with TS and found that the survival rate was lower

Table 2.

**Recommended Diagnostic Studies for Tuberous Sclerosis\***

Diagnostic Study	Asymptomatic Parent, Child, or First-Degree Relative of Affected Individual at Time of Diagnosis	Suspected Case or Initial Diagnostic Evaluation	Child		Adult	
			Known Case and No Symptoms in Referable Organ	Known Case and Symptoms or Findings Previously Documented	Known Case and No Symptoms in Referable Organ	Known Case and Symptoms or Findings Previously Documented
Funduscopy examination	+	+	-	+	-	+
Brain MRI scan	+	+	+	+	+	+
Brain EEG	-	-	-	+	-	+
Cardiac ECG, ECHO	-	+	-	+	-	+
Renal MRI scan, CT scan, ultrasound	+	+	+	+	+	+
Dermatologic screening	+	+	-	+	-	+
Neurodevelopment testing	-	+	+	+	-	+
Pulmonary CT scan	-	-	-	+	+	+

\* + indicates screening recommended; -, screening not recommended; MRI, magnetic resonance imaging; EEG, electroencephalogram; ECG, electrocardiogram; ECHO, echocardiogram; CT, computed tomography.

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than that of white Americans without TS. The excess mortality among patients with TS was largely due to status epilepticus, renal disease, or subependymal giant cell astrocytomas. Increased fatality caused by past seizures is thought to partly account for the absence of adults with TS in epidemiologic studies.<sup>13</sup>

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