

Diagnosis of Tuberous Sclerosis Complex

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ABSTRACT

Tuberous sclerosis complex is a dominantly inherited disorder affecting multiple organs; because of its phenotypic variability, the diagnosis of tuberous sclerosis complex can be difficult in the young or in individuals with subtle findings. Recently revised consensus diagnostic criteria for tuberous sclerosis complex reflect an improved understanding of its clinical manifestations and its genetic and molecular mechanisms. The diagnostic criteria are based on the premise that there are probably no truly pathognomonic clinical signs for tuberous sclerosis complex; signs that were once regarded as specific occur as isolated findings in individuals with no other clinical or genetic evidence of tuberous sclerosis complex. Consequently, the revised criteria require tuberous sclerosis complex–associated lesions of two or more organ systems or at least two dissimilar lesions of the same organ to confirm the diagnosis. The addition of DNA testing complements clinical diagnosis and allows more precise genetic counseling and, in some individuals, prenatal diagnosis. Nevertheless, the 15% false-negative rate for DNA testing and the occurrence of germline mosaicism in about 2% of individuals with tuberous sclerosis complex make it difficult to exclude the diagnosis of tuberous sclerosis complex in family members. (*J Child Neurol* 2004;19:643–649).

Tuberous sclerosis complex is a dominantly inherited disorder of cellular differentiation and proliferation that variably affects the brain, skin, kidneys, heart, and other organs. Because of its striking variability of clinical expression and severity, the diagnosis of tuberous sclerosis complex can be difficult, especially in young individuals or in those with subtle findings.¹ The genetics and biologic mechanisms of tuberous sclerosis complex are not nearly as straightforward as once believed. For these reasons, the diagnosis of tuberous sclerosis complex can be challenging.^{1–3}

In 1998, a panel of international experts revised the diagnostic criteria for tuberous sclerosis complex at the Tuberous Sclerosis Complex Consensus Conference in Annapolis, Maryland.^{4,5} The revised criteria (Table 1) reflect an improved understanding of the clinical manifestations of tuberous sclerosis complex and its genetic and molecular

mechanisms. Fundamental to the revised criteria was the agreement among the experts that there are no truly pathognomonic clinical signs for tuberous sclerosis complex; the signs that were once regarded as specific sometimes occur as isolated findings in individuals with no other clinical or genetic evidence of tuberous sclerosis complex. Consequently, the revised criteria require tuberous sclerosis complex–associated lesions of two or more organ systems or at least two dissimilar lesions of the same organ to confirm the diagnosis.

Another departure from earlier tuberous sclerosis complex diagnostic criteria was the panel's decision not to include epilepsy and mental retardation as indicators of tuberous sclerosis complex. The group concluded that epilepsy and mental retardation were both so common in the general population and their causes so numerous that neither had sufficient specificity to be useful in the criteria. Additionally, most patients with epilepsy and mental retardation have cortical brain lesions on neuroimaging studies, and the number of such lesions tends to increase in rough proportion to the severity of the neurologic problems. There was concern that including both the symptoms and the lesions that caused the symptoms amounted to counting the same item twice.⁴

The consensus criteria were designed to establish a consistent and reliable standard for the diagnosis of tuberous sclerosis complex. It is much more difficult, however, to devise criteria that will exclude the diagnosis in affected

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Table 1. Diagnostic Criteria for Tuberous Sclerosis Complex

Major features
Facial angiofibromas or forehead plaque
Nontraumatic ungual or periungual fibroma
Hypomelanotic macules (more than three)
Shagreen patch (connective tissue nevus)
Cortical tuber*
Subependymal nodule
Subependymal giant cell astrocytoma
Multiple retinal nodular hamartomas
Cardiac rhabdomyoma, single or multiple
Lymphangiomyomatosis†
Renal angiomyolipoma‡
Minor features
Multiple randomly distributed pits in dental enamel
Hamartomatous rectal polyps‡
Bone cysts§
Cerebral white-matter "migration tracts"¶§
Gingival fibromas
Nonrenal hamartoma‡
Retinal achromic patch
"Confetti" skin lesions
Multiple renal cysts‡

Adapted from Roach ES et al.⁴

*When cerebral cortical dysplasia and cerebral white-matter migration tracts occur together, they should be counted as one rather than two features of tuberous sclerosis.

†When both lymphangiomyomatosis and renal angiomyolipomas are present, other features of tuberous sclerosis should be present before a definite diagnosis is assigned.

‡Histologic confirmation is suggested.

§Radiographic confirmation is sufficient.

Definite tuberous sclerosis complex: Either two major features or one major feature plus two minor features.

Probable tuberous sclerosis complex: One major plus one minor feature.

Suspect tuberous sclerosis complex: Either one major feature or two or more minor features.

individuals with few tuberous sclerosis complex signs or in younger patients who have yet to develop the full array of manifestations. Nevertheless, the revised criteria are still useful, even in very young patients or when the diagnostic evaluation is incomplete, because once sufficient evidence of tuberous sclerosis complex accumulates, a definite diagnosis can still be made. It is important, however, to periodically reassess these individuals over time or when more evidence becomes available.^{6,7}

The revised diagnostic criteria (see Table 1) have been widely disseminated and have shown great utility in establishing the clinical diagnosis of tuberous sclerosis complex. Standardized criteria provide a quick, reliable, and economical method of establishing a diagnosis, and they help ensure uniformity in clinical tuberous sclerosis complex research. The addition of DNA-based testing complements clinical diagnosis and allows more precise genetic counseling and, in some cases, prenatal diagnosis. Our aim is to review the clinical features of tuberous sclerosis complex as they relate to diagnosis and the recent developments in confirmatory diagnosis.

CLINICAL FEATURES OF TUBEROUS SCLEROSIS COMPLEX

Skin Lesions

The cutaneous lesions of tuberous sclerosis complex include hypomelanotic macules, the shagreen patch, ungual fibromas, and facial angiofibromas (Figure 1). One or more of these

skin lesions occur in over 90% of individuals with tuberous sclerosis complex, although none is pathognomonic.⁴

Hypomelanotic macules (ash leaf spots) are found in over 90% of patients with tuberous sclerosis complex (see Figure 1A). They are usually present at birth but are often difficult to see in the newborn without an ultraviolet light. Other pigmentary abnormalities include the "confetti" lesions (an area with stippled hypopigmentation, typically on the extremities) and poliosis of the scalp hair or eyelids. Hypomelanotic macules are not specific for tuberous sclerosis complex because one or two of these lesions are relatively common in normal individuals.⁸

Facial angiofibromas (see Figure 1B) occur in about three fourths of patients but often appear several years after the diagnosis has been established by other means. These lesions typically become apparent during the preschool years as a few small red papules on the malar region; they gradually become larger and more numerous, sometimes extending down the nasolabial folds or onto the chin. Angiofibromas contain both vascular and connective tissue elements. Although facial angiofibromas are a strong indication of tuberous sclerosis complex when found with other manifestations, these lesions also occur in individuals with multiple endocrine neoplasia type I and thus are not pathognomonic for either condition.

The shagreen patch (see Figure 1C) is most commonly found on the back or flank area; it is an irregularly shaped, slightly raised, or textured skin lesion. The lesion is found in 20 to 30% of patients with tuberous sclerosis complex and occasionally other individuals. It might not be apparent in young children.

Ungual fibromas (see Figure 1D) are nodular or fleshy lesions that arise adjacent to or from underneath the nails. The lesion is usually considered specific for tuberous sclerosis complex, although a single lesion occasionally occurs after trauma. Ungual fibromas are seen in about 20% of unselected patients with tuberous sclerosis complex and are more likely to be found in adolescents or adults than in younger children. Sometimes the fibroma itself is not visible but creates a prominent longitudinal groove in the fingernail, a finding that also has diagnostic significance.

Retinal Lesions

The frequency of retinal hamartomas in tuberous sclerosis complex varies with the expertise and technique of the examiner. Under ideal circumstances, up to 87% of patients with tuberous sclerosis complex have retinal lesions, but especially in uncooperative children, these lesions can be difficult to identify without dilating the pupils and the use of indirect ophthalmoscopy.⁹ Retinal lesions vary from the classic mulberry lesions (Figure 2) adjacent to the optic disk to the plaquelike hamartoma or depigmented areas. Most retinal lesions are clinically insignificant, but occasional patients have visual impairment owing to a large macular lesion, and rare patients have visual loss owing to retinal detachment, vitreous hemorrhage, or hamartoma enlargement. Some patients have a pigmentary defect of the iris.



Figure 1. Cutaneous features of tuberous sclerosis complex include A, hypomelanotic macules and poliosis (in this case, the area of hypopigmentation and poliosis is unusually large; a more typical hypomelanotic macule is evidently inferior to the large lesion); B, facial angiofibromas (adenoma sebaceum); C, the shagreen patch, and D, an ungual fibroma. B reproduced with permission from Roach ES, Delgado MR: Tuberous sclerosis. *Dermatol Clin* 1995;13:151–161.

Cardiac Lesions

Roughly two thirds of newborns with tuberous sclerosis complex have one or more cardiac rhabdomyomas, but few of these lesions are clinically important. Cardiac rhabdomyomas are often multiple (Figure 3) but shrink over time and are identified much less often in older children and adults.¹⁰ These lesions are sometimes evident on prenatal ultrasonographic testing, and most of the patients with cardiac dysfunction present soon after birth with heart failure, usually owing to either obstruction of blood flow by an intraluminal tumor or to inadequate normal myocardium to

maintain perfusion. Some patients stabilize and improve after medical treatment; others require surgery. A few children later develop cardiac arrhythmias.

Renal Lesions

Renal angiomyolipomas occur in about 75 to 80% of patients with tuberous sclerosis complex over the age of 10 years; most of these lesions are histologically benign tumors with varying amounts of vascular tissue, fat, and smooth muscle (Figure 4).¹¹ Bilateral tumors or multiple tumors per kidney are typical. The prevalence of renal tumors increases with

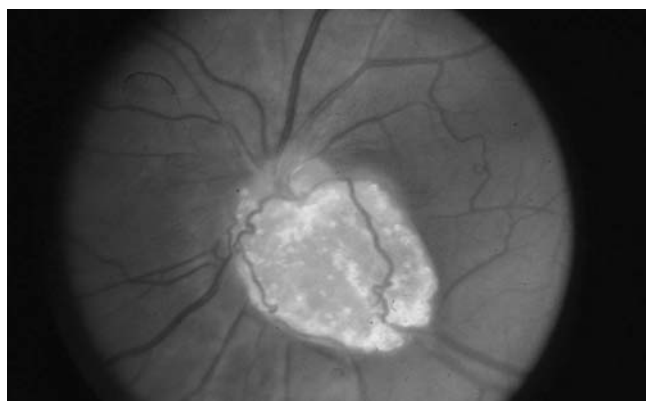


Figure 2. A retinal astrocytoma ("mulberry lesion") adjacent to the optic nerve is typical of those found with tuberous sclerosis complex. Reproduced with permission from Roach ES: Neurocutaneous syndromes. *Pediatr Clin North Am* 1992;39:591-620.

age, and tumors larger than 4 cm are much more likely to become symptomatic than smaller tumors. Renal cell carcinoma or other malignancies are less common.

Single or multiple renal cysts are also a feature of tuberous sclerosis complex; these tend to appear earlier than the renal tumors. Larger cysts are easily identified with ultrasonography or computed tomography (CT), and the combination of renal cysts and angiomyolipomas is characteristic of tuberous sclerosis complex. Individual renal cysts can disappear.

Pulmonary Dysfunction

At least 1% of patients with tuberous sclerosis complex develop symptomatic pulmonary dysfunction, and many

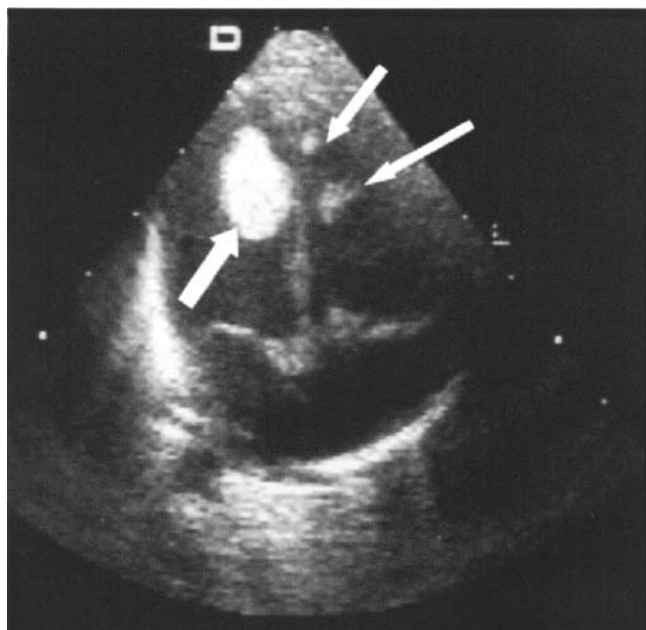


Figure 3. Ultrasonic demonstration of multiple cardiac rhabdomyomas (arrows). Reproduced with permission from Roach ES, Delgado MR: Tuberous sclerosis. *Dermatol Clin* 1995;13:151-161.

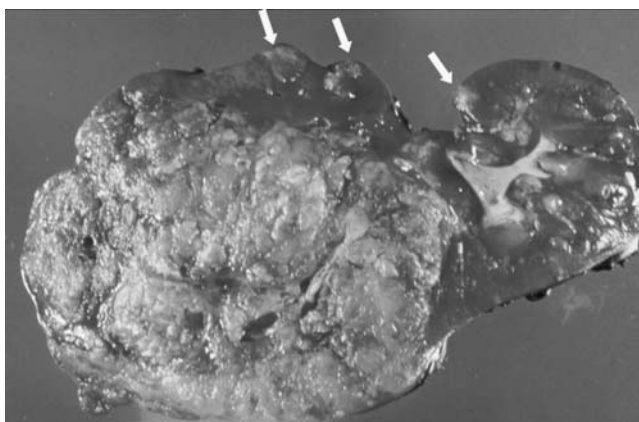


Figure 4. A large angiomyolipoma of the lower pole of a kidney removed at surgery; several smaller angiomyolipomas (arrows) are evident in the same specimen. Reproduced with permission from Weiner DM et al.⁷

others probably have asymptomatic lung lesions on diagnostic studies later in life. The classic pulmonary lesion of tuberous sclerosis complex is lymphangioleiomyomatosis; other patients have multifocal micronodular pneumocyte hyperplasia. Pulmonary disease is five times more common in female than in male patients. Spontaneous pneumothorax, dyspnea, cough, and hemoptysis are typical symptoms of pulmonary tuberous sclerosis complex, although these do not often develop before the third or fourth decade. CT of the chest commonly demonstrates lung lesions even in adults without symptoms.

Both renal angiomyolipomas and pulmonary lymphangioleiomyomatosis are strongly associated with tuberous sclerosis complex, but neither is specific; moreover, they tend to occur together in the absence of other signs of tuberous sclerosis complex. Thus, when both conditions occur in the same patient, they should be counted as one major feature of tuberous sclerosis complex, not two. Either condition can be considered a major feature of tuberous sclerosis complex without the other, but the diagnosis should not rest solely on the presence of these two lesions.⁴

Neurologic Dysfunction from Tuberous Sclerosis Complex

The predominant neurologic manifestations of tuberous sclerosis complex are mental retardation, epileptic seizures, and behavioral abnormalities, but affected individuals with little or no neurologic impairment are common.^{2,3} Neurologic lesions probably result from impaired neuronal migration along radial glial fibers and from abnormal proliferation of glial elements.

Neuropathologic lesions of tuberous sclerosis complex include subependymal nodules, cortical hamartomas, areas of focal cortical hypoplasia, and heterotopic gray matter.^{7,12} Although all of the superficial cerebral lesions of tuberous sclerosis complex are sometimes lumped together as cortical tubers, the actual pathologic picture is more complex. A classic tuber is a dysplastic lesion of a gyrus that has a firm, nodular feel; it often occurs at the apex of a gyrus

but does not always enlarge the gyrus. However, areas of focal cortical dysplasia that are not nodular and are less sharply demarcated are common, ranging from grossly visible defects of the cortical mantle to microscopic disruption of the cytoarchitecture.

Various types of seizures occur in 80 to 90% of patients. Most patients with mental retardation have epilepsy, but there are exceptions. On the other hand, many people with tuberous sclerosis complex have epilepsy but have normal intelligence. The number of subependymal lesions does not correlate with the clinical severity of tuberous sclerosis complex, but patients with numerous lesions of the cerebral cortex shown by magnetic resonance imaging (MRI) tend to have more cognitive impairment and more difficulty with seizure control.^{13,14} Children with infantile spasms are more likely to exhibit long-term cognitive impairment, but these patients, in turn, have more cortical lesions demonstrated by MRI.

The likelihood of mental retardation in patients with tuberous sclerosis complex is probably overestimated. Webb and colleagues, for example, found only 10 patients with mental retardation among 26 patients with tuberous sclerosis complex in a population survey.¹⁵ The severity of intellectual dysfunction ranges from borderline to profound mental retardation. Autism and various behavioral disturbances, including hyperactivity, aggressiveness, and frank psychosis, are common, either as isolated problems or in combination with epilepsy or intellectual deficit.¹⁶

The calcified subependymal nodules (Figure 5) that characterize tuberous sclerosis complex are best demon-

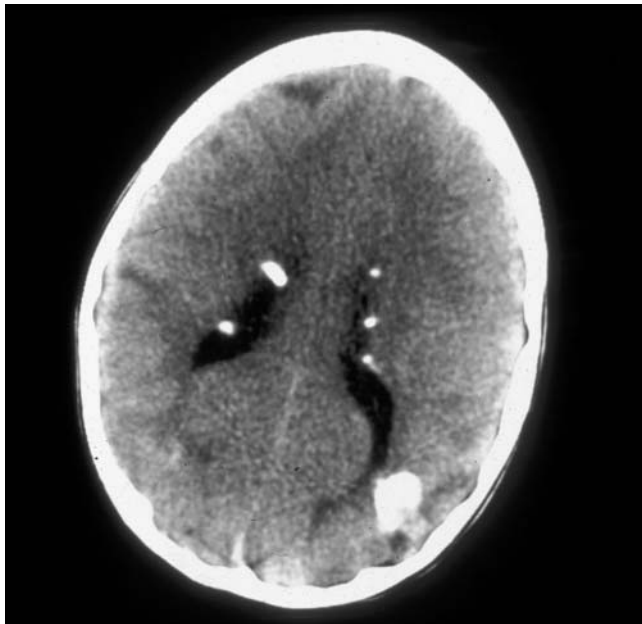


Figure 5. Computed tomographic scan from a child with tuberous sclerosis complex demonstrates typical calcified subependymal nodules, a large calcified parenchymal lesion, and smaller low-density cortical lesions. Reproduced with permission from Roach ES, Kerr J, Mendelsohn D, et al: Diagnosis of symptomatic and asymptomatic gene carriers of tuberous sclerosis by CCT and MRI. *Ann N Y Acad Sci* 1991;615:112-122.

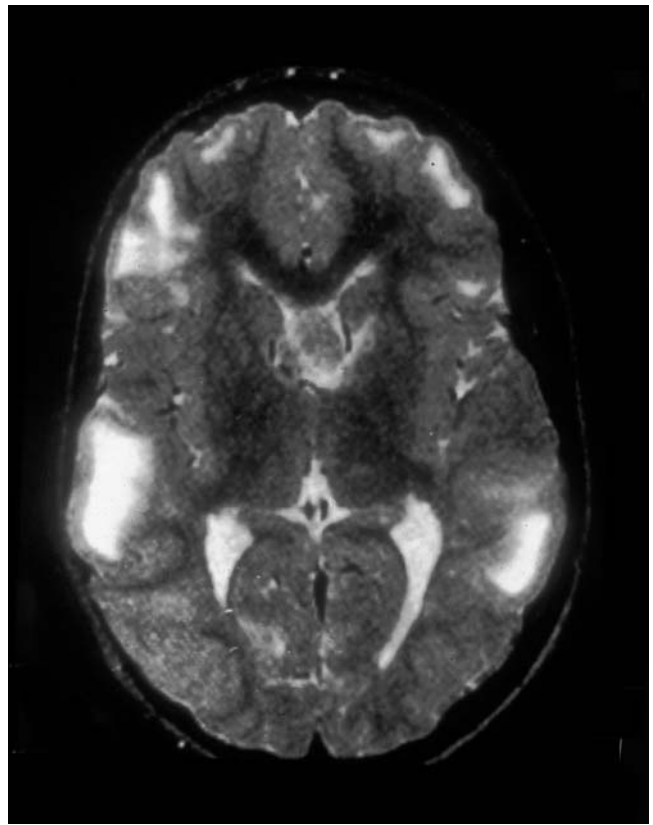


Figure 6. Noncontrast T_2 -weighted magnetic resonance image from a child with tuberous sclerosis demonstrates extensive high-signal cortical lesions typical of tuberous sclerosis. Reproduced with permission from Miller VS, Roach ES: Neurocutaneous syndromes, in Bradley WG, Daroff RB, Fenichel GM, Marsden CD (eds): *Neurology in Clinical Practice*, 3rd ed. Newton, MA, Butterworth-Heinemann, 1999, 1665-1700.

strated with cranial CT. Subependymal nodules arise adjacent to the ventricular wall and characteristically protrude into the ventricular lumen. They are most often found in the lateral ventricles and seem to occur more often anteriorly. Superficial cerebral lesions can sometimes be seen with cranial CT but are far more obvious with T_2 -weighted MRI (Figure 6). Cerebellar anomalies occur in about a fourth of patients with tuberous sclerosis complex. Nodular subependymal lesions that have not yet calcified produce a high-signal lesion with T_2 -weighted scans. Evidence of abnormal neuronal migration can be seen in some patients as a high-signal linear lesion running perpendicular to the cortex on T_2 -weighted scans.

Subependymal giant cell astrocytoma occurs in 6 to 14% of individuals with tuberous sclerosis complex and is more likely to develop during childhood. Unlike the more common cortical tubers, giant cell astrocytomas (Figure 7) can enlarge and cause symptoms such as increased intracranial pressure, new focal neurologic deficits, or deterioration of seizure control.¹⁷ Acute or subacute onset of neurologic dysfunction rarely results from sudden obstruction of the ventricular system by an intraventricular subependymal giant cell astrocytoma or from hemorrhage into the tumor

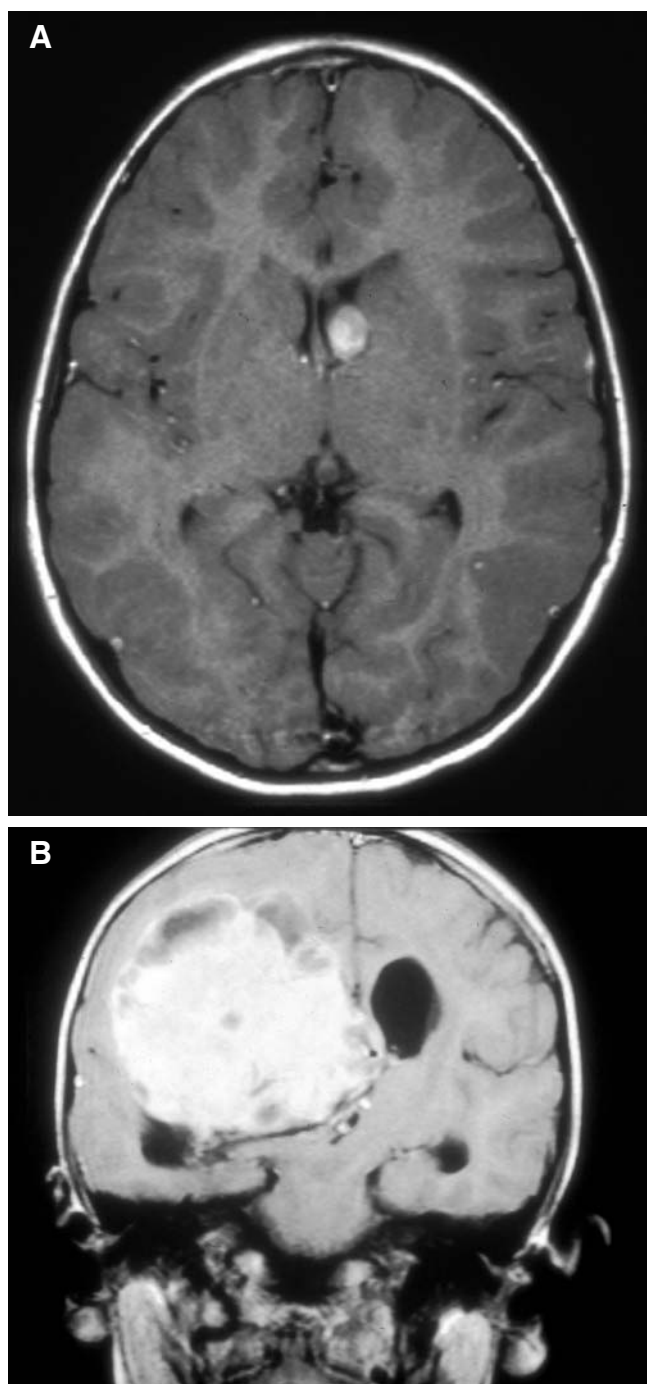


Figure 7. *A*, Gadolinium-contrast T₁-weighted magnetic resonance image (MRI) from a child with tuberous sclerosis complex shows an enhancing subependymal giant cell astrocytoma protruding into the left frontal horn. *B*, Another patient's MRI with gadolinium demonstrates a huge subependymal giant cell astrocytoma filling much of the lateral ventricle.

itself. Giant cell tumors are usually benign but locally invasive, and surgery, performed early, can be curative.

GENETICS OF TUBEROUS SCLEROSIS

Tuberous sclerosis complex was once thought to be a rare disease but is now known to occur in about 1 in 6000 live births,¹⁸ making it not quite as common as neurofibro-

matosis type 1 (1 in 4,000 births) but more common than von Hippel-Lindau disease (1 in 36,000 births). Improved diagnostic techniques (especially in imaging and genetic testing), as well as an ever-growing awareness of tuberous sclerosis complex among physicians and the public, might, in time, reveal an even greater prevalence.

Tuberous sclerosis complex is inherited as an autosomal dominant trait with variable penetrance, and two thirds to three fourths of the individuals with tuberous sclerosis complex arise via a spontaneous mutation. Two different genes cause tuberous sclerosis complex: *TSC2*, which encodes tuberin, and *TSC1*, which encodes hamartin.^{19,20} Multiple mutations of each gene have been identified. The phenotype for the two tuberous sclerosis complex genes overlap, although individuals with *TSC2* tend to have more severe neurologic impairment, and *TSC1* tends to be found more often in familial cases.²¹ Tuberin and hamartin physically interact at the Golgi apparatus and function together as a single molecular complex, probably explaining why a mutation on either gene causes such a similar phenotype.²²⁻²⁴

DIAGNOSIS OF TUBEROUS SCLEROSIS COMPLEX BY DNA ANALYSIS

Testing for *TSC1* and *TSC2* mutations has been available from Athena Diagnostics, Inc. (Worcester, MA) since 2002. Confirmatory testing for tuberous sclerosis complex is helpful in individuals who fail to meet the criteria for definite tuberous sclerosis complex and to improve genetic counseling. Prenatal genetic testing for tuberous sclerosis complex is also possible when there is a defined tuberous sclerosis complex mutation in a specific family. Preimplantation genetic diagnosis is a method of determining the genetic characteristics of an embryo created by in vitro fertilization. Although preimplantation genetic diagnosis is feasible for tuberous sclerosis complex, its use is not widespread.²⁵⁻²⁷

Several issues limit the usefulness of confirmatory testing for tuberous sclerosis complex, beginning with the fact that most patients develop the disorder via a spontaneous mutation. And although there are few false-positive tests, as much as 15 to 20% of the time the test fails to demonstrate a disease-causing mutation. Nevertheless, confirmatory testing in an individual who already fulfills the diagnostic criteria for definite disease can help identify a mutation that can then be sought in other family members or for subsequent prenatal diagnosis.

Somatic and germline mosaicism also complicate confirmatory testing for tuberous sclerosis complex. Somatic mosaicism occurs when an individual has a mutation in some, but not all, cells and tissues. Such an individual often has milder manifestations of tuberous sclerosis complex or manifestations limited to a single organ system but can have more severely affected progeny.²⁸ Germline mosaicism occurs when an individual carries a mutation only in the germ cells and has no other signs or symptoms of the given disease. Germline mosaicism probably accounts for about 2% of the patients,²⁹ making genetic counseling

more difficult even when a specific mutation has been identified. Hence, a conservative recurrence risk for seemingly unaffected couples with a single affected child, even when they have no demonstrable tuberous sclerosis complex mutation, is 2%.

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