Special Article

Tuberous Sclerosis Consensus Conference: Recommendations for Diagnostic Evaluation

E.S. Roach, MD; Francis J. DiMario, MD; Raymond S. Kandt, MD; Hope Northrup, MD

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From the Division of Child Neurology, University of Texas Southwestern Medical Center at Dallas (Dr Roach), Dallas, TX; the Division of Pediatric Neurology, University of Connecticut at Connecticut Children's Medical Center (Dr DiMario), Hartford, CT; the Johnson Neurological Clinic (Dr Kandt), High Point, NC; and the Department of Pediatrics, University of Texas Medical School-Houston (Dr Northrup), Houston, TX.

Address correspondence to Dr E.S. Roach, Department of Neurology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75235.

ABSTRACT

At the recent Tuberous Sclerosis Consensus Conference, a subcommittee proposed recommendations to guide the rational use of diagnostic studies in patients with tuberous sclerosis complex. Recommendations were made for diagnostic evaluation at the time of diagnosis, when testing helps both to establish the diagnosis and to identify potential complications. Additional guidelines were proposed for the ongoing surveillance of established patients to detect later complications of tuberous sclerosis complex. In the absence of comprehensive population studies to govern the use of diagnostic studies in individuals with tuberous sclerosis complex, the panel developed guidelines based on the disorder's natural history, concentrating on complications that are common, clinically significant, and more easily managed when found early. Finally, the group made suggestions for the use of diagnostic tests to identify family members who have tuberous sclerosis complex. Although these recommendations should standardize and improve our use of diagnostic studies in individuals with tuberous sclerosis complex, the clinical approach in a given patient must remain flexible enough to meet the needs of individual patients and families. (J Child Neurol 1999;14:401-407).

Virtually any part of the body can be affected by tuberous sclerosis complex, and the clinical manifestations are highly variable, even among affected members of the same family. Some features of tuberous sclerosis complex can be present at birth, while other complications tend to develop later in life.1,2 Although many of these problems are easily detected by readily available diagnostic techniques, rational use of these studies is handicapped by the lack of a standardized approach.

A subcommittee at the Tuberous Sclerosis Consensus Conference (sponsored by the National Institutes of Health in June 1998 in Annapolis, MD) developed recommendations for using diagnostic studies in three groups: (1) patients newly diagnosed with tuberous sclerosis complex, (2) established patients (to detect late complications of tuberous sclerosis complex), and (3) potentially affected family members of children who have tuberous sclerosis complex. Each of these categories will be discussed separately.

EVALUATION OF NEWLY DIAGNOSED PATIENTS

Diagnostic studies at the time of initial diagnosis are typically done either to confirm the presence of tuberous sclerosis complex or to evaluate presenting symptoms such as epileptic seizures or cardiac dysfunction. In addition, it is often useful to establish a baseline assessment in areas that could develop problems later. Unless specific areas of concern are identified with these initial studies, subsequent testing is targeted to areas with a significant risk of dysfunction and to lesions that can be treated. The panel considered several specific diagnostic studies and made the following recommendations for newly diagnosed patients (Table 1).

Computed Cranial Tomography

and Magnetic Resonance Imaging

Most patients with tuberous sclerosis complex undergo either cranial computed tomography (CT) or magnetic resonance imaging (MRI) at the time of initial presentation, either to evaluate a neurologic problem or to search for addi-
Table 1. Summary of Testing Recommendations

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<th>Assessment</th>
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<td>At adulthood (women only)</td>
<td>If pulmonary dysfunction occurs</td>
</tr>
<tr>
<td>Cranial computed tomography*</td>
<td>At diagnosis</td>
<td>Children/adolescents: every 1 to 3 years</td>
</tr>
<tr>
<td>Cranial magnetic resonance imaging*</td>
<td>At diagnosis</td>
<td>Children/adolescents: every 1 to 3 years</td>
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*Either cranial computed tomography or magnetic resonance imaging, but usually not both.

Tional evidence of tuberous sclerosis complex already suspected on some other grounds.3 But patients whose diagnosis is obvious also should be scanned because of the risk of subependymal giant cell astrocytoma, which is sometimes already present at the time of diagnosis. It is not usually necessary to do both scans initially, but occasionally both tests might be required to clarify specific concerns.

The number, size, and perhaps the location of the dysplastic cortical lesions shown with MRI tend to correlate with the severity of the clinical neurologic dysfunction.4-6 However, response to seizure treatment and possibly other factors also can influence the prognosis,7 and the panel recommended that the scan results not be used to predict the neurologic outcome of an individual patient.

Electroencephalography
Electroencephalography (EEG) is useful when the initial presentation includes epileptic seizures.8 However, children who are not suspected of having epileptic seizures usually do not need to undergo baseline EEGs.

Renal Ultrasonography
Adolescents and adults are more likely to develop symptomatic renal angiomyolipomas than children, but occasionally children develop sizable renal tumors and require treatment.9 Additionally, a few children have features of autosomal-dominant polycystic kidney disease,10,11 and these children tend to develop symptoms earlier. Renal tumors larger than 4 cm in diameter are more likely to become symptomatic than smaller lesions.12,13

Older patients in particular should be evaluated for renal tumors. The panel recommended that each patient undergo renal ultrasonography at the time of diagnosis. Patients who have already undergone MRI or CT scanning of the kidneys do not require renal ultrasonography.

Electrocardiography
Cardiac arrhythmias sometimes occur even in patients with tuberous sclerosis complex who do not have a demonstrable cardiac rhabdomyoma. An arrhythmia can be present at birth or develop later. Wolff-Parkinson-White syndrome seems to be the most commonly mentioned arrhythmia in patients with tuberous sclerosis complex, and at least one patient developed this pattern just after starting carbamazepine treatment for epileptic seizures.14 The electrocardiogram (ECG) is often abnormal before the patient develops symptoms, and the panel recommended that a baseline study be performed at the time of diagnosis or before a patient has surgery.

Echocardiography
Echocardiography reveals one or more cardiac rhabdomyomas in more than half of the younger individuals with tuberous sclerosis complex.15,16 These cardiac tumors tend to involute over time and often disappear altogether by adulthood17; the most rapid reduction in lesion size takes place during the first 3 years of life, and thereafter rhabdomyomas tend to change less dramatically.18 Neonates without cardiac compromise have a low risk of developing cardiac dysfunction later.19 Most of the older children and adults who do develop new cardiac dysfunction have an arrhythmia, a problem not demonstrated by echocardiography.

The panel recommended an echocardiogram for patients of any age with symptoms of a cardiac rhabdomyoma. However, most symptomatic patients are neonates, and it is usually not necessary to study newly diagnosed older children or adults unless confirmation of cardiac lesions is needed to confirm an otherwise dubious diagnosis.

Ophthalmic Examination
Detailed examination of the retina with an indirect ophthalmoscope after pupillary dilatation often provides evidence of tuberous sclerosis complex at the time of initial diagnosis. In addition, some patients have poor vision resulting from large macular lesions, and these patients might need continuing eye care and perhaps adaptations for the visually impaired. Most panel members felt that each patient with tuberous sclerosis complex should have a thorough ophthalmic examination at the time of diagnosis.

Dermatologic Examination
Most children do not have facial angiofibromas or ungual fibromas at the time of diagnosis, and typical hypomelanotic macules can be recognized by most clinicians who are knowledgeable about tuberous sclerosis complex. A dermatologic evaluation can be useful when the skin lesions are atypical or when the diagnosis of tuberous sclerosis complex is uncertain.
Neurodevelopmental Testing

Individuals with tuberous sclerosis complex have a great risk of neurodevelopmental and behavioral impairment. In addition, it is important to recognize the consequences of frequent seizures as well as the potential detrimental effects of seizure therapy on cognitive function and behavior.

The panel recommends thorough age-appropriate screening for behavioral and neurodevelopmental dysfunction at the time of diagnosis. Children with normal initial testing and developmental milestones can still have less conspicuous deficits that interfere with learning, and each child should be reassessed around the time school begins, even if the prior screening revealed no abnormalities. Older children with previous test abnormalities or children with abnormal cognitive function or behavior should beperiodically retested, and re-evaluation is also appropriate when there is a significant change in behavior or cognitive function.

Newly diagnosed adults and adolescents with a well-established pattern of completely normal social and cognitive function (as determined by educational achievement or job performance) might not require formal testing. Likewise, frequent re-evaluation of older individuals who have a well-characterized, stable cognitive deficit or behavior disturbance is probably not warranted.

Molecular Diagnosis

Although DNA-based testing is not yet routinely available, gene characterization eventually might identify patients at increased or decreased risk for particular complications. If so, additional diagnostic studies could be performed selectively on individuals at greatest risk for specific complications, reducing the number of unfruitful studies. Once molecular testing becomes available and there is sufficient data to determine which phenotypes correlate with which gene defects, gene typing at the time of initial diagnosis could be useful.

ONGOING EVALUATION OF ESTABLISHED PATIENTS

Early identification of a problem that cannot be treated serves little practical purpose, and long-term surveillance testing should concentrate on complications that are significant, relatively common, and more easily managed when found early. Hepatic hamartomas, for example, do not require surveillance. They occur in about one quarter of patients with tuberous sclerosis complex, but so few of these lesions become symptomatic that repeated ultrasound studies are unlikely to be helpful. Therefore, there is no reason to do repeated imaging studies on these lesions. Other tuberous sclerosis complex lesions can cause major problems, but usually only within a limited time frame. Cardiac dysfunction due to rhabdomyomas, for example, generally occurs just after birth or not at all, although there can be exceptions.

Often the population data needed to guide ongoing diagnostic testing is lacking, and a surveillance protocol based on the natural history of tuberous sclerosis complex provides some practical basis for ordering follow-up tests. The goals are to identify treatable lesions that occur often enough to justify the effort and to maximize the likelihood that treatable lesions will be identified early. The following guidelines are designed for long-term clinical management of an asymptomatic patient whose diagnosis is well established; additional studies, of course, could be clinically indicated.

Cranial Computed Tomography and Magnetic Resonance Imaging

Subependymal giant cell astrocytomas occur in 6% to 14% of patients with tuberous sclerosis complex. These tumors are histologically benign but locally invasive, and they can cause hydrocephalus because of their typical occurrence in the anterior lateral ventricle. Early identification of an enlarging giant cell tumor enables it to be removed before symptoms develop and before it becomes locally invasive, probably reducing the likelihood of tumor residual or recurrence.

The panel recommended that children undergo periodic cranial imaging with either CT or MRI scans every 1 to 3 years, depending on the level of clinical suspicion in a given child. Children seem to be more likely to develop subependymal giant cell astrocytomas than are adults, and it might be reasonable to scan asymptomatic adults less frequently, provided that their last scan showed no evidence of a tumor, but the panel reached no specific conclusion about the optimal frequency of cranial scans in adults with tuberous sclerosis complex.

Electroencephalography

Generally the need for EEG is dictated by the clinical features and treatment response of epilepsy, rather than by the diagnosis of tuberous sclerosis complex. Both EEG and video-EEG can be useful when treating patients with epilepsy, whether or not the patient has tuberous sclerosis complex. EEG is usually not necessary in patients with tuberous sclerosis complex who do not have epileptic seizures. However, most patients with tuberous sclerosis complex do have epilepsy, and EEG is often indicated.

Since seizures are not always clinically obvious, EEG should be considered in the evaluation of a patient with an unexplained decline of behavioral or cognitive function in whom epileptic seizures are suspected. During the first few years of life, the seizure pattern can change fairly quickly, and it might be necessary to repeat the studies at frequent intervals during this stage of the illness.

Neurodevelopmental Testing

Various patterns of neurodevelopmental and behavioral dysfunction occur as a result of tuberous sclerosis complex, and their combined risk is substantial. While mental retardation is a classic and common feature of tuberous sclerosis complex, learning disabilities, autism, attentional deficits, and other difficulties are probably under-recognized.
Children with these problems can benefit from early recognition and specific education and treatment plans.

The panel recommends thorough age-appropriate testing at the time of diagnosis to establish a baseline. However, adults and adolescents with well-established patterns of normal social and cognitive function do not require formal testing. When the diagnosis of tuberous sclerosis complex is made in infancy or early childhood, testing should be repeated around the time the child enters school.

Older children should be reassessed periodically in response to educational or behavioral concerns. However, it is usually not necessary to retest children whose initial testing identified no specific concerns and whose behavior, emotional state, and educational progress are completely normal.

Renal Ultrasonography

By age 10 years, nearly 75% of children with tuberous sclerosis complex have sonographic evidence of one or more renal angiomyolipomas, which is similar to the prevalence in adults with tuberous sclerosis complex. During the first decade of life, the number and size of the renal angiomyolipomas tend to increase, but symptomatic renal angiomyolipomas seem to occur less often in children than in adults. Additionally, large renal angiomyolipomas are more likely to cause symptoms than are smaller lesions, so it might be reasonable to monitor patients with larger tumors more closely than those with smaller lesions.

Urinalysis can show microscopic or gross hematuria in some patients, and blood urea nitrogen or serum creatinine determinations reveal renal failure in others. However, many patients with clinically significant renal tumors do not have hematuria, and their blood chemistries tend to remain normal until there is little remaining renal function. Thus, these studies are not reliable substitutes for ultrasonography or other renal imaging studies.

The panel recommended renal ultrasonography every 1 to 3 years. The frequency of testing within this time frame depends on the level of concern for a particular patient and the results of previous examinations. Regardless of age, patients who have larger renal lesions or lesions that seem to have grown substantially should have more frequent follow-up examinations. Patients with large or numerous renal tumors should be referred to a urologist or nephrologist; these patients might require CT scans or MRI to better define the extent of the kidney disease.

Echocardiography

Although about two thirds of infants with tuberous sclerosis complex have echocardiographic evidence of one or more cardiac rhabdomyomas, these tumors tend to regress over time and can disappear altogether by adulthood. Most patients with tuberous sclerosis complex who have a cardiac rhabdomyoma remain asymptomatic, and it is unusual to become symptomatic after the neonatal period. Occasional patients develop arrhythmias during adolescence or adulthood, and one patient developed an arrhythmia soon after starting carbamazepine treatment. However, periodic cardiac evaluations are unlikely to identify individuals at risk before the onset of symptoms.

One report described the enlargement of a cardiac rhabdomyoma in two patients during treatment with corticotropin for infantile spasms. Most panel members did not think this one report is sufficient to justify repeated echocardiography during treatment with corticotropin. Repeated cardiac evaluations are unnecessary for most asymptomatic tuberous sclerosis patients. Occasionally asymptomatic children might need follow-up echocardiography because the initial study raised specific concerns about the size or location of a rhabdomyoma, but most asymptomatic patients do not require repeated studies. Patients who have new symptoms that might indicate cardiac dysfunction and those with previous symptoms should be followed by a cardiologist and might benefit from periodic studies to evaluate heart function.

Lung Disease

Pulmonary disease (lymphangioleiomyomatosis) due to tuberous sclerosis complex is uncommon, especially in children and men. It occurs almost exclusively in women. Chest CT scans can demonstrate the pulmonary abnormalities of tuberous sclerosis complex more precisely than other methods. The pulmonologists on the panel felt that early identification of patients with lymphangioleiomyomatosis might allow symptomatic treatment to be started early.

Pulmonary function testing should be reserved for patients with suspected lung dysfunction and has no defined role in the routine management of asymptomatic patients. The panel recommended no routine testing in asymptomatic children or adolescents. Likewise, routine testing was not advocated for asymptomatic men. Women should undergo chest CT scans at least once on reaching adulthood. This test should be repeated if pulmonary symptoms develop. After lymphangioleiomyomatosis is identified, a pulmonologist should be consulted for further evaluation and management.

Ophthalmologic Consultation

About 75% of patients with tuberous sclerosis complex have retinal lesions, but it is uncommon for these lesions to result in progressive visual loss. Moreover, ophthalmic examination can be difficult to perform without sedation in a severely impaired child and is unlikely to identify impending visual loss from a treatable lesion. Patients whose initial evaluation revealed only minor lesions are arguably even less likely to benefit from repeated examinations.

While a few panel members felt that children with tuberous sclerosis complex should have annual examinations by an ophthalmologist, the majority considered repeated ophthalmologic evaluations, beyond those required for routine healthcare maintenance, as unnecessary unless there is some specific reason for concern.
Dermatologic Evaluation
Facial angiofibromas are benign skin tumors that can have major consequences for some patients. Laser therapy can limit the growth of these skin tumors, although often the treatments need to be repeated periodically as the lesions tend to regrow gradually after treatment. Occasionally, treatments need to be repeated periodically as the lesions cause significant problems, and these lesions also can be effectively treated. While routine annual visits to a dermatologist are unnecessary for most patients, it is appropriate to refer patients who might benefit from laser treatment to a physician who is experienced in the treatment of these cutaneous lesions.

EVALUATION OF FAMILY MEMBERS
Because some affected individuals have only subtle clinical features of tuberous sclerosis complex, it is not always easy to distinguish the patient who has a new mutation from one with familial disease. But this question is vitally important for accurate genetic counseling for this autosomal-dominant disorder, because a mildly affected parent whose diagnosis is not recognized will be given very different odds of having another affected child than will a parent known to harbor a tuberous sclerosis mutation (2% versus 50%).

Much attention has been focused on the use of diagnostic studies to detect evidence of tuberous sclerosis complex in parents with few physical findings. Nevertheless, most affected individuals who receive a thorough physical examination, including a skin examination with ultraviolet light and a retinal examination through dilated pupils, have at least subtle physical findings of tuberous sclerosis complex, and it is relatively unusual to establish the diagnosis solely on the basis of radiographic studies in a family member whose physical examination is entirely normal.

Even a completely normal physical examination and extensive radiographic testing cannot absolutely exclude tuberous sclerosis complex, for there is always a chance of germline mosaicism. In a family with only one affected child, the evaluation discussed below should focus on the parents rather than siblings or other relatives.

Cranial Computed Tomography
Evidence of tuberous sclerosis complex in parents can be provided by either cranial CT scan or MRI, but it is uncommon to discover compelling evidence of tuberous sclerosis complex with either test in a parent who has absolutely no signs of the disorder after a careful physical examination.

Fleury and colleagues,34 for example, performed physical examinations, cranial CT scans, and other studies on 48 couples with children with tuberous sclerosis complex and found evidence of tuberous sclerosis complex in 21 couples. Seven parents from these 48 couples had definite evidence of tuberous sclerosis complex seen on cranial CT scans, and two other parents had abnormalities that were considered possibly significant. However, all nine of these parents had physical findings of tuberous sclerosis complex.34

Similarly, Roach et al evaluated the usefulness of cranial MRI for the identification of minimally affected parents with tuberous sclerosis complex.35 Sixty couples (120 parents) with one or more children with tuberous sclerosis complex underwent physical examinations and cranial MRI. Eight parents were believed to have tuberous sclerosis complex, and six of these eight had evidence of tuberous sclerosis complex seen on MRI. However, MRI confirmed the diagnosis of tuberous sclerosis complex in only one parent who had no definitive physical findings of the disorder, and this person had more than one affected child.35 Nonspecific abnormalities were noted in eight additional parents, and these authors concluded that CT was preferable in this setting because of its lower cost and increased specificity.35

The consensus panel concluded that cranial CT is more likely to provide disease-specific information and thus is the preferred test when evaluating a family member who has no outward manifestations of tuberous sclerosis complex. MRI can be more sensitive than CT, but it often detects lesions that are not as specific to tuberous sclerosis complex.

Renal Ultrasonography
No systematic studies have addressed the usefulness of renal ultrasonography in identifying minimally affected individuals with tuberous sclerosis complex. Nevertheless, ultrasonography effectively demonstrates renal angiomyolipomas, and is widely available and cheaper than other studies. Renal lesions occur in up to 80% of adults with tuberous sclerosis complex, and these lesions tend to increase in size over time, making it likely that an ultrasound study in an adult would remain abnormal throughout adulthood. For these reasons, renal ultrasonography is recommended if diagnostic studies are to be done on potentially affected family members.

Echocardiography
Likewise, there are no studies on the usefulness of echocardiography in parents or other family members at risk for tuberous sclerosis complex. Although more than half of individuals with tuberous sclerosis complex have cardiac rhabdomyomas, these cardiac tumors tend to shrink over time and commonly disappear altogether by adulthood. This could be one reason that echocardiography so seldom provides evidence of tuberous sclerosis complex in adult family members. The yield of echocardiography in this setting seems to be low and it is not recommended for these individuals.

Molecular Diagnosis
Molecular diagnosis will be used increasingly to rule out tuberous sclerosis complex in clinically normal family members. Although molecular testing for tuberous sclerosis complex is not yet commercially available, it is soon should be feasible to identify some individuals with tuberous sclerosis complex who do not fulfill the clinical diagnostic criteria.3 In the meantime, various radiographic studies can help to establish the diagnosis.
Occasionally couples have more than one child with tuberous sclerosis complex, despite the fact that neither parent has either physical or radiologic evidence of tuberous sclerosis complex. Tuberous sclerosis complex in these families probably results from germline mosaicism. At least a dozen likely examples of germline mosaicism for tuberous sclerosis complex have been described, and the underlying mutation has been characterized in seven families. Unfortunately, neither routine diagnostic studies nor DNA-based testing is likely to detect germline mosaicism in these individuals, because the parent who carries the mutation will not have a detectable mutation in DNA extracted from leukocytes. Thus, genetic counseling for families with one affected child should include a small (1% to 2%) possibility of recurrence, even for parents who have no evidence of tuberous sclerosis complex after a thorough diagnostic evaluation.

CONCLUSION

Diagnostic studies play an important role in the assessment of patients with tuberous sclerosis complex. In newly diagnosed patients, diagnostic testing helps both to confirm the diagnosis of tuberous sclerosis complex and to identify clinically significant complications. For patients with a well-established diagnosis of tuberous sclerosis complex, diagnostic studies sometimes can identify treatable complications in their early stages, when treatment can be more effective. Diagnostic tests sometimes provide evidence of tuberous sclerosis complex in asymptomatic relatives of children with tuberous sclerosis complex. However, affected relatives who have abnormal test results usually have at least subtle clinical findings of the disease, and the occurrence of germline mosaicism makes it impossible to exclude absolutely a risk of these individuals having additional children with tuberous sclerosis complex with the currently available diagnostic studies. These recommendations will need to be reassessed periodically as additional clinical information becomes known and as new developments in molecular diagnosis continue.

PANEL MEMBERS

E. Martina Bebin, Birmingham, AL
Melvin Burton, Boston, MA
Harry Chugani, Detroit, MI
Paolo Curatolo, Rome, Italy
Francis J. DiMario, Hartford, CT
Olivier Dulac, Paris, France
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