Renal Lesions in Patients With

Tuberous Sclerosis Complex

A Review for Health Care Professionals
Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder that can cause noncancerous tumors, or hamartomas, in multiple organs—particularly the brain, kidneys, lungs, eyes, skin, and heart—over a patient’s lifetime. Clinical manifestations vary widely, but seizures and dermatologic manifestations are the most common presenting features that lead to initial consultation.

The graphic below highlights the clinical manifestations of TSC and the age at which the various organ systems are most commonly affected.

Prevalence of TSC

TSC affects an estimated 1 million people worldwide. But because of symptom variability and underrecognition of less-severe phenotypes, many TSC cases remain undiagnosed.

TSC is more prevalent than several better-known genetic disorders

The Role of Genetics in TSC

TSC is caused by mutations in 1 of 2 genes, TSC1 (hamartin) or TSC2 (tuberin), leading to dysregulation of the mTOR (mammalian target of rapamycin) pathway. The mTOR pathway controls cell growth and proliferation, angiogenesis, glucose uptake, and metabolism.

TSC1 and TSC2 mutations lead primarily to the formation of nonmalignant tumors (eg, hamartomas) in multiple organ systems.
Diagnosis of TSC

Historically, health care providers diagnosed TSC patients using Vogt’s triad, which consists of epilepsy, mental retardation, and adenoma sebaceum. However, less than 30% of patients actually meet these criteria.

Genetic criteria are also an integral part of the diagnostic paradigm for TSC. Comprehensive and reliable screens for TSC1 and TSC2 mutations are well established, and many pathogenic mutations have been identified. Current TSC consensus guidelines have made identification of a pathogenic mutation in either TSC1 or TSC2 an independent diagnostic criterion sufficient for the diagnosis or prediction of TSC regardless of clinical findings. It is important to note, however, that between 10% and 15% of TSC patients have no mutation identified by conventional genetic testing; thus, a normal result does not exclude TSC.

The wide range of clinical presentations in TSC patients needs to be considered. There are under-recognized groups of patients, including asymptomatic adults who are diagnosed based on physical examination and/or radiographic findings. Below, 2 hypothetical patient journeys are presented: 1 with a diagnosis made early in life, and 1 made in adulthood.

Genetic Testing

Genetic testing is available to identify the genes associated with TSC (TSC1 and TSC2). Tests are based on gene mutations or gene deletions, and under optimal circumstances, genetic testing identifies mutations in up to 80% of affected individuals. Testing may be appropriate for confirming clinical diagnosis, predicting at-risk asymptomatic family members, and for prenatal diagnosis. Testing costs, which may not be covered by private insurance, range from about $250 to about $6000.

Diagnostic Clinical Criteria

The diagnostic clinical criteria include 11 major features and 6 minor features, as shown in the chart below.

Patient A – Presentation in infancy/childhood

- Cardiac rhabdomyoma found during routine prenatal ultrasound at 26 weeks’ gestation
- Infantile spasms at 6 months of age
- Diagnosis of autism at 4 years of age
- Multiple retinal hamartomas
- Cortical dysplasias

Patient B – Presentation in adulthood

- Development of “confetti” lesions on the arms at age 25
- Numerous angiomyolipomas identified on computed tomography (CT) scan, occurring in both kidneys at age 32
- Development of facial angiofibromas at 5 years of age
- LAM diagnosis at age 40
- Numerous cysts revealed by ultrasound, occurring in both kidneys at age 28

Major Features

- Hypomelanotic macules (≥3, at least 3-mm diameter)
- Subependymal nodules (SENs)
- Angiofibromas (≥3) or fibrous cephalic plaque
- Subependymal giant cell astrocytoma (SEGA)
- Ungual fibromas (≥2)
- Cardiac rhabdomyoma
- Shagreen patch
- Lymphangioleiomyomatosis (LAM)
- Multiple renal cysts
- Angiomyolipomas (≥2)
- Nonrenal hamartomas

Minor Features

- “Confetti” skin lesions
- Dental enamel pits (>3)
- Retinal achromic patch
- Intracranial fibromas (≥2)
- Multiple renal cysts
- Nonrenal hamartomas

Many TSC cases are not diagnosed until adulthood. In one retrospective study of female patients, 59% were found to have been diagnosed as adults.

Although not part of the diagnostic criteria for TSC, epilepsy may be the most prevalent and challenging clinical manifestation. Epilepsy occurs in more than 90% of TSC patients and is a major sign that warrants further investigation of a potential TSC diagnosis.
Renal Imaging for TSC

The initial evaluation of a patient suspected of having TSC includes renal imaging, usually by ultrasound, CT, or MRI. Follow-up is scheduled based on clinical suspicion and the results of previous imaging tests. Renal imaging should be performed every 1 to 3 years. More frequent imaging is appropriate after a lesion is first detected, so that it can be monitored for stability or changes indicating progression. Because of the possibility of progression or development of new lesions, renal specialists may continue to monitor a patient through adulthood even if the imaging results obtained during adolescence are normal.

Renal Manifestations of TSC

The 3 renal manifestations of TSC are renal angiomyolipomas, renal cysts, and renal cell carcinoma (table below).33

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Age of Onset and Incidence</th>
<th>Key Points</th>
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<tbody>
<tr>
<td>Renal Angiomyolipomas</td>
<td>Onset: &lt;2 years (16%); however, the majority (70%-90%) of renal angiomyolipomas are found in adults with TSC1</td>
<td>Tend to grow more quickly than those that do not result from TSC29</td>
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<td></td>
<td>Overall Incidence: Up to 80%24</td>
<td>Tend to occur in both kidneys in up to 80% of patients and are often numerous34,36</td>
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<td>Renal angiomyolipoma cells have been shown to infiltrate normal renal tissue28,37</td>
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<td>Can cause serious, potentially life-threatening comorbidities27</td>
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<tr>
<td>Renal Cysts</td>
<td>Onset: Usually early childhood2,38</td>
<td>Often numerous and occur in both kidneys33</td>
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<td></td>
<td>Overall Incidence: 18% to 53%33</td>
<td>Usually asymptomatic1</td>
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<td></td>
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<td>May cause hypertension1</td>
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<td></td>
<td>In rare cases, may present with severe early-onset renal cystic disease, progressing to end-stage renal failure by early adulthood1</td>
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<td>Renal Cell Carcinoma</td>
<td>Onset: 28 to 30 years3</td>
<td>Occurs at a younger age in TSC patients than in the general population1,25</td>
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<td>Overall Incidence: 2% to 3% and is considered to be rare30,42</td>
<td>Has a female preponderance2</td>
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<td></td>
<td></td>
<td>Usually occurs in both kidneys3</td>
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<td></td>
<td>Has heterogeneous pathology33,41</td>
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<td></td>
<td></td>
<td>May be difficult to distinguish radiologically from renal angiomyolipomas41</td>
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<th>Imaging Technique</th>
<th>Features At a Glance</th>
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<td>MRI16</td>
<td>More conclusive than CT in differentiating renal angiomyolipomas from renal cell carcinoma27</td>
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<td>Can detect fat-poor lesions28</td>
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<td>Effective in detecting both the macroscopic and microscopic fat components of renal angiomyolipomas28</td>
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<td>Adequate for diagnosis of renal angiomyolipoma when contrast enhancement is contraindicated or CT is inconclusive27,29</td>
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<td></td>
<td>Can provide better visualization of involved areas (compared with ultrasound) when numerous lesions are involved27</td>
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<td>Useful during pregnancy27</td>
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<tr>
<td>Ultrasound30</td>
<td>Can quickly monitor changes in renal angiomyolipomas and renal cysts14</td>
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<td>Preferred for use in children; does not expose patients to ionizing radiation21</td>
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<td>CT32</td>
<td>Can detect fat in a tumor, which is key to diagnosing renal angiomyolipoma27</td>
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<td>Imaging modality of choice when hemorrhage is suspected27</td>
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<td>Highly sensitive for identifying mass and hematomas27</td>
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<td>Can provide better visualization of involved areas (compared with ultrasound) when numerous lesions are involved27</td>
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<td>Helical CT with thin-cut sectioning has the greatest sensitivity, especially for tumors with lower fat content or with hemorrhage27</td>
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Angiomyolipomas are highly vascularized tumors composed of fat and smooth-muscle cells most commonly found in the kidneys. These tumors may vary in size from 1 mm to more than 20 cm in diameter. Renal angiomyolipomas occur in up to 80% of TSC patients, and increase in number and size with age.

Renal Angiomyolipomas in TSC Are More Likely to Have Serious Risks Than Those Not Associated With TSC

Renal angiomyolipomas not related to TSC may occur in patients without the clinical features or genetic mutations characteristic of TSC, and occur almost exclusively in middle-aged women.

TSC-associated renal angiomyolipomas tend to:
- Occur in both kidneys
- Occur at numerous sites in the same kidney
- Occur at a younger age
- Be larger at presentation

Comparison of TSC-Associated Renal Angiomyolipoma to Those Not TSC-Associated

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TSC-Associated</th>
<th>Sporadic</th>
<th>P Value</th>
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<tr>
<td>Mean age (yr)</td>
<td>26 ±3.2</td>
<td>49.4 ±2</td>
<td>&lt;0.001</td>
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<td>Mean lesion size (cm³)*</td>
<td>19.3 ±4.8</td>
<td>4.1 ±0.7</td>
<td>&lt;0.001</td>
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<td>Mean rate of growth/year (cm)</td>
<td>1.25</td>
<td>0.19</td>
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<tr>
<td>Multiple bilateral tumors (%)</td>
<td>100</td>
<td>13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic at follow-up (%)</td>
<td>42.9</td>
<td>8.7</td>
<td>&lt;0.01</td>
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*Lesion size correlates to volume and was measured using orthogonal diameter technique.

Data from a review of 60 patients diagnosed with renal angiomyolipomas. The differences of clinical spectrum between TSC-associated renal angiomyolipomas and sporadic renal angiomyolipomas were identified. Parameters including age, tumor size, multiplicity, symptoms, complications, association with TSC, and treatment modality were reviewed.

Complications of TSC-Associated Renal Angiomyolipomas

Renal complications are the most common cause of TSC-related death or disability and the second after neurologic complications. Renal angiomyolipomas do not spontaneously regress and are associated with serious, potentially life-threatening morbidities.

The Serious Risks of Renal Angiomyolipomas

- The estimated risk of hemorrhage from renal angiomyolipomas in patients with TSC is between 25% and 50%. The risk increases with tumor size and vascularity.
- Once the diameter of a renal angiomyolipoma reaches 4 cm, 68% to 80% of patients may develop symptoms.
- The risk of renal insufficiency may lead to chronic kidney disease and renal failure.
- There is a heightened risk of hypertension and renal failure if glomerular function is impaired.
- Approximately 1% of individuals with TSC develop end-stage renal disease.

The most common presenting symptoms of patients with TSC-associated renal angiomyolipomas are flank pain, palpable masses, and hematuria.

Other presentations include nausea or vomiting, fever, hypertension, anemia, renal failure, and hemorrhage.

Angiomyolipomas Can Migrate Beyond the Kidneys

In patients with TSC, renal angiomyolipoma cells have been shown to infiltrate normal renal tissue both adjacent to and distant from existing tumors. These angiomyolipoma cells may be exhibiting an atypical migratory phenotype. Renal insufficiency may occur as a result of compression and replacement of normal renal tissue with angiomyolipoma tissue.
Adopting a Multidisciplinary Approach to TSC

The unpredictable nature of TSC manifestations requires a multidisciplinary approach and regular lifelong follow-up as adopted by TSC centers of excellence nationwide. Renal specialists play a crucial role in the identification and surveillance of renal lesions and their complications. These specialists often receive referrals from other members of the multidisciplinary TSC care team to evaluate and monitor renal manifestations associated with the disease. Regular follow-up with adult TSC patients is needed to detect changes in renal structure and function as well as monitor for potentially life-threatening disease manifestations, as these may develop at any time and can cause serious complications.25,43

LAM can be associated with TSC-related renal angiomyolipomas.50 Up to 40% of adult women with TSC are affected by LAM.22 Renal specialists should refer their TSC patients to a pulmonologist, particularly their female patients who have a much higher risk.

Connecting Patients With Optimal Care5,9,51,52

Novartis Pharmaceuticals Corporation is committed to understanding and improving the lives of people with tuberous sclerosis complex through clinical research, education, and collaboration with the TSC community.
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References: