A 15-year-old girl presented with yellowish papules on the cheeks and nose. The papules, which first appeared at age 5 years, had become more prominent and profuse in the past 4 years. The patient had recurrent episodes of generalized tonic-clonic seizures from age 2 to 6 years but had been seizure-free since then. She had no headache, chest pain, shortness of breath, or hematuria. Her intelligence was normal. There was no family history of similar skin lesions or seizure disorder.

PHYSICAL EXAMINATION
Vital signs normal. Multiple small, skin-colored papules noted over the nose and both cheeks; 4 hypomelanotic macules and 7 café au lait spots present on the trunk. Remaining physical examination findings unremarkable.
The clinical diagnosis of tuberous sclerosis complex (TSC) in this patient is based on the presence of facial angiofibromas and hypomelanotic macules (Figure). The history of seizures is suggestive of the diagnosis. MRI scans performed when the patient was 3 years of age showed cortical tubers, which are pathognomonic of the disease.

**EPIDEMIOLOGY AND ETIOLOGY**

TSC is an inherited neurocutaneous multisystem disorder characterized by the development of hamartomas in almost every organ, notably in the skin, brain, kidneys, heart, and eyes. TSC affects both sexes and all ethnic groups. The prevalence is estimated to be 1 case per 6000 to 10,000 children.

TSC is caused by a mutation in TSC1 or TSC2; genes that encode for hamartin and tuberin, respectively. TSC has an autosomal dominant mode of inheritance with almost complete penetrance but variable expressivity. Approximately 70% of cases are caused by spontaneous mutations.

Both TSC1 and TSC2 have tumor suppressor activity, which when inactivated, leads to uncontrolled cell cycle progression and the proliferation of hamartomas throughout the body. Mutations in TSC2 are 4 to 5 times more common than those in TSC1 and generally result in a more severe phenotype.

**CLINICAL MANIFESTATIONS**

The Table provides a summary of the primary manifestations of TSC in various organ systems and the frequency of their occurrence.

**DIAGNOSIS**

Diagnosis of TSC requires the presence of 2 major features or 1 major feature plus 2 minor features. Additional diagnostic categories include probable TSC (1 major feature plus 1 minor feature) and possible TSC (1 major feature or 2 or more minor features). The presence of hamartomas in 2 different organ systems is considered by some clinicians to be sufficient for diagnosis.

The major features are:
- Facial angiofibromas or forehead plaque.
- Nontraumatic ungual or periungual fibroma.
- Hypomelanotic macules—more than 3.
- Shagreen patch (connective tissue nevus).
- Cortical tuber.
- Subependymal nodule.

---

Figure – The hypopigmented patches of tuberous sclerosis may occur anywhere on the body and are often present at birth, as shown in this infant.

---

www.Consultant360.com
What’s Your Diagnosis?
ANSWER: TUBEROUS SCLEROSIS COMPLEX

Table – Clinical features of tuberous sclerosis complex (TSC)

<table>
<thead>
<tr>
<th>System</th>
<th>% of patients</th>
<th>Clinical feature</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dermatologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>Hypomelanotic macules (ash leaf spots): these are often round at one end and tapered at the other, usually present at birth; almost all are evident within the first 2 years of life</td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>Facial angiofibromas: typically appear during preschool years in the malar area as small, pink to red, dome-shaped papules in a butterfly distribution; they gradually enlarge and become more numerous with age</td>
</tr>
<tr>
<td></td>
<td>20% to 30%</td>
<td>Shagreen or “leather” patches: these result from an accumulation of collagen and develop in the lumbosacral region; they are irregularly shaped, grayish-green or light brown, unevenly thickened plaques, with a cobblestone or orange-peel appearance and pigskin texture</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>Periungual and ungual fibromas (Koenen tumors): smooth, firm, nodular, or fleshly lesions; they are more common in adolescents and adults than in young children</td>
</tr>
<tr>
<td></td>
<td>30%</td>
<td>Café au lait spots</td>
</tr>
<tr>
<td><strong>Varies</strong></td>
<td></td>
<td>Other dermatologic abnormalities: Molluscum fibrosum pendulum (large, soft, pedunculated, flesh-colored papules and nodules that resemble skin tags), “confetti” lesions (stippled hypopigmentation), poliosis (hypopigmented hair or white forelock), and thumbprint hypopigmented macules</td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td>75% to 90%; 70% have seizure onset in first year of life</td>
<td>Seizures: infantile spasms, partial motor seizures, and generalized tonic clonic seizures are the most frequent types; atonic seizures (drop attacks) and myoclonic seizures also may occur</td>
</tr>
<tr>
<td></td>
<td>About 50%</td>
<td>Mental retardation: this is profound (IQ less than 21) in 30% of patients</td>
</tr>
<tr>
<td></td>
<td>17% to 63%</td>
<td>Autism spectrum disorder</td>
</tr>
<tr>
<td></td>
<td>30% to 60%</td>
<td>Attention-deficit/hyperactivity disorder</td>
</tr>
<tr>
<td><strong>Varies</strong></td>
<td></td>
<td>Other behavior disorders: Sleep disturbance, aggressiveness, memory deficits, and anxiety disorders</td>
</tr>
<tr>
<td><strong>Varies</strong></td>
<td></td>
<td>Intracranial tumors: cortical or cerebellar hamartomas (tubers), subcortical glioneuronal hamartomas, and subependymal giant cell astrocytomas</td>
</tr>
</tbody>
</table>

(Continued on next page.)
• Subependymal giant cell astrocytoma.
• Multiple retinal nodular hamartomas.
• Cardiac rhabdomyoma, single or multiple.
• Pulmonary lymphangioleiomyomatosis.
• Renal angiomyolipoma.

In patients with both lymphangioleiomyomatosis and renal angiomyolipomas, other features of TSC should be present before a definite diagnosis is assigned.20

The minor features are:
• Multiple randomly distributed pits in dental enamel.

<table>
<thead>
<tr>
<th>Table – Clinical features of tuberous sclerosis complex (TSC), continued</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System</strong></td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Cardiac and vascular</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Oral</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Ophthalmic</td>
</tr>
<tr>
<td>Pulmonary</td>
</tr>
<tr>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>GI</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
• Multiple renal cysts (histologic confirmation is suggested).

When a cortical tuber and cerebral white matter migration tracts occur together, they should be counted as 1 rather than 2 features of TSC.20

DIAGNOSTIC STUDIES

The following tests are recommended in the initial evaluation and in follow-up care of patients with TSC:

• Echocardiography to check for cardiac rhabdomyomas and other cardiac anomalies.
• ECG to identify arrhythmias.
• MRI or CT scans of the brain for confirmatory evidence of TSC, such as cortical tubers.
• Renal ultrasonography is performed at the time of diagnosis and repeated every 1 to 3 years, depending on the level of concern.7,19 Monitoring of renal function is important in those children with structural renal abnormalities. Small angiomylipomas usually do not cause symptoms; lesions larger than 4 cm are associated with an increased risk of serious hemorrhage, which may present as flank pain or hematuria.8 Renal tumors may also obstruct urine outflow or distort renal parenchyma.21
• Chest and skeletal radiographs can be ordered when indicated.
• Molecular genetic studies for TSC1 and TSC2 mutations are helpful in patients who do not meet the criteria for definite TSC and in clinically normal family members of an affected child to improve genetic counseling.

MANAGEMENT

Treatment is symptomatic and organ-specific and focuses on improving patient outcome and quality of life. Patients with TSC benefit from a multidisciplinary approach. Early intervention is important for the family—to help parents organize the most appropriate educational placement, when necessary, and plan specialist referral and follow-up.

Facial angiofibromas and forehead plaques, the potentially embarrassing cosmetic stigmata of TSC, can be treated with dermabrasion, laser surgery, or cryosurgery.9 Shagreen patches can be treated with laser surgery, shave excision, or dermabrasion.

Of the available antiepileptic medications, vigabatrin is often used as first-line therapy and has been shown to be especially effective for infantile spasms and partial seizures.10 Consider neurosurgical intervention for patients with intractable seizures, hydrocephalus, increased intracranial pressure, and interval or rapid enlargement of a subependymal giant cell astrocytoma or neurological deficits attributable to the tumor.1

REFERENCES: