

## Review article

# Tuberous sclerosis complex: Bourneville's disease

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**Abstract** Tuberous sclerosis complex is an autosomal dominant neurocutaneous syndrome due to mutations in two genes, tuberin and hamartin, involved in tissue growth. It is characterized by hamartomas in multiple organs including skin. Cutaneous lesions e.g. angiofibromas, ash-leaf macules, shagreen patches, unguis fibromas are quite characteristic and may herald other systemic features. The present article reviews the clinical profile, laboratory work-up, diagnosis and management of this multisystem disease.

**Key words**

Tuberous sclerosis, Bourneville's disease

### Introduction

Tuberous sclerosis complex (TSC), also known as Bourneville's Disease and epiloia, is a dominantly inherited, multisystemic, genetic disorder characterised by the development of hamartomatous lesions in multiple organ systems including skin (hypomelanotic macules, facial angiofibromas, shagreen patches, fibrous facial plaques, unguis fibromas), heart (rhabdomyomas, arrhythmias), eyes, brain (cortical tubers, subependymal nodules, seizures, mental retardation/developmental delay) and kidneys (angiomyolipomas, cysts).

The term "tuberous sclerosis" was first used in 1882 by Bourneville to describe a syndrome consisting of seizures, mental retardation and facial rash in a young girl. It is interesting to note here that this complex disorder had already been identified in 1862 by von Recklinghausen.<sup>1</sup>

The disorder, being second most common neurocutaneous syndrome after neurofibromatosis, affects about one in 10,000 persons in the general population and has an estimated incidence of one case per 6,000 live births.<sup>2</sup> No predilection for sex or race has been noted.

### Molecular pathogenesis and genetics

TSC is inherited as an autosomal dominant genetic condition and the affected individuals have a 50% chance of passing their condition on to each of their children. It would be pertinent to note here that two-thirds of affected individuals have TSC as the result of a de novo gene mutation.<sup>3</sup> It has been determined to result from mutations in two genes, hamartin (TSC1) and tuberin (TSC2).<sup>4,5</sup> The TSC1 gene is located on chromosome 9q34 and the TSC2 gene on chromosome 16p13. The precise location of the TSC2 gene was found in 1993 and it is now known to be responsible for the production of the protein tuberin which suppresses the growth of tumors. Mutations in this gene prevent the

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production of tuberin and allow certain tissues to grow unchecked.

### Clinical Description

Clinical features of TSC are most commonly seen in the skin, central nervous system, kidneys, heart, and the lungs.

#### Skin

The skin is affected in virtually 100% of patients. Skin lesions include: hypomelanotic macules (87-100% of patients), facial angiofibromas (47-90%), shagreen patches (20-80%), fibrous facial plaques, and unguis fibromata (17-87%).<sup>6</sup>

The facial angiofibromas are pink or skin-colored telangiectatic papules commonly observed in the nasolabial folds and on the cheeks and chin. They usually appear in children younger than 10 years and increase in size and number until adolescence, remaining unchanged thereafter. Other areas in which they may be observed include in and around nails (unguis fibromas), scalp, and forehead, in the latter location reaching sizes up to several centimeters. Dental pitting occurs in about 90% of patients. A hand lens examination aids detection of these pits, which are less obvious in deciduous teeth.

Hypomelanotic macules are ovoid, hypopigmented, ash leaf-shaped macules usually found on the trunk or limbs. These may be found at birth or early infancy. The use of Wood's lamp accentuates these macules. The possibility of TSC should be considered if 3 or more hypomelanotic macules are present at birth.

Shagreen patches are flesh-colored soft plaques with pebbly surface that are frequently found in

the lumbosacral area but may occur anywhere on the trunk.



**Figure 1** Ash leaf-shaped hypomelanotic macules in TSC



**Figure 2** Multiple angiofibromas over face

Periungual fibromas are smooth, firm, flesh-colored papules emerging from the nail folds.

#### CNS

CNS tumors are the leading cause of morbidity and mortality in TSC. The tuberosclerotic nodules of glial proliferation occur in the

cerebral cortex, basal ganglia, and ventricular walls but are rare in the cerebellum, medulla, or spinal cord. Subependymal glial nodules occur in 90% of individuals and cortical or subcortical tubers in 70%.<sup>7,8</sup> The cortical tuber count detected on MRI may be a marker to predict the severity of cerebral dysfunction.<sup>9</sup> Subependymal giant cell astrocytomas occur in 6-14% of all patients with TSC. These giant cell astrocytomas may enlarge, causing pressure and obstruction and resulting in significant morbidity and mortality.<sup>10</sup>

More than 80% of individuals with TSC have been reported to have seizures. At least 50% of patients suffer from developmental delay or mental retardation. The leading cause of premature death (32.5%) among patients with TSC is a complication of severe mental retardation, e.g., status epilepticus and bronchopneumonia.<sup>11</sup> Individuals with TSC have a great risk of neurodevelopmental and behavioral impairment.<sup>12,13</sup> The behavioral and psychiatric disorders that are common in TSC include pervasive developmental disorders and autism, hyperactivity or attention deficit hyperactivity disorder, and aggression.<sup>14</sup>

### **Heart**

Cardiac rhabdomyomas are observed in over 50% of infants.<sup>15</sup> They may be detected prenatally by fetal echocardiography. Up to 50-60% of patients with TSC have cardiac disease, mainly rhabdomyomas. These may cause mechanical problems because of their size or defects in conducting system caused by their infiltrating nature. Rhabdomyomas usually undergo spontaneous resolution in the first few years of life even though residual areas of histologically abnormal myocardium may persist.<sup>16</sup>

### **Kidneys**

Renal disease is the second leading cause of early death (27.5%) in patients with TSC.<sup>11</sup> Renal involvement is usually manifested by an angiomyolipoma, less commonly by renal cysts. Five different renal lesions occur in TSC: benign angiomyolipoma (70% of affected individuals), epithelial cysts (20%), oncocytoma (benign adenomatous hamartoma) (<1%), malignant angiomyolipoma (<1%), and renal cell carcinoma (<1%). Malignant angiomyolipoma and renal cell carcinoma may result in death. Although rare, these two tumors are much more common in TSC than in the general population.<sup>17</sup>

### **Lungs**

Pulmonary changes are estimated to occur in 1-6% of cases and primarily affect women between the ages of 20 and 40 years. These include lymphangiomatosis with cyst formation. This may be progressive and result in dyspnea, cor pulmonale, recurrent pneumothorax, and respiratory failure.

### **Eyes**

The retinal lesions of TSC are hamartomas characterized by proliferation of astrocytes and hypopigmented spots in the iris (equivalent to the ash-leaf macule in the skin). One or more of these lesions may be present in up to 75% of patients. These lesions are usually asymptomatic.

### **Diagnostic criteria**

The diagnostic criteria for TSC were revised at the Tuberous Sclerosis Complex Consensus Conference, July 1998.<sup>7</sup> The new criteria have eliminated non-specific features (e.g., infantile spasms and myoclonic, tonic, or atonic seizures) and have made certain features more specific

(e.g., non-traumatic ungual or periungual fibroma; three or more hypomelanotic macules). A diagnosis is considered *definite* when a patient has either two "major features" of TSC or one "major feature" and two "minor features". The clinician should consider TSC *probable* when the patient has one "major feature" and one "minor feature," while a *possible* diagnosis results from the presence of either one "major feature" or two or more "minor features."

### **Major features**

- Facial angiofibromas or forehead plaque
- Non-traumatic ungual or periungual fibromas
- Hypomelanotic macules (three or more)
- Shagreen patch (connective tissue nevus)
- Multiple retinal nodular hamartomas
- Cortical tuber
- Subependymal nodule
- Subependymal giant cell astrocytoma
- 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 radial migration lines
- Gingival fibromas
- Nonrenal hamartoma
- Retinal achromic patch
- "Confetti" skin lesions
- Multiple renal cysts<sup>7</sup>

## **Differential Diagnosis of TSC**

### **Skin**

*Hypomelanotic macules:* vitiligo, nevus depigmentosus, nevus anemicus, piebaldism, and Vogt-Koyanagi-Harada syndrome.

*Angiofibromas:* acne vulgaris, acne rosacea, multiple trichoepithelioma.

*Shagreen patches:* other connective tissue nevi

*Ungual fibromas:* traumatic ungual fibromas, epithelial inclusion cysts, verruca vulgaris, and infantile digital fibromatosis.

### **CNS**

Multiple lesions (cortical tubers, subependymal nodules, subependymal giant cell astrocytomas or radial migrating lines) in the CNS are definitive and distinctive features of TSC.

### **Kidneys**

Renal cysts are seen commonly in the population (1-2%), but uncommonly in persons under 30 years of age. Renal angiomyolipomas are rare tumors.

### **Lungs**

Patients affected with lymphangiomyomatosis and angiomyolipomas who have no other features of TSC do not meet diagnostic criteria for TSC.

### **Heart**

Infants with cardiac rhabdomyomas have a 50% chance of being affected with TSC. The other 50% have cardiac rhabdomyomas as an isolated finding.

## **Management of TSC**

A multidisciplinary approach is necessary to address the many organ systems that may be

affected because pathologic manifestations of TSC can cause variable symptoms based on the size and the location of the hamartomas. It is recommended that individuals suspected of having TSC have the following initial evaluation to establish the diagnosis and to identify potential complications for timely treatment.<sup>7</sup>

- Medical history, especially for features of TSC.
- Family history especially for features of TSC.
- Physical examination with use of a Wood's lamp (ultraviolet light) in a darkened room and special attention to dermatologic findings.
- Cranial CT/MRI Renal ultrasonography.
- Ophthalmologic examination.
- Electrocardiography and echocardiography, if cardiac symptoms indicate.
- Electroencephalography, if seizures are present.
- Neurodevelopmental and behavioral evaluation.
- Chest CT for adult females.

Early identification of an enlarging giant cell astrocytoma permits removal before symptoms develop and before it becomes locally invasive, and is the reason for performing routine brain imaging of children and adolescents with documented subependymal nodules.<sup>18</sup>

The seizure disorder in TSC may be intractable to anticonvulsants; selected patients have benefited from epilepsy surgery.<sup>18,19</sup> Renal angiomyolipomas greater than 3.5 to 4.0 cm in diameter have the greatest risk of hemorrhage. Such patients should be considered for prophylactic renal arterial embolization or renal sparring surgery.<sup>20</sup>

Facial angiofibromas may require repeated dermal abrasion or other cosmetic procedures including laser treatment.<sup>18</sup> The argon and pulsed-dye lasers are more effective on vascular lesions, while the carbon dioxide laser is effective in lesions with increased fibrous content.

### Genetic counselling

Genetic counselling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. Given the unpredictability of symptoms and the complicated genetic nature of TSC, all affected individuals and their immediate family should be referred for genetic counselling with a medical geneticist or genetic counsellor. Genetic testing will play a major role in clarifying diagnosis, accurately diagnosing family members of affected individuals and allowing families to make use of reproductive testing options, when desired. Unfortunately, no specific prenatal laboratory test is available.

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