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# Tuberous sclerosis: Case report and literature review

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**Abstract**
Tuberous sclerosis complex (TSC) is a rare, multisystem genetic disorder caused by pathogenic variants in the *TSC1* or *TSC2* genes, leading to mTOR pathway dysregulation and the development of benign tumors in multiple organs. Clinical presentation is highly heterogeneous, often involving the central nervous system, skin, heart, kidneys, eyes, and oral cavity. Early diagnosis and individualized, multidisciplinary management are essential to minimize morbidity and improve prognosis.
This case report describes a male infant with prenatal diagnosis of a cardiac rhabdomyoma detected on routine fetal ultrasound. Postnatal evaluation revealed multiple hypomelanotic macules, facial angiofibromas, a Shagreen patch, and dental anomalies. Neuroimaging identified multiple cortical tubers and subependymal nodules, with calcifications typical of TSC. Seizures began within the first year of life, manifesting as infantile spasms, and were later controlled. Ophthalmologic assessment confirmed retinal hamartomas. Despite early prenatal diagnosis, multidisciplinary follow-up was only initiated after the patient's migration to Portugal, highlighting disparities in access to healthcare.
TSC-related neuropsychiatric disorders, including epilepsy, intellectual disability, autism spectrum disorder, and behavioral dysregulation, are major contributors to disease burden. In this case, developmental delay was noted, reinforcing the need for early developmental monitoring and intervention. Cutaneous, neurologic, cardiac, renal, and dental features supported the clinical diagnosis based on the 2012 consensus criteria.
Genotype-phenotype correlations indicate that *TSC2* mutations are associated with more severe clinical phenotypes, including early-onset epilepsy and cognitive impairment. Multisystemic imaging and clinical surveillance remain essential for ongoing care.
This case underscores the importance of early detection, thorough clinical evaluation, and coordinated multidisciplinary follow-up in improving outcomes for children with TSC. Delayed access to specialized care can impact long-term prognosis, emphasizing the need for equitable healthcare access, particularly in migratory populations.

**Keywords:** Tuberous sclerosis complex (TSC), Neurocutaneous syndromes, Infantile spasms, Cardiac rhabdomyoma, Cortical tubers, Multisystem involvement

## Introduction
Tuberous Sclerosis (TS), also known as epiloia, was first described by Von Recklinghausen in 1862. Its incidence is estimated at 1 in 6,000 to 10,000 live births, with a prevalence of approximately 1 in 20,000 individuals. In Portugal, it is estimated to affect around 500 people, with no differences in distribution by sex or race. TS is a multisystemic disorder of genetic origin, exhibiting highly variable clinical expressivity [1–3].
Genetically, it is an autosomal dominant disorder, with approximately two-thirds of cases resulting from de novo variants. The molecular diagnosis is associated with mutations in the TSC1 and TSC2 genes, which encode the proteins hamartin and tuberin, respectively. These proteins function as tumor suppressors by regulating cell proliferation and differentiation. However, in about 5% of patients, no genetic cause has been identified to date. Regarding genotype-phenotype correlations, pathogenic variants in the TSC2 gene are associated with a more severe clinical presentation. Moreover, the majority of these individuals carry de novo variants, i.e., without a family history of the condition [4, 5].
TS is characterized by multisystemic involvement, which may include the skin, heart, kidneys, eyes, lungs, liver, and brain. Neurodevelopmental comorbidities such as autism spectrum disorder, epilepsy, and intellectual disability are also commonly associated. Nonetheless, there is a wide phenotypic variability both between and within families,

including intra-familial differences in the number and severity of clinical manifestations. The classic Vogt triad—comprising seizures, intellectual disability, and facial angiofibromas—is present in fewer than one-third of patients, making cutaneous findings essential for raising suspicion of TS [5–7]. We present the clinical case of a 5-year-old boy diagnosed with TS.

**Case Report**

A 5-year-old boy of Brazilian nationality, residing in Portugal since the age of five, was referred to the Pediatric Department due to a suspected diagnosis of TSC. The suspicion arose in the prenatal period following the identification of cardiac rhabdomyomas and neurocutaneous findings suggestive of the disease. Regarding prenatal and neonatal history, the pregnancy was monitored, and three cardiac rhabdomyomas were identified during second-trimester prenatal ultrasounds, with no other notable complications. He was delivered by cesarean section at 38 weeks of gestation in Rio de Janeiro, with good postnatal adaptation. At 3 months of age, he began experiencing seizure episodes that persisted until the age of 24 months, despite treatment with antiepileptic medications (vigabatrin and sodium valproate). In terms of neurodevelopment, a global developmental delay was noted, with more significant impairment in language, as well as behavioral abnormalities consistent with autism spectrum disorder. There was no relevant family history. On physical examination, the patient presented with hypomelanotic macules on the right thigh and 4–5 on the left lower limb, all measuring more than 5 mm in diameter (Figure 1-A). A slightly pigmented plaque in the lumbar region, compatible with a Shagreen patch, was also observed (Figure 1-B), along with facial angiofibromas (Figure 1-C). Dental anomalies were noted, including agenesis of the lower incisor (Figure 1-D). Basic laboratory investigations—including liver and kidney function tests, and complete blood count—were unremarkable. Brain Magnetic Resonance Imaging with contrast (MRI) revealed “encephalic features consistent with tuberous sclerosis, particularly multiple cortical tubers distributed bilaterally across the cerebral hemispheres, with evidence of mineralization/calcification in the right fronto-opercular region. Multiple subependymal nodules were also observed, showing calcification; the largest measured approximately 8 mm in diameter and was located at the transition between the body and the left trigone” (Figure 2). An abdominal and pelvic MRI with paramagnetic contrast showed no abnormalities. Fundoscopy revealed a hamartoma at the optic disc (nasal margin) and two additional hamartomas adjacent to the inferior temporal arteriole.

Transthoracic echocardiography demonstrated the presence of a rhabdomyoma located at the apex of the right ventricle, measuring 16 × 12 mm, as illustrated in Figure 3. No other intracardiac rhabdomyomas were identified.

The patient is currently under multidisciplinary follow-up, involving Pediatric Neurology, Dermatology, Ophthalmology, Pediatric Nephrology, Developmental Pediatrics, Medical Genetics, Pediatric Cardiology, General Pediatrics, and Stomatology. Vigabatrin has been discontinued, and sodium valproate is in the process of being tapered.

A formal developmental assessment was conducted using the Griffiths II Mental Development Scales, revealing a chronological age of 89 months and a developmental age of 45 months, corresponding to a general developmental quotient (DQ) of 50 (below the 1st percentile, >1 standard deviation), indicating global developmental delay. The developmental quotients across various subscales also fell within the range consistent with developmental delay. Genetic testing identified the following variant:* *TSC2* (NM_000548.5): c.328C>T (p. (Gln110))**, in heterozygosity, classified as pathogenic.

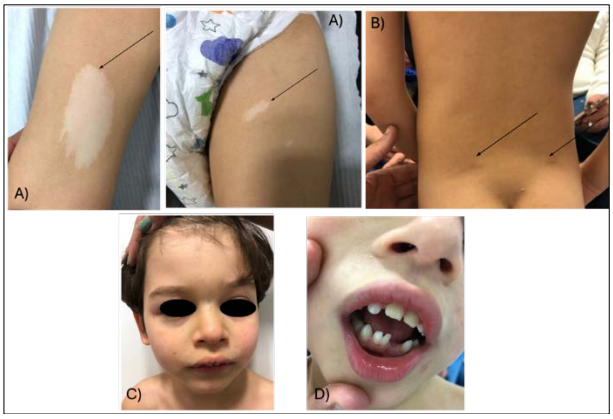


**Fig 1:** A) Hypomelanotic macules on the right thigh and left lower limb. B) Slightly pigmented plaque in the lumbar region, consistent with a Shagreen patch. C) Facial angiofibromas with a "butterfly-shaped" distribution, sparing the upper lip. D) Agenesis of the lower incisor.

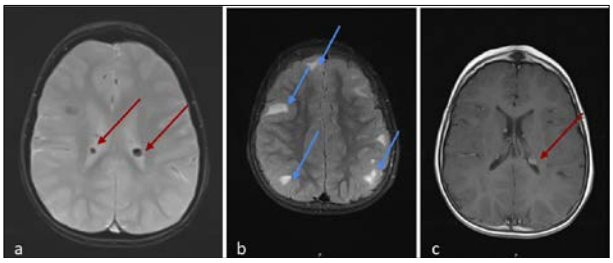


**Fig 2:** Cerebral MRI in T2-weighted sequences (a and b) showing multiple cortical tubers (blue arrow) scattered throughout the cerebral hemispheres and multiple subependymal nodules (red arrow) with evidence of calcification; and T1-weighted imaging (c).

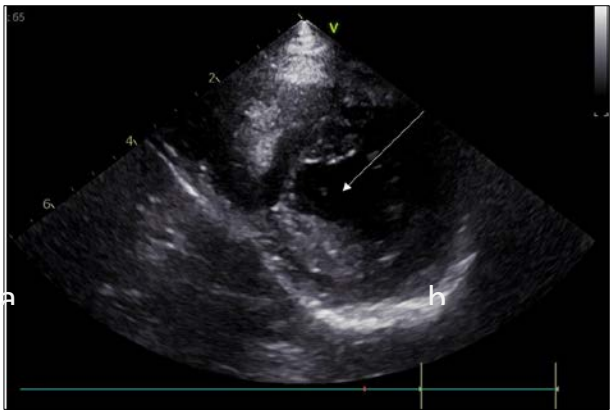

**Fig 3:** Transthoracic echocardiogram showing a mass at the apex of the right ventricle, measuring up to 16 x 12 mm, consistent with a cardiac rhabdomyoma.

**Table 1:** Diagnostic criteria as defined in the 2012 Tuberous Sclerosis Complex Diagnostic Criteria Update [4].

| Major Features | Minor Features |
|---|---|
| Hypomelanotic macules (≥3, at least 5 mm in diameter, including poliosis);<br>Facial angiofibromas (≥3) or fibrous cephalic plaque;<br>Ungual fibromas (≥2);<br>Shagreen patch;<br>Multiple retinal hamartomas;<br>Cortical dysplasia;<br>Subependymal nodules;<br>Subependymal giant cell astrocytoma;<br>Cardiac rhabdomyoma;<br>Lymphangioleiomyomatosis;<br>Angiomyolipomas (≥2) | Confetti skin lesions (hypomelanotic macules);<br>Dental enamel pits (≥3);<br>Intraoral fibromas (≥2);<br>Retinal achromic patch;<br>Multiple renal cysts;<br>Nonrenal hamartomas |

## Discussion

TSC is a progressive, multisystem disorder with variable phenotypic expression. Individual disease manifestations follow distinct natural histories, and the clinical presentation can differ markedly both between patients and within affected families. As such, it is not possible to accurately predict the comorbidities in a child at the time of initial diagnosis. Nonetheless, given the disease's complete penetrance, multidisciplinary surveillance is strongly recommended [1–3].

TSC results from pathogenic mutations in either the TSC1 tumor suppressor gene or, more commonly, the TSC2 gene. These mutations disrupt the inhibition of the mammalian target of rapamycin (mTOR) signaling pathway, leading to abnormal cellular proliferation and the formation of hamartomas in multiple organs. Affected organs include the brain (cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas), kidneys (renal angiomyolipomas), lungs (lymphangioleiomyomatosis), heart (cardiac rhabdomyomas), and skin (angiofibromas, Shagreen patches, and hypomelanotic macules).

The diagnostic criteria for TSC, as defined by the 2012 Tuberous Sclerosis Complex Diagnostic Criteria Update (Table 1), are as follows: 1. The presence of a pathogenic mutation in either TSC1 or TSC2 confirms the diagnosis of TSC. 2. A clinical diagnosis of TSC can be established by the presence of two major features or one major feature plus two or more minor features. 3. A possible diagnosis of TSC should be considered when one major feature or two or more minor features are present [4, 6, 10, 13].

On childhood, common presenting features of TSC include epileptic seizures, hypopigmented macules, and cardiac rhabdomyoma, as demonstrated in the present clinical case. The primary neurological manifestations of TSC comprise epilepsy, autism spectrum disorder, and a range of behavioral and psychiatric disturbances. Epileptic seizures occur in approximately 80–90% of individuals with TSC and typically begin within the first year of life, as occurred in this case. The most frequent initial seizure type is infantile spasms, reported in 36–69% of cases. Other common seizure types include focal seizures, generalized tonic-clonic seizures, subclinical seizures, and, less frequently, other forms of generalized seizures.

Importantly, patients with TSC remain at increased risk for new-onset seizures in adulthood. Epilepsy is one of the most prevalent and significant sources of morbidity in TSC, affecting 79–90% of individuals.

The main risk factors for epilepsy development include the presence of cortical glioneuronal hamartomas and pathogenic variants in the TSC2 gene. However, it should be noted that not all cortical hamartomas are epileptogenic, and some patients with both TSC and epilepsy may have a normal brain MRI, leaving aspects of the role of glioneuronal hamartomas in epileptogenesis yet to be fully elucidated [7, 8].

As in the present case, although seizure control was achieved, typical neuroimaging findings, including subependymal nodules and cortical tubers, persist. Therefore, ongoing follow-up in pediatric neurology is essential.

Neuropsychiatric disorders associated with TSC include intellectual disability, autism spectrum disorder, attention-deficit/hyperactivity disorder, and various behavioral disturbances such as hyperactivity, impulsivity, sleep disturbances, anxiety, aggression, mood disorders, poor eye contact, repetitive or ritualistic behaviors, and language delay. Additionally, patients may present with neurophysiological deficits as well as academic and occupational difficulties. These clinical features are frequently associated with brain lesions, particularly cortical glioneuronal hamartomas, periventricular subependymal giant cell astrocytomas, and white matter abnormalities.

Intellectual disability is reported in approximately 44–65% of patients with TSC and has been associated with a history of infantile spasms, refractory seizures, and, to a lesser extent, the burden of cortical hamartomas [4, 10].

Cutaneous manifestations of TSC include hypomelanotic macules (90%), facial angiofibromas (75%), and Shagreen patches (20–30%). Hypomelanotic macules are typically present at birth, with most cutaneous lesions becoming evident within the first two years of life. Facial angiofibromas typically appear during the preschool years, most often affecting the malar region as a cluster of small pink or red papules on the cheeks and nose, in a "butterfly-shaped" distribution, characteristically sparing the upper lip—as observed in this case (Figure 3).

Among prenatal screening findings, cardiac rhabdomyoma is the second most common presenting feature, accounting for approximately 14% of cases [4, 9].

TSC presents with four major neuroimaging features: cortical tubers, white matter lesions, subependymal nodules, and subependymal giant cell astrocytomas. Cortical tubers are glial hamartomas of the brain that may involve both the gray and white matter, and their development has been associated with overexpression of microRNA-34a in cortical cells. These lesions are most commonly distributed in the frontal and parietal lobes, although they can affect the entire brain.

Based on magnetic resonance imaging (MRI) findings, cortical tubers have been classified into three types:

1. Type A tubers show isointense signal on T1-weighted imaging, hyperintense signal on T2/FLAIR, and no

restricted diffusion on apparent diffusion coefficient (ADC) maps.
2. Type B tubers exhibit hypointense signal on T1, hyperintense signal on T2/FLAIR, and similarly no diffusion restriction on ADC imaging.
3. Type C tubers are characterized by T1 hypointensity, T2/FLAIR hyperintensity with central hypointense nuclei and homogeneous halos, and increased diffusion on ADC sequences.

In addition to the common imaging findings, approximately 1% to 5% of patients with TSC present with rare neuroradiological features, including parenchymal calcifications, hemimegalencephaly, mild lateral ventricle dilatation secondary to atrophy or dysplasia, Chiari malformation, microcephaly, macrocephaly, arachnoid cysts, neurofibromas, and chordomas [4, 15, 16].

With regard to ophthalmological manifestations, these include both retinal and non-retinal abnormalities, though they rarely impair vision and generally do not require specific treatment. As in our clinical case, retinal hamartomas are frequently observed, affecting approximately 44% of patients with TSC [5, 11].

TSC is also associated with intraoral fibromas, gingival hyperplasia, dental enamel pits, and mandibular bone cysts. In the present case, the patient exhibited hypoplasia of a lower incisor, which, although not commonly described in the literature, may fall within the spectrum of reported dental anomalies [12].

The cardiac hallmark of TSC is the rhabdomyoma, a benign tumor that typically appears in a multifocal pattern. Although the majority of children with cardiac rhabdomyomas have TSC, the presence of such tumors is not pathognomonic for the condition. Characteristically, cardiac rhabdomyomas develop in utero and are often detected during prenatal ultrasound screening, as occurred in the present case. Cardiovascular morbidity and mortality may result from hemodynamic compromise due to tumor size or location. To date, our patient remains asymptomatic, requiring no specific treatment, but is under regular surveillance.

Other less frequent cardiac manifestations include aortic coarctation, stenosis of major arteries (e.g., renal artery stenosis), and aortic aneurysms [4, 10].

Renal involvement is common in TSC, with its prevalence increasing with age. The most frequent renal lesions are angiomyolipomas, followed less commonly by benign renal cysts, lymphangiomas, and renal cell carcinomas. Patients with TSC and renal lesions may develop renin-dependent hypertension and are at increased risk of chronic kidney disease [4, 5].

Genotype–phenotype correlations have been identified in the literature. Pathogenic variants in the TSC2 gene are associated with a more severe clinical phenotype than TSC1 mutations. A higher proportion of individuals with severe TSC features harbor de novo TSC2 mutations compared to de novo TSC1 mutations. Sporadic cases (i.e., single affected individuals in a family) are more likely to have TSC2 mutations, whereas familial cases tend to show an approximately equal distribution of TSC1 and TSC2 variants.

Individuals with TSC2 pathogenic variants have an increased risk of:

- Renal involvement
- Significant developmental delay by 24 months
- Severe intellectual disability
- Autism spectrum disorder
- Cardiac rhabdomyomas
- Facial angiofibromas [13, 14]

TSC is a progressive disorder with highly individualized clinical features, and its prognosis is closely tied to the extent of systemic involvement. Involvement of major organ systems is associated with greater morbidity, particularly during adolescence and early adulthood, and contributes to increased mortality.

Early diagnosis is crucial to enable tailored multidisciplinary surveillance, which allows for optimized treatment, timely identification of comorbidities, and ultimately, improved prognostic outcomes for patients diagnosed with TSC. In the present case, although the diagnosis was made in utero, multidisciplinary follow-up could only be initiated after the family emigrated to Portugal.

## Conclusion

In this case, despite an already established diagnosis, multidisciplinary care was only initiated following an emergency visit due to a viral illness, highlighting the challenges that immigrant populations face in accessing healthcare, as well as the broader systemic issues related to continuity of care.

Beyond a detailed clinical history and the identification of cutaneous markers during physical examination, neuroimaging assessment remains essential for both diagnosis and ongoing monitoring of individuals with TSC. Although there is currently no cure for this condition, comprehensive multidisciplinary follow-up with regular multisystemic surveillance enables early intervention when needed, helping to prevent or mitigate complications.

Importantly, early diagnosis and timely intervention during childhood can have a significant positive impact on the long-term quality of life of individuals affected by TSC.

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