

## CASE REPORT

# Tuberous Sclerosis Complex – a Multidisciplinary Conundrum: Case Reports

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## Abstract

**Introduction:** Tuberous sclerosis complex (TSC) is a genetic disorder with a heterogenous clinical phenotype, with possible involvement of virtually any organ. Although recent advancement in genetics has allowed a better understanding of the pathophysiology of TSC, enabling a genetic diagnosis, TSC is primarily diagnosed on clinical grounds. Neurological manifestations amount to over 90% of people with TSC. Ensuing surveillance and treatment of TSC imply a multidisciplinary team of specialists. **Case reports:** We report 2 cases of TSC, both admitted to our Neurology Department on account of poor seizure control. One was diagnosed early in his infancy having a typical onset with infantile spasms and subsequent generalised seizures whereas the other was diagnosed with TSC in our department, at 56 years of age. They both also have skin and renal involvement as major clinical features. **Conclusion:** Recognition of the clinical hallmarks of TSC, albeit variable, is important for early diagnosis and subsequent multidisciplinary management. Neurological involvement, as illustrated in our case reports, is frequent and is largely responsible for morbidity and mortality in TSC.

**Keywords:** genetic, hamartoma, tuberous sclerosis complex.

## Rezumat

**Introducere:** Scleroza tuberoasă (ST) este o afecțiune genetică cu fenotip clinic heterogen, cu posibilă implicare multiorganică. Deși dezvoltarea recentă în domeniul geneticii a condus la înțelegerea mai bună a mecanismelor fiziopatologice a ST și a permis diagnosticul genetic al acesteia, ST este diagnosticată mai ales pe baza criteriilor clinice. Manifestările neurologice apar la peste 90% dintre persoanele cu ST. Monitorizarea și tratamentul ST presupun o echipă multidisciplinară de specialiști. **Prezentări de caz:** Prezentăm două cazuri de ST, ambele admise în Secția noastră de Neurologie din cauza controlului suboptimal al crizelor epileptice. Primul a fost diagnosticat precoce, în copilărie, având un debut tipic cu spasme infantile urmate de crize generalizate, iar cel de-al doilea caz a fost diagnosticat cu ST în secția noastră, la vârsta de 56 de ani. Ambii pacienți asociază afectare cutanată și renală între criteriile majore de diagnostic. **Concluzie:** Recunoașterea semnelor clinice de ST, în pofida variabilității fenotipice, este importantă pentru diagnosticul precoce și managementul multidisciplinar aferent. Afectarea neurologică, după cum ilustrăm în cazurile prezentate, este frecventă și este responsabilă în mare parte de morbiditate și mortalitate în ST.

**Cuvinte-cheie:** genetic, hamartom, scleroză tuberoasă.

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## INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder with a wide spectrum of clinical manifestations, primarily affecting the skin, brain, eyes, heart, kidneys, liver and lungs. The incidence of TSC is roughly between 1 in 6000 and 1 in 10000 births<sup>1,2</sup>.

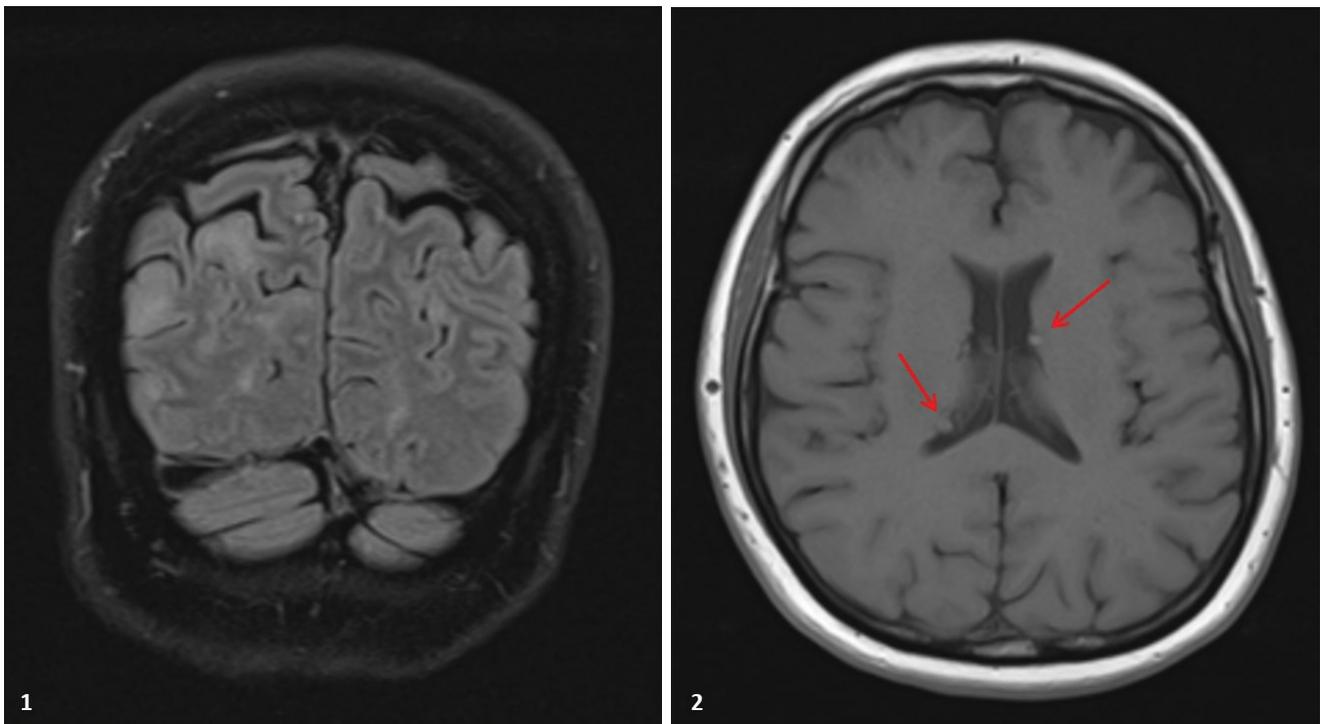
TSC is caused by mutations in the TSC1 or the TSC2 gene, which encode hamartin and tuberin, respectively. These proteins form a complex functioning as a tumour suppressor of the mammalian target of rapamycin (mTOR) pathway<sup>3,4</sup> which is involved in cellular homeostasis, proliferation, and within the nervous system, in neuronal differentiation, synaptogenesis and apoptosis<sup>3,5</sup>. Therefore, mutations in these genes cause hyperactivation of the mTOR signalling pathway and subsequent tumour formation.

In this report we present 2 cases of TSC highlighting the importance of clinical diagnosis and that of monitoring and treating people with TSC within a functional multidisciplinary team. Moreover, we discuss the major causes of morbidity in TSC.

## CASE REPORT 1

A 56-year old woman was admitted to our Neurology Department with clinical suspicion of TSC. She had epilepsy with generalised tonic seizures beginning at 20 years of age and poor clinical control (about 3 seizures monthly over the past 9 months), undergoing treatment with levetiracetam 2500 mg daily and lamotrigine 400 mg daily. Additionally, she had neuropsychiatric disorder with anxiety and depression treated with selective serotonin reuptake inhibitor and mirtazapine. She had performed brain magnetic resonance imaging (MRI) revealing cortical glioneuronal hamartomas and subependymal nodules (SEN) (Figure 1). She was monitored nephrologically for bilateral renal cysts and also had hepatic lesions suggestive of biliary hamartomas on abdominal computed tomography.

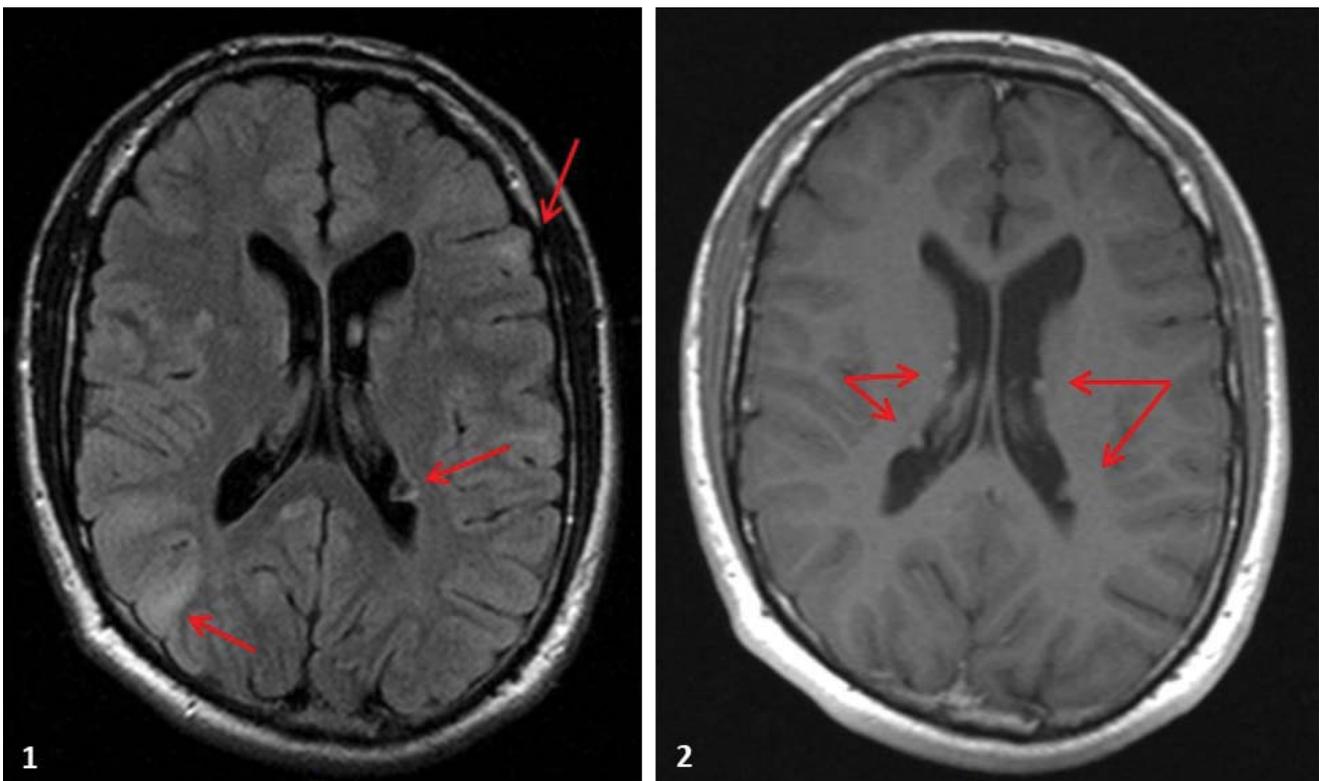
We adjusted the antiepileptic treatment with good seizure control. Dermatologic assessment revealed unequal angiofibromas and hypomelanotic macules (Figure 2). Therefore, we diagnosed definite TSC as the patient had major neurologic criteria, i.e. SEN and cortical glioneuronal hamartomas, the aforementioned dermatologic features, and one minor criterion – multiple renal cysts, in accordance with the 2012 International TSC Consensus Conference diagnostic criteria<sup>6</sup>.



**Figure 1.** Brain MRI. Coronal fluid attenuation inversion recovery (FLAIR)-weighted image showing cortical glioneuronal hamartomas (1) and axial T1-weighted image showing subependymal nodules (2).



**Figure 2.** Right foot with unguis angiofibroma of the first finger and hypomelanotic macule.



**Figure 3.** Brain MRI. Axial FLAIR-weighted image showing subependymal nodules and cortical glioneuronal hamartomas (1) and axial T1-weighted image showing subependymal nodules (2).



**Figure 4.** Shagreen patch and hypomelanotic macules over the lower back.

## CASE REPORT 2

A 28-year old man diagnosed with TSC at the age of 1.5 years had infantile spasms and developed generalised tonic-clonic seizures in his youth, resistant to treatment with levetiracetam 1000 mg daily and valproate 1000 mg daily. He had SEN and cortical glioneuronal hamartomas (Figure 3) and was under nephrological surveillance for a left renal angiomyolipoma under 3 cm and multiple renal cysts. He also had skin lesions, i.e. Shagreen patch over his lower back and hypomelanotic macules (Figure 4).

We increased the dosage of levetiracetam to 1500 mg daily with good clinical outcome and performed a systemic workup, which was normal.

## DISCUSSION

Both cases were diagnosed on clinical grounds, underscoring the importance of clinical appraisal across different medical specialties.

In both cases there is neurological involvement fulfilling major diagnostic criteria for TSC, i.e. cortical glioneuronal hamartomas and SEN<sup>6</sup>. Approximately 90% of people with TSC have central nervous system manifestations<sup>7</sup>. The SEN, occurring in about 80% of TSC cases, present a 5-15% risk of evolving into sube-

pendymal giant cell astrocytoma (SEGA)<sup>6</sup>. Our second patient has more prominent SEN than the first one, however, they do not exceed 10 mm in diameter, which is deemed a radiological criterion for distinguishing these two histologically identical entities<sup>8</sup>. Furthermore, after 25 years of age, surveillance imaging every 1-3 years for SEGA may cease<sup>9</sup>.

Despite not classifying as a diagnostic criterion for TSC, epilepsy is among the most common neurologic manifestations in TSC and a major cause of morbidity and mortality<sup>10</sup>. Our second patient presented typically with infantile spasms at 1.5 years, in agreement with the reported seizure onset before 2 years of age in most TSC cases<sup>10</sup>, whereas the first patient began having seizures in her early adulthood, and less commonly, they were generalised. However, TSC patients are at increased risk of developing epilepsy throughout their life<sup>10,11</sup> and may present with virtually any type of seizure<sup>7</sup>.

Significant burden of disease is also caused by a wide range of neuropsychiatric manifestations termed TSC-associated neuropsychiatric disorders (TAND), as is the case of our first patient. TAND occur in about 90% of people with TSC, but only around 20% of them are properly diagnosed and managed<sup>12</sup>. It is therefore necessary to increase awareness of these manifestations and to screen for them early.

Renal involvement in TSC is another important cause of morbidity and mortality through renal failure due to angiomyolipomas and cysts, haemorrhage in large ruptured angiomyolipomas, and renal cell carcinoma. Assessment by abdominal MRI every 1-3 years is necessary and renal angiomyolipomas over 3 cm require an mTOR inhibitor as first-line therapy<sup>9</sup>.

Better understanding of the pathophysiology of TSC has significantly improved diagnostic and management strategies, leading to molecularly targeted therapies. Inhibition of the mTOR pathway is a promi-

sing approach and further research might additionally advance current practice.

**Compliance with ethics requirements:** The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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