

# Tuberous sclerosis complex presenting as convulsive status epilepticus followed by hypoxic cerebropathy

## A case report

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### Abstract

**Rationale:** Tuberous sclerosis complex (TSC) is a relatively rare, autosomal dominant, and progressive neurocutaneous disorder involving multiple organs. Heterozygous mutations in the *TSC1* gene located on chromosome 9 (9q34.13) or the *TSC2* gene located on chromosome 16 (16p13.3) have been shown to be responsible for this disorder. The most common clinical manifestations are abnormalities of the skin, brain, kidney, heart, and lungs. Although all seizure types have been observed in TSC patients, the present case is the first in the literature to present with convulsive status epilepticus followed by hypoxic cerebropathy.

**Patient concerns:** A 33-month-old girl presented with fever and seizure followed by unconsciousness for 6 hours. Physical examination showed 4 hypopigmented macules with diameters exceeding 5 mm. Initial magnetic resonance imaging of the brain revealed diffuse edema in the bilateral cerebral cortex, cortical tubers, and subependymal nodules. Video electroencephalography showed no epileptiform activity, but diffuse slow waves intermixed with small fast waves were seen for all leads. Computed tomography brain scanning revealed bilateral cortex edema and calcified subependymal nodules.

**Diagnosis:** Combined with her clinical presentation, the patient was diagnosed with TSC after molecular analysis revealed she had inherited the *TSC2* c.1832G>A (p.R611Q) mutation from her mother.

**Interventions:** The patient received anti-infection therapy, mannitol dehydration, hyperbaric oxygen treatment, and topiramate.

**Outcomes:** One month later, the patient was in a decorticate state, presenting with unconsciousness and bilateral arm flexion and leg extension. At 6 weeks, repeated electroencephalography was normal.

**Lessons:** In addition to the present case report, rare studies have reported cases of TSC presenting as convulsive status epilepticus followed by hypoxic cerebropathy, which may be strongly associated with a poor prognosis. Patients with the characteristic skin lesions and epilepsy should be carefully evaluated for the possible diagnosis of TSC.

**Abbreviations:** CT = computed tomography, MRI = magnetic resonance imaging, TSC = tuberous sclerosis complex.

**Keywords:** convulsive status epilepticus, hypopigmented macules, hypoxic cerebropathy, tuberous sclerosis complex

## 1. Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant and progressive neurocutaneous disorder that involves multiple

Editor: N/A.

Informed written consent was obtained from the patient's guardians for publication of this case report and accompanying images.

The authors of this work have nothing to disclose.

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Medicine (2019) 98:19(e15545)

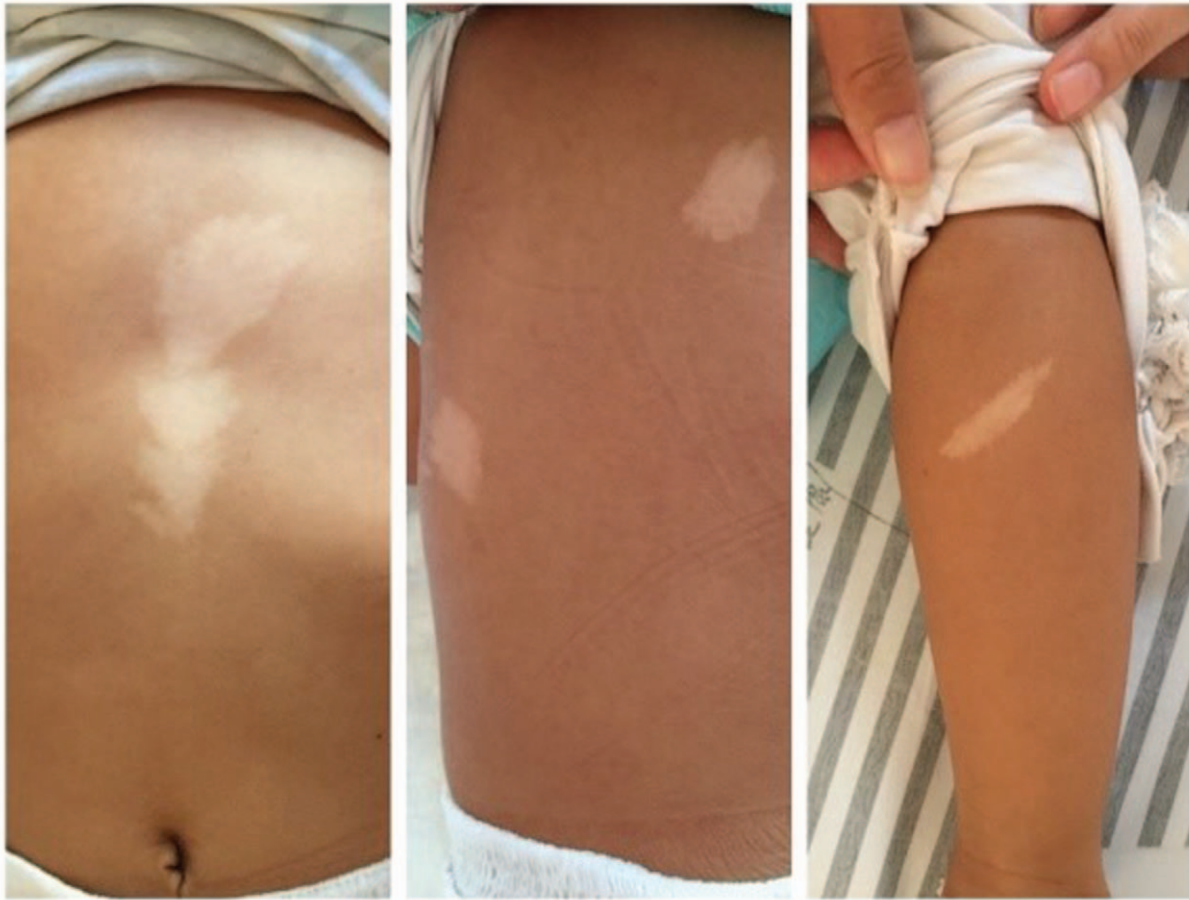
Received: 6 December 2018 / Received in final form: 1 April 2019 / Accepted: 10 April 2019

<http://dx.doi.org/10.1097/MD.00000000000015545>

organs, and its estimated incidence and prevalence are 1 in 6000 to 10,000 live births and 1 in 20,000 persons, respectively.<sup>[1]</sup> The most common clinical manifestations are abnormalities of the skin (e.g., hypomelanotic macules, facial angiofibromas, shagreen patches, fibrous cephalic plaques, and unguis fibromas), brain (e.g., cortical tubers, subependymal nodules and subependymal giant cell astrocytomas, seizures, and intellectual disability/developmental delay), kidney (e.g., angiomyolipomas, cysts, and renal cell carcinomas), heart (e.g., rhabdomyomas and arrhythmias), and lungs (lymphangiomyomatosis).<sup>[1]</sup> Heterozygous mutations in the *TSC1* gene located on chromosome 9 (9q34.13) or the *TSC2* gene located on chromosome 16 (16p13.3) have been shown to be responsible for this disorder.<sup>[2,3]</sup> At present, the diagnosis of TSC is based on both clinical findings and genetic testing. Although all seizure types have been observed in TSC patients, the present case is the first in the literature to present with convulsive status epilepticus followed by hypoxic cerebropathy.

## 2. Case presentation

A 33-month-old girl who experienced fever and seizure followed by unconsciousness for 6 hours was admitted to the Department of



**Figure 1.** Hypopigmented macules on chest, abdomen, back, and lower limb.

Pediatric Neurology. She had flu-like symptom for several days before admission, including cough, runny nose, and sneezing. Her temperature increased to 41°C, and then she experienced a tonic-clonic seizure persisting for 40 minutes as well as cyanosis of the whole body. Diazepam was given to control the seizure; however, her unconsciousness was not improved. Physical and neurological examinations revealed coma (Glasgow Coma Scale 3), decreased tone in bilateral limbs, loss of deep tendon reflexes, absence of bilateral Babinski signs or meningeal irritation signs, and 4 hypopigmented macules with diameters greater than 5 mm, with one each on the chest, abdomen, back, and lower limb (Fig. 1).

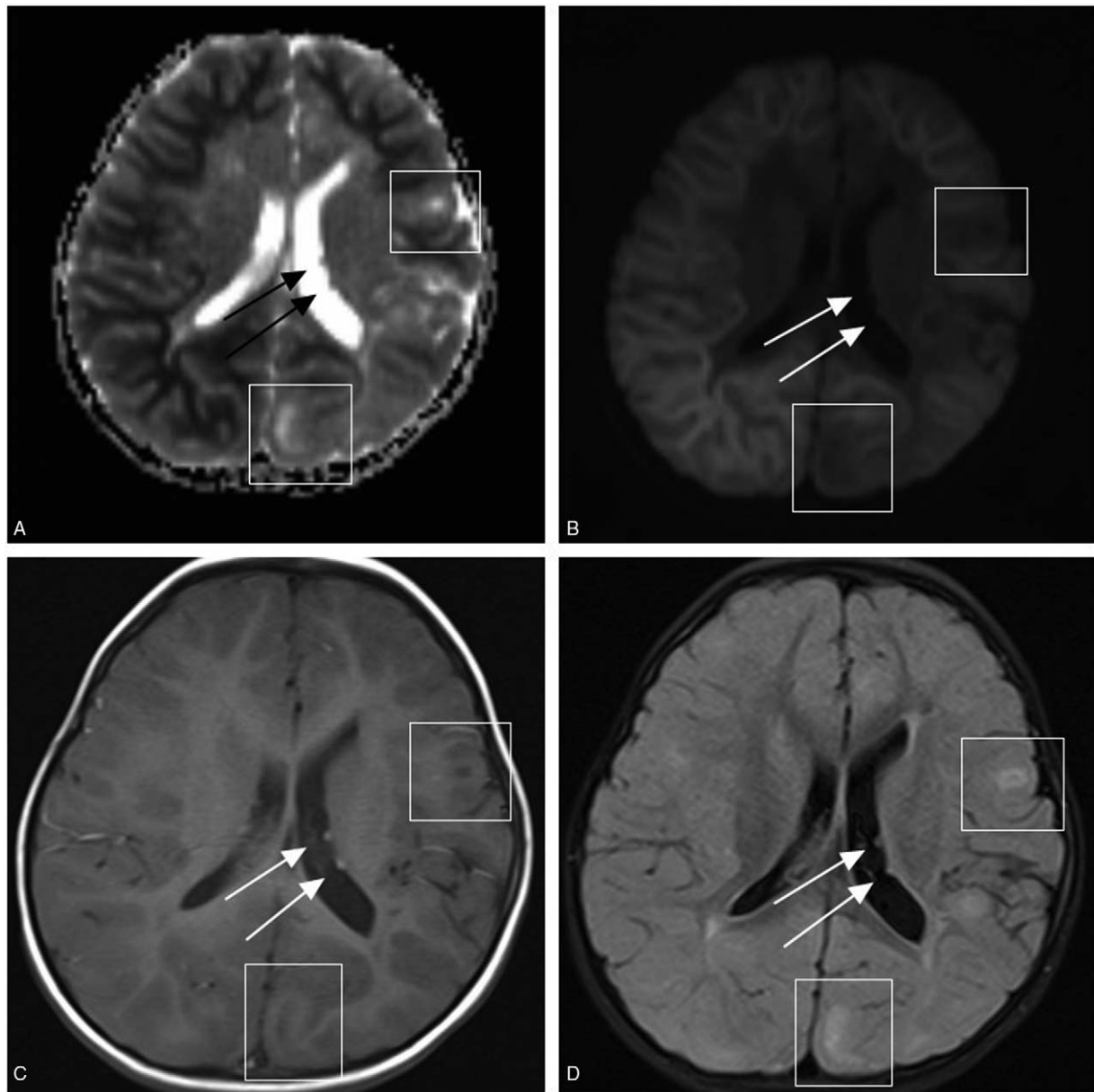
Initial magnetic resonance imaging (MRI) of the patient's brain revealed diffuse edema in the bilateral cerebral cortex, cortical tubers, and subependymal nodules (Fig. 2). Video electroencephalography showed no epileptiform activity but diffuse slow waves intermixed with small fast waves seen for all leads. Biochemical examination showed the cerebrospinal fluid was normal, and all microbiological tests were negative, including those for TORCH antibody, mycoplasma pneumonia antibody, chlamydia antibody, Epstein-Barr virus antibody, fungi, and tuberculosis. Combined with the patient's history and examination results, we diagnosed the patient with an acute upper respiratory tract infection, convulsive epileptic status, and hypoxic encephalopathy. She was treated with anti-infection therapy, mannitol dehydration, hyperbaric oxygen treatment, and topiramate.

Two weeks after admission, computed tomography (CT) brain scanning revealed bilateral cortex edema and calcified subependymal nodules (Fig. 3A, B). Findings on other examinations, including cardiac ultrasonography, abdominal CT scanning, and chest CT scanning, were normal. One month after admission, a repeat MRI showed cerebral atrophy, ventricle dilation, cortical tubers signal, and subependymal nodules (Fig. 3C, D), and the patient presented with coma vigil and a decorticate state, with unconsciousness and bilateral arm flexion and leg extension. At 6 weeks, repeated electroencephalography was normal.

Regarding the patient's medical history, the antenatal period was uneventful. The child was born at term via natural birth with a birth weight of 3.0 kg. Her cognition and motor development were age appropriate. She had no family history of seizures, developmental delay, or any other neurologic illness. Genetic analysis revealed that the patient had inherited the TSC2 c.1832G>A (p.R611Q) mutation from her mother, who was clinically unaffected. Therefore, her terminal diagnosis was TSC.

### 3. Discussion

TSC is an autosomal dominant, neurocutaneous disorder characterized by the development of hamartomatous tumors in multiple organs and abnormalities in neuronal migration. The present case met the clinical and genetic criteria for a definitive



**Figure 2.** Axial views of ADC, DWI, T1, and FLAIR at approximately the same level. (A) Diffuse hypointense signal in the bilateral cortex and hyperintense cortical tubers (white square frame) were observed on ADC images. (B) Diffuse hyperintense areas were seen in the bilateral cortex and hypointense cortical tubers (white square frame) on DWI images. Cortical tubers (white square frame) were hypointense on T1 images (C) and hyperintense on FLAIR images (D). Subependymal nodules along the wall of the ependymal lining of the lateral ventricle are indicated by arrows in all panels.

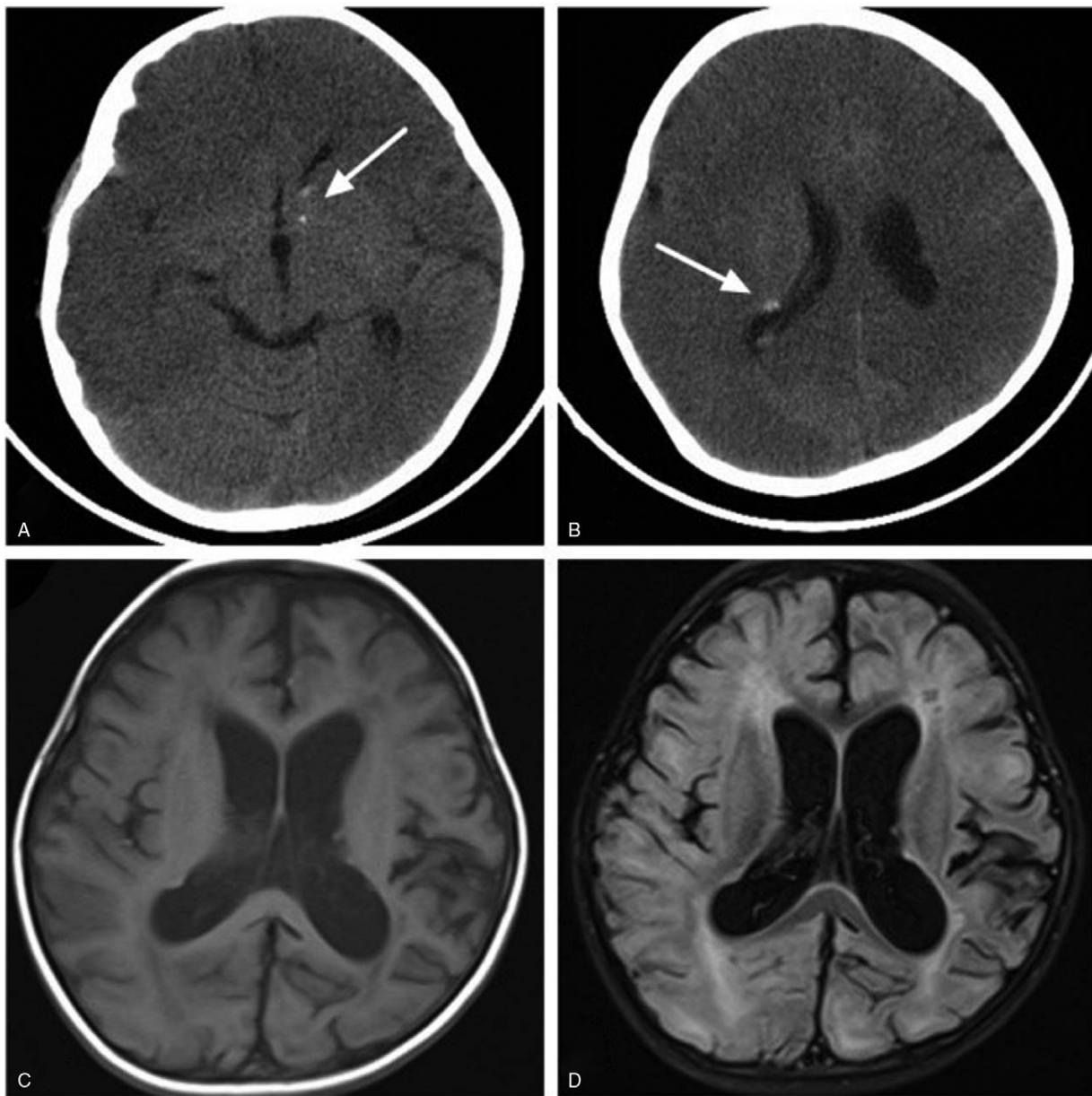
diagnosis of TSC according to the recommendations of the 2012 International Tuberos Sclerosis Complex Consensus Conference.<sup>[11]</sup> Three major features meeting the clinical diagnostic criteria were the 4 hypomelanotic macules with diameters exceeding 5 mm, cortical tubers, and subependymal nodules.

This type of neurocutaneous syndrome is caused by mutations in the *TSC1* or *TSC2* gene, and over 300 and 900 mutations, respectively, in the genes been recorded in the Human Gene Mutation Database.<sup>[4]</sup> *TSC2* mutations are 3 times more common than *TSC1* mutations in tumor suppressor genes and associated with more severe neurodevelopment impairment.<sup>[5]</sup> The cause for TSC in patients without *TSC1/TSC2* mutation remains unknown and may be related to either a third gene and/or regulatory DNA controlling *TSC1* or *TSC2*.<sup>[6]</sup> In the present case, genetic

molecular analysis revealed a missense mutation on the *TSC2* gene (R611Q) that has been reported previously in other populations. In general, two-thirds of TSC cases are sporadic.<sup>[4]</sup> The present case was familial, given that the patient's mother carried the same mutation as her daughter.

The typical skin lesions of TSC include hypomelanotic macules, angiofibromas, and shagreen patch. Hypomelanotic macules are a significant feature, because they are observed in about 90% of individuals with TSC. Also, they typically appear at birth or infancy, and they may be a presenting sign of TSC.<sup>[7]</sup> In the present case, hypomelanotic macules were the most dominant finding of physical examination. Notably, when such typical skin lesions are observed, it is necessary for pediatricians to further review the case history and complete an imaging examination.





**Figure 3.** CT images showed some calcified subependymal nodules (white arrows) (A and B). T1 images (C) and FLAIR images (D) showed cerebral atrophy, ventricle dilation, signal for cortical tubers, and subependymal nodules.

Neurological manifestations of TSC are also prominent, such as epilepsy and neuropsychiatric disorders, including learning disability, autism spectrum disorders, and attention-deficit hyperactivity disorder.<sup>[6,8]</sup> Epilepsy occurs in approximately 90% of TSC patients, making it the most common manifesting symptom. Epilepsy often appears in the first year of life. Patients with TSC can experience almost all seizure types, and two-thirds of infants with TSC develop epilepsy as infantile spasms or focal-onset seizures.<sup>[8]</sup> The patient in the present case experienced generalized convulsive status epilepticus followed by anoxia and unconsciousness. No report has been published yet of a case presenting with convulsive status epilepticus as the initial symptom of TSC. It was reported that the initial type and severity of epilepsy may be associated with the *TSC2* mutation as well as the size, location, and number of tubers. Perhaps, the worse

neurological prognosis in the present case could be attributed to the *TSC2* gene mutation.

Cortical tubers, subependymal nodules, and white matter lesions are commonly encountered in TSC. Less common manifestations include cerebellar atrophy, dysgenesis of corpus callosum, Chiari malformation, arachnoid cyst, and infarctions due to occlusive vascular disorders. MRI is the most sensitive modality for identifying these intracranial lesions. However, CT is more sensitive for detecting calcified subependymal nodules.<sup>[9]</sup> Cortical tubers and subependymal nodules were seen in the present case, and these features were reported to both be present in approximately 90% of children with TSC. The calcified subependymal nodules were difficult to detect on MRI in this case, but readily detected on CT imaging. Furthermore, initial brain MRI revealed diffuse edema in the bilateral cerebral cortex,

which presented the evidence of hypoxic cerebropathy and might be the interference factor that leads pediatricists to detect cortical tubers. No other published reports of TSC cases with such serious hypoxic cerebropathy could be found in the literature.

In addition to the present case report, rare studies have reported cases of TSC presenting as convulsive status epilepticus followed by hypoxic cerebropathy, which may be strongly associated with a poor prognosis. Patients with the characteristic skin lesions and epilepsy should be carefully evaluated for the possible diagnosis of TSC.

### Author contributions

**Conceptualization:** Xuncan Liu, Yanfeng Zhang, Yunpeng Hao, Yinbo Chen, Chen Chen.

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**Writing – review & editing:** Xuncan Liu, Yanfeng Zhang, Yunpeng Hao, Yinbo Chen, Chen Chen.

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