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Case Report

A case of tuberous sclerosis complex revealed by epilepsy ☆☆☆

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ABSTRACT

Tuberous sclerosis complex is a multisystem genetic disease with autosomal dominant inheritance, characterized by the development of benign tumors known as hamartomas that affect multiple organs. It is a condition with a wide phenotypic spectrum, and its clinical presentation varies over time within the same individual. Hence, the importance of early screening and rigorous monitoring of evolving clinical manifestations. Diagnosis can occur at any age. These tumors are generally benign, but their size and location can have a significant impact on the prognosis and, in some cases, even on life expectancy. Cardiac, neurological, and cutaneous manifestations are most common in childhood. The onset of early and severe epilepsy within the first year of life is associated with neurodevelopmental disorders that impact the quality of life for affected individuals and their families. We present a case of a 22-year-old female patient experiencing inaugural epileptic seizures in adulthood, with magnetic resonance imaging revealing subependymal hamartomas, cortical tubers and radial migration bands accompanied by polycystic kidney disease; the diagnosis of tuberous sclerosis complex was established based on the association of these lesions, which constitute major and minor criteria.

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Introduction

Tuberous sclerosis complex (TSC) is a genetic disorder classified under phakomatoses. It is inherited in an autosomal dominant manner, and its incidence does not exceed 1 in

10,000 births. The characteristic triad of symptoms includes sebaceous adenomas, intellectual disability, and epilepsy [1]. The disease was first described in 1880 by Désiré Magloire Bourneville. During an autopsy of a young girl, he identified “tuberous sclerosis of the cerebral convolutions”. She initially presented with seizures and intellectual delay [2].

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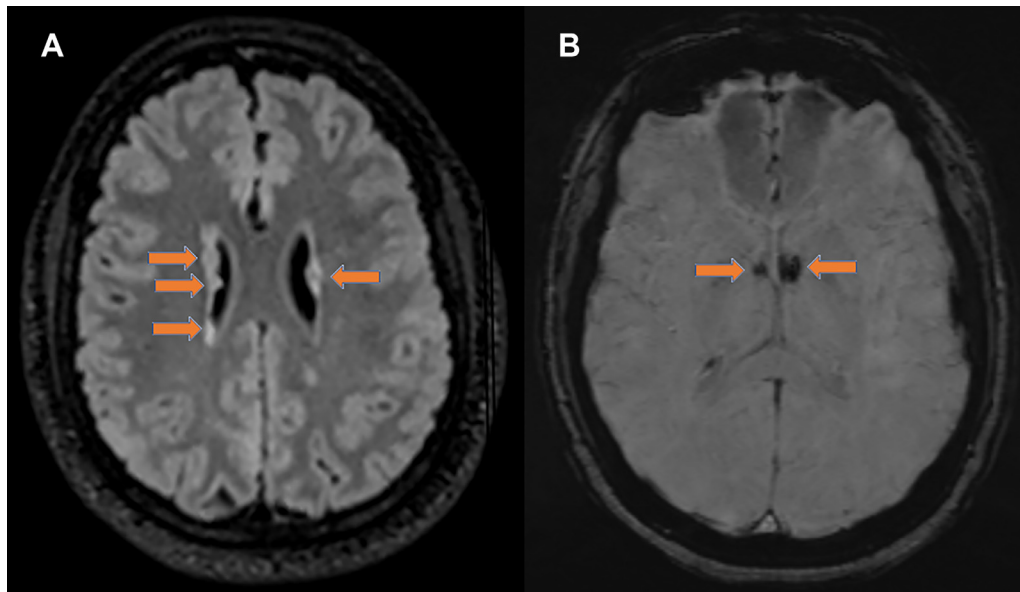


Fig. 1 – Axial FLAIR (A) and SWI images (B) showing calcified subependymal hamartomas (arrows).

Bourneville was a psychiatrist, a medical specialist in the study and treatment of mental illnesses, a neurologist at Bicêtre Hospital, and a deputy in Paris [3]. The main organs affected are the brain, skin, lungs, and kidneys, with a wide range of symptoms. The most severe morbidity is associated with brain and kidney lesions [4].

Case report

We present a case of a 22-year-old female patient with no notable personal or family medical history, who has been experiencing recurrent generalized tonic-clonic epileptic seizures for the past two months; no etiological investigation was conducted previously, given the self-resolution of these epileptic episodes. Over the last 2 weeks, she has also been suffering from partial seizures, which led to her admission to the emergency department. She was initially prescribed carbamazepine. A thorough clinical examination, including skin observation and cognitive function assessment, did not reveal any specific abnormalities.

A brain computed tomography (CT) was performed, showing no apparent lesion; the laboratory tests, notably the metabolic panel, were within the normal range.

The brain Magnetic resonance imaging (MRI) revealed subependymal hamartomas (Fig. 1) as nodular lesions with hyperintensity on T1 and FLAIR weighted images and isointensity on T2-weighted images (1a), they appear calcified on the SWI sequence (1b). It also showed cortical and subcortical signal abnormalities with hyperintensity on T2-weighted and FLAIR images; located in frontoparietal lobes; these findings did not correlate with any abnormalities on diffusion-weighted sequences and are consistent with cortical tubers (Fig. 2). They are associated with radial signal abnormalities of the periventricular white matter extending to the bifrontal subcortical region related to radial migration bands (Fig. 3).

A thoracoabdominal-pelvic CT scan and an abdominal MRI were subsequently performed, revealing the presence of multiple bilateral renal cysts, some of which were hemorrhagic related to polycystic kidney disease (Fig. 4).

These criteria provided a sufficient basis to confirm the diagnosis of tuberous sclerosis complex.

Discussion

TSC is caused by a mutation that affects 2 genes: TSC1 (Tuberous Sclerosis Complex, located on chromosome 9) or the TSC2 gene (located on chromosome 16). These are referred to as “tumor suppressor genes” and are responsible for encoding 2 proteins known as hamartin and tuberlin [5]. These 2 proteins form a complex that synergistically regulates the appropriate control of cell proliferation by physiologically inhibiting the mTOR signaling pathway (mTOR stands for mammalian Target Of Rapamycin, a target for rapamycin in mammals) [5]. If 1 of these 2 proteins is absent or abnormal due to a mutation in 1 of the 2 genes, the hamartin-tuberlin complex cannot form or is ineffective. This results in overactivation of mTOR, leading to the development of benign tumors [5].

The variety of clinical features presented by a given patient depends not only on the type of germline mutation but also on the timing and location of the second somatic mutation [6]. Clinical manifestations change as patients age. The phenotype varies significantly from one individual to another, ranging from isolated skin involvement to a much more severe presentation that can lead to profound disability [7], the initial assessment is intended to identify the various organ involvements [8]; regular and multidisciplinary follow-up will enable the early detection of manifestations and their potential complications in order to provide timely intervention [8].

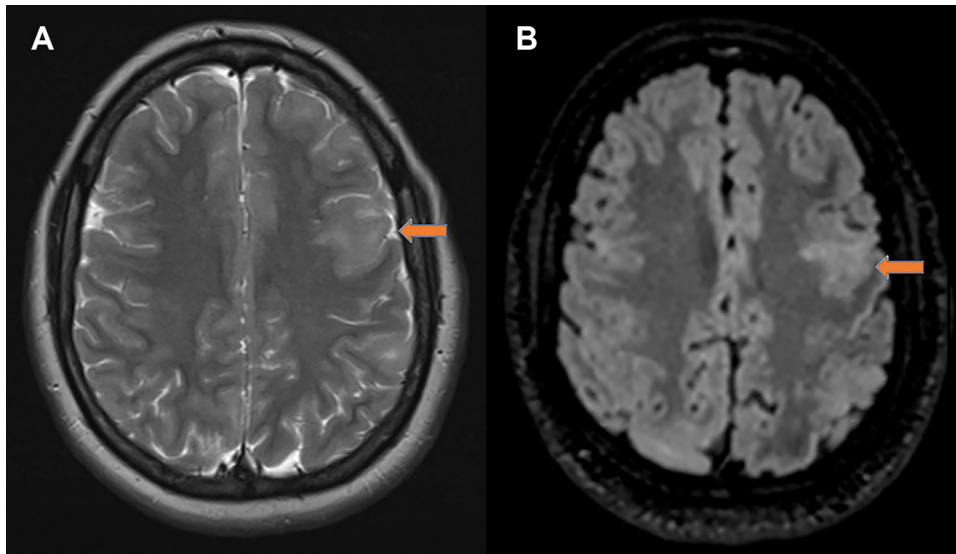


Fig. 2 – Axial T2 (A) and FLAIR (B) MRI images showing cortical tubers (arrows).

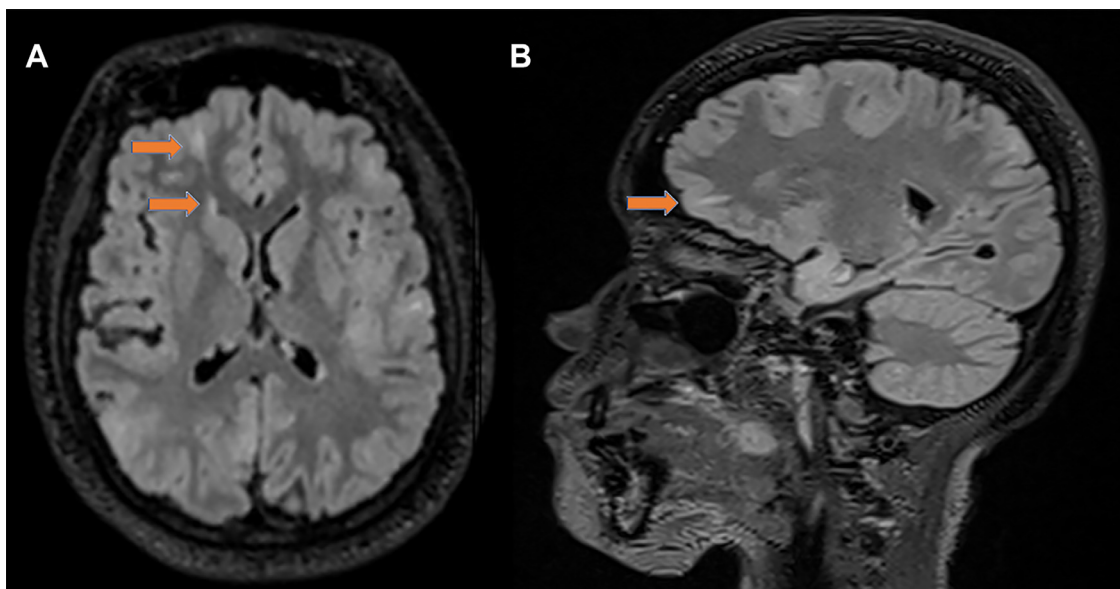


Fig. 3 – Axial (A) and sagittal (B) FLAIR MRI images showing radial migration bands (arrows).

The diagnosis of TSC is established using clinical criteria, which are categorized into 2 types: major and minor criteria. The updated clinical criteria now include 11 major criteria and 6 minor criteria [8,9] (Table 1). Therefore, the diagnosis can be based solely on clinical features.

As previously noted, our patient presented subependymal hamartomas, cortical tubers, and radial migration lines on MRI, meeting 2 major validation criteria for the disease. Additionally, abdominal CT and MRI revealed multiple renal cysts, aligning with diagnostic criteria outlined in the table. Altogether, our case fulfilled 2 major criteria and 1 minor criterion which largely confirms the diagnosis of tuberous sclerosis.

Brain lesions

The brain is frequently the organ most profoundly impacted by various disorders, and its wide range of neurological symptoms contributes significantly to the overall disability burden associated with this disease [10]. Additionally, these manifestations have a substantial adverse effect on the quality of life and psychosocial well-being of both patients and their families, often resulting in negative consequences for education and career prospects [10]. When there is a failure to regulate cellular growth and proliferation processes, and an inability to control neuronal development within the brain, it can lead to abnormal differentiation of neuronal stem cells, disturbances

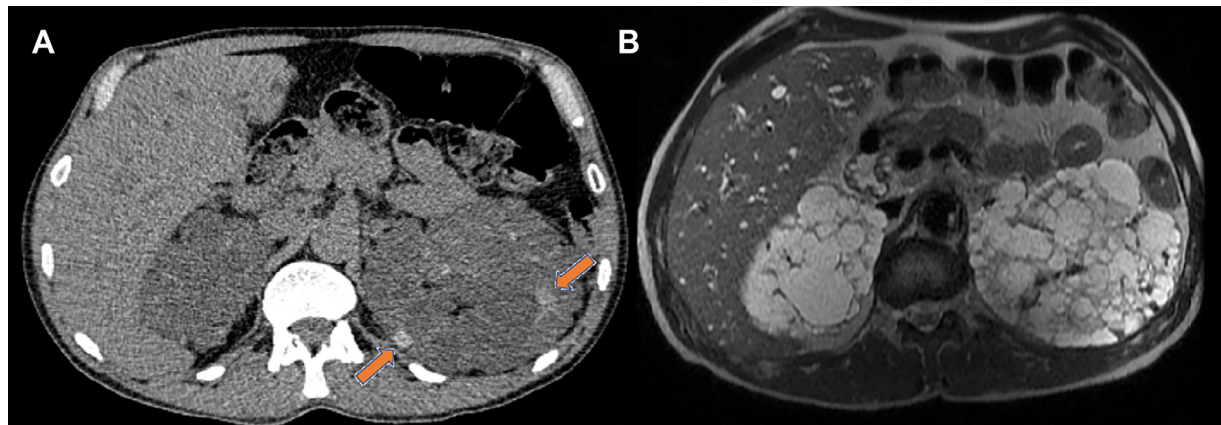


Fig. 4 – Polycystic kidney disease: scannographic image displaying bilateral renal cysts, some of which are spontaneously hyperdense indicating hemorrhage (A, arrows); axial T2-weighted MRI image showing the bilateral renal cysts (B).

Table 1 – Diagnostic criteria according to the 2021 International Tuberous Sclerosis Complex Consensus Conference.

Major criteria	Hypomelanotic macules ($n \geq 3$, at least 5 mm in diameter) - Angiofibromas ($n \geq 3$) or fibrous cephalic plaque - Ungual fibromas ($n \geq 2$) - Shagreen patch - Multiple cortical tubers and/or radial migration lines - Subependymal nodules ($n \geq 2$) - Subependymal giant cell astrocytoma - Cardiac rhabdomyoma - Lymphangiomyomatosis - Angiomyolipoma ($n \geq 2$) - Multiple retinal hamartomas
Minor criteria	Confetti skin lesions - Dental enamel pits ($n \geq 3$) - Intraoral fibromas ($n \geq 2$) - Multiple renal cysts - Retinal achromic patch - Nonrenal hamartomas - Sclerotic bone lesions
Genetics	Identification of either a TSC1 or a TSC2 pathogenic variant in DNA from normal tissue is sufficient to make a definite diagnosis regardless of clinical findings
Definite diagnosis:	2 major features or 1 major feature with 2 minor features
Possible diagnosis:	either 1 major feature or ≥ 2 minor features

in neuronal migration, synapse formation and plasticity [10].

Brain damage often appears in early childhood and is easily identified using imaging. They include subependymal nodules, cortical and subcortical tubers, subependymal giant cell astrocytomas, radial white matter migration lines and brain cysts [11]. These lesions give rise to a spectrum of neurological and neuropsychiatric manifestations, including conditions like epilepsy, intellectual disability, and neurodevelopmental disorders [12]. Seizures typically serves as the initial clinical sign of the disease, often becoming evident as early as the first few months of life allowing the diagnosis in 15%-35% of infants [13], it is also the most frequent symptom, with reports of occurrence in around 80%-90% of patients, and up to 75% of them showing drug resistance [14].

For our case, the mode of revelation of the disease in our patient was indeed seizures but a late age, on the other hand she presented no cognitive deficit since her childhood.

Renal lesions

Renal involvement develops gradually during the initial decades of the disease and is present in 90% of adults; it encompasses angiomyolipomas (AMLs) (present in 80% of patients), cysts (present in 40% of patients), and cancer (present in 3% of patients). It can lead to renal insufficiency, progressing to end-stage disease in approximately 5% of patients

[6,15–17]. AMLs are often bilateral and multifocal [18], their vascular anomalies, often of an aneurysmal type, might cause hemorrhage. The risk of bleeding, estimated in 20% of affected patients [6], is correlated with the size of the AML (>3 -4 cm), its rate of growth (>0.5 cm/year), and the presence of aneurysms larger than 0.5 cm [19]. Cancers that develop as complications of TSC typically manifest around the age of 40, and they histologically differ from conventional hypernephromes. They are most frequently of the papillary or oncocytic type [5]. Among the less common but more severe renal manifestations are polycystic kidney disease and renal cell carcinoma [20].

For our case, the patient's imaging showed bilateral renal cysts, some of which were hemorrhagic. There was no suspected lesion, and even the renal assessment was normal.

Cardiac lesions

The most frequent cardiac involvement seen in TSC is the presence of one or more rhabdomyomas. These cardiac rhabdomyomas (CR) can be identified in as many as 90% of infants with the condition and may undergo spontaneous regression within the first few years of life [21]. The tumors typically have a diameter ranging from 5 to 15 mm, although their size can vary from a few millimeters to several centimeters. They can originate within the heart muscle or be located intracavitarily [22]. CR develop in utero and are frequently identified during prenatal ultrasound examinations or before the

child reaches 1 year of age. These growths can impact the myocardium of both ventricles and the interventricular septum, potentially affecting ventricular function. On occasion, they may also involve the atria, usually appearing as a distinct and well-defined mass [23,24], CRs often remain asymptomatic, yet their presence in larger sizes or specific locations can result in disruptions in heart function, potentially causing arrhythmias, obstruction of intracardiac blood flow, or congestive heart failure [25].

Skin lesions

A well-recognized aspect for dermatologists, serves as the diagnostic clue in 90% of cases [16], These encompass hypomelanotic macules, also known as 'ash leaf spots,' which are observed in as many as 90% of patients [26], They are observed at birth or in early infancy, although in some cases, they can be challenging to identify, especially in fair-skinned individuals or small infants. Therefore, the use of ultraviolet light (Wood's lamp) can be beneficial [16], Other skin-related clinical characteristics encompass forehead plaques, shagreen patches, and facial angiofibromas [27,28]. Koenen fibromas are reported in up to 50% of TSC cases, typically appearing during puberty [27].

In our case, the clinical examination did not reveal the presence of skin lesions typical of tuberous sclerosis, something which would probably help to make an early diagnosis of the disease before the onset of convulsions in adulthood.

Involvement of other organs

Retinal astrocytic hamartomas are found in 35%-50% of patients and are typically noncancerous unless they exert pressure on the optic disc, potentially leading to vision impairment or blindness [29] Additionally, 'retinal achromic patches,' which are areas of hypopigmentation around the retina, are observed in 39% of individuals with TSC [30].

TSC may lead to liver AML, colonic polyps, hamartomas; and it can also result in lung-related conditions such as lymphangioleiomyomatosis [31,32].

Spinal bone lesions are a common discovery in individuals with TSC and are primarily located in the posterior regions of the vertebrae. They are typically discovered incidentally during chest CT scans performed as part of TSC surveillance for lung disease [33].

Other organs that may be impacted include the thyroid, pituitary gland, pancreas, and gonads [34].

Conclusion

Tuberous sclerosis complex should be considered in any patient, child or adult, in the context of seizures, when cerebral lesions are identified as tubers or subependymal nodules; this consideration is especially relevant if these cerebral lesions are accompanied by polycystic kidney disease; these already serve as sufficient major and minor criteria for the diagnostic, but their precision and validation can be enhanced through additional genetic studies.

Ethical Approval

No ethical approval is required for deidentified single case reports based on our institutional policies.

Patient consent

Written informed consent was obtained from the patient.

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