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Bourneville Tuberous Sclerosis and Brain MRI: a Case Report

Fadoua Ijim[1*], Mehdi El Kourchi[1], Said Adnor[1], Chahbi Zakaria[1], Soukaina Wakrim[1]

[1]Radiology Department - Chu Souss Massa - Faculty of Medicine and Pharmacy, University Ibn Zohr Agadir, Morocco

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***Corresponding author:** Fadoua Ijim
Radiology Department - Chu Souss Massa - Faculty of Medicine and Pharmacy, University Ibn Zohr Agadir, Morocco

Abstract **Case Report**

Summary: Tuberous sclerosis (TS) is a rare genetic disease of autosomal-dominant transmission. Mutations in either the tuberous sclerosis complex 1 (TSC1) or tuberous sclerosis complex 2 (TSC2) genes result in hamartomas affecting many organs, such as the brain, heart, kidneys, skin, lungs and liver. We report the observation of a 17-year-old girl with facial angiofibromas, hypo-pigmented skin lesions on the lower back and back of the right wrist and a history of seizures. The patient was admitted to the emergency department for treatment-resistant status epilepticus and was referred to our training for magnetic resonance imaging (MRI) of the brain. Brain MRI revealed subependymal nodules, cortical tubercles, and white matter abnormalities.

Keywords: Tuberous sclerosis Bourneville, brain MRI.

INTRODUCTION

Tuberous sclerosis of Bourneville (TSB) is one of the most common phacomatoses (approximately 1/10,000 births). It is inherited in an autosomal dominant fashion. Loss-of-function mutations in either of the two genes, TSC1 and TSC2, which code for the proteins hamartin and tuberin, respectively, cause TSB. These proteins are tumour growth suppressors, which are agents that regulate cell proliferation and differentiation. TSB is marked by the presence of hamartomas in almost all tissues, but especially in the brain, skin, kidneys and heart.

The classic triad of TSB is seizures, mental retardation and angiofibromas, but these occur in only 29% of TSB patients.

The most common warning sign is neurological and four characteristic lesions can be found on cross-sectional imaging of the brain (CT, MRI).

These are cortical tubers, subependymal nodules, giant cell astrocytomas and white matter abnormalities.

The aim of this case report is to present the imaging findings and to raise awareness of the value of early diagnosis by identifying these characteristic lesions in order to predict the risks involved and to institute appropriate treatment or monitoring.

PATIENT AND OBSERVATION

Patient Information:

A 17-year-old female patient was admitted to the emergency department for treatment-resistant status epilepticus. She had multiple generalised tonic-clonic seizures that lasted for a few minutes. There was no family history of seizure disorder.

Clinical Findings

On clinical examination, the patient was found to be obnoxious (OS 12/15), normocardic (HR 80 beats/min), normotensive and slightly tachypneic (FR 22 Cycles/min), apyretic (36°).

Physical examination revealed multiple skin lesions (angiofibromas) on the face, hypo-pigmented skin lesions on the lower back and back of the right wrist.

Chronology:

The onset of the symptomatology was one week ago with the onset of generalized tonic-clonic seizures associated with urinary leakage.

Diagnostic approach:

The patient was admitted to the intensive care unit and received conditioning with antiepileptic therapy. After a satisfactory assessment of her renal

function and a baseline biologic workup, the patient was referred to the radiology department for a brain MRI. A brain MRI with the following sequences was performed:

A T1/T2 spin echo weighted sequence, a fluid attenuation inversion recovery (FLAIR) weighted sequence, a T2 gradient echo weighted sequence (T2 EG), a diffusion weighted sequence, apparent diffusion coefficient (ADC and a 3D T1 FSPGR weighted sequence. An intravenous gadolinium-based contrast agent was administered.

Brain MRI showed

Peripherally based, diffuse bilateral supratentorial cortico-subcortical triangular signal abnormalities, T2 hyper signal and FLAIR in the periphery with an iso signal centre with increased ADC in DIFFUSION sequence. These lesions do not enhance after injection of contrast medium (Figure 1).

Multiple nodular formations protruding from the lateral ventricles, bilaterally asymmetric, in T1, T2 and FLAIR iso signal, some of which enhance homogeneously nodularly after injection of PDC and the largest of which measures 4.2 x 2.5 mm (Figure 2).

Radial and patchy white matter signal abnormalities, bilaterally with T2 and FLAIR hyper signal (Figure 3). Discrete dilatation of the ventricular system.

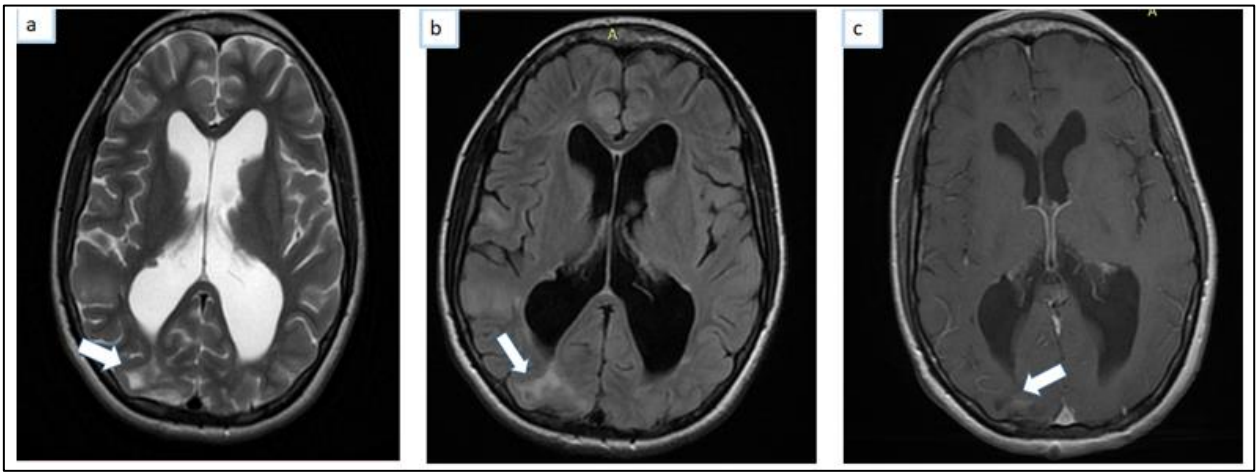

Figure 1: Diffuse bilateral supratentorial cortico-subcortical signal abnormalities with peripheral base, T2 hyper signal and FLAIR in the periphery with a center in iso signal with increased ADC in DIFFUSION sequence. These lesions do not enhance after injection of contrast medium

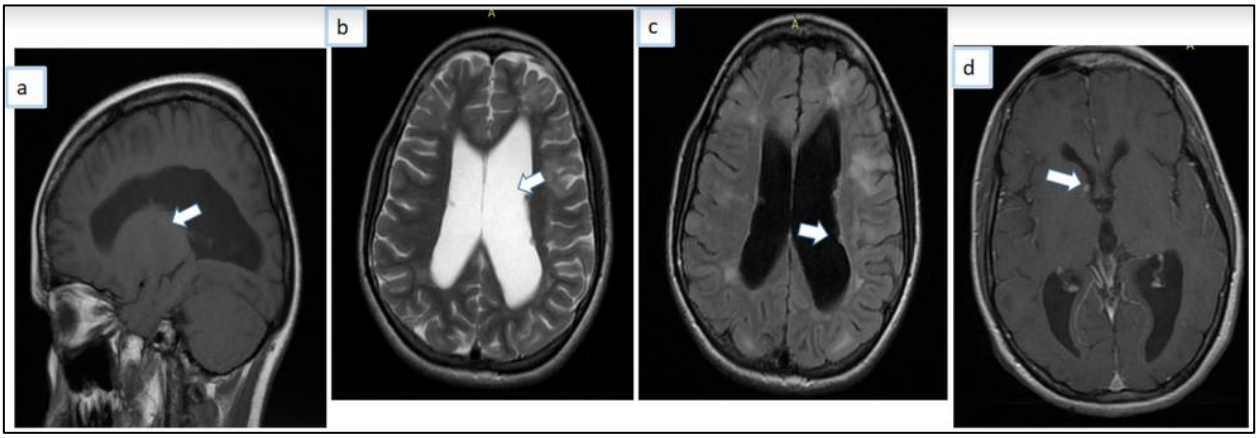

Figure 2: Multiple nodular formations protruding from the lateral ventricles, bilaterally asymmetric, in T1, T2 and FLAIR iso signal, some of which enhance in a homogeneous nodular fashion after PDC injection and the largest of which measures 4.2 x 2.5 mm

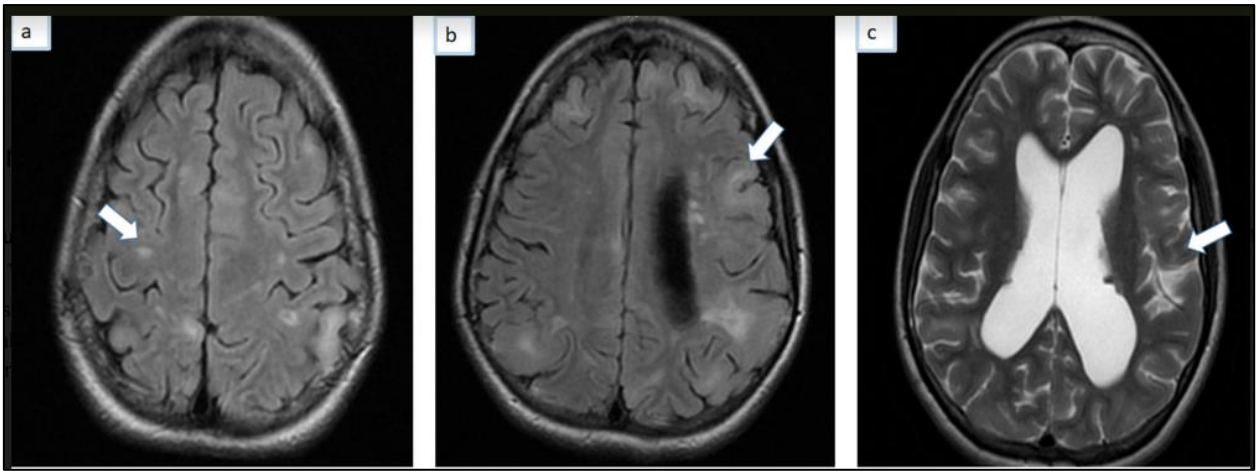

Figure 3: Radial and patchy white matter signal abnormalities, bilateral T2 and FLAIR hyper signal

Therapeutic intervention, follow-up and outcome:

Given our imaging findings, which are typical of STB, we made a diagnosis of STB in our radiology report and the patient was managed by the neurology and dermatology team with a good clinical course.

DISCUSSION

Tuberous sclerosis is a rare autosomal dominant neurocutaneous syndrome consisting of hamartomatous lesions in the brain, kidney, skin and heart. No predilection for gender or ethnic group. The estimated prevalence ranges from 1 in 6,000 to 1 in 12,000 and about two-thirds of cases are sporadic, which may explain why the patient had no family history of TSB [1, 2].

1. PATHOGENY

STB is characterised by a disorder of neuronal and glial formation, migration and organisation, leading to the main brain lesions: tubers, subependymal nodules, giant cell astrocytomas and white matter abnormalities [3, 4].

Neuronogenesis takes place in three main stages:

- Proliferation phase: pluripotent cells differentiate into neuronal and glial precursors.
- Migration phase of immature neurons and glial cells along radial glial fibres to the future cortex.
- Phase of formation of the mature cortex.

In STB, these different mechanisms appear defective. Some abnormal germline precursor cells do not migrate and form subependymal nodules and giant cell astrocytomas. Others may undergo incomplete migration and form heterotopic bands of abnormal cells extending from the subependymal region into the subcortical white matter. Cortical tubers are the result of abnormal migration and organisation of neurons and glial cells, responsible for the production of a focally disordered cortex [5, 6].

Cortical tubers

These are regions of focal cortical dysplasia. They consist of dysmorphic neurons, giant cells, and gliosis and myelin loss that may extend into the underlying white matter.

Subependymal nodules and giant cell astrocytomas

These are benign masses of astrocytes and giant cells, located in the ventricular wall and covered by an intact layer of ependyma. Giant cell astrocytomas grow from a pre-existing subependymal nodule.

White matter abnormalities

These are clusters of heterotopic giant cells aligned radially between the ependyma and the normal tuber or cortex, following the path of neuronal migration.

2. Brain MRI

Brain MRI is fundamental to the diagnosis by showing the major signs [7]. On MRI, tubers are typically hypointense to iso intense in T1 and hyperintense in T2. They rarely enhance after injection of gadolinium. In T1, there is a hypointense area within enlarged grooves: this signal is probably related to gliosis and reduction of myelin sheaths. The tubers are peripherally located, cortical, and have a characteristic triangular shape. In case of multiple tubers and drug-resistant epilepsy, functional studies (SPECT) allow the localization of the epileptogenic zone.

Proton spectroscopy can also be used: there is a low ratio of N-acetyl/(Creatinine+phosphocreatinine) and N-acetyl/[Choline + (Creatinine+phosphocreatinine)] in the cortical tubers compared to the contralateral healthy side.

In childhood, subependymal nodules are often calcified and a CT scan is sometimes useful in case of a single or suspicious nodule; they protrude into the ventricles and may be symmetrical or asymmetrical and require regular monitoring because of the risk of hydrocephalus, especially if they are located close to

the foramen of Monro and progressively increase in volume. Other predictive criteria for progression have been proposed, including size greater than 12 mm, incomplete calcification and enhancement after contrast injection [8].

Enhancement is considered evidence of transformation to giant cell astrocytoma, especially for nodules located near Monro's foramen [9].

On MRI, nodule enhancement is more common. Therefore, this finding cannot be used to differentiate a nodule from an astrocytoma. The subependymal nodule may be homogeneous or heterogeneous in signal. It is typically hypointense on T1 and especially on gradient echo. On T2, it is heterogeneous in target, with a hypointense centre and a hyperintense crown [10].

Giant cell tumours are benign tumours, which are simply nodules with growth potential. White matter abnormalities are present in 93% of cases. They are best seen on MRI and appear as iso to hypo T1 signal and hyper T2 signal. They appear as linear or curvilinear bands extending radially from the ventricular wall towards the cortex. These lesions may become calcified and enhanced on CT and MRI. They may correspond to demyelination and gliosis [11, 12].

CONCLUSION

Sclerosis tuberous of Bourneville is a neurocutaneous syndrome. It is a rare genetic disease. In addition to the clinical history of attacks and skin lesions, imaging, and essentially cerebral MRI, plays an important role in the diagnosis by highlighting these four lesions. The interest in recognising these lesions makes it possible to predict the risks involved and to institute appropriate treatment or monitoring.

Conflicts of Interest: The authors declare no conflict(s) of interest.

Author Contributions:

All authors contributed to the conduct of this research work. The authors have read and approved the final version of the manuscript.

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