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Case Report

All tubers are not created equal: Cerebellar tubers in a pediatric patient with tuberous sclerosis ☆,☆☆

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ABSTRACT

Tuberous sclerosis complex (TSC) is a rare autosomal dominant disease characterized by multiple tumors throughout the body. Supratentorial hamartomas (or tubers), are a very common CNS feature of TSC. Cerebellar tubers are much less common in TSC. We present an interesting case of cerebellar tuber in a 14-year-old patient with TSC, highlighting clinical and diagnostic criteria for TSC and review the unique features of cerebellar tubers, differentiating these lesions from their more common supratentorial counterparts. This case serves as an educational tool to improve awareness of cerebellar tubers in patients with tuberous sclerosis.

Introduction

Tuberous sclerosis complex (TSC) is the second most common neurocutaneous syndrome (phakomatoses) and is characterized by the formation of predominately benign tumors in multiple organ systems. It has a prevalence of about 1/6000 and affects 1.5 million people worldwide [1]. This disease is an autosomal dominant disorder with high penetrance and variable gene expression. It results from a mutation in either the *TSC1* or *TSC2* gene on chromosome 9p or 16q respectively [2]. The 3 most common clinical manifestations of this disease (Vogt's triad) are epilepsy, intellectual disability, and facial angiofibromas [1]. Because of the variable expression of TSC, some patients may receive a diagnosis at birth while others may elude diagnosis for decades [1]. The vast majority of patients have brain lesions, which can be asymptomatic or manifest as seizures, learning or behavioral difficulties [3].

Intracranial features of TSC include cortical or subcortical tubers, white matter radial migration lines, subependymal nodules, and subependymal giant cell astrocytomas [4]. Tubers are present in greater than 80% of patients with TSC [1]. These tubers consist of glial and neuronal elements such as atypical giant astrocytes and bizarre giant cells [1].

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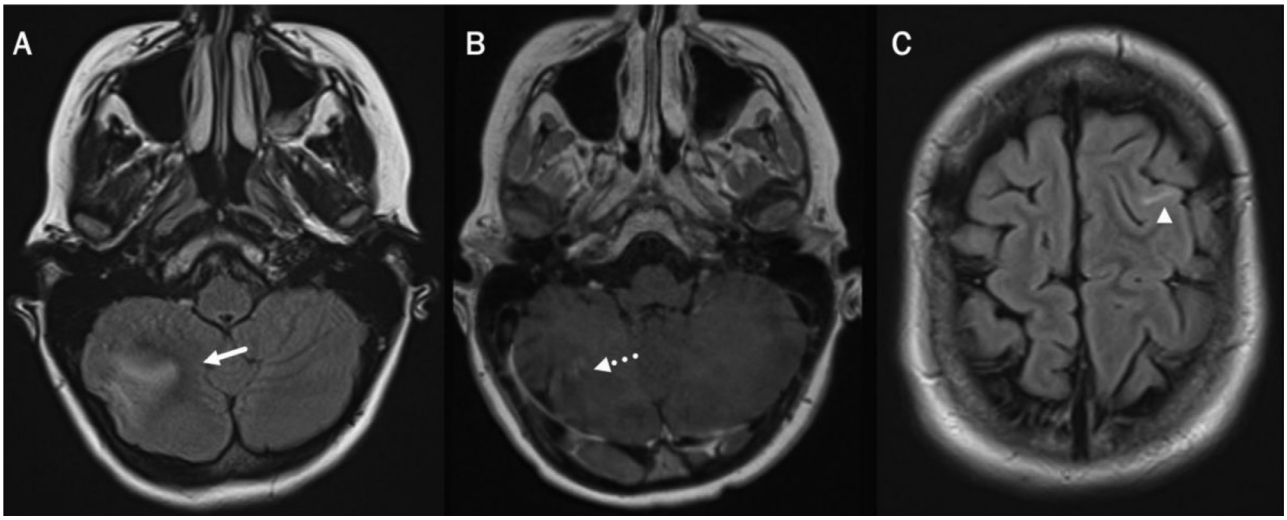

Fig. 1 – Axial FLAIR images (A) of the cerebellum revealed a wedge shaped area of increased FLAIR signal in the right cerebellum (arrow). Postcontrast imaging (B) demonstrated patchy contrast enhancement with folial retraction (dotted arrow). Supratentorial axial FLAIR imaging(C) revealed additional lesions in the supratentorial subcortical white matter, suspicious for hamartomas and a diagnosis of TSC (arrowhead).

Cerebellar tubers are less common than supratentorial cortical tubers (9%-30% vs 82.2%-94%) and have imaging and clinical features that differ from their supratentorial counterparts [3,5–7].

Case report

A 14-year-old male with medically well-controlled cryptogenic focal epilepsy underwent a brain magnetic resonance imaging to evaluate for pituitary abnormalities in the setting of growth hormone deficiency. The pituitary gland was normal, but incidentally seen was a large ill-defined wedge-shaped lesion without mass effect in the right lateral cerebellum demonstrating high FLAIR signal with patchy enhancement (Figs. 1A and B). In addition, there were small regions of high FLAIR signals in the temporal lobe and subcortical white matter of the left and right frontal lobe, concerning for cortical and subcortical tubers (Fig. 1C). A focused physical examination revealed 4 hypopigmented lesions found on his back. Based on these clinical and radiological findings, the patient satisfied 2 major criteria (>3 hypopigmented lesions and cortical dysplasia [tuber]) resulting in a definite diagnosis of tuberous sclerosis.

Upon review of the patient's family history, an extensive seizure history was identified on his maternal side. Indeed, his mother had seizures and hypopigmented macules. His 8-year-old brother also has seizures, hypopigmented macules, and a learning disability.

Discussion

Supratentorial cortical or subcortical tubers are a common finding in patients with TSC and are present in 82.2%-94% of cases [5,6]. These tubers represent cortical glioneural hamartomas with focal distortion in cellular organization and morphology, which extend into the subcortical white matter [4]. These are benign lesions but can serve as epileptogenic foci. Therefore, it is important for a radiologist to identify these lesions as they may be surgically resected in some cases of medically refractory epilepsy.

Magnetic resonance imaging is the most common modality to diagnose tubers [9]. These lesions are typically triangular shaped, centered on the cortex with apex oriented toward the ventricles. It has been suggested that this appearance may be secondary to abnormal neuronal migration [9]. These tubers most commonly involve the frontal and parietal lobes [10]. Tubers tend to be hypointense on T1 and hyperintense on T2 and FLAIR sequences with variable contrast enhancement [2].

Infratentorial tubers are less common than their supratentorial counterparts with prevalence between 9% and 30% [3,7]. Cerebellar tubers are primarily seen in pediatric patients over 11.5 years of age and are rare in patients under the age of 8 [3]. Patients with cerebellar tubers are known to have a high association with TSC2 mutations, with one study showing 41 of 42 patients with cerebellar tubers demonstrating TSC2 mutations [2]. However, no mechanism of causation has been established between TSC2 mutations and cerebellar tubers.

Cerebellar tubers are usually found in posterior cerebellar lobules associated with Crus I, Crus II, or lobule VIIa of the cerebellum [8]. They are also associated with cerebellar atrophy that is not otherwise observed in supratentorial tubers. Patients who have cerebellar tubers in the setting of TSC tend to have more cortical tubers than other TSC patients without cerebellar tubers [11]. Patients with cerebellar tubers also have an increased incidence of subependymal giant cell astrocytomas (20%) compared to other patients with TSC (8.2%) [12].

Imaging characteristics of cerebellar tubers have been reported to be somewhat similar to supratentorial tubers, with

low T1 signal, high T2/FLAIR signal and variable contrast enhancement. Two unique features that have been reported in cerebellar tubers are retraction, which was seen in 84% of patients and variable "zebra striped" enhancement seen in 51% of patients [2,12].

The clinical significance of cerebellar tubers is unknown and their overall contribution to the phenotype of tuberous sclerosis is also unknown [13]. Some studies have demonstrated a correlation with autism but there have only been few investigations to establish this relationship and elucidate a possible pathological mechanism [13].

Further studies need to be conducted to demonstrate a relationship between cerebellar lesions and phenotypic expression. A better understanding of the cerebellar contribution to TSC is needed before considering surgical resection [2].

Infratentorial tubers are increasingly being recognized in patients with TSC. It is important for radiologists to be familiar with these lesions and understand unique features that differentiate supratentorial and infratentorial tubers from both an imaging and clinical perspective.

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