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ORIGINAL ARTICLE

Cerebellar abnormality in children and young adults with tuberous sclerosis complex: MR and diffusion weighted imaging findings

Anomalie cérébelleuse chez des enfants et adultes jeunes présentant une sclérose tubéreuse complexe : aspects en IRM cérébrale et imagerie de diffusion

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KEYWORDS
Tuberous sclerosis complex;
Cerebellum;
Children;
Diffusion weighted imaging

Summary
Objectives. — The goal of our study was to: determine the incidence of cerebellar lesions in a cohort of children and young adults with TSC, and analyze the magnetic resonance imaging (MRI) findings of cerebellar TSC lesions including their contrast behavior and diffusion characteristics.
Material and Methods. — MRI studies of 27 TSC patients (mean age, 10.6 years) were evaluated for: cortical/subcortical tubers, white matter lesions, subependymal nodules, and giant cell astrocytomas. Patients with cerebellar involvement were further analyzed for the imaging and diffusion characteristics. ADC measurements of the cerebellar tubers were performed and compared with the contralateral normal appearing cerebellum. The clinical charts were revisited for symptoms suggesting cerebellar involvement.
Results. — Cerebellar tubers were seen in 8/27 patients, cerebellar atrophy in 1/27 patients. Cerebellar tubers showed a pyramidal/wedge appearance with a broad base reaching the cortex. The majority of the cerebellar tubers (11/12, 92%) showed a ''zebra-like'' contrast enhancement. All cerebellar tubers had increased ADC values (mean ADC 1472 $\times 10^{-6}$ mm^2/s). None of the patients had ''typical'' cerebellar symptoms.
Conclusion. — Thirty-three percent of TSC patients had cerebellar lesions, most of them being cerebellar tubers. Cerebellar tubers differ from supratentorial tubers both concerning shape and contrast behavior. The exact etiology of contrast enhancement remains unclear. Future studies have to determine the impact of cerebellar lesions on neurocognitive development.

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Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome characterized by multiple hamartomas in numerous organ systems [1]. TSC primarily affects the skin, brain, retina, heart, kidneys and lungs [2]. The genetic abnormality of this syndrome is a mutation of either the TSC1 or TSC2 gene. These tumor suppressor genes are found on chromosomes 9q,16p and encode for hamartin and tuberin proteins [2].

Involvement of the central nervous system (CNS) is the most common cause of morbidity and mortality in TSC. Clinically, TSC patients may present with seizures, developmental delay, behavioral problems and autism [2]. The major structural brain abnormalities of TSC include cortical and subcortical tubers, white matter lesions (linear radial bands and wedge-shaped white matter lesions), subependymal nodules (SEN) and subependymal giant cell astrocytomas (SGCA) [1].

Tubers are the hallmark of TSC. They are present in 80—95% of children with TSC and can be either cortical or subcortical [3,4]. They vary in size, number and location, with most of them located in the supratentorial brain, in particular in the frontal lobe [5]. Few reports studied the imaging findings of cerebellar TSC lesions [4,6,7]. Cerebellar tubers are reported to be uncommon, are not found in the absence of cerebral tubers and may be associated with global cerebellar volume loss. Jurkiewicz et al. [4] and Castillo et al. [6] both noted that cerebellar tubers may show different degrees of contrast enhancement. The exact etiology of the contrast enhancement is unclear. Castillo et al. [6] discussed that cerebellar tubers are areas of dysgenetic cortex without a normally developed blood-brain-barrier. Reviewing the literature, the reported incidence of contrast enhancement varies significantly. Braffman et al. [7] who studied 42 patients concluded that 3.4% of tubers showed a contrast enhancement. Jurkiewicz et al. [4] who focused on cerebellar findings in 73 children concluded that 52% of the cerebellar lesions showed a contrast enhancement.

The goal of our study was:

- to determine the incidence of cerebellar lesions in a cohort of children and young adults with confirmed TSC;
- and to systematically analyze the magnetic resonance imaging findings of cerebellar TSC lesions including their contrast behavior and diffusion characteristics.

Material and methods

Study design

Patients from birth to 25 years of age with an established diagnosis of TSC who underwent MRI/CT at the Johns Hopkins Hospital between January 2000 and January 2009 were retrospectively ascertained using a computer assisted search of all radiological reports using various keywords related to TSC. In addition, the hospital discharge records were electronically searched for TSC using the ICD-9-CM code.

Inclusion criteria for the study were confirmed diagnosis of TSC by clinical, radiological and neurological criteria, available MRI and DWI data sets and patient age less than 25 years. Patients were excluded if TSC was not definitely confirmed, imaging data were incomplete or of poor quality and if the clinical records were unavailable.

Demographic characteristics, clinical findings and relevant neurological data related to TSC were gathered from the electronic patient records.

Institutional review board approval was obtained for this Health Insurance Portability and Accountability Act (HIPAA) compliant study; a waiver of informed consent was granted.

Imaging and analysis

All patients were examined on a 1.5 Tesla MRI unit using the standard departmental protocols, which consisted of pre- and postcontrast T1-weighted, T2-weighted, Fluid Attenuated Inversion Recovery (FLAIR) and Diffusion Weighted Imaging (DWI) sequences. All DWI measurements used a balanced diffusion-weighted single-shot spin-echo echo-planar sequence, which was sampled along at least three, up to 18 different geometric directions. Apparent diffusion coefficient (ADC) maps were reconstructed using two b-values, 0 and 1000 sec/mm^2.

All patients were systematically evaluated for the presence, number, and location of supratentorial and infratentorial lesions by two experienced pediatric neuroradiologists in consensus (AT, TH). Following lesions were evaluated:

- cortical/subcortical tubers;
- white matter lesions;
- subependymal nodules;
- and giant cell astrocytomas.

A tuber was defined as a focal T1-hypointense, T2- and FLAIR-hyperintense lesion within the cortex or subcortical white matter, possibly associated with expansion of the involved gyri/folia [8]. In neonates the lesions may demonstrate opposite signal intensities because of the ongoing myelination.

White matter lesions were defined as linear or wedge shaped T1-hypointense, T2- and FLAIR-hyperintense radial, glial bands extending from the periventricular white matter towards the overlying cortex. Radial bands may terminate in a subcortical tuber [2,7,9].

Table 1 MRI Findings.

Variables	Number of patients, $n = 27$	
	Total	Enhancing
Supratentorial lesions, # (%)		
Subcortical cerebral tubers	26 (96%)	6 (23%)
White matter lesions	16 (59%)	0
Subependymal nodules	23 (85%)	20 (87%)
Giant cell astrocytomas	10 (37%)	9 (90%)
Infratentorial lesions, # (%)		
Subcortical cerebellar tubers	8 (29.6%)	7 (87.5%)
White matter lesions	0	0
Subependymal nodules	0	0
Cerebellar atrophy	1 (3%)	0