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 ± 10^{-6} mm²/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 including their contrast behavior and diffusion characteristics. The exact etiology of the contrast enhancement is unclear. Castillo et al. [6] discussed 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/mm2.

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>
<thead>
<tr>
<th>Variables</th>
<th>Number of patients, n = 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial lesions, # (%)</td>
<td></td>
</tr>
<tr>
<td>Subcortical cerebral tubers</td>
<td>26 (96%)</td>
</tr>
<tr>
<td>White matter lesions</td>
<td>16 (59%)</td>
</tr>
<tr>
<td>Subependymal nodules</td>
<td>23 (85%)</td>
</tr>
<tr>
<td>Giant cell astrocytomas</td>
<td>10 (37%)</td>
</tr>
<tr>
<td>Infratentorial lesions, # (%)</td>
<td></td>
</tr>
<tr>
<td>Subcortical cerebral tubers</td>
<td>8 (29.6%)</td>
</tr>
<tr>
<td>White matter lesions</td>
<td>0</td>
</tr>
<tr>
<td>Subependymal nodules</td>
<td>0</td>
</tr>
<tr>
<td>Cerebellar atrophy</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Table 1 MRI Findings.
Cerebellar lesions in children with TSC were defined as focal, non-obstructing, nodular hamartomatous subependymal lesions along the ventricles typically isointense to the gray matter but may be T1- and T2-hypointense due to calcifications [2,7].

SGCA's were defined as focal T1-hypointense, T2-hyperintense, strongly contrast enhancing mass lesions typically at the foramen of Monro with possible obstructive hydrocephalus [2].

In addition, images were studied for cerebellar atrophy, which is characterized by a widening of the cerebellar fissures and/or fourth ventricle [10].

Those patients who had cerebellar TSC involvement were further analyzed in detail. In these patients the observed cerebellar lesions and their imaging findings including contrast enhancement behavior were carefully studied and documented as well as their diffusion characteristics. ADC

| Table 2 | Clinical and Imaging findings of patients with cerebellar tubers (n = 8). |
|---|---|---|---|---|---|---|
| Patient | Age (months) | Cerebral tubers/SEN enhancement | Cerebellar tubers/GCA enhancement | SEN/GCA | Clinical findings |
| | | Right | Left | Right | Left |
| 1 | 32 | 26/1 | 20/0 | 1/1 | 1/1 | Present/absent |
| 2 | 48 | 13/0 | 8/0 | 1/1 | 0 | Present/absent |
| 3 | 59 | 10/0 | 11/0 | 0 | 1/1 | Present/absent |
| 4 | 88 | 7/1 | 9/1 | 0 | 3/3 | Present/absent |
| 5 | 103 | 10/0 | 5/0 | 1/1 | 1/1 | Present/present |
| 6 | 106 | 15/0 | 12/0 | 0 | 1/0 | Present/absent |
| 7 | 173 | 18/0 | 14/0 | 0 | 1/1 | Present/absent |
| 8 | 301 | 8/0 | 7/0 | 1/1 | 0 | Present/absent |

SEN: subependymal nodules; GCA: giant cell astrocytomas.
measurements of the cerebellar lesions were performed. For purpose of comparison, the ADC values of the normal appearing white matter of the contralateral cerebellar hemisphere were measured. FLAIR images were used as anatomical references for placement of the regions of interest (ROI). These ROI’s were superimposed to the corresponding ADC maps. The size of the (ROI’s) varied between 10–40 mm². Finally, in the patients with cerebellar lesions, the characteristics and incidence of supratentorial lesions was studied.

In those patients in whom cerebellar lesions were noted on imaging, the clinical charts were evaluated for symptoms suggesting cerebellar involvement (e.g. ataxia, tremor). All charts were reevaluated by an experienced pediatric neurologist (LJ).

Results

A total of 67 patients less than 25 years of age were identified with a confirmed or suspected diagnosis of TSC in the surveyed time period. After applying the exclusion criteria, 27 patients (14 males, 13 females, mean age, 10.6 years) who had high quality MRI/DWI images could be included in the study sample.

Table 1 summarizes the frequency of all studied TSC lesions in the patient group both for the supra- and infratentorial brain.

In the supratentorial region 26/27 (96%) had subcortical tubers. On postcontrast images, 6/26 patients (23%) showed a matching contrast enhancement.

Sixteen out of 27 patients (59%) had white matter lesions. Eight out of 16 patients (50%) had radial gial bands, the remainder of the patients (eight out of 16) (50%) had nonspecific foci. Twenty-three out of 27 (85%) patients had SEN’s and 10/27 (37%) patients had SGCA’s. Twenty out of 23 (87%) patients with SEN’s and nine out of 10 patients (90%) with SGCA’s showed a corresponding contrast enhancement.

Infratentorial lesions were seen in nine out of the 27 (33%) patients (two males, seven females, mean age, 10 years). Eight had cerebellar tubers and one had focal cerebellar atrophy. Table 2 summarizes the detailed imaging and clinical findings of patients with cerebellar tubers. All of the eight patients with cerebellar tubers also had cerebral tubers. None of the patients had isolated cerebellar tubers. All cerebellar tubers were triangular shaped with their base directing towards the cerebellar cortex (Figs. 1 and 2). The total number of cerebellar tubers observed in these eight patients was 12. Eleven (92%) of these tubers showed a contrast enhancement (Figs. 1 and 2). In the seven patients with enhancing cerebellar tubers two had simultaneous enhancing supratentorial tubers as well. However the percentage of supratentorial tubers with contrast enhancement was significantly lower, only three out of 166 supratentorial tubers showed an enhancement (1.8%). One patient who had focal cerebellar atrophy also had cerebral tubers (Fig. 3).

Six out of eight patients had clinical/neurological symptoms related to TSC. None of the patients had “typical” cerebellar symptoms. Three patients had cardiac lesions (rhabdomyomas), two patients had renal lesions (angiomyolipomas) and seven patients had cutaneous lesions typical of TSC. The patient with the non enhancing cerebellar tuber had no neurological symptoms; this patient was imaged for routine TSC screening based on findings outside of the CNS.

Table 3 summarizes the detailed MRI findings of the cerebellar tubers. Most cerebellar tubers were T1-hypointense/isointense, while T2-hyperintense or heterogeneous hypo/hyperintense. The cerebellar tubers were predominantly isointense or hypointense on FLAIR images (six out of eight patients).

All enhancing tubers of the cerebellum were pyramidal/wedge shaped with the broad base reaching the cerebellar cortex (Figs. 1 and 2). The tip of the tubers directed towards the fourth ventricle. The mean maximal diameter of the tubers was 1.5 cm, ranging between 1 and 2 cm. None of the cerebellar tubers exerted a local mass effect; the adjacent folial pattern was however distorted in

Figure 1  Axial T1 weighted pre- (a) and post-contrast (b) MR image of the cerebellum. A wedge shaped, T1-isointense cortical/subcortical tuber is seen in the right paramedian cerebellar hemisphere with a “zebra-like” contrast enhancement (b, arrowhead).
Cerebellar lesions in children with TSC

Figure 2  Axial T1-weighted pre- (a) and post-contrast (b) MR image of the cerebellum. Two T1-hypointense, wedge-shaped, cortical/subcortical tubers are seen in the left cerebellar hemisphere (a). Both tubers show a "zebra-like" contrast enhancement (b, arrows). The deepest part of the more medial tuber does not enhance.

Table 3  MRI findings of patients with cerebellar tubers.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (months)</th>
<th>T1</th>
<th>T2</th>
<th>FLAIR</th>
<th>T1 post contrast</th>
<th>Cerebellar tuber ADC (10^−6 mm²/sec)</th>
<th>Contralateral cerebellar ADC (10^−6 mm²/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>Iso/hypointense</td>
<td>Hyperintense</td>
<td>Isointense</td>
<td>Enhancing</td>
<td>1606—1182</td>
<td>779—779</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>Hypointense</td>
<td>Hyperintense</td>
<td>Hypointense</td>
<td>Enhancing</td>
<td>No DWI</td>
<td>No DWI</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>Isointense</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Enhancing</td>
<td>954</td>
<td>682</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
<td>Hypointense</td>
<td>Heterogenous</td>
<td>Heterogenous</td>
<td>Enhancing</td>
<td>1200—1122</td>
<td>672—701</td>
</tr>
<tr>
<td>5</td>
<td>103</td>
<td>Hypointense</td>
<td>Heterogenous</td>
<td>Heterogenous</td>
<td>Enhancing</td>
<td>1841</td>
<td>794</td>
</tr>
<tr>
<td>6</td>
<td>106</td>
<td>Hypo/isointense</td>
<td>Hyperintense</td>
<td>Hypo/isointense</td>
<td>Non enhancing</td>
<td>1084</td>
<td>905</td>
</tr>
<tr>
<td>7</td>
<td>173</td>
<td>Hypointense/heterogenous</td>
<td>Hyperintense/heterogenous</td>
<td>Hynointense</td>
<td>Enhancing</td>
<td>1650</td>
<td>552</td>
</tr>
<tr>
<td>8</td>
<td>301</td>
<td>Hypointense</td>
<td>Hyperintense</td>
<td>Hypointense</td>
<td>Enhancing</td>
<td>2228</td>
<td>700</td>
</tr>
</tbody>
</table>

seven out of eight (88%) patients and in nine out of 12 tubers (75%). The cerebellar tubers showed an inhomogeneous, "zebra-like” contrast enhancement involving both the cortical gray and subcortical white matter (Figs. 1 and 2). The only non-enhancing cerebellar tuber appeared significantly smaller than the contrast enhancing lesions.

The mean ADC value of all enhancing cerebellar tubers was 1472 × 10^−6 mm²/sec (varying between 954 and 2228 mm²/sec) while the mean ADC value of corresponding contralateral normal appearing cerebellar hemisphere was 706 × 10^−6 mm²/sec (Fig. 4). The ADC value of the non-enhancing tuber was 1080 × 10^−6 mm²/sec while the ADC value of the corresponding contralateral normal appearing cerebellar hemisphere was 905 × 10^−6 mm²/sec.

Discussion

Despite the fact that TSC represents a systemic disease, the supratentorial brain appears to be much more frequently affected than the cerebellum. Several previous studies have reported that cerebellar tubers occur in 9—44% of children with TSC [4,11—14], while supratentorial tubers are seen in 80—95% of children [3,4]. In our study cerebellar lesions were noticed in nine out of 27 (33%) children with TSC. Eight of them had cerebellar tubers and one had cerebellar atrophy. The incidence of cerebellar lesions as observed in our study matches with the previously reported studies.

We also noted that the MR imaging characteristic of cerebellar tubers differ from the supratentorial tubers. In our study we have noticed that 11/12 (92%) cerebellar tubers were wedge shaped with a broad basis towards the cerebellar cortex and a tip directing towards the fourth ventricle. The shape may be related to the complex cerebellar neuronal migration, which differs from the neuronal migration in the supratentorial brain. Compared to the supratentorial brain, the migration of granule cell neurons is in the reverse direction; from the external surface inward past the Purkinje dendrites and somas. Therefore, the wedge shape of the cerebellar lesions may be a result from the specific neuronal migration characteristics within the cerebellum [15].
In addition, the majority of the cerebellar lesions showed a "zebra-like" contrast enhancement (11/12, 92%). The "zebra-like" enhancement can be explained by the closely packed, alternating (horizontal) bands of cerebrospinal fluid within the cerebellar fissures, and cerebellar gray matter and white matter. The incidence of contrast enhancement differs however significantly from the supratentorial tubers of which only 23% showed a contrast enhancement. Contrast enhancement of cerebellar tubers has been studied previously. The reported incidence varies however considerably. Jurkiewicz et al. [4] reported in his study that 52% of the cerebellar lesions showed contrast enhancement; Girard et al. [16] observed enhancement in less than 10% of cerebellar tubers while Castillo et al. [6] identified three different sites of simultaneous contrast enhancement in one cerebellar tuber. In our study we noticed a higher percentage of contrast enhancement of the cerebellar tubers (11/12, 92%).

The exact etiology and significance of the contrast enhancement remains unclear. Few histological studies on the cerebellar lesions are available. Castillo et al. [6] discussed that cerebellar tubers represent areas of dysgenetic cortex without a blood-brain-barrier. One detailed histological study of Jay et al. on cerebellar tubers found a disorganization of the cerebellar neuronal architecture with maloriented Purkinje cells of different size and shape. In addition the Purkinje cells were distributed in various levels of the molecular and granular cell layers in an abnormal location. Moreover, multiple granule cells were seen intermixed with areas of gliosis and giant neurons with bizarre morphology. Finally, the affected cerebellum showed a marked depletion of myelin with white matter vacuolation and gliosis. Some of the affected cerebellar folia showed a severe atrophy [17,18]. These findings may support the thesis of Castillo et al. that the cerebellar cortex is maldeveloped/dysgenetic and may lack a normal development of a functional blood-brain-barrier, which explains the observed contrast enhancement. Due to the nature of the disease, rarely pathological specimens are available. In our patient population, no cerebellar biopsies had been performed. Future studies using functional studies including perfusion and permeability MRI sequences may possibly answer the mystery why cerebellar lesions in TSC enhance.

Contrast enhancing cerebellar lesions have been reported in Lhermitte- Duclos disease (LDD) which is a rare neoplastic-like entity affecting the cerebellum. LDD is closely associated with Cowden disease (CD) which is a multiple hamartoma-neoplasia syndrome affecting multiple organs [19—21]. Mutations of the PTEN gene, which result in an abnormal signaling pathway, are known to be present in both LDD and CD. Interestingly a similar mutation of the PTEN gene affecting the same signaling pathway has been described in TSC as well [3,22]. Despite the fact that currently no evidence is available suggesting that TSC may be linked to LDD/CD, further chromosomal analysis/studies may be of interest.

Cerebellar atrophy in TSC has been reported in the literature [4,10,23,24]. Focal atrophy can be seen more often around cerebellar tubers [4,10]. Cerebellar atrophy is found in approximately 4—12% of TSC patients. We noted mild cerebellar atrophy in only one of eight patients. This patient had no focal cerebellar lesions. Possibly, the cerebellar atrophy is an incidental finding.

Previous studies showed that cerebellar tubers do not seem to occur in the absence of cerebral cortical tubers [4,10,23,24]. We confirm these results; all our patients with cerebellar tuber had simultaneous cerebral involvement. This may indicate that patients with a cerebellar affection possibly represent a more severe form of TSC.

Diffusion weighted imaging is an advanced application of MRI used for evaluation of the microstructure of the brain [25]. ADC values may be altered by changes in the tissue integrity that occurs as a result of pathologic processes. Several studies in the past have analyzed the ADC values of the tubers in TSC [25—27]. They found that the ADC values of cerebral cortical tubers were significantly higher compared to matching normal appearing brain tissue. In our study the cerebellar tubers also showed significantly increased ADC.

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values. The previous studies discussed that the increased ADC values may result from focal gliosis combined with areas of hypomyelination and loss of the structural barriers to water motion, which was also confirmed by histological studies [17]. The described giant neurons with bizarre morphology could also contribute to the increased ADC values. Correlative histological-clinical-DWI studies appear mandatory to evaluate the significance of these findings.

Interestingly, none of our patients with cerebellar findings had focal neurological symptoms that would indicate cerebellar involvement. Several previous studies have described cerebellar symptoms in TSC patients [17,28]. However, in the majority of cases cerebellar lesions are known to be clinically silent [4,23]. This may however also be due to the fact that TSC patients are not explicitly examined for discrete focal cerebellar signs. However, it has been debated that early cerebellar injuries/ malformations may have an impact on the overall cognitive development of children. In our patients five patients had signs of developmental delay. Future studies are mandatory to determine the exact relation between cerebellar affection in TSC and the degree and incidence of developmental delay. In addition, the relation between cerebellar lesions and autism should be studied in detail. Several previous studies have suggested a relation between cerebellar pathology and autism [29]. A recent study of Eluvathingal comparing TSC patients with and without cerebellar lesions confirmed that patients with cerebellar affection had higher overall autistic symptomatology [30]. Moreover, they also showed that children with right-sided cerebellar lesions had higher social isolation and communicative and developmental disturbances compared to children with left-sided cerebellar lesions.

Our study has several limitations. Our study is retrospective in design, consequently imaging protocols changed slightly over time, our stated study goals may have biased/increased the observed incidence of cerebellar TSC lesions, no detailed prospective neuropsychological evaluation was performed, no follow up examinations were performed and no correlative pathological specimens were available. Future prospective studies are mandatory.

Conclusion

The cerebellum is less frequently involved than the cerebrum in TSC patients. The cerebellar tubers differ in shape and contrast behavior compared to cerebral tubers. Similar patterns of contrast enhancement are noted in LDD and Cowden’s disease; further genetic analysis may reveal a possible overlap. In addition it is debated that cerebellar lesions may result from an altered cerebellar neuronal migration with incomplete blood brain barrier development which would at least partially explain the higher incidence of contrast enhancement of cerebellar tubers compared to cerebral tubers as well as the elevated ADC values within these cerebellar tubers. The impact of cerebellar lesions on the neurocognitive development of children has still to be determined. In our cases, no “typical” cerebellar signs were noted. Future, prospective studies correlating normal cerebellar and neurocognitive development are mandatory.

Conflicts of interest

The authors declare to have no conflict of interest.

References


