**Tuberous sclerosis: evaluation of intracranial lesions**

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**Abstract**

Tuberous sclerosis is a neurocutaneous disease characterized by the clinical triad (Vogt triad) of mental retardation, seizures and skin lesions (sebaceous adenoma). It is also characterized by typical intracranial findings that lead to this diagnosis.

The aim of this pictorial essay is to describe and provide examples of intracranial findings characteristic of tuberous sclerosis using images from our case series.

**Keywords:** cortical tubers; subependymal hamartomas; intracranial lesions; neurocutaneous disease

**Introduction**

The objective of this pictorial essay is to describe and provide examples of intracranial imaging findings of tuberous sclerosis (TS) extracted from our case series.

Tuberous sclerosis is a neurocutaneous syndrome formerly described by Bourneville in 1880 (also known as Bourneville disease). This entity is an inherited autosomal dominant disease caused by mutation or deletion of two genes: one on chromosome 9, known as TSC1, and the other one on chromosome 16, known as TSC2. This neurocutaneous disease is characterized by the presence of a clinical triad (Vogt triad) of mental retardation, seizures and skin lesions (sebaceous adenoma, also called facial angiofibroma). All three signs are present in 30% of the cases. Diagnosis of the tuberous sclerosis complex (TSC) is made on the basis of clinical features, using major and minor diagnostic criteria (table 1). Based on these parameters, clinical diagnosis is considered to be:

- **Definite:** when either two major criteria or one major criterion with two minor criteria are met.
- **Probable:** when one major criterion and one minor criterion are met.
- **Possible:** when wither 1 major criterion or two or more minor criteria are met.

In our study, only intracranial findings are detailed. Within neurological signs and symptoms, seizures are the most common (82%). Seizures may be of any type except the so-called petit mal (absence seizures). Mental retardation occurs in 48% of cases and it may be very severe, mainly in patients who had a very early seizure onset.

**Table 1: Diagnostic criteria for tuberous sclerosis**

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Age at onset</th>
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<tbody>
<tr>
<td>Facial angiofibroma</td>
<td>Infancy to adulthood</td>
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<tr>
<td>Ungual fibroma</td>
<td>Adolescence to adulthood</td>
</tr>
<tr>
<td>Shagreen patch</td>
<td>Infancy</td>
</tr>
<tr>
<td>Hypomelanotic macule</td>
<td>Infancy</td>
</tr>
<tr>
<td>Cortical tuber</td>
<td>Fetal life</td>
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<tr>
<td>Subependymal hamartoma</td>
<td>Childhood to adolescence</td>
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<tr>
<td>Subependymal giant-cell astrocytoma</td>
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<tr>
<td>Retinal hamartoma</td>
<td>Infancy</td>
</tr>
<tr>
<td>Cardiac rhabdomyoma</td>
<td>Fetal life</td>
</tr>
<tr>
<td>Renal angiomylipoma</td>
<td>Childhood to adulthood</td>
</tr>
<tr>
<td>Lymphangiomylipomatosis</td>
<td>Adolescence to adulthood</td>
</tr>
<tr>
<td>Minor criteria</td>
<td></td>
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<tr>
<td>Multiple pits in dental enamel</td>
<td></td>
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<tr>
<td>Hamartomatous rectal polyps</td>
<td></td>
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<tr>
<td>Bone cysts</td>
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<tr>
<td>Cerebral white-matter</td>
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<tr>
<td>radial migration lines</td>
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<tr>
<td>Gingival fibromas</td>
<td></td>
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<tr>
<td>Retinal achromatic patch</td>
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<tr>
<td>“Confetti” skin lesions</td>
<td></td>
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<tr>
<td>(groups of small, lightly pigmented spots)</td>
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<tr>
<td>Multiple renal cysts</td>
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</table>
There is a correlation between the number and volume of cortical tubers, the age of onset of seizures and the degree of mental retardation: the earlier cortical tubers develop the earlier seizures occur, hence, the greater degree of mental retardation. The number and anatomic location of cortical tubers may play an important role in the development of mental retardation\textsuperscript{4}.

However, some individuals with TS never had seizures and have a normal intelligence quotient. In addition, other neurological findings may occur, such as hyperactivity, behavioral abnormalities, autism and attention deficit.

**Development**

The main cerebral abnormality in TS is related to dysplastic stem cells, which give rise to dysplastic glia and neurons that are unable to differentiate, migrate or organize properly\textsuperscript{5}.

**Subependymal hamartomas**

Subependymal hamartomas, also known as subependymal nodules, are small lesions which histologically consist of giant cells with features of neurons and astrocytes. These hamarto-
Figure 3 Axial MRI in a 7-year-old female patient. The scan shows a large, ovoid and solid intraventricular mass located on the right lateral ventricle. The mass is hyperintense on T2, isointense on T1 and is significantly enhanced after the administration of paramagnetic contrast agents. This image is consistent with a subependymal giant cell astrocytoma.

Figure 4 Cortical tubers. The axial T2-weighted image shows a hyperintense lesion on the left frontal subcortical white matter involving two adjacent gyri and called “sulcal island” (black arrow). The coronal T2-weighted image sows a hyperintense lesion located in the core of an expanded gyrus, called “gyral core” (white arrow).
mas are located on the wall of the lateral ventricles and their appearance on computed tomography (CT) and magnetic resonance imaging (MRI) varies with the age of the patient. Their size is variable, but no greater than 10 mm in diameter. On CT scans, subependymal hamartomas are isodense to the white matter, but in older patients they may calcify and become hyperdense (fig. 1). Even if hamartomas calcify progressively during the first two decades of life, a calcified nodule is hardly found in patients younger than 1 year of age. Regarding the location of hamartomas, they either protrude into the lateral ventricles or are “embedded” in the contour of the caudate nuclei, being bilateral in 95% of the cases. On MRI, subependymal hamartomas in newborns are slightly hyperintense on T1-weighted images compared with the

Figure 5 Parenchymal cyst. Cystic lesion, which is hyperintense on T2-weighted image (b) and hypointense on T1-weighted image (a) and FLAIR (c), located in the periventricular white matter, adjacent to the occipital prolongation of the right lateral ventricle (arrows).

Figure 6 White matter hamartomas. CT scan and MRI in a 2-year-old patient with a lesion in the white matter located on the left external capsule (arrows). CT scan shows a hyperdense lesion correlated with calcification, while on MRI, the lesion appears hypointense on T2-weighted imaging and hyperintense on T1-weighted imaging.
white matter and of heterogeneous intensity on T2-weighted images, due to the hypomyelination of the white matter. As myelination occurs, nodules become isointense to the white matter on T1- and T2-weighted images. If they calcify, they are markedly hypointense on gradient echo sequences (GRE). Post-contrast paramagnetic uptake is variable (fig. 2), with an absence of enhancement being more frequent.

**Subependymal astrocytomas**

Subependymal giant cell astrocytomas are histologically benign tumors formed by giant cells which present features of astrocytes and neurons. The age of onset is between 8 and 18 years old, and their typical location is near the foramen of Monro. Subependymal astrocytomas may cause obstructive hydrocephaly. Compared with subependymal hamartomas, astrocytomas are larger and tend to grow slowly. Their diagnosis and follow-up are important, because if they grow and produce obstructive hydrocephaly, neurosurgery may be required.

On CT and MRI, subependymal astrocytomas are similar to subependymal hamartomas. Despite their larger size, they are usually enhanced by paramagnetic contrast agents, and they may calcify and bleed. Differential diagnosis with subependymal hamartomas is determined by the follow-up of their evolution, since subependymal astrocytomas grow whereas hamartomas do not. Subependymal astrocytomas may also appear as large heterogeneous intraventricular masses that enhance after intravenous contrast administration (fig. 3).

**Cortical tubers**

Cortical tubers are benign hamartomatous lesions, which rarely become malignant. They may be single or multiple (more frequent) and they most commonly occur in the frontal lobes, followed by the parietal, occipital and temporal lobes (in decreasing order). Histologically they consist of bizarre giant cells, dense fibrillary gliosis and disorganized myelin sheaths.

On CT scan, tubers appear hyperdense in newborns and infants, while adjacent subarachnoid spaces are usually widened. However, they become hypodense throughout years and may also calcify.

On MRI, in the first years of life cortical tubers appear slightly hyperintense on T1-weighted sequences with respect to the white matter, and hypointense on T2-weighted images. As the brain myelinates, tubers become iso-hypointense on T1-weighted images and hyperintense on T2-weighted images.
FLAIR sequence has an enhanced sensitivity in the diagnosis of cortical tubers both in children and adults. Cortical tubers appear as hyperintense images of diffuse limits at the site where the lesions are located. When tubers calcify, they often appear hypointense on GRE sequences and slightly hyperintense on T1-weighted images.

Some authors divide cortical tubers into two types (fig. 4): gyral core and sulcal island. A gyral core appears hyperintense on T2-weighted images and hypointense on T1-weighted images, located in the inner core of an expanded (widened) gyrus, with a cortex of normal thickness. Sulcal islands are lesions in which the subcortical white matter appears hyperintense on T2-weighted images and iso-hypointense on T1-weighted images, involving two adjacent gyri. Their cortex is of normal thickness.

Parenchymal cysts

Even if these lesions are ubiquitous in its location, they are mostly found in the periventricular white matter. The clinical significance of these lesions is unknown.

On CT scan, parenchymal cysts appear as round hypodense images. On MRI, they appear hyperintense on T2-weighted images and hypointense on T1-weighted images and FLAIR (fig. 5).

White matter hamartomas

These lesions are formed by giant cells that are 5 to 10 times larger than astrocytes with features of neurons and glial cells. White matter hamartomas are of variable size. While small lesions are punctiform, hyperintense on T2-weighted images and FLAIR, large lesions have various appearances: they can be linear, cuneiform or form a conglomerate. However, the most common appearance is a linear pattern extending from the periventricular region to the cortex, known as “radial migration lines”.

Figure 10 (a) Axial T2-weighted image in a 1-year-old patient with subependymal hamartomas in both lateral ventricles (white arrows), and cortical tubers (circle). (b) On diffusion weighted imaging, subependymal hamartomas are isointense to the white matter (arrows), while on apparent diffusion coefficient, subependymal hamartomas are isointense or slightly hypointense to the white matter (arrows). This might be related to calcification of hamartomas. Cortical tubers are hyperintense on apparent diffusion coefficient (circle), with facilitated diffusion.
Figure 11 Monovoxel Spectroscopy with PRESS sequences, echo time 25ms; (a) normal side and (b) assessment of a cortical tuber, showing a decrease in the N-acetyl aspartate peak, an increase in the myo-inositol peak and a normal choline peak.
On CT scan, these lesions are usually slightly hypodense and may also calcify (fig. 6), while on MRI they are hyperintense on T2-weighted images and FLAIR (figs. 7 and 8). They rarely enhance after contrast administration.

Some authors report that these lesions are identical to transmantine cortical dysplasias\textsuperscript{10}.

**FLAIR and susceptibility-weighted imaging**

In MRI, FLAIR and GRE sequences play a key role. On the one hand, the FLAIR sequence is more sensitive than T2-weighted imaging for the diagnosis of cortical tubers (which appear as hyperintense with diffuse borders at the subcortical level) and more accurate for identifying white matter lesions. GRE imaging is particularly helpful for diagnosing calcified lesions. Calcium appears as hypointense on GRE sequences, while on all other conventional sequences it may appear with various signal intensities or even be undetected. Nevertheless, new magnetic susceptibility sequences are currently available, known as susceptibility weighted imaging (SWI) and susceptibility weighted angiographies (SWAN), which are more sensitive than echo gradient sequences for the detection of calcification.

On GRE sequences, calcified subependymal hamartomas usually appear as hypointense small nodules along the walls of the lateral ventricles (fig. 9).

**Magnetic resonance diffusion weighted imaging and spectroscopy**

On diffusion weighted imaging (DWI), cortical tubers show an increase in the apparent diffusion coefficient (ADC), which reflects an expansion of the extracellular space and is due to the presence of astrogliosis and hypomyelination\textsuperscript{11}. Subependymal hamartomas may, in turn, have changes in diffusion as a result of calcification. These lesions are generally isointense to healthy parenchyma on DWI and ADC (fig. 10).

As regards to the magnetic resonance spectroscopy findings in cortical tubers, there is no increase in choline (Cho) that might suggest increased mitosis; instead, there is a significant reduction in the N-acetyl aspartate/creatinine (NAA/Cr) and NAA/(Cho+Cr) ratios at the expense of a decrease in NAA (fig. 11). The reduction in NAA is due to the fact that cells forming cortical tubers produce less NAA than neurons\textsuperscript{12}.

An increase in myo-inositol has also been found in cortical tubers, which might be explained by the presence of gliosis or immature neurons\textsuperscript{13}.

Subependymal hamartomas cannot be assessed by spectroscopy because of their periventricular location, since the cerebrospinal fluid alters the spectrum.

**Conclusion**

We should be aware of and keep in mind the typical intracranial findings of tuberous sclerosis, since these constitute the major and minor diagnostic criteria for this disease.

The most frequent intracranial findings are subependymal hamartomas and cortical tubers. We should also be aware of the fact that intraventricular giant cell astrocytomas may cause hydrocephaly and that these lesions are usually located near the foramen of Monro, causing its obstruction.

**Conflicts of interest**

The authors declare no conflicts of interest.

**References**