

Imaging of central nervous system manifestations of Tuberous Sclerosis: a current pictorial review for an “old” disease

Imagem em manifestações de Esclerose Tuberosa no sistema nervoso central: um ensaio pictórico atual para uma doença “antiga”

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ABSTRACT

Tuberous Sclerosis is a genetic multisystemic disease that mainly affects the central nervous system (CNS) of patients at any age. This study illustrates the neuroimaging findings that are included in the clinical diagnostic criteria in a group of patients with tuberous sclerosis (TS) of two tertiary university hospitals. The neuroimaging findings, in order of frequency, are cortical tubers, subependymal nodules, white matter abnormalities and subependymal giant cells astrocytomas. All these lesions represent disorganized neurons and glial cells. Cerebellar and

hippocampal abnormalities have also been described in TS. Neuroimaging, particularly magnetic resonance imaging (MRI), has a crucial role in the evaluation and diagnosis of tuberous sclerosis, especially in atypical clinical presentations or in cases of inadequate therapeutic response.

Keywords: Tuberous Sclerosis Complex, computed tomography, magnetic resonance imaging.

RESUMO

A esclerose tuberosa é uma doença genética multissistêmica que afeta principalmente o sistema nervoso central (SNC) de pacientes em qualquer idade. Este estudo ilustra os achados de neuroimagem que estão incluídos nos critérios de diagnóstico clínico em um grupo de pacientes com esclerose tuberosa (ET) de dois hospitais universitários terciários. Os achados de neuroimagem, em ordem de frequência, são tubérculos corticais, nódulos subependimários, anormalidades da substância branca e astrocitomas subependimários de células gigantes. Todas essas lesões representam neurônios e células gliais desorganizados. Anormalidades cerebelares e hipocampais também foram descritas na ST. A neuroimagem, particularmente a ressonância magnética (RM), tem um papel crucial na avaliação e no diagnóstico da esclerose tuberosa, especialmente em apresentações clínicas atípicas ou em casos de resposta terapêutica inadequada.

Palavras-chave: Complexo de Esclerose Tuberosa, tomografia computadorizada, imagem por ressonância magnética.

1 TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex (TSC) is a neurocutaneous autosomal dominant disorder with heterogenous manifestations in each individual affecting many systems. It is caused by a mutation in the TSC1 or TSC2 genes, which are responsible for the transcription of a hamartin/tuberin dimer, mostly associated with “de novo” mutations. It is characterized by the occurrence of multiple benign tumors of the embryonic ectoderm involving the brain, heart, skin, eyes, kidney, liver and lungs⁽¹⁾.

Although most patients are diagnosed in infancy or early childhood, TSC can vary substantially in its age of onset and severity of disease, even among individuals within the same family⁽²⁾. TSC can be diagnosed by genetic testing and/or a combination of clinical and imaging criteria. A TSC1 or TSC2 pathogenic DNA mutation detected in normal tissue is sufficient for the diagnosis of TSC. The clinical and imaging criteria include 11 major and 6 minor features, requiring two major features or one major and two minor features to establish a definite diagnosis⁽³⁾ (Table 1).

Magnetic resonance imaging (MRI) is the main tool to evaluate lesions of the central nervous system and has been the subject of a series of papers in the radiology literature⁽⁴⁻³³⁾.

2 CLINICAL FEATURES

There is no typical presentation of TSC due to the wide range of clinical features and organ involvement. Brain, kidneys, lungs, skin, eyes, liver and heart are the most common organs affected. Severity and age of the onset of the signs and symptoms are highly variable⁽³⁴⁾.

Neurological manifestations are the most common, with epilepsy affecting up to 90% of patients. Other neurological symptoms include behavioral disorders, cognitive impairment and autism, which are present in 50-60% of the individuals. Early recognition and control of seizures is associated with a better cognitive development^(35,36).

Non-neurological manifestations include cutaneous lesions, like facial angiofibromas, and ungueal or gingival fibromas, and renal lesions, like angiomyolipomas (AMLs), isolated renal cysts, autosomal dominant polycystic kidney disease (PKD), and renal cell carcinoma (RCC). Cardiac, ophthalmic and pulmonary systems are also affected with rhabdomyomas, retinal hamartomas, proliferation of type II pneumocytes, pulmonary cysts, and lymphangiomyomatosis (LAM)⁽³⁷⁾.

Clinical diagnostic criteria are important, as the genetic evaluation currently available may not detect a mutation in up to 25% of patients⁽³⁸⁾.

3 CNS LESIONS

CNS characteristic lesions of TSC included in the diagnostic criteria are cortical tubers, white matter abnormalities, subependymal nodules (SENs) and subependymal giant cells astrocytomas (SEGAs)⁽³⁾ (Figures 1 and 2).

We revisited the main neurological findings of TSC based on a review of the literature and cases with a definitive diagnosis of two tertiary university hospitals.

4 CORTICAL TUBERS

Cortical tubers are benign hamartomas of the cerebral cortex and are associated with the neurological manifestations of TSC, including epilepsy, cognitive impairment and behavioral symptoms. They are composed by abnormal neurons and glial cells, shaped like triangles with the apex pointed towards the ventricle, and can appear anywhere in the brain parenchyma, about half of them located in frontal lobes⁽³⁹⁾. Cortical tubers are observed in 95% of the patients⁽³⁸⁾.

On computed tomography (CT), cortical tubers present as areas of decreased attenuation or eventually as calcified lesions after 2 years of age. On MRI, adult patients usually demonstrate lesions with increased signal intensity on T2-weighted images (WI) and FLAIR WI, decreased or intermediate intensity on T1 WI, and only 10% show enhancement after

contrast administration⁽⁴⁰⁾ (Figure 3). Due to the scarce myelination in neonates and infants under 3 months, cortical tubers are seen as hypointense on T2 WI and hyperintense on T1 WI, an opposed pattern of signal intensity in adults⁽⁴¹⁾ (Figure 4).

5 WHITE MATTER ABNORMALITIES

White matter abnormalities are less frequent than cortical tubers and subependymal nodules, but more frequent than SEGAs⁽⁴²⁾.

Among the spectrum of white matter abnormalities, which includes superficial abnormalities associated with cortical tubers and cyst-like white matter lesions, the most important in our review are radial white matter bands or radial migration lines (RML).

RMLs are a minor diagnostic feature of TSC, representing linear bands on MRI, extending from the periventricular white matter to the subcortical region. They appear as thin lines or bands of hyperintensity signal on T2 WI and isointensity signal on T1 WI, usually running from juxta-ventricular white-matter extending to the deep surface of cortical tubers. RMLs are more common in frontal lobes⁽³⁹⁾ (Figure 5).

Cyst-like white matter lesions are seen on MR images as round, oval, or linear structures with signal intensity similar to cerebrospinal fluid and are usually found in the deep white matter⁽⁴²⁾ (Figure 2).

6 SUBEPENDYMAL NODULES AND SUBEPENDYMAL GIANT CELLS ASTROCYTOMAS

SENs are constituted of abnormal swollen glial cells and giant cells that cannot be differentiated from normal neural tissue. They tend to calcify over the time and are thought to progress into SEGAs, which would explain why they are histologically indistinguishable^(39,43).

One of the most relevant complications in TSC patients is the development of SEGAs. Usually, the prognosis is good as they grow slowly, but its location, usually at foramen of Monro, can cause ventricular obstruction and hydrocephalus^(44,45).

The typical appearance of SENs on unenhanced CT is small calcified periventricular lesions while SEGAs are similar, but larger (Figure 6). MR imaging shows variability but usually demonstrates iso/hyperintense signal on T1 WI and iso/ hyperintense signal on T2 WI^(39,40) (Figure 7).

Although histologically indistinguishable, image findings are helpful to identify a transformation of a SEN into a SEGAs. Serial imaging is used to monitor growth and lesions

with 10 mm or larger, incompletely calcified or with enhancement are suspicious for SEGA⁽⁴⁶⁾ (Figure 8, 9 and 10).

In a previous report, the ¹H-MRS of SEGA showed high choline to creatine ratio (1.60) and low NAA/Cr (0.93) ratio, similar to other brain neoplasms⁽⁴⁷⁾. The authors suggested the ¹H-MRS might be a valuable tool for early detection of neoplastic transformation in subependymal nodules arising near to the foramen of Monro. However, there are few papers that assessed the ¹H-MRS features in this region, trying to establish the role of ¹H-MRS for monitoring TSC patients, although ¹H-MRS has theoretically the potential to detect changes in cellular turnover even before the nodule grown, allowing a precocious diagnosis of a SEGA⁽⁴⁷⁾.

7 HIPPOCAMPAL AND CEREBELLAR ABNORMALITIES

Other structures of the CNS are often affected as well. Cerebellum is involved in approximately 30% of patients. Cerebellar lesions also represent tubers and are usually wedge-shaped masses with or without calcification and mostly seen in the posterior lobe, which has mainly cognitive functions and are associated with autistic manifestations⁽⁴⁸⁾. The lesions are hypointense on T1 W1 and can be hyperintense on T2 W1 and FLAIR if non-calcified or hypointense, if calcified⁽⁴⁸⁾ (Figure 11).

Hippocampal abnormalities also are described in patients with TS. Mesial temporal sclerosis (MTS) is the main finding, but hippocampal malrotation (HIMAL) can eventually be seen (Figure 11). HIMAL is a failure of hippocampus to properly fold around the hippocampal sulcus, which is completed by the 25th gestational week. Hippocampal abnormalities are associated with epileptic symptoms^(49,50).

8 CONCLUSION

Multimodal brain MRI, echocardiography, skin examination and genetic testing should be performed early in every patient suspected of having TS. Besides the classic lesions (cortical tubers in cerebral hemispheres, subependymal nodules, white matter abnormalities and subependymal giant cells astrocytoma), cerebellar and hippocampal abnormalities have also been described in TS. The role of spectroscopy to depict SEGA must be established.

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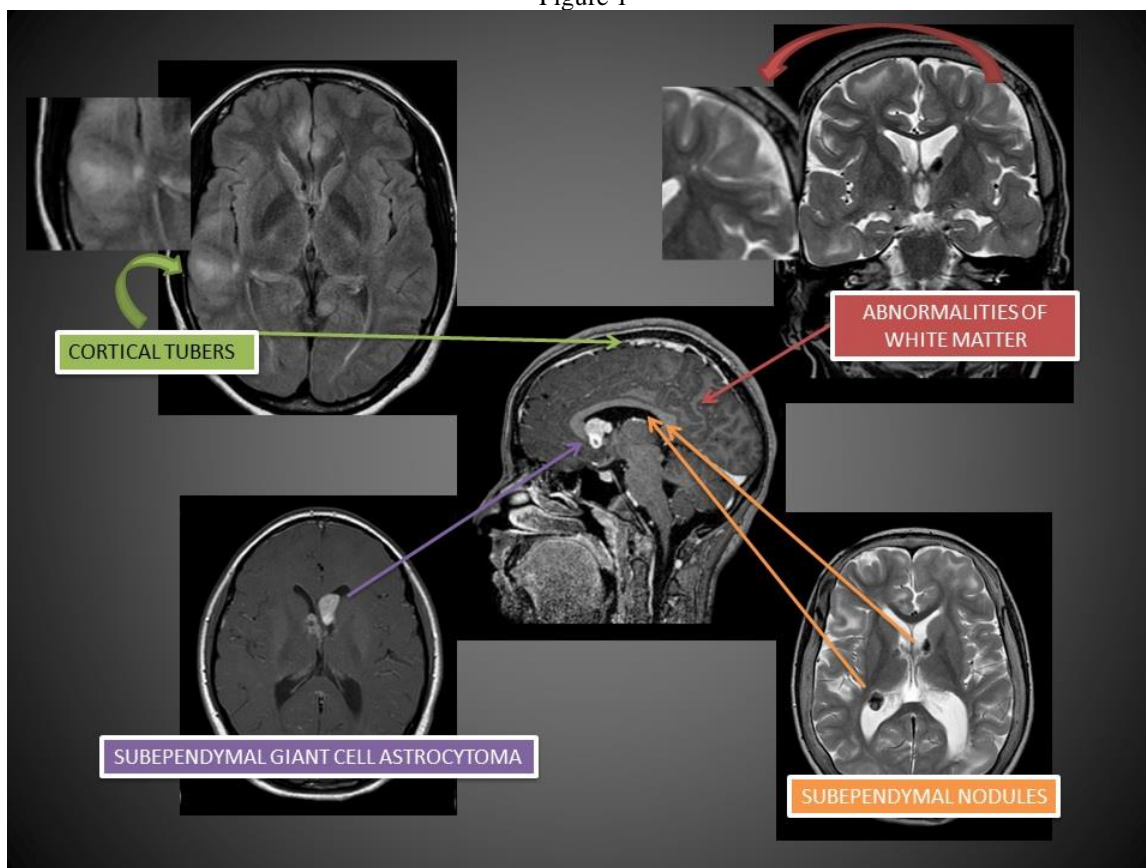
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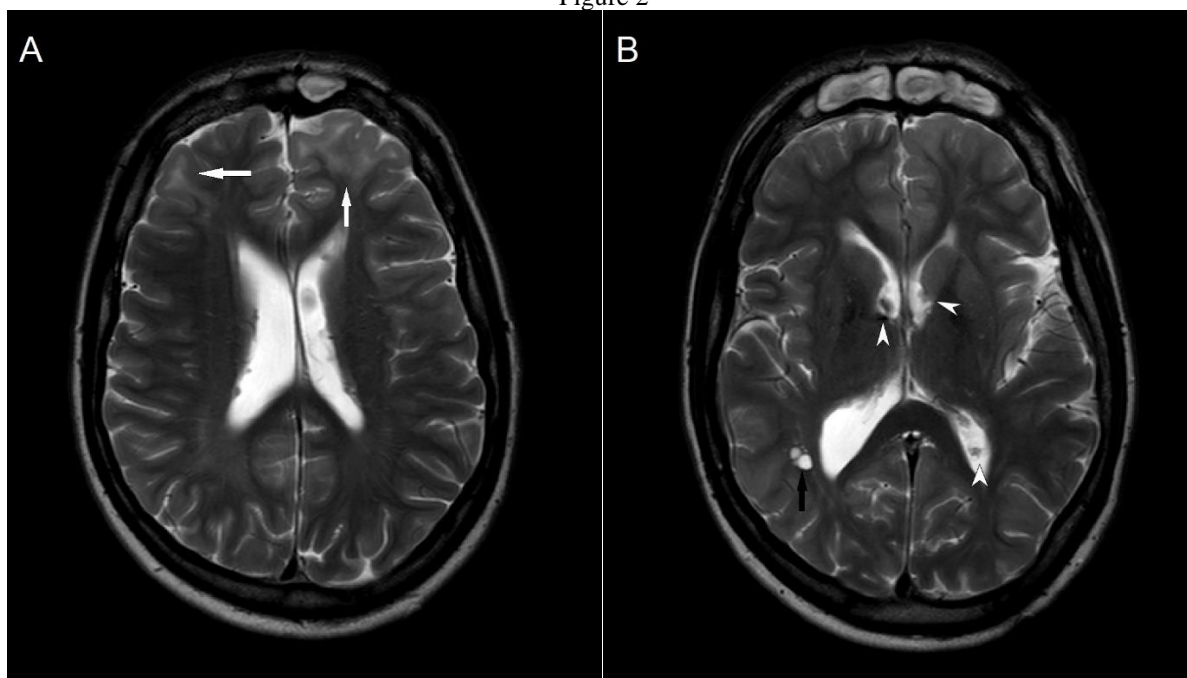
ANEXOS

Figure 1



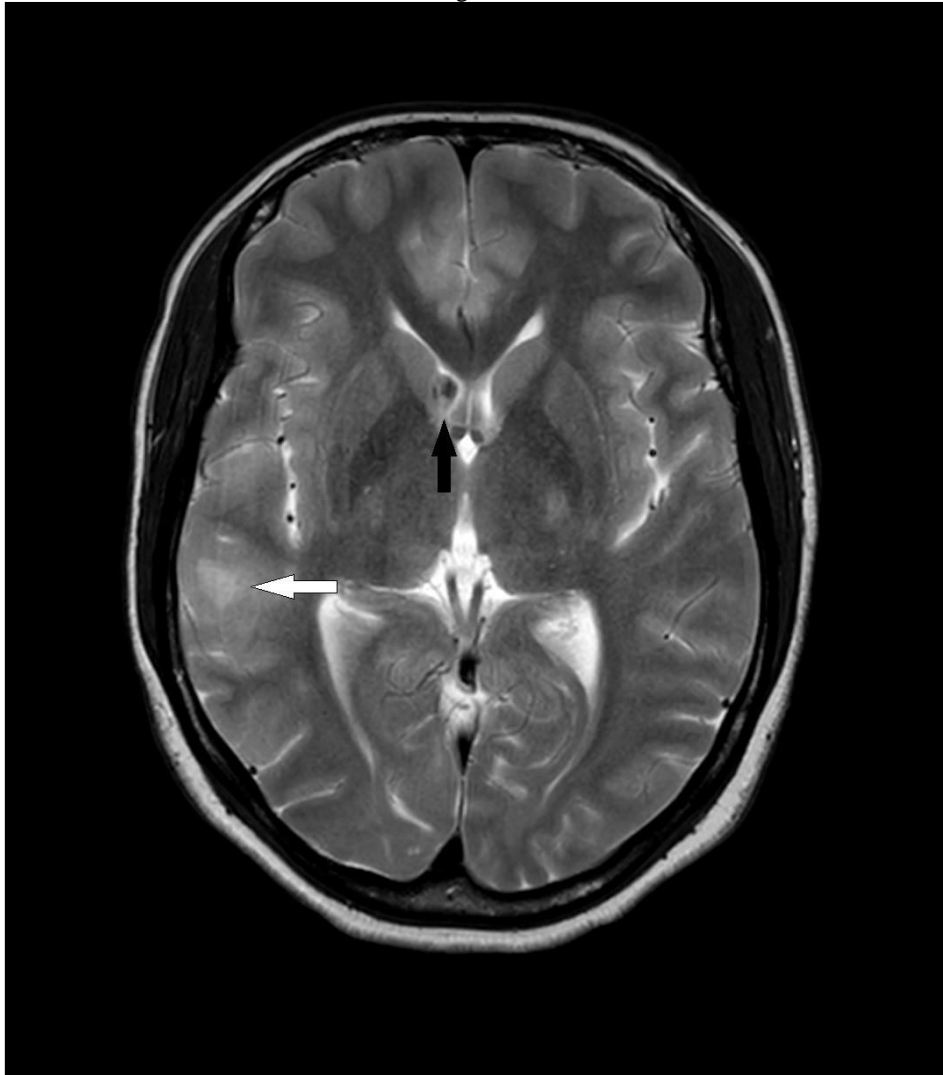
MRI images of the central nervous system characteristic lesions of tuberous sclerosis complex.

Figure 2



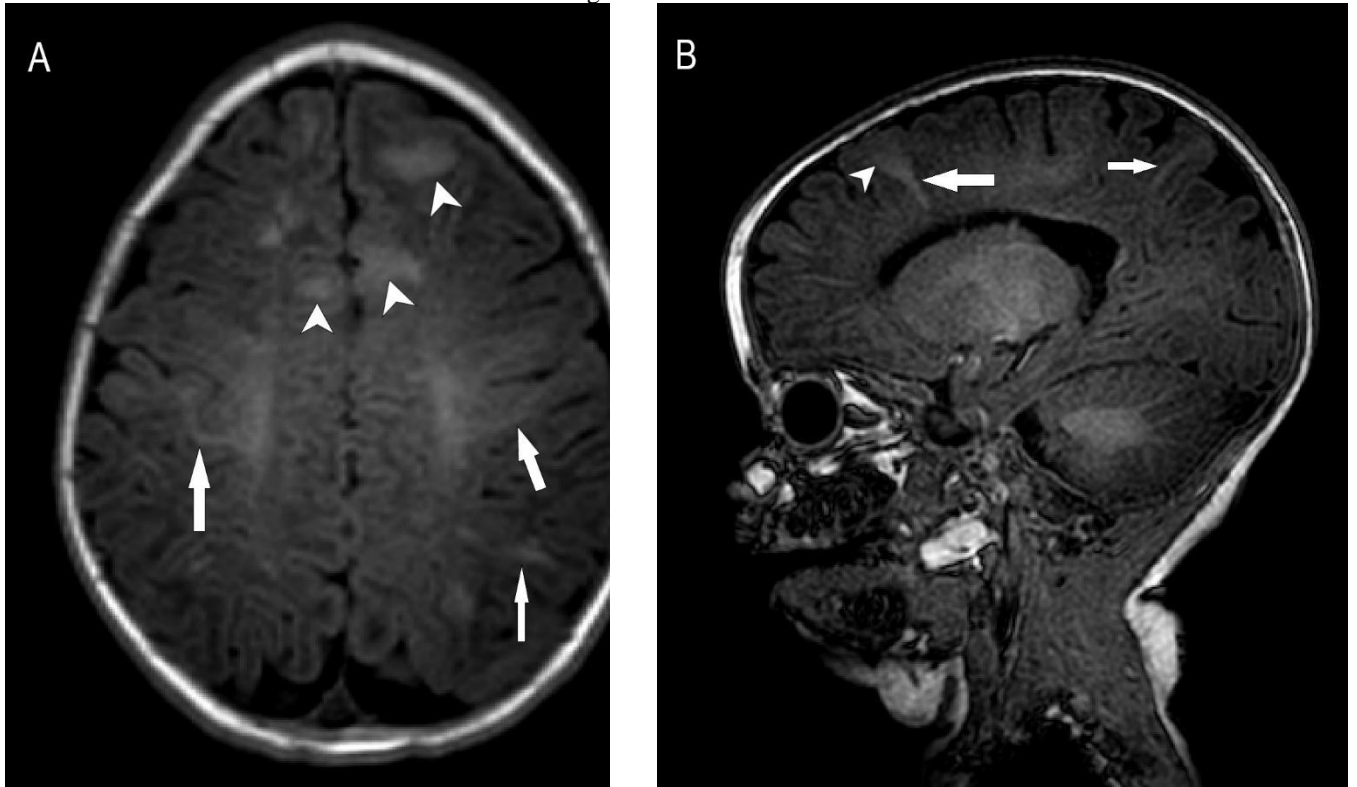
A 35-year-old man with tuberous sclerosis complex. Axial T2-WI shows cortical tubers in (A) (white arrows), cystlike lesions in the white matter (black arrows) and subependymal nodules in (B) (arrowheads).

Figure 3



A 28-year-old man with tuberous sclerosis complex. MR Axial T2-WI shows a cortical tuber, shaped like a triangle, with increased signal intensity (white arrow). It can also be seen a nodular lesion in the right frontal horn of the lateral ventricle near the Monro foramen that may correspond to a subependymal giant cell astrocytoma (black arrow).

Figure 4



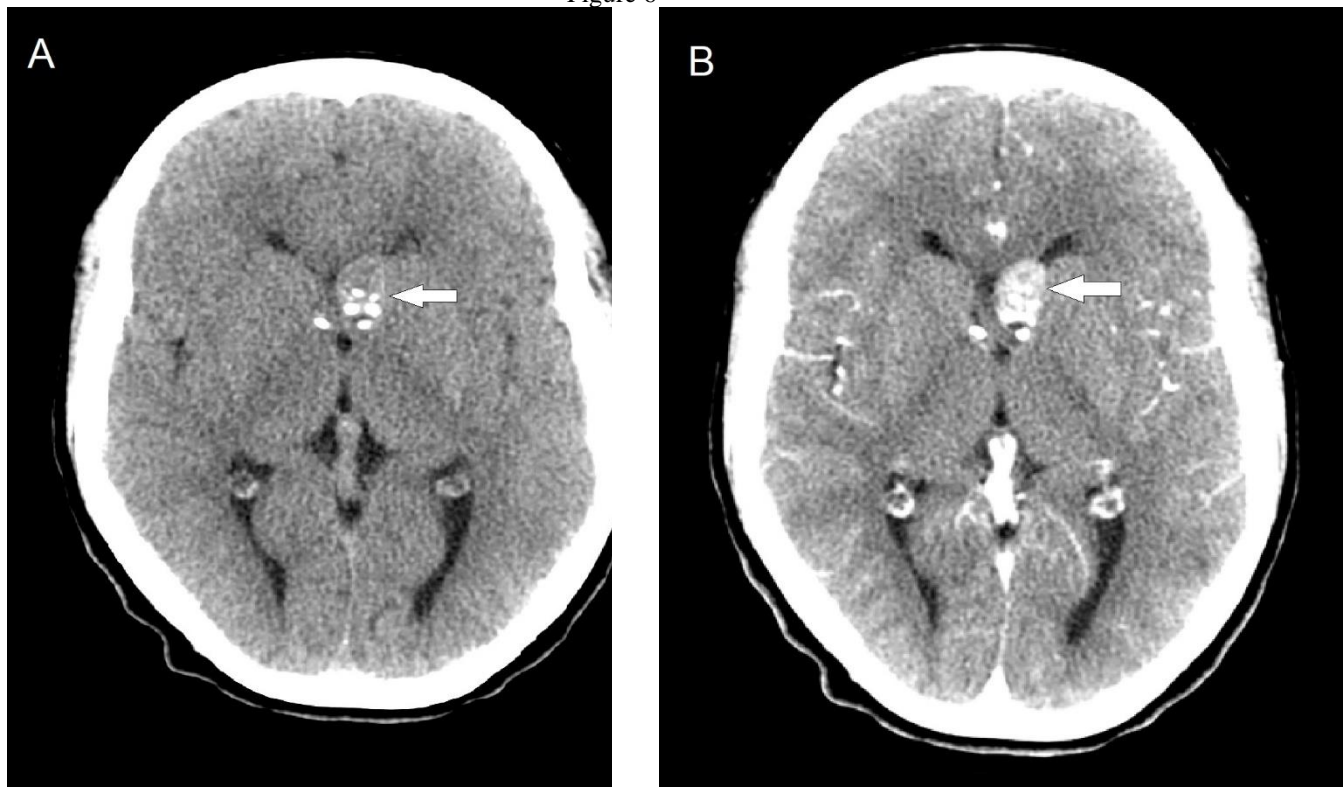
A 3-month-old baby with tuberous sclerosis complex. Axial (A) and Sagittal (B) T1 WI show cortical tubers (arrowheads) and linear bands (white arrows), with an increased signal intensity (in adults these lesions demonstrate hypointensity on T1 WI).

Figure 5



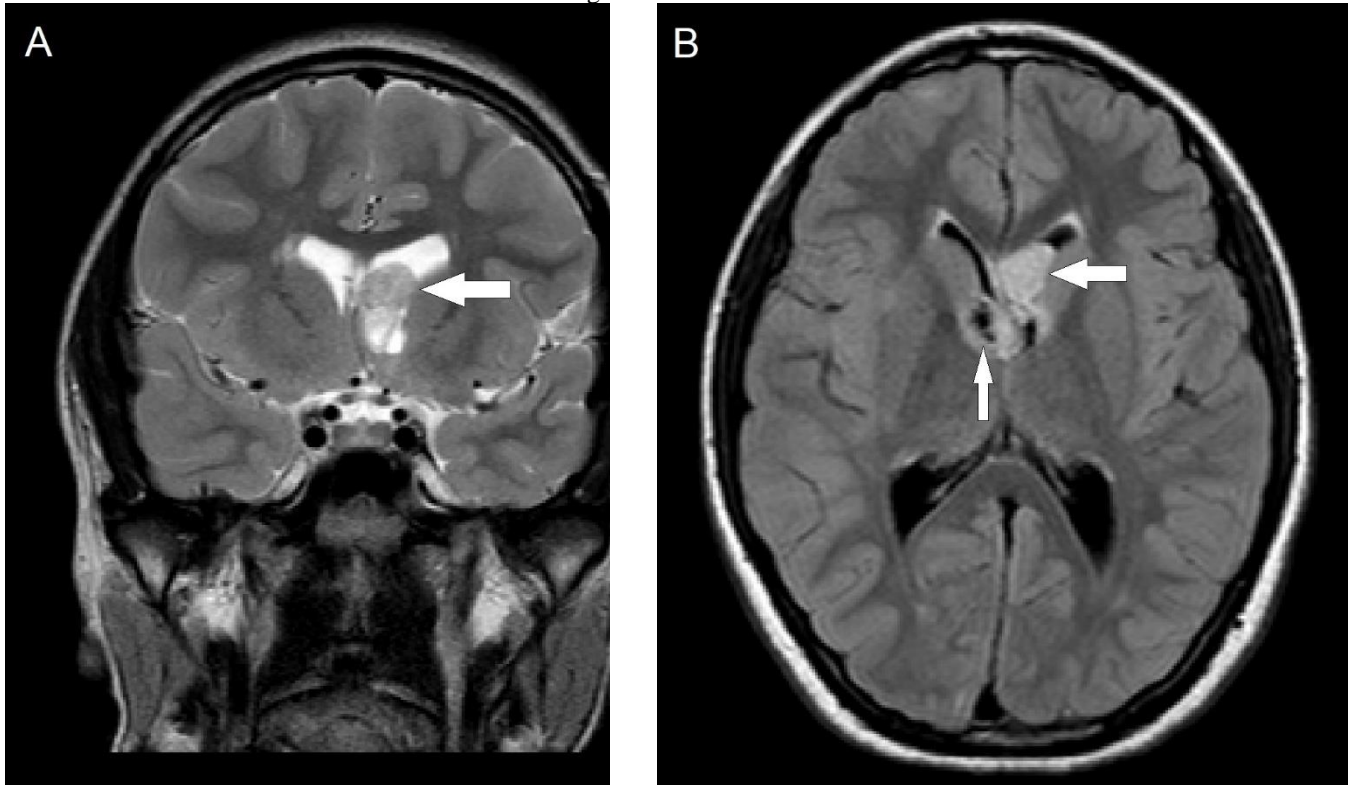
A 12-year-old boy with tuberous sclerosis complex. Axial T2-WI shows linear bands (black arrow), cortical tubers (white arrows) and subependymal nodules (arrowheads).

Figure 6



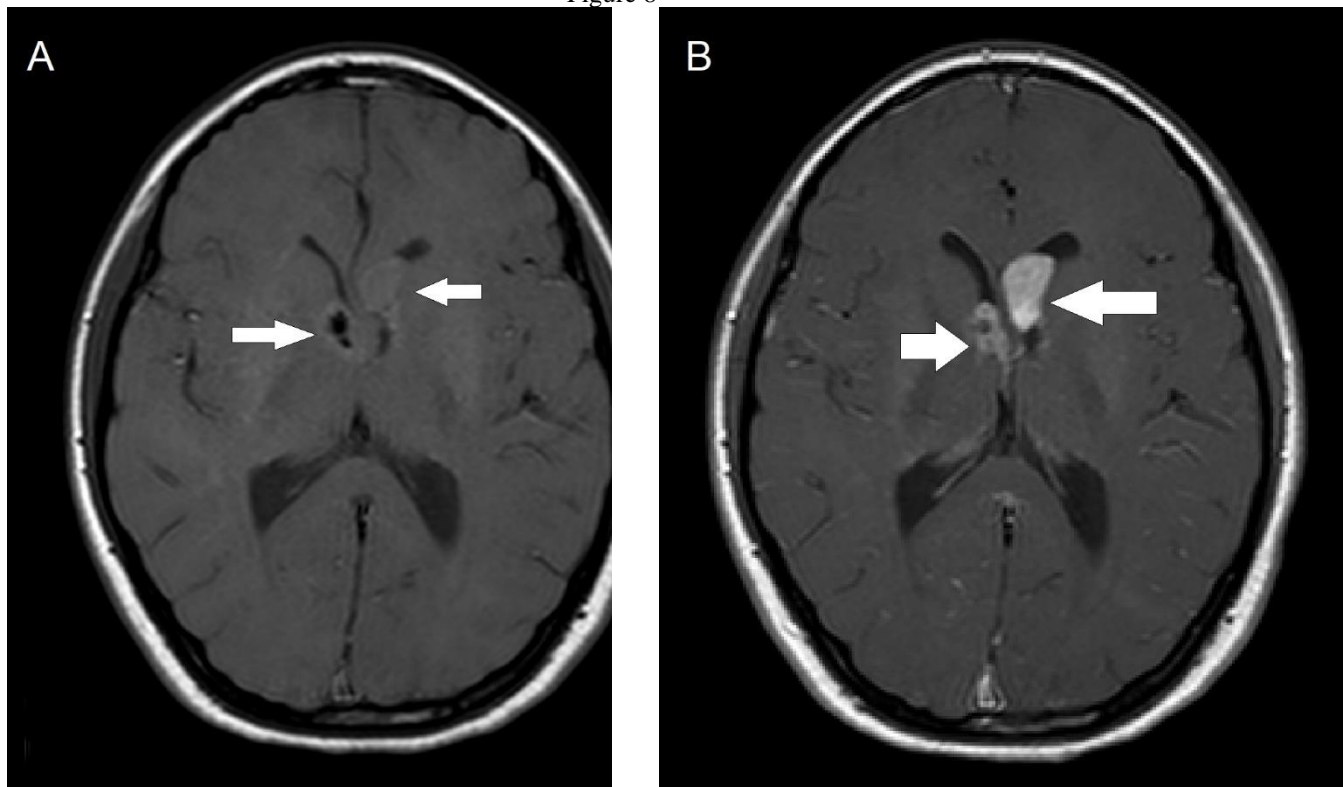
An 18-year-old man with tuberous sclerosis complex. Unenhanced (A) and post-contrast (B) CT shows a subependymal giant cell astrocytoma (white arrow) as a nodular lesion, larger than 10 mm, with calcifications, near the foramen of Monro and with intense enhancement.

Figure 7



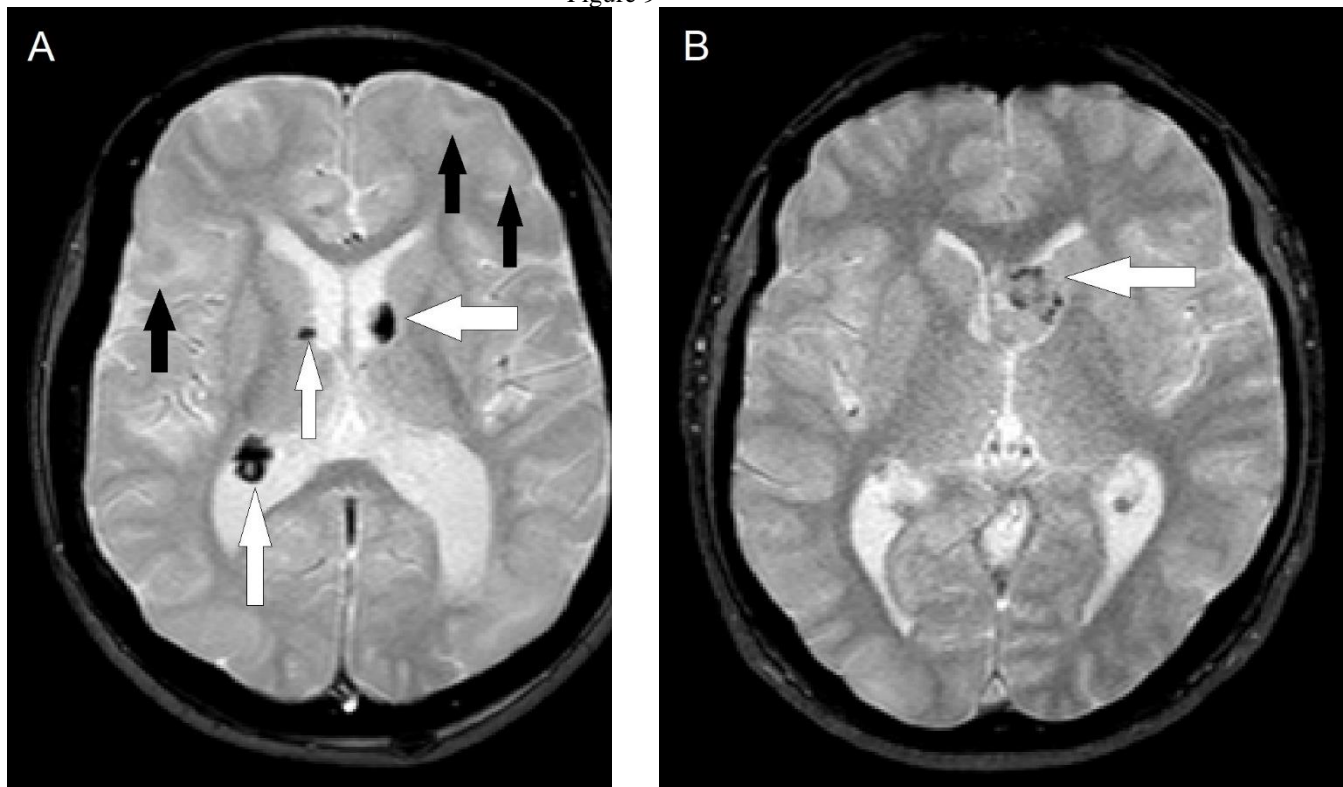
A 12-year-old boy with tuberous sclerosis complex. Coronal T2-WI (A) and axial FLAIR WI (B) show intraventricular nodular lesions (white arrows) with increased signal intensity on T2-WI and FLAIR WI consistent with subependymal giant cells astrocytomas.

Figure 8



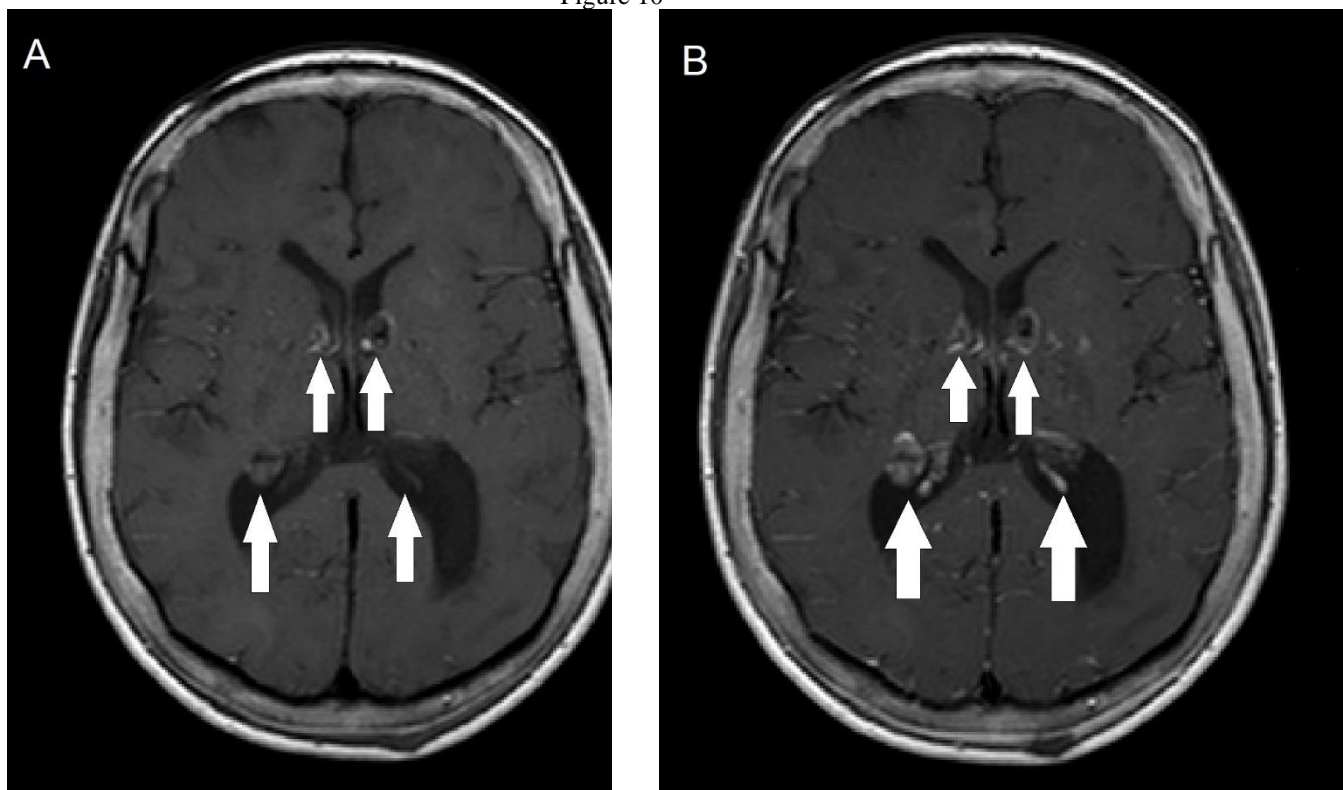
A 12-year-old boy with tuberous sclerosis complex. T1-WI without contrast shows hyperintense intraventricular SEGAs, larger than 10 mm, with calcification (depicted as a hypointense component), near the foramen of Monro (A), with intense enhancement post-gadolinium (B).

Figure 9



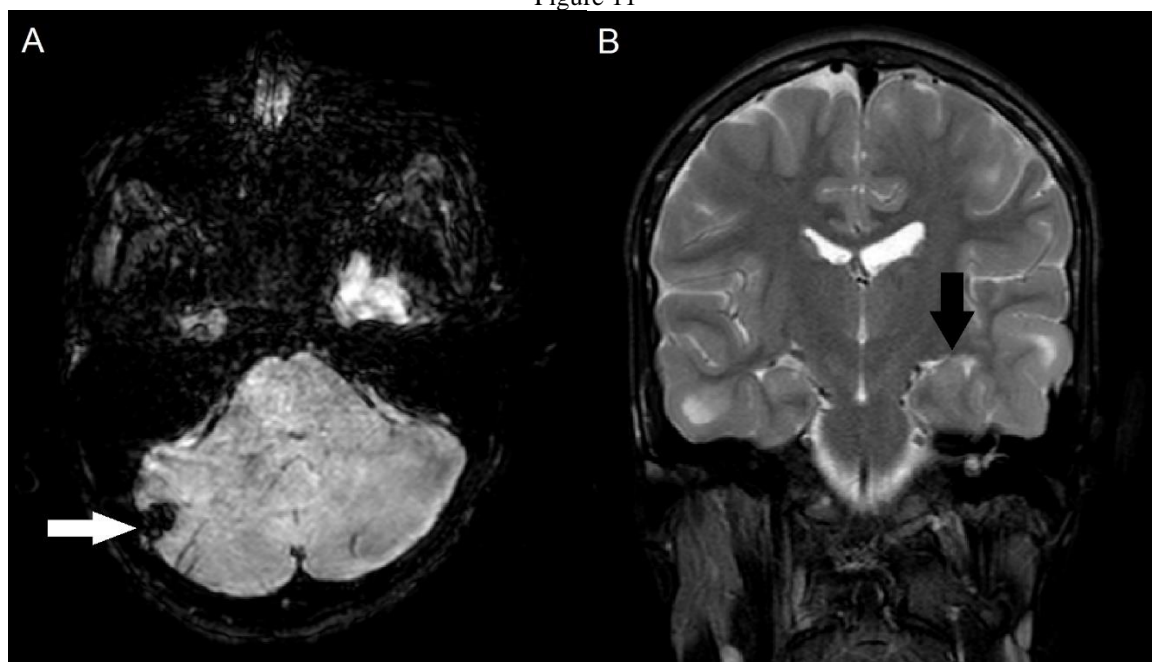
A 12-year-old boy (A) and a 28-year-old man (B) with tuberous sclerosis complex. T2 gradient echo (GRE) sequences show SEGAs (white arrows) with hypointense signal corresponding to calcifications. There are also cortical tubers demonstrated as hyperintense foci (black arrows).

Figure 10



A 12-year-old boy with tuberous sclerosis complex. T1 WI show intraventricular hyperintense nodular lesions (A) that demonstrate peripheral enhancement post-gadolinium (B).

Figure 11



A 12-year-old boy with tuberous sclerosis complex. MR Susceptibility Weighted Imaging (SWI) (A) shows a calcified cerebellar lesion (white arrow). Left hippocampal malrotation (black arrow) can also be seen on coronal T2-WI (B).

Table 1

Major features	Minor features
Hypomelanotic macules (≥ 3 , at least 5 mm diameter)	“Confetti” skin lesions
Angiofibromas (≥ 3) or fibrous cephalic plaque	Dental enamel pits (≥ 3)
Ungual fibromas (≥ 3)	Intraoral fibromas (≥ 2)
Shagreen path	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Cortical dysplasias ^(a)	Nonrenal hamartomas
Subependymal nodules	
Subependymal giant cells astrocytoma	
Cardiac rhabdomyoma	
Lymphangiomyomatosis (LAM) [†]	
Angiomyolipomas (≥ 2) ^(b)	

Definite diagnosis: Two major features or one major feature ≥ 2 minor features.

Possible diagnosis: Either one major feature or ≥ 2 minor features.

^(a)Includes tubers and cerebral white matter radial migration lines.

^(b)A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.