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Intracranial Manifestations of Tuberous Sclerosis: A Pictorial Essay

Tuberous sclerosis is an autosomal dominant genetic disease that involves multiple organs. Hamartomas are the predominant lesions. Classically, tuberous sclerosis has been characterized by a classical clinical triad of facial angiofibromas (90%), mental retardation (50-80%), seizure (80-90%) and all three in 30% of the patients. Two major features or one major feature plus two minor features are necessary for the definite diagnosis of this disease. We had some patients admitted with different presentations of tuberous sclerosis and a past history of convulsion from childhood, skin lesions and also mental retardation with a new onset headache and a changed pattern of convulsion. In physical examination, facial angiofibromas and subungual fibromas were apparently detected. Brain CT scan study with contrast showed multiple calcified nodules associated with tubers, ventriculomegaly and also enhancing enlarged nodules at the foramen of Monro, which were suggestive of subependymal giant cell astrocytoma (SGCA). MRI showed the same brain findings (tubers, white matter lesions and subependymal nodules associated with SGCA), which were detected better. After surgery, SGCA was proved. In abdominal and pelvic CT scan and ultrasonography, massive bilateral angiomyolipomatosis and focal hypodense hyperechoic liver lesions were detected.

Keywords: Tuberous Sclerosis Complex, Tubers, Subependymal Nodules, Subependymal Giant Cell Astrocytoma, White Matter Lesions

Introduction

Tuberous Sclerosis Complex (TSC) or Bourneville-Pringle Syndrome is an inherited tumoral disorder with multi-organ hamartomas, in which the spectrum of CNS hamartomas all contain giant balloon cells.[1] This complex is occasionally seen in association with other cortical dysplasias (hemimegalencephaly, focal cortical dysplasia).[2-4] Approximately 50% of TSC cases are inherited with De novo or spontaneous mutation/germ-line mosaicism and autosomal dominant, high but variable penetrance; mutations in TSC tumor suppressor genes cause abnormal cellular differentiation and proliferation.[1]

It affects 1 in 7,000 to 10,000 live births. It involves many of the body systems. Outwardly you may not know that someone has TSC and the diagnosis is usually made on what the patient complains of and the findings on examination. However, many patients will be referred for their brain imaging to confirm the clinical diagnosis, evaluate the extent of the abnormality, look for associated abnormalities and to follow-up patients with the known abnormality. The common initial problems in TSC are seen in the brain and this can also be the site of important complications.[1,5]

Classically, tuberous sclerosis has been characterized by a classical clinical triad of facial angiofibromas (90%), mental retardation (50-80%), seizure (80-90%) and all three (epiloia) in 30% of patients. Associated abnormalities should be considered (Table 1). The definite diagnostic criteria for this syndrome are two major or one major with two minor features (Table 2).[4]

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These patients may be diagnosed at any age; in the first year of life, with infantile spasms or surveillance for positive family history; in childhood, with an autistic-like behavior, mental retardation, seizures, or skin lesions; and in adults, with demonstration of symptomatic SGCA on brain imaging.[6]

We could help them by treating the seizures; resecting isolated tubers if the seizure focus is identifiable, and also resecting SGCAs which obstruct the foramen of Monro. The best diagnostic clue is the classic imaging appearance: calcified subependymal nodules—98% have subependymal nodules (SEN)—subependymal giant cell astrocytoma (SGCA)—15%—cortical/subcortical tubers, white matter lesions—70-95%—especially in the frontal, parietal, occipital, temporal lobes and the cerebellum. One tuber is the same as one neurologic symptom, also white matter lesions along lines of neuronal migration and cystic white matter lesions (cystoid brain degeneration) are other imaging findings. Also sometimes you can see thickened cortex, enlarged gyri associated with cortical/subcortical tubers.[3,7-10]

Gross pathologic & surgical features include firm cortical masses ("tubers") with dimpling ("potato eye"), cortical dysplasias, hemimegalencephaly and transmantle dysplasia. Microscopic features consist of balloon cells, myelin loss, vacuolation, gliosis and ectopic neurons.[5]

We encountered a 51-year-old male who was admitted for the first work-up of convulsion. His family history of convulsion was negative. He studied economics and graduated with a good grade. In the physical examination, multiple skin tags were noted, especially in the axillary and inguinal folds (Fig. 1A). In the hands and feet you could see multiple subungal fibromas (Fig. 1B). Routine laboratory tests were negative for seizure. Then imaging studies were performed. In abdominal and pelvic ultrasonography we detected multiple hyperechoic lesions in both kidneys in favor of angiomyolipomas (Figs. 1C&D) which were confirmed by CT scan (Figs. 1E&F). In brain CT scan studies, we found multiple calcified subependymal nodules (Figs. 1G&H). Therefore, the patient filled the diagnostic criteria for TSC. His family was studied with brain CT scan without contrast and two of his girls (he had three girls) had subependymal calcified nodule without any symptoms.

In addition a 21-year-old mentally retarded male was admitted for further evaluation of a new onset headache. His past history was negative. In physical examination, facial angiofibroma was noted (Fig. 2A). In his hands and feet you could see multiple subungal fibromas (Fig. 2B). Routine paraclinic tests for seizure were negative. Then imaging studies were performed. In abdominal and pelvic ultrasonography, multiple hyperechoic lesions were noted in both kidneys, which were in favor of angiomyolipomas and were confirmed by CT scan (Fig. 2C). The same hyperechoic hypodense lesions were also noticed in the liver (Fig. 2D). In the brain CT scan study, we found mul-

Table 1. Associated Abnormalities

Renal: Angiomyolipoma and cysts (40-80%)
Cardiac: Rhabdomyoma (50-65%); majority involute over time
Lung: Cystic lymphangiomyomatosis/fibrosis
Solid organs: Adenomas, leiomyomas
Skin: Ash-leaf spots (majority) including scalp/hair; facial angiofibromas; shagreen patches (20-35%); post pubertal
Extremities: Subungual fibromas (15-20%), cystic bone lesions, undulating periosteal new bone formation
Ocular: "Giant drusen" (50%)
Dental pitting: Permanent teeth in most adults with TSC

Table 2. Diagnostic Criteria

Major features: Facial angiofibroma/forehead plaque, sub-/periungual fibroma, hypomelanotic macules, shagreen patch, multiple retinal nodular hamartomas, cortical tuber, SEN, SGCA, cardiac rhabdomyoma, lymphangiomyomatosis, renal angiomyolipoma
Minor features: Dental enamel pits, hamartomatous rectal polyps, bone cysts, cerebral white matter radial migration lines (>3=major sign), gingival fibromas, non-renal hamartoma, retinal achromic patch, confetti skin lesions, multiple renal cysts

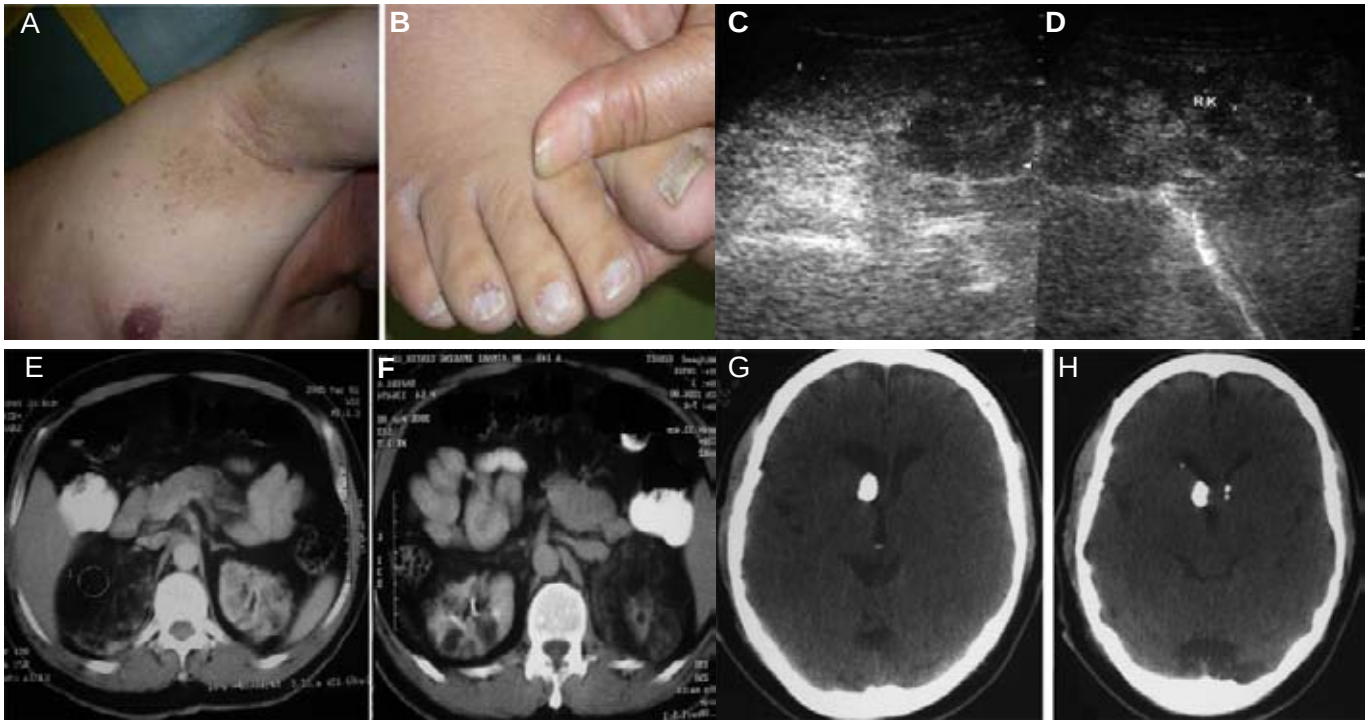


Fig. 1. A 51-year-old male who was admitted for the first work-up of convulsion.

A&B. Dermatologic manifestations of TS. (A: Subungal fibromasand B: Multiple skin tags).

C&D. Ultrasound study shows hyperechoic lesions in both kidneys: angiomyolipomatosis.

E&F. Abdominal CT scan with contrast showed angiomyolipomatosis.

G&H. Multiple calcified subependymal nodules.

tiple calcified subependymal nodules, calcified tubers and a large enhancing, partially calcified nodule adjacent to the foramen of Monro, in favor of subependymal giant cell astrocytoma (Figs. 2E&F), which was histologically confirmed after surgery. MRI study showed subependymal signal void lesions related to subependymal calcified nodules (Figs. 2I-L), bright white matter (WM) lesions as streaky linear or wedge-shaped hyperintensities on T2W and especially on FLAIR (along radial migration lines from the ventricle to the cortex) (Figs 2I,K&L), some cortical and subcortical tubers showed bright signal on T2W but no signal on T1W (Fig. 2K), and also a heterogeneous enhancing large subependymal nodule which was a subependymal giant cell astrocytoma, as noticed earlier (Figs 2G&H). He was one of the typical cases of TSC.

Another patient was admitted for further evaluation of new onset headache and dizziness with a past history of convulsion. He was a 19-year-old boy who was mentally retarded.

In physical examination, he had facial angiofibroma and a forehead plaque with shagreen patches (Figs. 3A-D). Routine paraclinical tests were negative for seizure. Bone lesions as patchy flame like sclerosis were confirmed in the iliac bone (Figs. 3E-F). In abdominal and pelvic ultrasonography, multiple hyperechoic lesions were detected in both kidneys, which were in favor of angiomyolipomas (Figs. 3G-H), and were confirmed by CT scan. In the brain CT scan, multiple calcified subependymal nodules and calcified tubers (Figs. 3I&J) were noticed. A large enhancing nodule was identified adjacent to the foramen of Monro, which mentioned subependymal giant cell astrocytoma (SEGCA) and was histologically confirmed after surgery. MRI study also confirmed subependymal nodules, some of the tubers and SEGCA (Figs. 3K&L).

A 9-year-old boy was admitted for further evaluation of convulsion. He did not study well at school and failed. His facial angiofibroma (Fig. 4A) was the first positive sign everyone encountered. Routine laboratory tests were negative for seizure. On brain imaging studies you could see multiple calcified subependymal nodules (Fig. 4B), calcified tubers and also a large calcified subcortical tuber (Fig. 4C) in the left

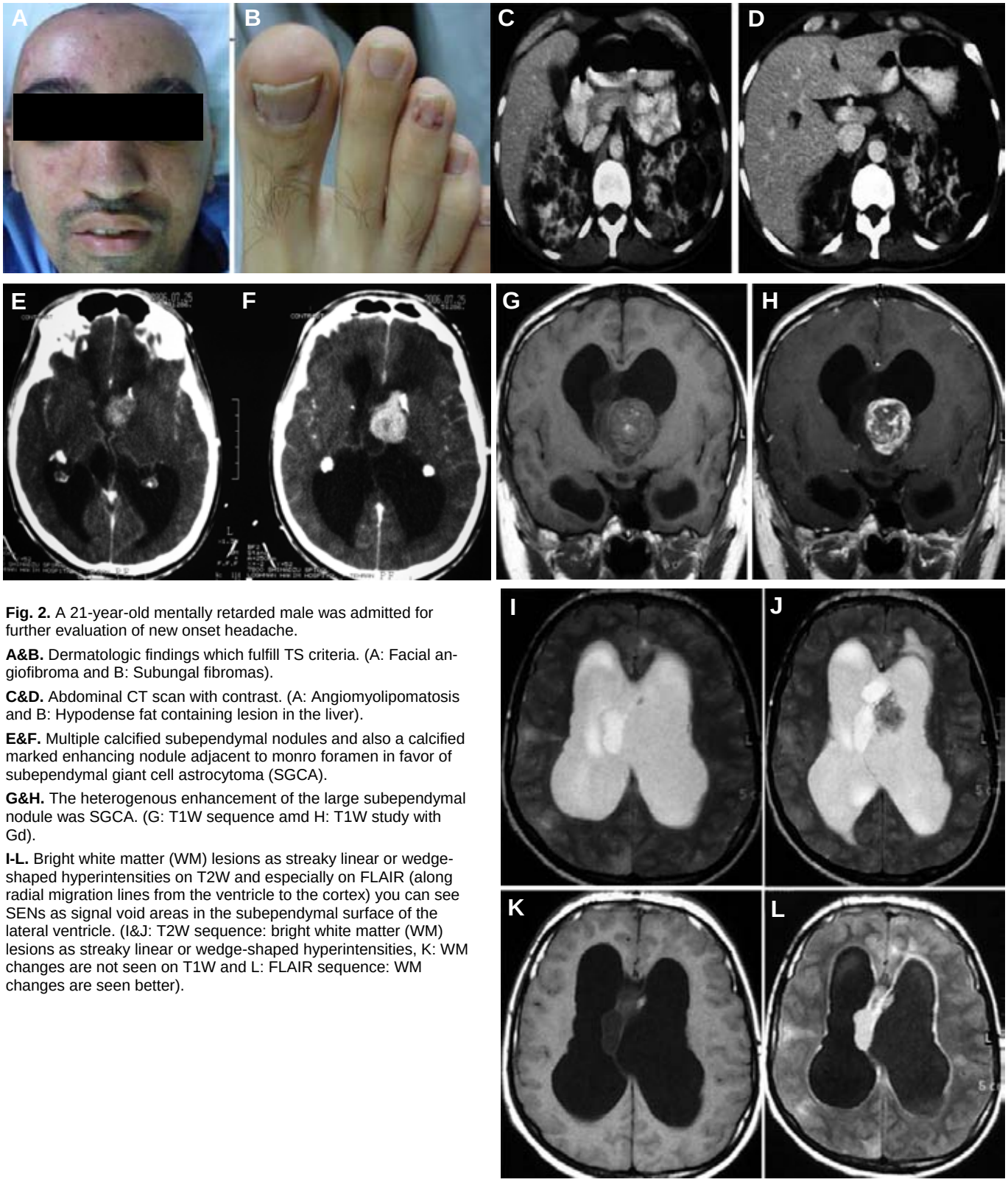


Fig. 2. A 21-year-old mentally retarded male was admitted for further evaluation of new onset headache.

A&B. Dermatologic findings which fulfill TS criteria. (A: Facial angiofibroma and B: Subungal fibromas).

C&D. Abdominal CT scan with contrast. (A: Angiomyolipomatosis and B: Hypodense fat containing lesion in the liver).

E&F. Multiple calcified subependymal nodules and also a calcified marked enhancing nodule adjacent to monro foramen in favor of subependymal giant cell astrocytoma (SGCA).

G&H. The heterogenous enhancement of the large subependymal nodule was SGCA. (G: T1W sequence amd H: T1W study with Gd).

I-L. Bright white matter (WM) lesions as streaky linear or wedge-shaped hyperintensities on T2W and especially on FLAIR (along radial migration lines from the ventricle to the cortex) you can see SENs as signal void areas in the subependymal surface of the lateral ventricle. (I&J: T2W sequence: bright white matter (WM) lesions as streaky linear or wedge-shaped hyperintensities, K: WM changes are not seen on T1W and L: FLAIR sequence: WM changes are seen better).

parietal lobe, which had an interesting presentation on MRI study. MRI showed subependymal signal void lesions related to subependymal calcified nodules , bright white matter (WM) lesions as streaky linear or wedge-shaped hyperintensities on T2W and especially on FLAIR (along radial migration lines from the ventricle to the cortex), and the subcortical calcified tuber as a low signal/signal void lesion with

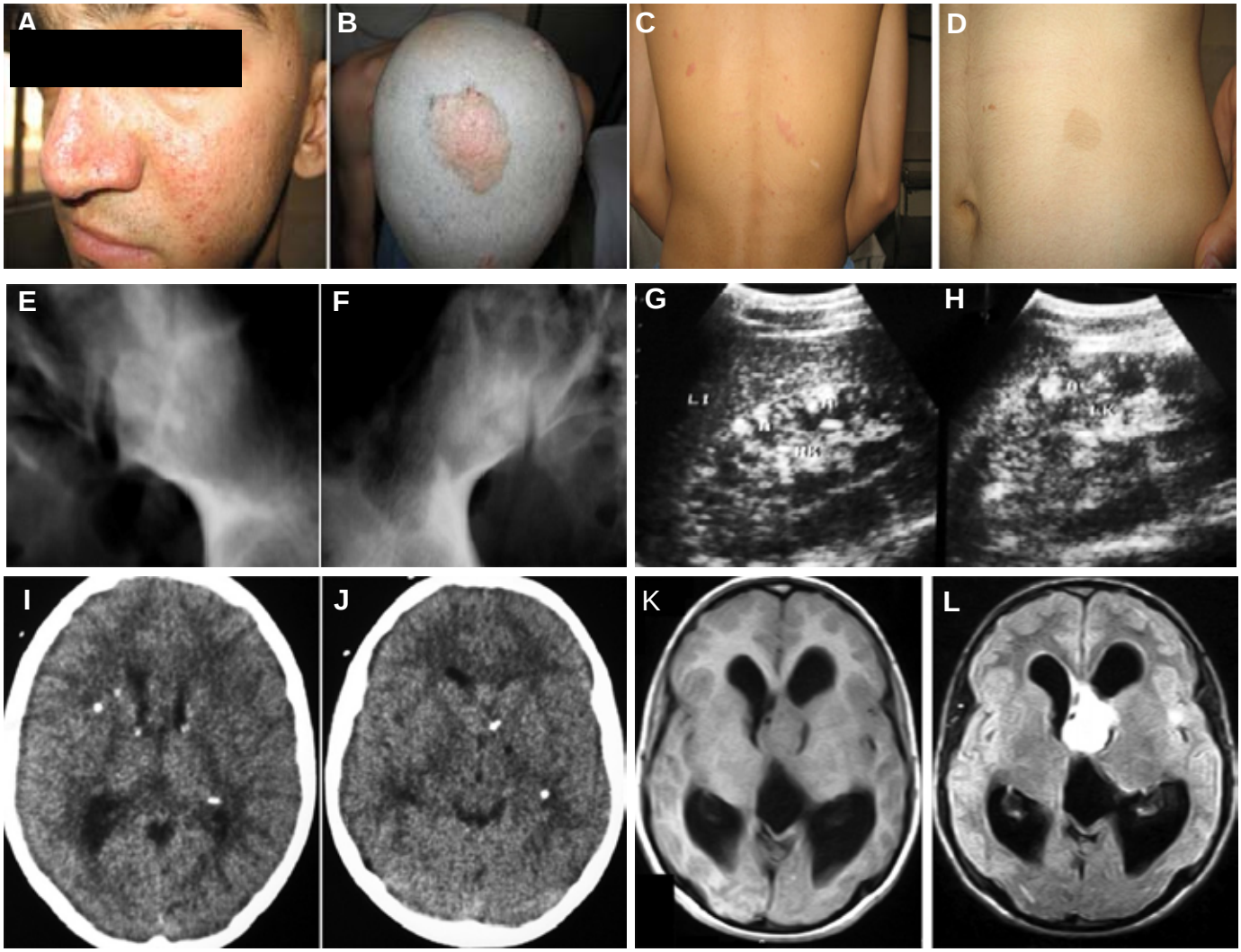


Fig. 3. A 19-year-old mental retarded boy was admitted for further evaluation of new onset headache and dizziness with a past history of convulsion.

A-D. Skin manifestations of TSC. (A. Facial angiofibroma, B**.** Forehead plaque, C**.** Shagreen patch and D**.** Pigmented macula).

E&F. Bone lesions as patchy flame like sclerosis in the iliac bone.

G&H. Ultrasonography shows multiple hyperechoic lesions in both kidneys (angiomyolipomas)

I&J. Brain CT scan: multiple calcified subependymal nodules and calcified tubers.

K&L. MRI: subependymal nodules and SGCA. (T1w & T1w with Gd)

peripheral bright signal on T2W and FLAIR, which you could not differentiate from other differential diagnoses without positive findings about TSC (Figs. 4D-G).

A 20-year-old mentally retarded boy presented with a new onset headache. Brain MRI showed a large enhancing subependymal nodule situated near the foramen of Monro (Figs. 5A&B). Abdominal CT scan study revealed hypodense lesions in the liver and angiomyolipomatosis of both kidneys (Figs. 5C-E), which were confirmed by MRI (Figs. 5F-H).

A 9-year-old boy with seizure from infancy was admitted for further evaluation. He was mentally retarded. Routine paraclinic tests were negative for seizure. In brain imaging studies you could see multiple hamartomas, especially the subependymal type. Subcortical calcified tubers were also detected in the right frontal lobe (Figs. 6A&B). Subependymal nodules showed enhancement after Gd-enhanced MRI study (Figs. 6C-F).

A 38-year-old woman was admitted in our hospital with acute abdominal pain. She had the same symptoms 13 years ago, after NVD, in which laparatomy revealed retroperitoneal hematoma. Routine laboratory data showed no specific findings. Abdominal and pelvic CT scan with contrast revealed angiomyolipo-

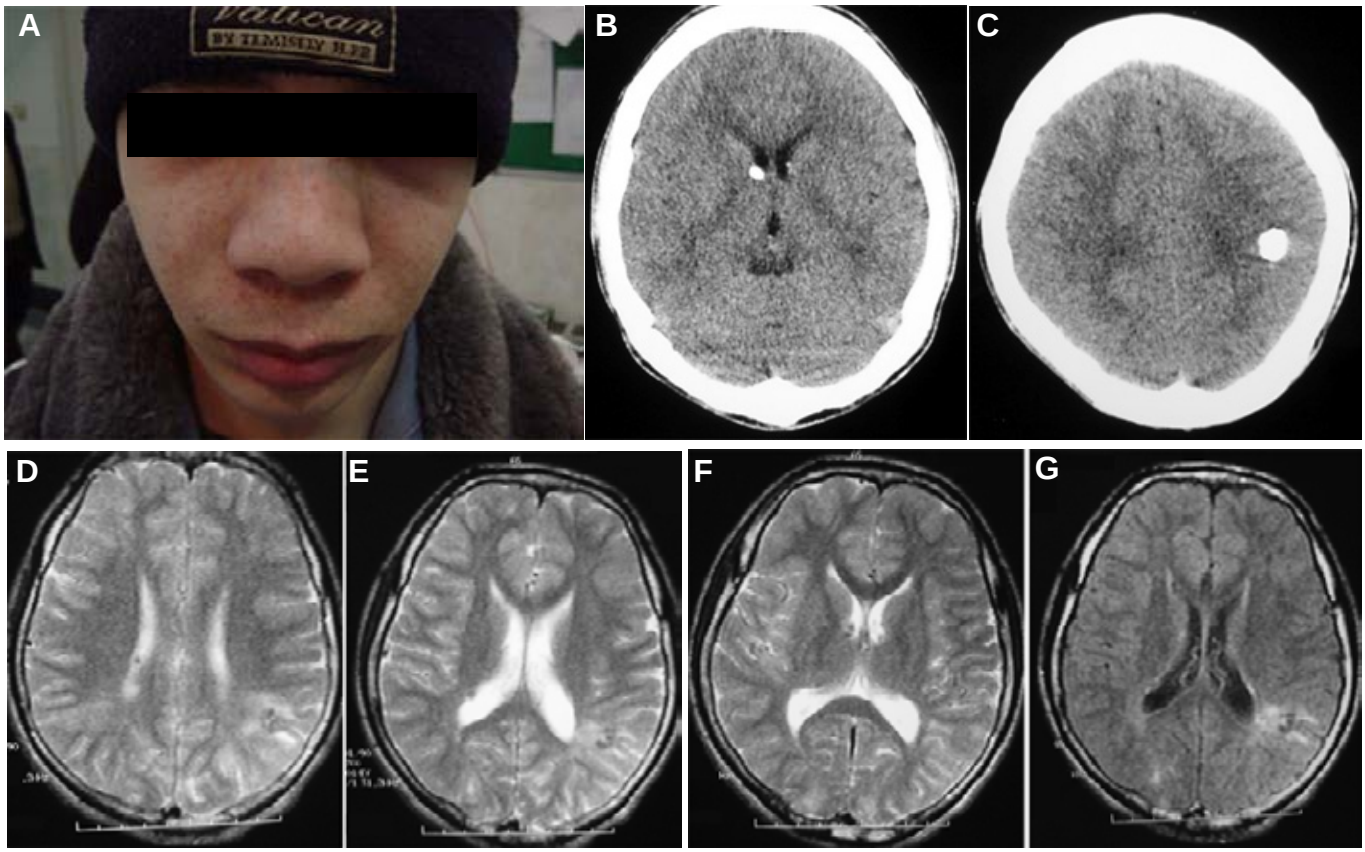


Fig. 4. A 9-year-old mentally retarded boy admitted for further evaluation of convulsion.
A. Facial angiofibroma.

B&C. Brain CT scan without contrast. (A**.** Calcified cortical tuber and B**.** Subependymal calcified nodules).

D-F. MRI study: Subependymal signal void lesions related to subependymal calcified nodules and bright white matter (WM) streaky linear hyperintensities on T2W & a subcortical calcified tuber as a low signal/signal void lesion with peripheral bright signal.

G. High lightened above changes on FLAIR.

matosis in both kidneys (Fig. 7A), left kidney subcapsular hematoma (Fig. 7B), and hemoperituneum (Fig. 7D). A hypodense lesion was also noted in her liver (Fig. 7C). Brain CT scan showed subependymal calcified nodules (Fig. 7E).

Discussion

Tuberous sclerosis is an autosomal dominant disorder with variable expressions and a predilection for diffuse hamartomatous development.[1] Multiple organs are often involved. The classic diagnostic criteria consist of facial lesions, seizures, and mental retardation, but this is actually seen in less than 50% of cases.[4] The exact etiology is not known, but it seems to represent abnormal migration of neurons. There are four major intracranial findings consisting of cortical tubers, white matter abnormalities, subependymal nodules and giant cell astrocytomas. Other rare findings are: parenchymal cysts, cerebellar lesions and vascular lesions.

The subependymal nodules are found in approximately 95% of patients with tuberous sclerosis, as the most common lesion. They tend to be located along the ventricular surface of the caudate nuclei. Less commonly, the nodules may be detected along the frontal and temporal horns, the third ventricle and/or the fourth ventricle. The imaging appearance of subependymal hamartomas on CT and MR varies with the age of the patient. They are rarely calcified in the first year of life. The number of calcified lesions typically increase with age. The lesions do not grow, but appear to calcify progressively. By 20 years of age, most of them are calcified. On MR scans, these appear as irregular subependymal nodules that protrude into the adjacent ventricles. Their appearance changes as the signal of the surrounding white matter changes. In infants who have unmyelinated white

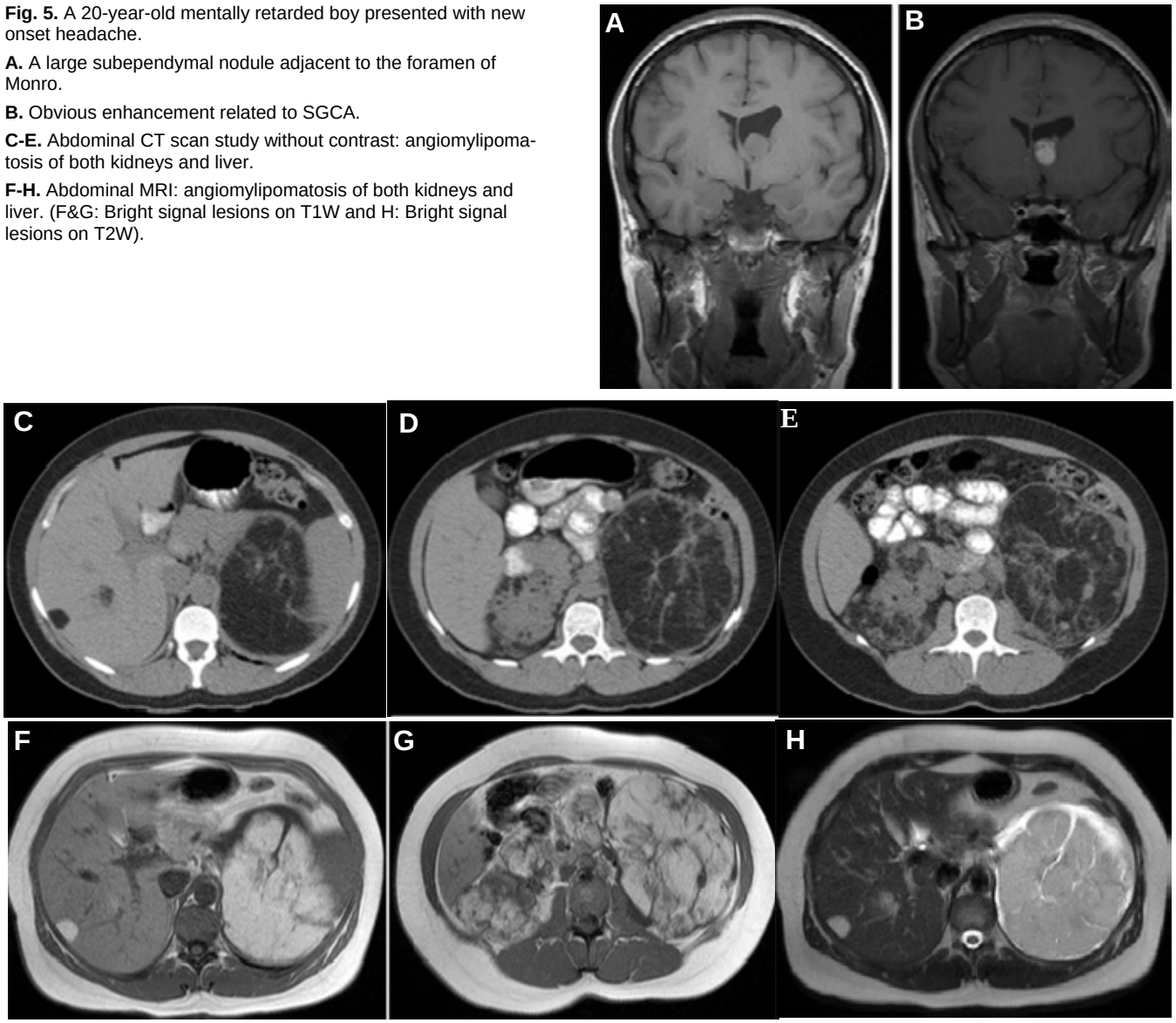


Fig. 5. A 20-year-old mentally retarded boy presented with new onset headache.

A. A large subependymal nodule adjacent to the foramen of Monro.

B. Obvious enhancement related to SGCA.

C-E. Abdominal CT scan study without contrast: angiomylipomatosis of both kidneys and liver.

F-H. Abdominal MRI: angiomylipomatosis of both kidneys and liver. (F&G: Bright signal lesions on T1W and H: Bright signal lesions on T2W).

matter, the hamartomas are relatively hyperintense on the T1W images and hypointense on the T2W images. As the brain myelinates, the subependymal nodules gradually become isointense with the white matter. They are most easily visualized on the T1W images. A few lesions may be hyperintense on the T1W images, related to the dispersed microcalcifications. Small nodules may not be apparent on the T2W images. Larger subependymal nodules manifest as variably low signal intensity on the T2W images, depending on the extent of calcification. A few lesions may have a target appearance, with a central hyperintensity, on the T2W images. After intravenous administration of contrast, these nodules show variable enhancement, some will enhance markedly, some mildly, some not at all. The presence or absence of enhancement has no clinical significance. Subependymal grey matter heterotopias do not calcify, are isointense to normal grey matter and do not enhance.[7,9]

Subependymal giant cell astrocytoma is the term given to the enlarging subependymal nodules that are usually situated near the foramen of Monro. These tumors differ from subependymal hamartoma in their size and tendency to enlarge, which results in the clinical presentation of hydrocephalus. The incidence is 15% in tuberous sclerosis. Lesions greater than 12 mm should be classified as a giant cell tumor. However, progressive enlargement is a more reliable criterion. On imaging, these tumors are identified by a demonstration of tumor growth on serial studies. Most of them are located near the foramen of Monro.

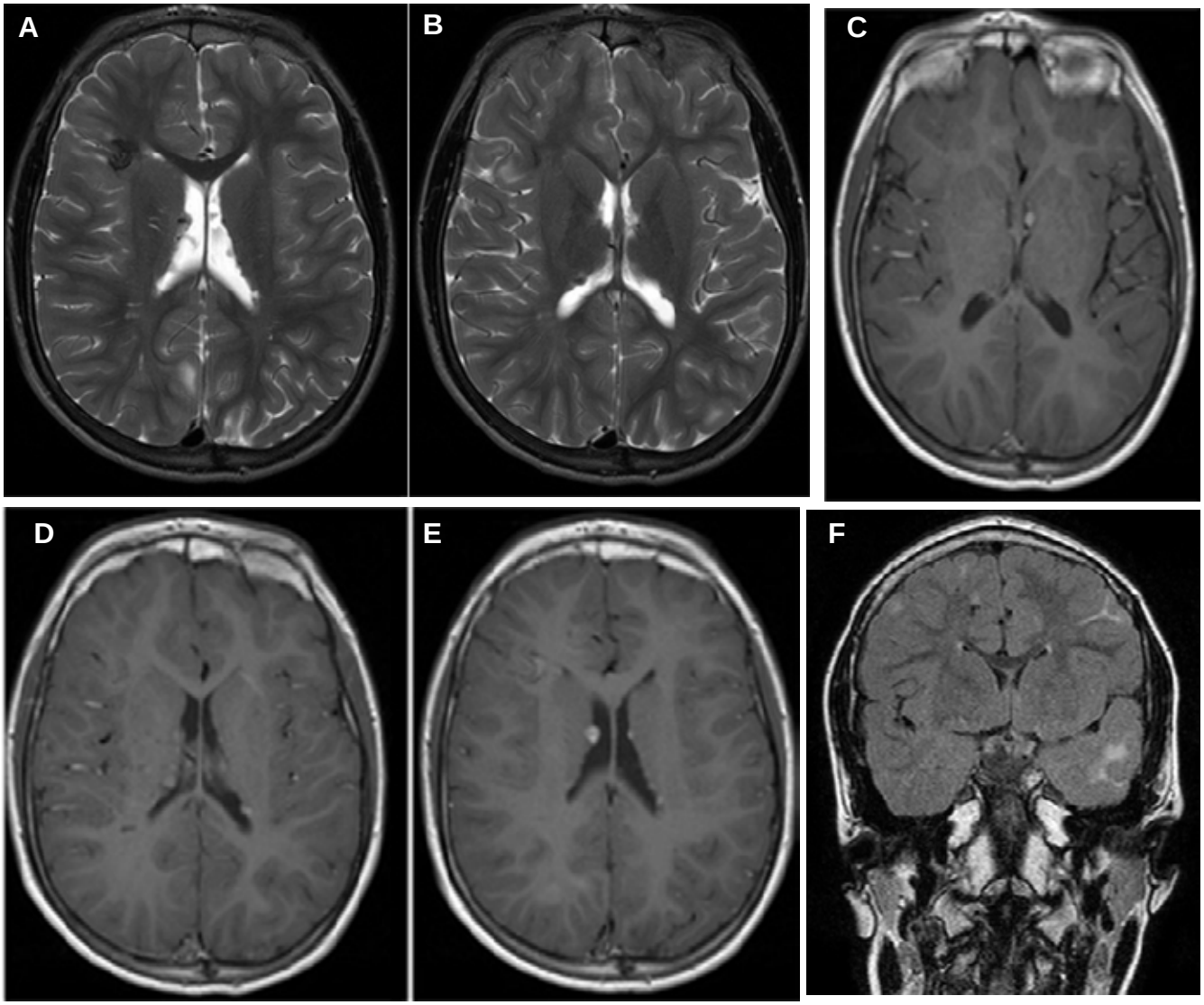
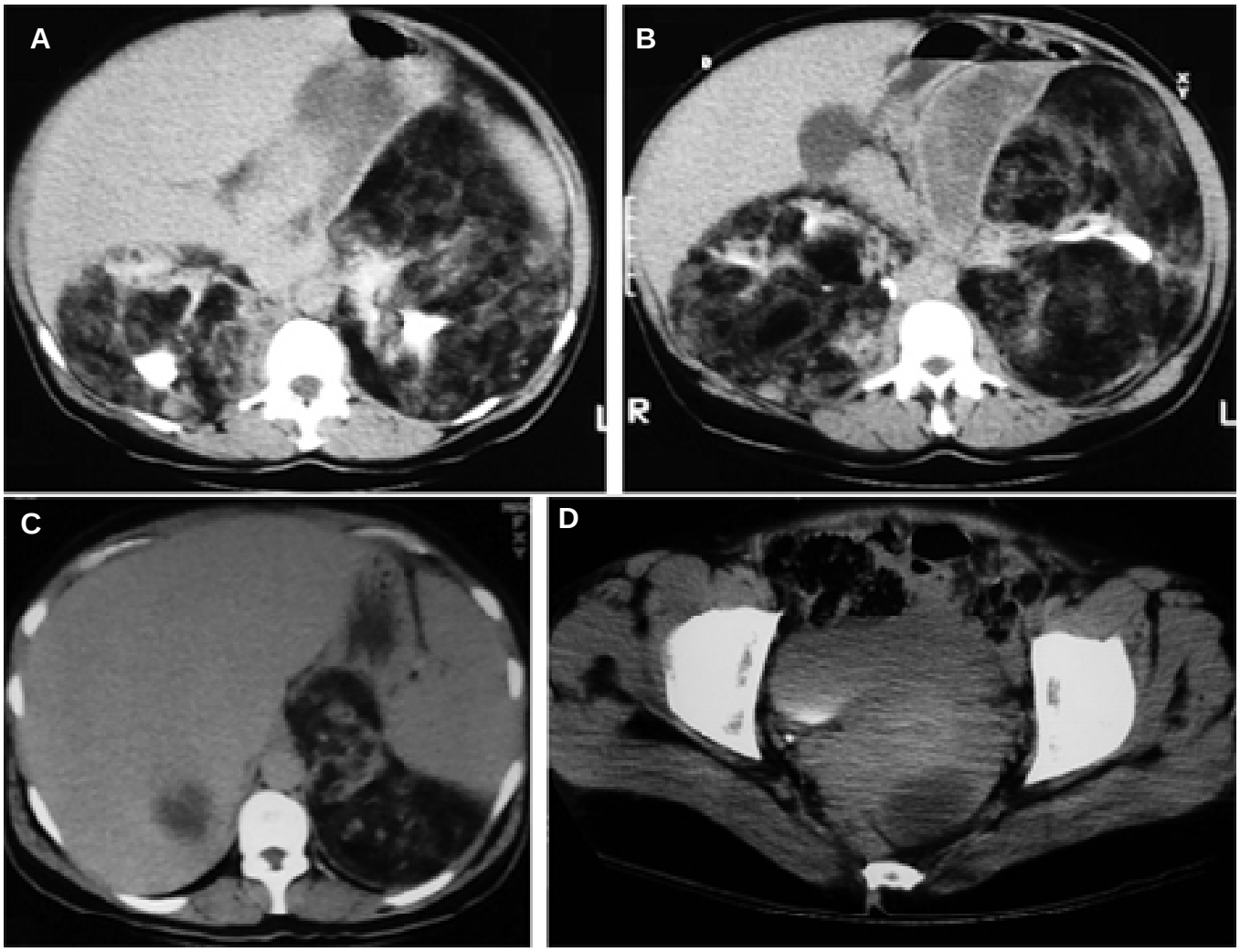


Fig. 6. A 9-year-old boy with seizure from infancy.
A. MRI T2W. Right frontal lobe subcortical tuber.
B. MRI T2W. Multiple subependymal nodules.
C-E. MRI T1W with Gd. Subependymal nodules show enhancement.
F. Coronal FLAIR shows cerebral white matter radial migration lines.

However, they can occur anywhere along the ependymal surface. Neither signal intensity nor the presence or absence of enhancement is useful in making the distinction between hamartomas and giant cell tumors. These tend to grow into the ventricle as a polypoid mass and only rarely invade the brain parenchyma. They do not seed the CSF. Occasionally degeneration into a high grade or infiltrating neoplasm can occur.[1,6,7,9]

Cortical tubers (or hamartomas) are the most characteristic lesions of tuberous sclerosis. They are found in approximately 95% of patients with tuberous sclerosis. They are most commonly supratentorial. Cerebellar lesions are seen in 8-15% of the patients. The number of calcified lesions seen on CT increases with age. The MR appearance of cortical tubers changes with age. In neonates, they appear as gyri that are hyperintense to the surrounding unmyelinated white matter on the T1W images and hypointense on the T2W images. About 20% of the affected gyri are enlarged. The appearance changes as the brain myelinates, the signal of the lesions slowly becomes isointense. After suppression of the high intensity signal of the myelinated brain, application of a magnification transfer pulse may result in more apparent parenchymal lesions than on the standard



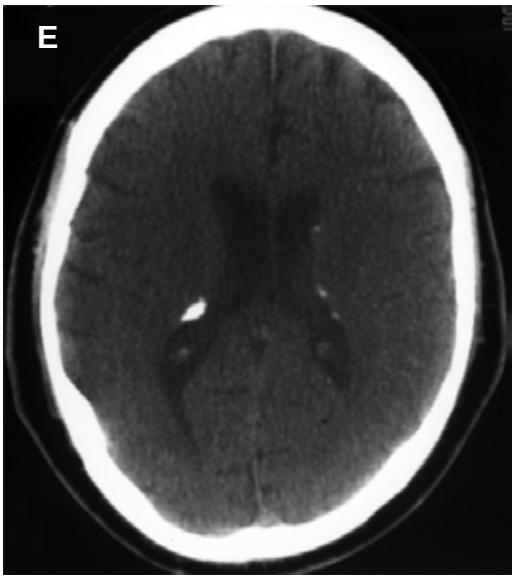


Fig. 7. A 38-year-old woman with acute abdominal pain.

A. Abdominal CT scan with contrast showed bilateral angiomyolipomatosis of the kidneys.

B. Abdominal CT scan with contrast: subcapsular hematoma of the left kidney.

C. Abdominal CT scan with contrast: hypodense lesion in the liver.

D. Pelvic CT scan with contrast: hemoperituneum.

E. Brain CT scan without contrast revealed subependymal calcified nodules.

T1W and T2W images. FLAIR images are also more sensitive in detecting parenchymal lesions in children and adults. The tubers are predominantly subcortical, separate from the overlying cortex. The inner margin of the tuber is poorly defined on all pulse sequences. Although cortical tubers may become isointense with the normal white matter on the T1W images, they usually remain hyperintense on the T2W images in

the mature brain. Neoplastic degeneration of these tubers is rare. When cortical tubers calcify, they may appear bright on the T1W images, presumably because of the T1 shortening caused by the calcium crystals. Degenerated calcified cortical tubers may enhance after contrast administration.[6,7,9]

White matter lesions are islets consisting of a group of neurons and glial cells which are usually present in the white matter. These white matter foci contain areas of hypomyelination and different types of cells. On MR these white matter lesions have the same characteristics as cortical tubers. In older patients, they may be difficult to see on the T1W images. They can sometimes be identified as low signal intensity regions. On the T2W images, they appear as well defined areas of high signal intensity. If the lesion is calcified, the calcification may appear as low or high signal intensity on the short TR images depending upon the characteristics of calcium crystals. They have short T1 and T2 relaxation times in neonates and young infants. Degenerated lesions may enhance. On the T2W, FLAIR and magnetization transfer images they will be often seen as linear or curvilinear regions of hyperintensity in the cerebral white matter, extending from the subependymal hamartomas to the cortical tubers. These are believed to represent bands of unmyelinated disordered cells, along the pathway of the linear radial glial-neuronal unit (similar to focal transmantle dysplasia-formes fruste).[10]

Parenchymal cysts consisted of cyst like structures may be seen in the cerebral white matter (usually periventricular).[8]

Cerebellar lesions are less common, occurring in about 10% of patients. MR features are similar to cerebral lesions.[5]

Vascular lesions are rare. Cerebral aneurysms have been seen in internal carotid arteries and the anterior cerebral artery distribution. These are usually seen in children.[3]

Neuroimaging plays an important role in the diagnosis, especially because CNS abnormalities have been present since birth, whereas cutaneous malformations may not develop until much later in childhood. Knowing more about this syndrome, the clinical presentation, criteria and imaging findings could help us in our work process.

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