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TUBEROUS SCLEROSIS COMPLEX -RADIOLOGICAL FEATURES IN DIFFERENT BODY SYSTEMS

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Abstract

Tuberous sclerosis (TS) is a rare genetic disorder of autosomal - dominant inheritance. Tuberous sclerosis complex is characterized by the development of benign tumors affecting different body systems who results in hamartomas involving many organs, like the brain, heart, kidneys, skin, lungs and liver. The management of these patients is often multidisciplinary, involving specialists from various fields. TSC presents at any age as a wide range of clinical and phenotypic manifestations with varying severity. The most common manifestations are facial angiofibroma, seizures, cortical tubers, cardiac rhabdomyoma, renal cysts and tumor of the kidneys. We present four patients with characteristic clinical and radiological features of multilocular tuberous sclerosis.

***Keywords*:** Tuberous sclerosis complex (TSC), tuberous sclerosis (TS), cortical tubers, angiofibromas, renal angiomyolipomas (AML).

Introduction

Tuberous sclerosis complex (TSC) is a rare autosomal dominant disorder first described by von Recklinghausen in 1862. In 1880, Bourneville coined the term “sclerose tubereuse” based on the pathologic features of the sclerotic tubers found in the postmortem investigation of patients with epilepsy and mental retardation, henceforth known as Bourneville's disease [1].

TSC is classified as a phakomatoses (neurocutaneous disorder) and which is characterized by the presence of glial cell tumors arising in the cerebral hemispheres and retina [2]. It is clinically characterized by the triad of epilepsy (EPI), intellectual disability (LOI), and adenoma sebaceum (A), therefore, encompassing these features Sherlock coined the term EPILOIA [3].

It is known that mutations on either of the two genes, TSC1 and TSC2, which encode for the proteins hamartin and tuberin, respectively, are the causes of TS. These proteins are tumor growth suppressors, which are agents that regulate cell proliferation and differentiation [4]. The classic triad of TS is seizures, mental retardation, and angiofibromas but this occurs in only 29% of patients with TS [5]. It is important to note that skin involvement is crucial for suspecting the diagnosis of TS [6,7].

The frequency of TSC has been estimated to be 1 in 10,000 live births and is about a third as common as neurofibromatosis type 1 [8]. It is a multisystem disorder which becomes perceptible only in late childhood, limiting the expediency for early diagnosis in infancy [9].

We will present four cases with tuberous sclerosis in different organ systems.

Case 1

A 32-years-old female patient presented with epilepsy since the age of 2 years old when she was hospitalized in University clinic for Pediatrics and under anticonvulsant therapy. The patient did not have seizures for the last 5 years. There were not any radiological findings for the disease, just it was labeled as tuberous sclerosis.

In 2016 on general physical examination, dermatologist noticed multiple well-defined, reddish-brown sessile nodular growths on the forehead, nose and cheeks in a characteristic "butterfly pattern". There was also nevocellular nevus on the back and cherry angiomas. He ordered an MRI.

MRI findings noticed bilateral cerebellar cortical tubers. There were also calcified subependymal nodules frontally right with dimensions 11mm, and 8mm on the left side.

In 2021 in abdominal ultrasonography was noticed enlarged right and left kidney which have heterogeneous echo pattern due to well-defined, rounded hyperechoic masses in both renal parenchyma. To define the masses it was ordered multiphase CT.

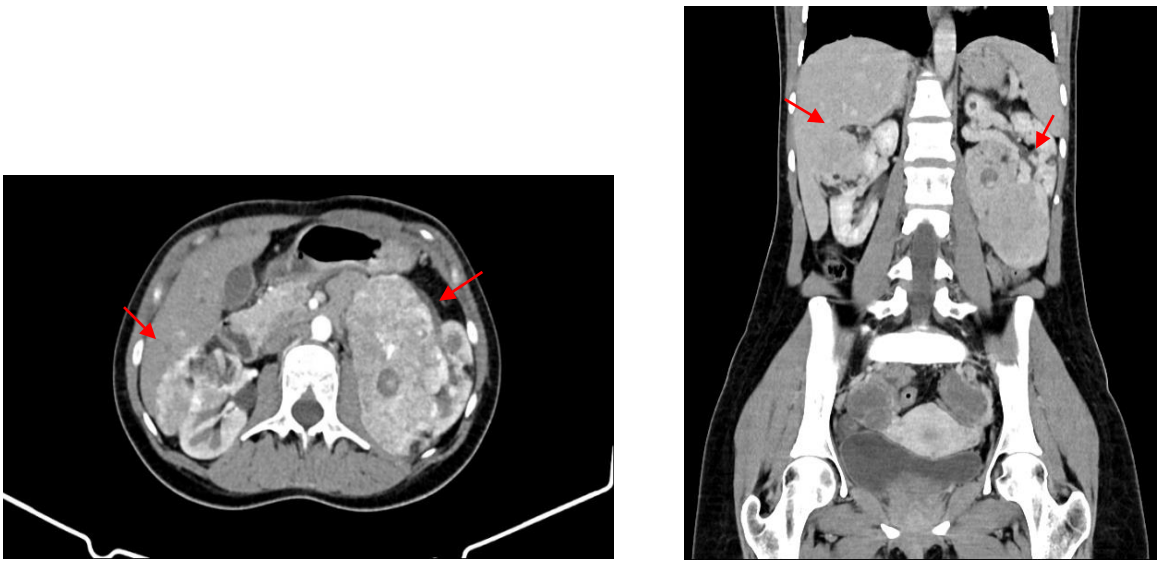
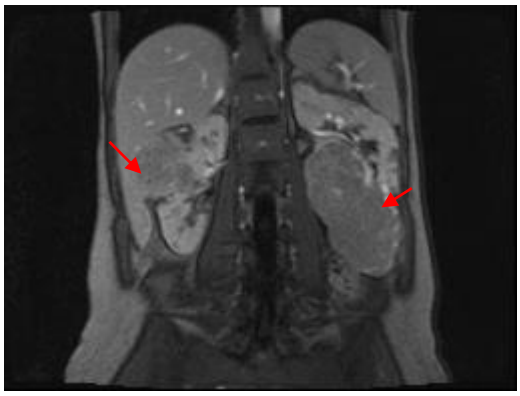


Figure 1a and 1b. CT arterial phase, axial and coronal plane– bilateral angiomyolipomas and cystic lesions on both ovaries (arrows)

CT evaluation noticed multiple lesions in the renal parenchyma, the largest two masses measured 62 x 63 x 50 mm on the right and 129 x 103 x 54 cm on the left, under the left renal artery. They were parenchymal fat-containing lesions, some of them partially exophytic and showed heterogeneous post-contrast enhancement. (Fig.1a, 1b)

On MRI these intrarenal masses were confirmed as angiomyolipomas. (Fig. 2a, 2b)



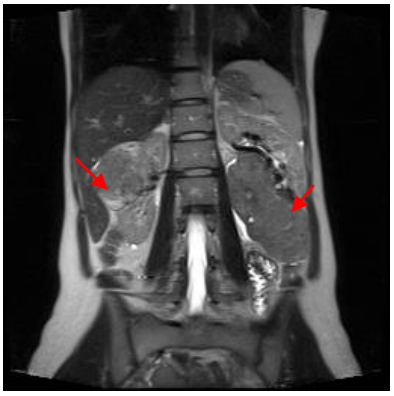


Figure 2a, 2b. MRI, Coronal plane -bilateral angiomyolipomas with predominantly fat component (arrows)

On chest CT scan was detected proliferation of smooth muscle cells throughout the peribronchial, perivascular, and perilymphatic regions of the lung in correlation with TS-LAM complex, consistent with lymphangioleiomyomatosis early stage. (Fig. 3)

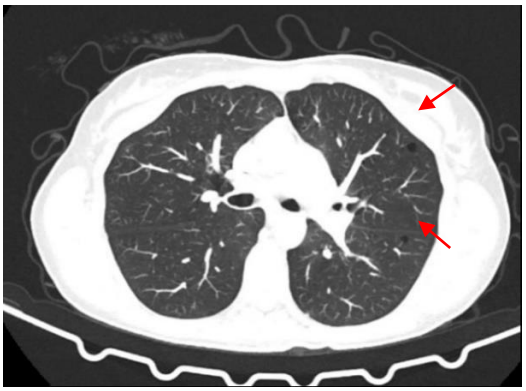


Figure 3. Chest CT scan, axial plane – diffuse small, thin-walled pulmonary cysts in both lungs, lymphangioleiomyomatosis (arrows)

On a control CT scan in 2022 there were no changes in dimensions of renal angiomyolipomas, but also were noticed cystic lesions on both ovaries with 35 x 45 mm left, and 28 x 35 mm on the right one.

Case 2

10-years-old boy was hospitalized in order to investigate the seizures. The pediatrician ordered a MRI that showed multiple subcortical nodules with hyperintensity on T2 and TIRM, hypointensity on T1 puls sequences and linear hyperintense white matter lesions extending from the cortex. Lesions were frontotemporally bilaterally, especially on the left side, parietooccipitally bilaterally, with restriction on DWI. All these findings indicate to subcortical tubers and white matter heterotopia in correlation to the primary diagnose TS. (Fig.4a, 4b) [10]

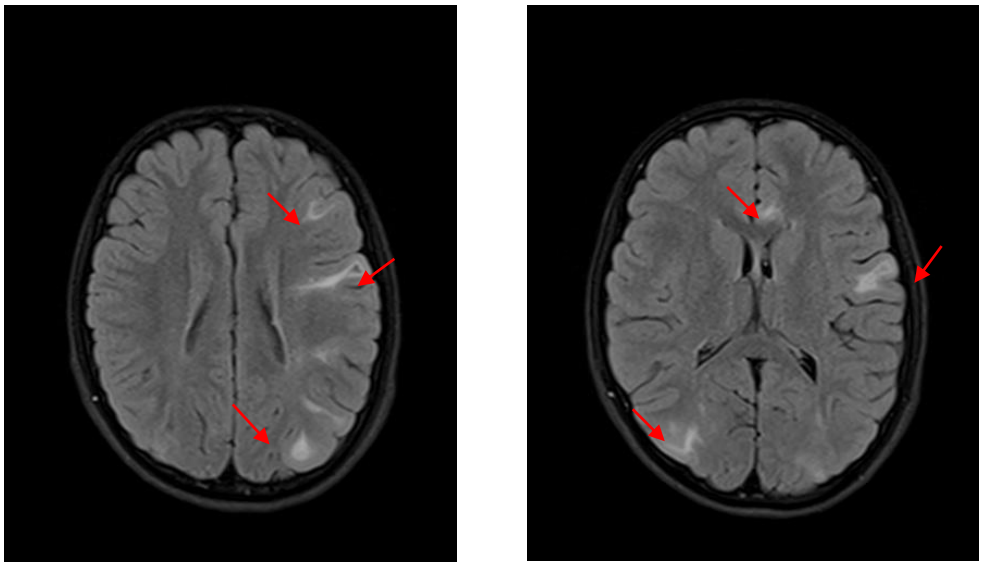


Figure 4a, 4b. MRI t2-tse-FLAIR, axial plane – hyperintense frontooccipital subcortical tubers bilaterally and linear hyperintense white matter lesions frontotemporoparietooccipitally bilaterally predominant lat. sin. (arrows)

The patient also had dermatological changes as brown nodular growths.

In 2021 MR urography was performed in standard pulse sequences and planes where the kidneys were presented with regular MR signals and no focal changes. Post-contrast signal enhancement was not observed.

In 2022 the pediatrician prescribed anticonvulsant and immunosuppressive therapy.

A control MRI of the brain was performed, showing again subcortical gyriform lesions in T2 and FLAIR sequences frontotemporally bilaterally, predominantly left and occipitally bilaterally. The ventricular system and the subarachnoid spaces were shown in orderly width, free.

In March of this year, an EEG was performed where the basic activity is shown with a stable alpha rhythm. A focal spot was isolated mostly on the right side. The EEG finding did not change even with stimulation methods. New skin efflorescences were not observed. The therapy prescribed by the pediatrician is continued.

Case 3

To 11-years-old girl with cerebral palsy was ordered an MRI in 2015 that showed bilateral occipital, subcortical and paraventricular, also, frontal bilateral hyperintense nodules in T2 and FLAIR puls sequence consistent with Tuberous Sclerosis. (Fig. 5). The patient had seizures and was on anticonvulsant therapy. From the other investigation, the patient had aphtous changes in her mouth.

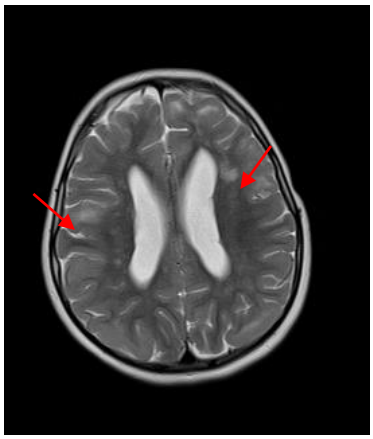


Figure 5. MRI t2-tse, axial plane – multiple hyperintense lesions (arrows) in the cortex, cortical tubers

On control MRI check in 2019 the changes in the brain were with the same MRI characteristics. There were also multiple hyper to isointense subependymal nodules along the ependymal surface of the lateral ventricles. (Fig. 6). The ventricular system was dilated.

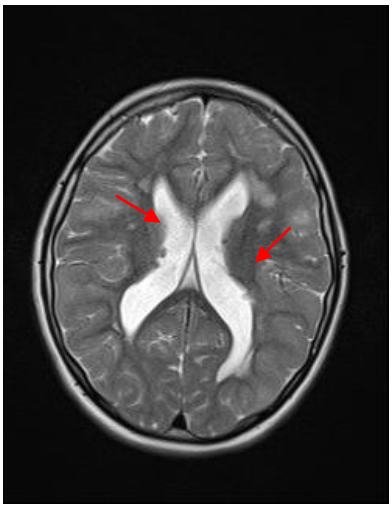


Figure 6. MRI t2-tse-tra – hyper to isointense subependymal nodules (arrows)

On MRI of kidneys, both were with regular form and dimensions. There were multiple small cystic changes, especially on the right one.

In the last 3 years, the patient did not have any control radiological examinations.

And this year, the patient continues with the anticonvulsant therapy prescribed by the pediatrician.

Case 4

2-years old boy in 2021 was hospitalized at University clinic for Pediatrics. It was ordered a MRI of the brain and MRI urography. The brain MRI showed hyperintense cortical tubers and hyper to isointense subependymal nodules in T2 puls sequence, and in the both kidneys had multiple hiperintense lesions with no internal enhancement, polycystic kidney bilateral. (Fig.7a, 7b, 7c)

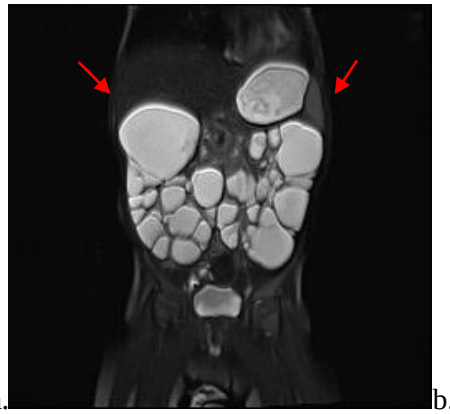
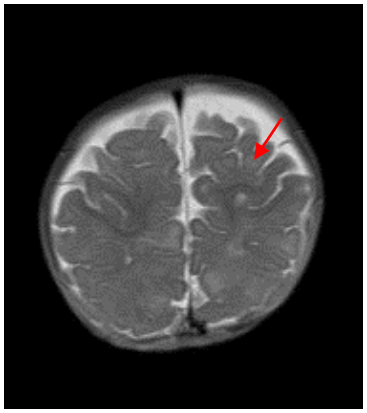
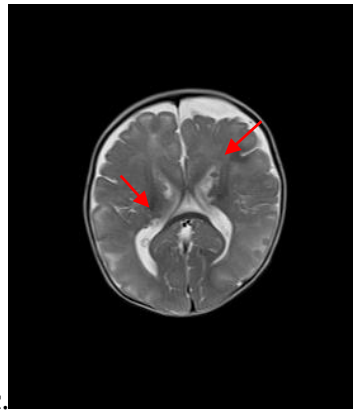
a.  b.  c. 

Figure7 a. MRI t2-haste-cor – multiple hiperintense with no internal enhancement lesions on both kidneys, as polycystic kidney bilateral; b. MRI t2-tse-tra – hyperintense lesions in cortex, cortical tubers; c. MRI t2-tse-tra – hyper to isointense tumefactions along the ependymal surface of the lateral ventricles, subependymal nodules. (arrows)

The child was hospitalized again at University clinic for Pediatrics in late 2022 and early 2023 due to convulsions. From the family anamnesis, we note a finding of neonatal death in an older brother, also a cystic kidney and cardiac disease in an older sister of the patient. In addition to neurological examination, he was also examined by a cardiologist and a nephrologist. Due to the dilated cardiomyopathy and anomaly of the coronary blood vessels, it was prescribed therapy to the patient. Other controls are carried out at the Sistina Hospital for which we have no data.

Discussion

TSC is characterized by the development of unusual tumor-like growths (hamartomas) in brain, skin, retina, and viscera. The term “tuberous sclerosis” refers specifically to the presence of multiple sclerotic masses scattered throughout the cerebrum. The diagnosis of TSC is based on the identification of hamartomas in more than one organ system [11].

At the Tuberous Sclerosis Consensus Conference of 1998, the clinical diagnostic criteria of TSC were revised and a new classification system based on major and minor findings was established as ‘The presence of two major features or one major and two minor features was considered sufficient for a definitive diagnosis.’ (Fig.8)

Major criteria	Minor criteria
Hypomelanotic macules (≥3, ≥5 mm in diameter)	"Confetti" skin lesions
Angiofibromas (≥3) or fibrous cephalic plaque	Dental enamel pits (>3)
Ungual fibromas (≥2)	Intraoral fibroma (≥2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Cortical dysplasia	Nonrenal hamartomas
Subependymal nodules	
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangioleiomyomatosis	
Angiomyolipomas (≥2)	

Figure 8. Clinical criteria for the diagnosis of tuberous sclerosis complex.

Our first case was presented with three major features – LAM, AML and subependymal nodules with cortical tubers and two minor features – multiple renal cysts and 'confetti' skin lesions.

LAM is the most common pulmonary manifestation of TSC, occurring in 26%–57% of affected patients. It should be noted that LAM may also occur sporadically and needs to be distinguished from TSC-associated LAM. On chest CT, LAM exhibits numerous thin-walled, fairly homogeneous pulmonary cysts in all lung zones and is devoid of internal structures. The cyst size correlates with the disease extent. Larger cysts are associated with more severe and extensive disease[12].

Renal AMLs can be identified in 55%–75% of patients with TSC. They are often asymptomatic and can multiply and grow during puberty, suggesting an estrogenic influence. Renal AMLs represent the second most frequent cause of morbidity among patients with TSC owing to the risk of spontaneous hemorrhage and rupture[13].

The second case was a girl which have skin changes and cortical tubers.

Cortical and subcortical tubers occur in 90% of persons with TSC and are composed of enlarged atypical and disorganized neuronal and glial elements with astrocytosis.

They occur as a result of disorganized cortical lamination and can appear anywhere, from the cortex to white matter. Similar to white matter heterotopia, cortical and subcortical tubers are regarded as cortical dysplasia, which are a major feature in the clinical diagnosis of TSC. Cortical tubers may serve as the epileptogenic focus and are generally resected in cases of intractable epilepsy. Subependymal nodules have a histologic composition that is similar to that of cortical tubers, and they occur in more than 90% of individuals with TSC [13,14].

The third case, the boy had (major feature) subependymal nodules with cortical tubers and minor feature – multiple renal cysts. Renal cysts are the second most prevalent renal feature of TSC, occurring in 17%–47% of pediatric patients with TSC [15].

Because of their low specificity, they are considered a minor feature of TSC.

The last one is a baby boy who had the same features as the third case, plus dilated cardiomyopathy which is prove that cardiovascular system is also affected.

Conclusion

Tuberous sclerosis is a neurocutaneous syndrome and it is a rare genetic disorder. In addition to the clinical history of seizures, renal and cutaneous lesions, imaging plays an important role in diagnosis.

The moment TS is suspected, the individual's parents should be counselled and enrolled in multi-disciplinary treatment programs. It is true there is no cure but symptomatic treatment is available.

The essential role in early diagnosis and lifelong follow-up of patients with these conditions have the radiologists.

The possibilities and values of radiological procedures are enormous in the diagnosis of pathological changes that are manifested multiloculary.

Radiological features make the process of diagnosing easier and faster so the clinical doctor can continue with treatment in such a rare disease. CT and MRI as leading radiological procedures are necessary for diagnosing the changes in the brain, kidneys, lungs and heart.

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