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Case Report

The importance of imaging in tuberous sclerosis complex (tsc) in children: Two cases [☆]

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ABSTRACT

Tuberous sclerosis complex (TSC) is an inherited, multisystemic, hamartomatous neurocutaneous disorder, with an autosomal dominant inheritance pattern. It affects multiple organs, however the most susceptible ones include the brain, skin, kidneys, lungs, the retina, and the heart. TSC is characterized by considerable clinical heterogeneity. The majority of patients present with a constellation of clinical signs and symptoms, most prominently central nervous system manifestations including epilepsy, cognitive impairment and autism spectrum disorders, cutaneous, cardiac, renal and ophthalmic manifestations. Epilepsy affects 70%–90% of patients, representing the primary neurological feature and 1 of the foremost clinical findings of the disorder. Cardiac rhabdomyomas are the most frequent cardiac manifestations, appearing as isolated or multiple lesions.

Herein, we present 2 patients diagnosed with tuberous sclerosis. A 3-month-old male patient with cardiac rhabdomyomas and hypopigmented macules and a 19-month-old male patient with partial epilepsy and mild psychomotor retardation. As brain lesions represent some of the most prevalent clinical features and early onset seizures are associated with

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more severe cognitive, function delay, through this article we hope to emphasize the potential role MRI can play in the diagnostic workup of TSC, to ensure a more timely diagnosis, thus modifying the natural course of the disorder and its prognosis.

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Introduction

Tuberous Sclerosis Complex (TSC) is an autosomal dominant, multisystemic, hamartomatous, neurocutaneous disease. The most commonly affected organs include the brain, skin, kidney, lung, retina, and heart[1]. The prevalence of TSC is reported to be approximately 1:6000 – 10,000 live births[1]. The condition shows no ethnic or sex predisposition[2]. It manifests with high intra-familial clinical heterogeneity and variable severity, due to the numerous possible mutations in the TSC1 and TSC2 genes and the varying level of penetrance[2].

The term Tuberous Sclerosis of the cerebral convolutions was first used more than a century ago to describe the distinctive autopsy findings in some patients with seizures and mental, subnormality[3]. The term tuberous describes the potato-like consistency of gyri with hypertrophic sclerosis[3].

It is caused by loss-of-function mutations affecting genes TSC1 and TSC2, encoding for hamartin and tuberin respectively, 2proteins that make up the TSC complex[2,4,5]. The TSC complex plays an important inhibitory role in the mTOR signaling cascade that mediates cell proliferation and differentiation, translation, protein and lipid synthesis, autophagy and stress response[2,4,5].

Disruptions in this pathway lead to unregulated cell proliferation, giving rise to benign tumors affecting multiple organs[2,4,5].

The vast majority of patients show central nervous system (CNS) manifestations including epilepsy, subependymal giant cell astrocytomas, subependymal nodules, cortical dysplasias, neurodevelopmental impairment and autism spectrum disorders[2,4-6,8]. Epilepsy affects 70% – 90% of patients and is the most prominent neurologic feature in patients with TSC and a significant source of morbidity[6-8].

Manifestation in other organs include cardiac rhabdomyomas, renal angiomyolipomas, pulmonary lymphangiomyomatosis, multiple retinal hamartomas, hypomelanotic macules, angiofibromas, ungual fibromas and shagreen patch[2,4-6,8]. These manifestations represent the major diagnostic criteria. Minor criteria include confetti skin lesions, dental enamel pits, intraoral fibromas, multiple renal cysts, retinal achromic patch and hamartomas in other organs[2,4-6,8]. Diagnosis is established by the presence of two major criteria and 1 minor 1[8].

Tuberous sclerosis displays almost complete penetrance and high clinical variability, even among members of the same family[2]. Certain lesions such as cardiac rhabdomyomas and rarely cortical tubers, appear in the antenatal period, cardiac rhabdomyomas almost always regress spontaneously in infancy[9]. In contrast other lesions such as renal angiomyolipomas, or facial angiofibromas do not occur until a certain age and progressively worsen over time[9].

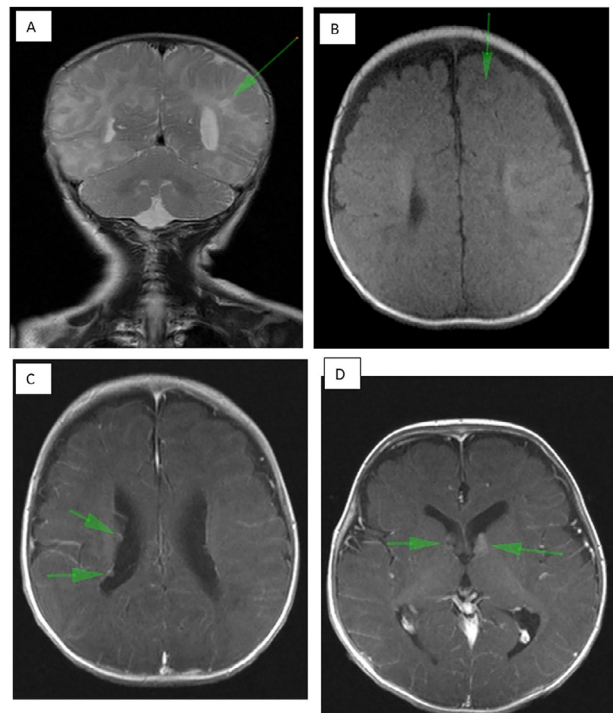


Fig. 1 – (A) 3-month-old boy with tuberous sclerosis. (A) Coronal T2-weighted images of the brain at multiple levels. There are dominant hyperintense T2 lesions in the left parietal cortex and subcortical region consistent with cortical tuber (green arrows). (B, C) Axial T1-weighted images of brain, cortical tubers are also seen in the left frontal lobe (green arrows). There is a prominent subependymal nodule at foramen Monro (green arrows). (D) Axial T1-weighted images of brain after contrast administration shown smaller subependymal nodules are identified along the walls of the lateral ventricle (green arrows) (Color version of figure is available online)

Sometimes, an antenatal diagnosis can be based on fetal ultrasound and MRI, which show cardiac and brain lesions [10]. Definitive diagnosis is established based on a strict criteria system and genetic testing.

Treatment of Tuberous sclerosis is mainly symptomatic, consisting in the management of symptoms associated with the presence of hamartomas in multiple organs and preventing serious functional impairment of these affected organs[6]. A proactive approach involving a multidisciplinary team of doctors from several specialties is imperative in the symptomatic, prophylactic and surgical treatment of TSC. Recently, a lot of progress has been made in the understanding of the genetic mechanisms underpinning the pathogenesis

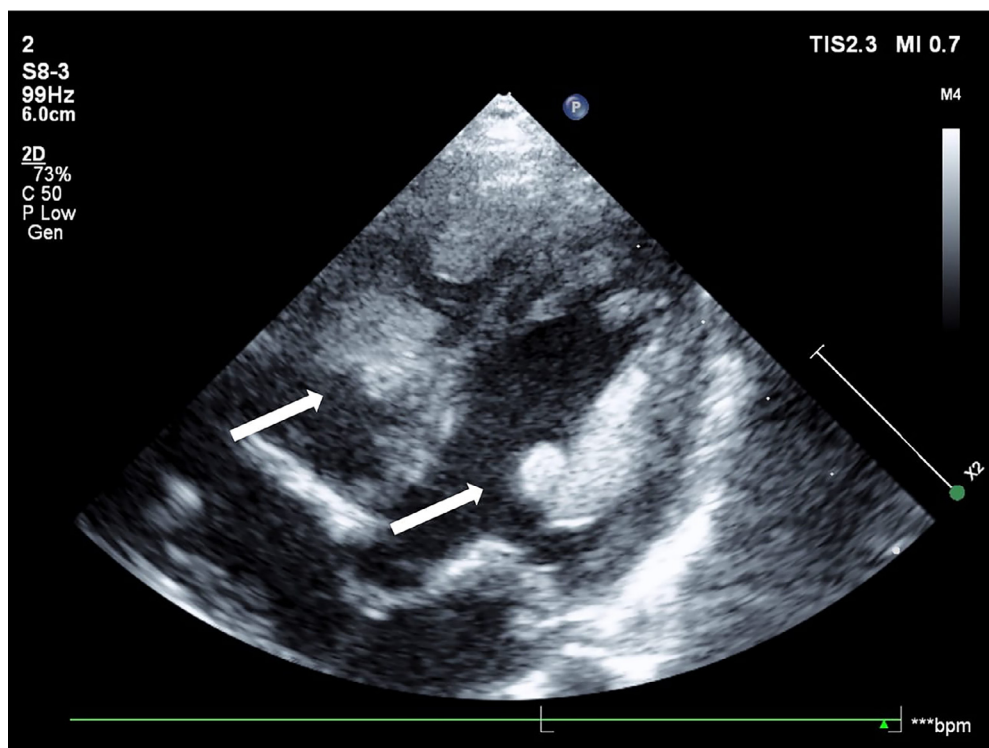


Fig. 2 – (A) 3-month-old boy with tuberous sclerosis.

Multiple bright hyperechoic pseudotumoral images with the myocardium, in the interventricular septum, the right atrium, and both ventricles (white arrows) (Color version of figure is available online)

of TSC, particularly in regards of the mTOR signaling pathway, with new, mTOR inhibitory medications promising to revolutionize the treatment of multiple tumors including renal angiomyolipomas, giant cell, subependymal astrocytomas and lymphangioliomyomatosis and cutaneous manifestations[15,16].

Case report

Case 1

A 3 month-old male patient was admitted to the Pediatrics Clinic with complaints of ongoing seizures and multiple skin lesions. The patient had an uncomplicated perinatal history and no significant family history of inherited genetic conditions. On physical examination, hypopigmented macules and a small distinctive shagreen patch in the lumbar region were present, along with episodes of partial seizures. Routine laboratory examinations were within normal limits. The patient was referred to the Radiology Clinic for a head MRI, which revealed multiple hyperintense lesions in T2-weighted images in the left parietal cortex and subcortical regions consistent with cortical tubers. (Fig 1) These lesions were also evident in the left frontal lobe, some of them appeared to be contrast-enhancing. (Fig. 1) A prominent subependymal nodule at foramen Monro was evident as well, associated with smaller subependymal nodules along the walls of the lateral

ventricle. (Fig. 1) There were also patchy areas of demyelination in several cerebral lobes, potentially related to this pharmacosis.

In the light of these findings, additional imaging was ordered, namely a cardiac ultrasound to identify the presence of other TSC features. Echocardiography revealed multiple solid, hyperechoic masses, in the ventricular septum and ventricular wall, consistent with cardiac rhabdomyomas. (Fig. 2) No obstruction of the inflow or outflow tracts, arrhythmias or otherwise anomalies and impairment of the cardiac function were noted.

Case 2

A 19-month-old patient was referred to the Radiology Clinic, for additional imaging exams, to investigate the origin of his seizures. He presented with a history of partial epilepsy and psychomotor retardation. MRI revealed multiple cortical tubers involving all the lobes presenting as areas of gyral expansion with thickening of the overlying cortex and abnormal signals in the underlying white matter.

Hyperintense signal intensity was evident in T2/Flair in the underlying white matter involving almost all the lobes and cortex of the brain and right basal ganglia. The lesions showed low signal intensity in axial T1-weighted images, with minimal faint contrast enhancement (Fig. 3).

There was an intense contrast enhancement in the subcortical white matter of the left inferior frontal lobe. There were multiple subependymal tuberous nodules in periven-

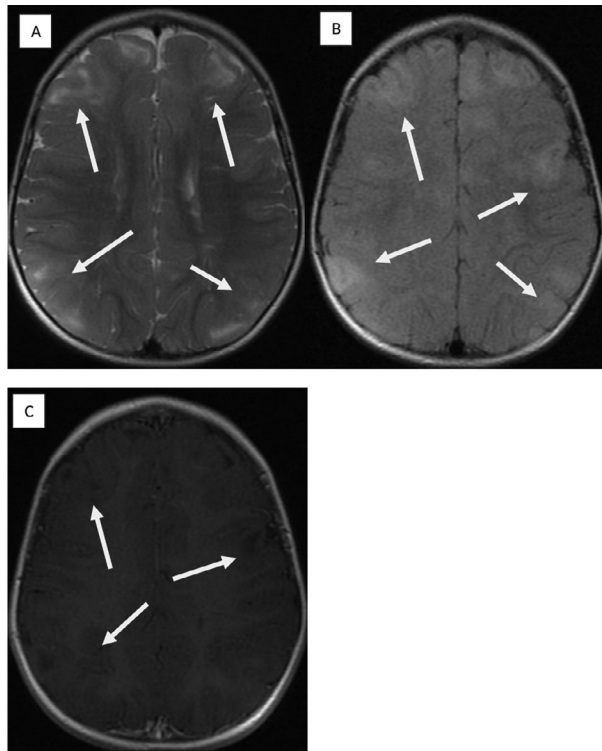


Fig. 3 – (A) 19-month-old male with tuberous sclerosis. A) Axial T2-weighted images of the brain at multiple levels almost all the lobes (white arrows); (B) Axial FLAIR of the brain showed multiple levels almost all the lobes (white arrows); (C) The lesions showed low signal intensity in T1-weighted with minimal faint contrast enhancement (white arrows) (Color version of figure is available online)

tricular deep white matter, showing contrast enhancement in the post-contrast study. Overall findings were consistent with tuberous sclerosis.

Discussion

Tuberous sclerosis is a rare, multisystemic, neurocutaneous genetic disorder defined by the presence of cellular and tissue dysplasia, in the form of hamartomas, involving multiple organs.

[2]. Oftentimes, establishing the diagnosis may be challenging, due to the inconspicuous presentation of the condition, associated with mild symptomatology. Consequently, genetic testing is of the essence in reaching a conclusive diagnosis.

Tuberous sclerosis arises from loss-of-function mutations involving the *TSC1* and *TSC2* genes.

[2,4-6] Approximately 70% of cases are caused by mutations affecting the *TSC2* gene, mutations in *TSC1* gene are present in 20% of patients and it has been recently elucidated that the remaining 10% of cases may be caused by mutations in non-encoding areas including intron or promoter regions, as well as somatic mosaicism[4]. De novo mutations account for two-thirds of all affected patients, inherited mutations constitute

the remaining one-third[2]. These mutations are inherited in an autosomal dominant fashion and the condition shows almost complete penetrance[2]. Mutations involving the *TSC1* gene are more often small nonsense, insertion or deletion mutations, with a few missense and frameshift ones, whereas mutations affecting the *TSC2* gene are frequently large deletions, missense mutations and rearrangements[2,4].

TSC1 and *TSC2* genes encode the proteins hamartin (*TSC1*) and tuberin (*TSC2*), respectively[2,4-6]. These proteins, along with TBC1D7 compose a heterotrimeric complex, the TSC complex, that plays an inhibitory role in the mTOR signaling cascade[2,4,5]. The TSC complex inhibits mTORC1, through the activity of the GTPase-activating protein (GAP) domain on RAS homologue enriched in brain (Rheb), the functional mediator between the TSC complex and mTORC1[2,4,5]. When Rheb is bound to GTP, it activates mTORC1 and the entire downstream signaling pathway, whereas when it is bound to GDP it is inactive, unable to stimulate mTORC1[2,4,5]. The TSC complex works by inducing hydrolysis of the GTP bound to Rheb, maintaining it in a GDP-bound state, thereby inhibiting the activation of mTORC1 [2,5]. Mutations in the

GAP domain, located in the *TSC2* gene, in addition to mutations in *TSC1* gene render the formation of the TSC complex impossible[5]. The lack of the inhibitory, tumor suppressing role of TSC complex, leads to an overdrive of the mTOR signaling pathway, that is associated with excessive proliferation, protein synthesis and translation and metabolic reprogramming[2,4,5].

Clinical presentation varies widely among the affected population, nevertheless distinctive clinical features include neurological anomalies, namely seizures, cortical tubers, subependymal tumors, neurodevelopmental anomalies and autism spectrum disorder, cardiac rhabdomyomas, renal angiomyolipomas and cysts, pulmonary lymphangiomyomatosis, retinal hamartomas, and typical cutaneous lesions including hypopigmented lesions, facial angiofibromas, ungual fibromas and shagreen patch [2,4,6].

Rhabdomyomas in children should be differentiated from other cardiac tumors, such as cardiac myxoma, pericardial teratoma, haemangioma, and fibroma[10]. MRI may be helpful but cardiac ultrasound is generally sufficient to establish the diagnosis of cardiac rhabdomyomas in the setting of Tuberous Sclerosis[10,11]. The diagnosis of multiple cardiac rhabdomyomas in the antenatal period points to the potential diagnosis of Tuberous Sclerosis, well before the development of neurocutaneous signs [10]. Despite the predominantly favorable prognosis of patients with cardiac tumors like rhabdomyomas, their presence should be sought in patients with Tuberous Sclerosis, especially when extracardiac surgery is planned. It should also be noted that symptomatic patients generally have a poorer prognosis than those who are asymptomatic[11].

The onset of infantile spasms in 4-to-6-month-old infants with hypomelanotic macules should strongly suggest the diagnosis of Tuberous Sclerosis Complex[12]. Usually, the epileptic fits lead rapidly to psychomotor deterioration and loss of acquired motor function[13]. Neurological anomalies including cortical tubers, subependymal nodules in the walls of the lateral ventricles and subependymal giant cell tumors are present in approximately 95% of neuroimaging studies of pa-

tients with TSC, revealing a correlation between the number of cortical tubers, their location in the temporal lobe or bilaterally and the severity of neurological manifestations[14]. Our second case underscores the causal epileptogenic role of tubers and reveals a topographic correlation between electroencephalographic spike foci and areas of abnormal MRI signals.

A timely diagnosis of TSC is essential, to allow early diagnostic assessments (neuroimaging studies, electroencephalogram, electrocardiography, renal ultrasonography, and chest computed tomography) and therapeutic interventions to modify the natural progression of the disease and potentially prevent serious complications. TSC neuroimaging assists in identifying early diagnostic findings preceding seizure onset, to improve cognitive outcomes and seizure control. Imaging techniques and advances in genetic technology aid in providing new insights on the disease and offering new perspectives for a better understanding of disease pathophysiology and future therapeutic approaches.

Conclusion

The early diagnosis of Tuberous Sclerosis Complex (TSC) continues to pose a challenge in the majority of cases, as diagnostic workup often begins after seizure onset. Through this article, we hope to emphasize the role high-resolution imaging techniques, in particular MRI, have to play in the early diagnosis of Tuberous Sclerosis in the pediatric population before seizure onset, considering neurological manifestations represent the most prevalent clinical features of the condition, to enable the modification of its natural course and prognosis.

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