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Tuberous sclerosis complex: a case report

Hanna Sebesi[1], Réka Borka-Balás[1], Micheu Cristian Ion[2]

[1]Department of Pediatrics, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Targu Mures, Romania
[2]Department of Pediatric Neuropsychiatry, Mures County Emergency Clinical Hospital, Targu Mures, Romania

ABSTRACT

Background. Tuberous sclerosis complex (TSC) is a rare genetic disorder diagnosed in 6000-10000 children annually, marked by hamartomas in various organs due to hyperactivity of the mTOR pathway.

Case report. A 9-year-old male with TSC exhibited developmental delays, skin lesions, vision and hearing impairments, and neurological symptoms. Extensive evaluations confirmed the diagnosis, and treatment included mTOR inhibitors, symptomatic management, and psychotherapy, resulting in condition improvement.

Conclusions. TSC, caused by mutations in TSC1 and TSC2, significantly impacts organ function and quality of life, requiring comprehensive, multidisciplinary care.

Keywords: sclerosis tuberosa, hamartoma, genetic, mTOR, pediatrics

Abbreviations

ADHD	– Attention Deficit Hyperactivity Disorder	SGCA	– Subependymal Giant Cell Astrocytoma
ASD	– Autism Spectrum Disorder	TSC	– Tuberous Sclerosis Complex
Mtor	– Mammalian Target of Rapamycin		

INTRODUCTION

Tuberous sclerosis complex (TSC) is a rare genetic multisystem condition diagnosed in about 6000 to 10000 children a year. It is characterized by a widespread appearance hamartomas affecting the brain, heart, kidneys, lungs, eyes, skin, and oral cavity [1]. The pathognesis is based on the hyperactivity of the mTOR pathway due to its faulty inhibition.

TSC is also known as Bourneville-Pringle disease, a name which stands for the Frenchdoctors who better defined the disease in 1880 after it was originally discovered in 1862 by a german pathologist, Friedrich Daniel [2].

Our article aims to describe the case of a 9-year-old male patient presenting a complicated case of this condition.

CASE REPORT

A 3-year-old male patient, the first child born after a high-risk pregnancy (hypertension and oedema), presented with a significant heredocolateral history, including a mother with vitiligo and a brother and maternal aunt with epileptic seizures. The patient was born at term by natural delivery, weighing 2800 grams. The developmental trajectory was marked by some delays, with independent walking at 1 year of age and the utterance of first words at 2 years.

In 2017 with a medical history of otitis media, the patient presented at the ENT clinic with complaints of oral breathing, chronic nasal obstruction, persistent nocturnal stertor, and rhinorrhea. Upon medical examination, inflamed pharyngeal lymphoid tis-

Corresponding author:
Reka Borka-Balas
E-mail: reka.borka-balas@umfst.ro

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sue was evident, leading to a diagnosis of chronic hypertrophic adenoiditis. Subsequently, the patient underwent surgical treatment under general anesthesia, and a classic adenoidectomy was performed. Medical management involved the administration of parenteral anti-inflammatory, antibiotic, and analgesic drugs. Post-operative audiometry confirmed the patient's favorable condition, prompting discharge.

At 8 years old, in August 2022, the patient visited a dermatology specialist for a consultation accusing multiple tuberous formations. The patient had numerous skin changes, including macules and reddish-brown, hyperpigmented lesions, facial, left palpebral, and right gingival fibromas, clustered and isolated right lumbar papules, and a dorsal penile papilloma. During the clinical examination, representative features were observed, including hypomelanotic spots, Koenen's tumor, an elastic nevus, Shagreen's spot in the right lumbar region, angiofibromas, and confetti lesions.

The patient also accused vision and hearing impairment predominantly affecting the left eye and ear. These findings, combined with the cognitive slowness and systemic involvement observed in the patient, supported the diagnosis of TSC and warranted further specialist evaluations.

In August 2023 the patient presented at the emergency services for three paroxysmal manifestations:

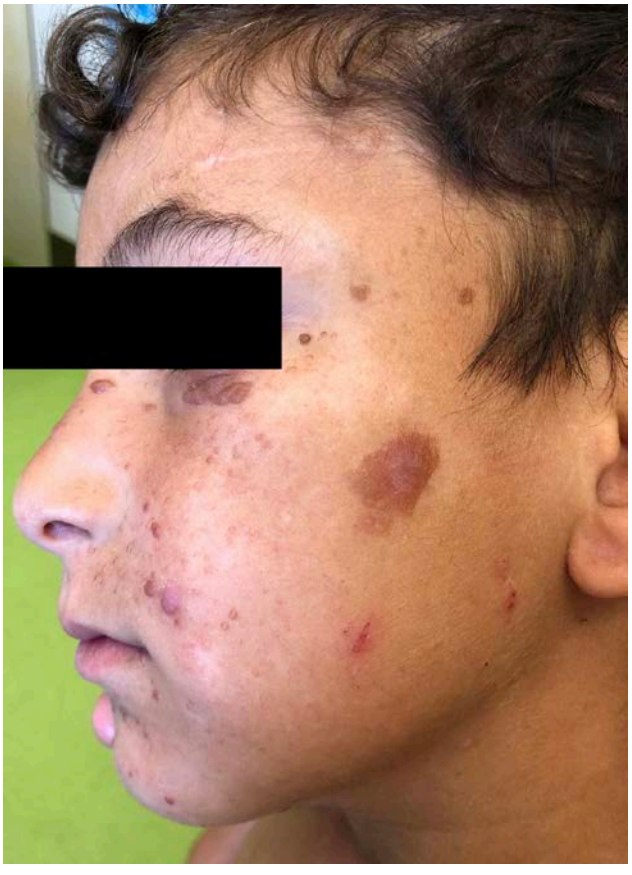

FIGURE 1. Hyperpigmanted facial lesions

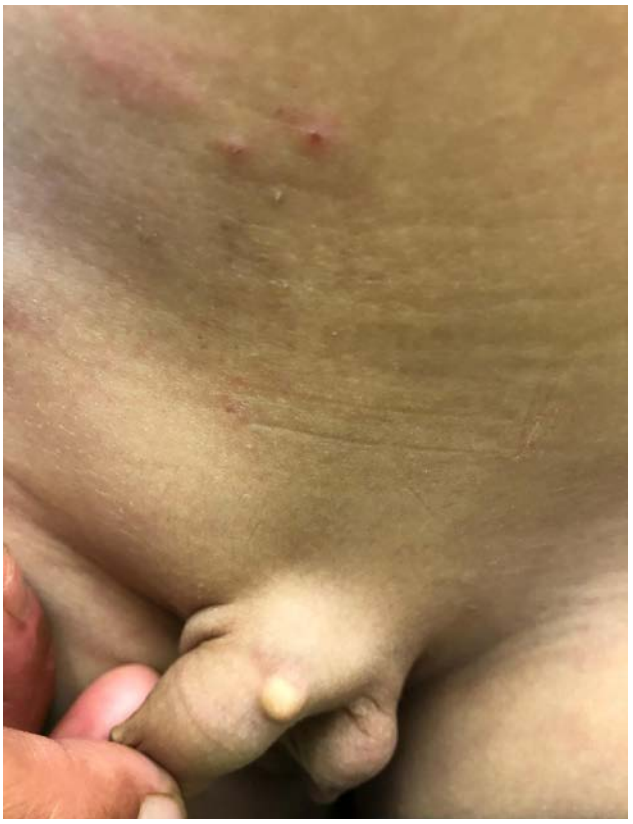

FIGURE 2. Dorsal penile papilloma

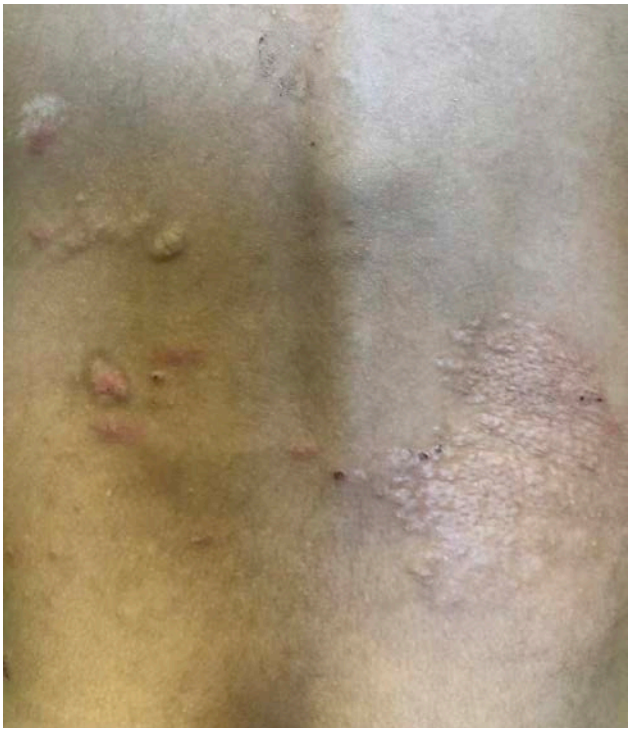

FIGURE 3. Shagreen's spot

first upon awakening, manifested by the deviation of the buccal commissure to the left, sialorrhea and several clones of the cephalic region. Two other manifested in sleep by hypertonia, sialorrhea, followed by palpebral myoclonus and clonus of the cephalic region, affirmatively without loss of consciousness. The patient underwent a series of

comprehensive investigations, including a brain MRI, EEG, ocular ultrasound, fundus examination, psychological evaluation, oro-maxillo-facial surgery consult, cardiac ultrasound, abdominal ultrasound, and genetic testing.

The neurological examination revealed several findings such as left eye divergent strabismus, and mild generalized hypotonia. An additional cranial MRI was performed, revealing multiple space-occupying lesions in the lateral ventricles, ranging between 6-27 mm with the largest being in the right ventricle. Ventricles III and IV were of normal size, without any abnormalities. No infratentorial lesions were observed. Bilateral carotid stenoses were noted, particularly on the right side, as well as fluid collections in the right mastoid, indicating right-sided mastoiditis. EEG examination shows delta theta font tracing with medium-hyperintense bursts of sharp slow waves.

The ophthalmologic consultation revealed chorioretinitis in the left eye and divergent strabismus in both eyes, predominantly the left eye, with significant amblyopia. The fundus examination revealed multiple yellowish-white, prominent retinal hamartomas with relatively well-defined contours, indicative of possible retinal astrocytoma. An ocular ultrasound was recommended by the specialist, which later confirmed this suspicion, showing minimal slightly prominent peripapillary retinal lesions in the left eye and multiple retinal formations in the posterior pole, which were hyperreflective and nonhomogeneous with a posterior shadow cone.

During the psychological evaluation the 3rd grader exhibits poor academic performance, mental latency, and anxiety. The child struggles with understanding Romanian, preferring their mother tongue, and lacks social skills. An IQ of 61 is revealed, indicative of mild mental retardation, difficulty understanding instructions, dyslexic speech, and infantile behavior. The child also suffers from nocturnal enuresis.

The oro-maxillo-facial surgeon diagnosed the patient with a 4,0 × 4,0 cm wide odontogenic vestibular abscess. The lesion was drained in local anesthesia followed by antimicrobial and anti-inflammatory treatment.

Cardiac ultrasound showed no signs of intraventricular or intravascular malformations. Abdominal ultrasound showed no abnormalities.

The diagnosis of tuberous sclerosis was then genetically confirmed through a peripheral blood sample, which was analyzed using the Next-Generation Sequencing (NGS) analysis method, specifically the TruSight One gene panel kit. The patient continues to receive appropriate medical care and undergo necessary follow-up evaluations to monitor their condition and adjust treatment as needed.

The patient is currently being treated with a regimen of Carbamazepine, Spironolactone, Omega 3, and Gingko Biloba supplement while also being in psychotherapy. Due to proliferation of the patients' tumors, an mTOR inhibitor (Everolimus) was also introduced to his treatment. This management approach led to a favorable evolution of the patient's condition.

DISCUSSION

Genetic view-point

TSC stems from alterations in tumor suppressor genes, namely TSC1 or TSC2, through rearrangements, deletions, or inactivating mutations. These genetic changes give rise to abnormal proteins, hamartin, and tuberin, whose typical function involves regulating cellular growth by modulating the phosphatidylinositol 3-kinase signaling pathway [3]. This pathway's modulation results in the inhibition of the mammalian target of rapamycin (mTOR), a pivotal regulator of cellular processes. The hamartin/tuberin complex acts as an inhibitor of tumor growth by suppressing the activity of the mTOR pathway, thereby controlling cellular proliferation and preventing cellular apoptosis [4]. However, in individuals with TSC, these proteins undergo alterations, leading to sustained activation of the mTOR pathway and subsequent formation of hamartomas across multiple organs. Interestingly, while TSC can be hereditarily transmitted, a significant portion (70%) of patients develop the condition due to spontaneous mutations. Familial cases often trace back to germline mutations, indicating a genetic predisposition within affected families [5]. Research highlights a notable discrepancy: mutations in the TSC2 gene tend to be more prevalent and correlate with more severe neurological impairments compared to those in TSC1 [6]. Moreover, familial transmissions frequently present a higher frequency of changes in the TSC1 gene, thereby aligning with distinct diagnostic criteria [5]. These findings shed light on the intricate genetic mechanisms underlying both sporadic and familial occurrences of TSC, contributing to our understanding of its pathogenesis and potential diagnostic approaches.

Neurological manifestations

The neurological manifestations of TSC represent a significant cause of impairment for many patients. These manifestations include epilepsy, structural brain abnormalities, intellectual disability, autism spectrum disorder, and psychological problems [7]. Epilepsy stands out as the foremost neurological symptom in TSC, affecting approximately 90% of patients, with onset typically occurring before the age of one. Various seizure types can mani-

fest in TSC, with infantile spasms being the most common in early life, affecting nearly 40% of patients with TSC-associated epilepsy [8]. These epileptic spasms are characterized by symmetric and synchronous clusters of neck, trunk, or limb flexion or extension, often coinciding with periods of awakening or falling asleep. Vigabatrin is used as the first-line treatment for epileptic spasms due to its superior efficacy compared to steroids [9]. The age of seizure onset and the severity of seizures are key predictors of long-term cognitive and behavioral outcomes. Despite earlier theories suggesting a correlation between seizures and cortical tubers, the exact origin and mechanism of epileptogenesis remain subjects of debate [1]. Structural brain abnormalities include cortical tuber, found in 80% of patients, subependymal nodule, present in 90% of patients, and subependymal giant cell astrocytoma (SGCA). The latter is a rare type of slow-growing benign tumor most often found near the foramen of Monro, seen in up to 20% of the cases. The symptoms caused by these astrocytomas are not specific, resulting mostly from obstruction, and can include focal neurological deficits, headache, and emesis alongside fatigue, brain fog, and increased risk of further seizures [10].

Dermatological manifestations

Dermatological manifestations often lead to early diagnoses as most of them are detectable at birth and during early infancy [11]. The majority of these lesions are included in the 2017 diagnostic criteria for TSC [12]. Among these, hypomelanotic macules, also called ash leaf spots, are present in 90% of cases. These lesions are round and can vary in size from a few millimeters to as much as 5 cm in length. Occasionally, they may have an irregular, reticulated appearance resembling scattered white confetti paper (confetti lesions) [13]. As these macules are harder to identify on fair skin, using Wood's lamp for a precise diagnosis is recommended [14]. 3 or more of these white macules present at birth warrant further evaluation for TSC. Furthermore, 75% of patients over the age of 9 will develop facial angiofibromas. These lesions typically appear as flat reddish macules on the center of the face and evolve into erythematous nodular growths over time [15]. Other cutaneous manifestations include fibrous plaques on the forehead, confetti skin lesions, shagreen patches in the lumbosacral region, and gingival or periungual fibromas, all found in approximately 20% of cases [10].

Cardiovascular manifestations

Cardiac involvement in TSC typically peaks at birth or during early infancy, often serving as the initial sign alongside cutaneous manifestations [16]. Approximately 50–60% of individuals with TSC demonstrate signs of cardiac involvement, primarily in the form of rhabdomyomas, which are detected in prenatal ultrasounds between 20 to 30 weeks gestation in at least 50% of newborns with TSC [6]. Typically, these lesions tend to group in small clusters, reaching sizes ranging from 3 to 25 mm, predominantly located within the ventricles of the heart along the septum. While these noncancerous tumors are usually asymptomatic, they possess the potential to cause heart failure or arrhythmia [17]. Rhabdomyomas typically undergo spontaneous regression within the first 3 years of life, although residual areas of histologically abnormal myocardium may persist despite regression [5].

Ophtalmic manifestations

Ophthalmic lesions are common in TSC, retinal astrocytic hamartomas being the most common, found at any age in up to 50% of patients [18]. These typically benign lesions are composed of glial astrocytes and blood vessels, usually appearing on funduscopic examination as nodular or lobulated areas prone to calcification. In rare instances when visual acuity is impacted, the retinal hamartoma might be discovered compressing the retinal fovea and/or optic nerve. Other ophthalmic manifestations include retinal achromic patches, seen in up to 39% of cases, iris depigmentation, and palpebral angiofibroma [19].

Cognitive and behavioral manifestations

TSC presents a wide array of cognitive, behavioral, and psychiatric symptoms [20]. In the realm of neuropsychiatric manifestations, autism spectrum disorder (ASD) holds particular significance, both clinically and in research. Approximately 26–50% of individuals with TSC meet the criteria for ASD. The overlap between ASD in TSC and idiopathic ASD underscores TSC's importance as a genetic model for studying this condition [21]. Key factors linked to poorer cognitive outcomes include a history of resistant seizures and the presence of cortical tubers in specific brain regions like the frontal and temporal lobes. Roughly 30% of patients exhibit profound impairment (mean IQ 30–40), with minimal or no noticeable improvements over time. Over 50% have average intelligence (IQ >70) but may experience specific cognitive deficits in memory, attention, or executive function [20]. ADHD and related behaviors, including impulsivity, hyperactivity, and attention issues in daily life, are present in approximately half of children with TSC. These behaviors tend to be more prevalent in individuals with severe disabilities but are also disproportionately common among those with normal abilities [22]. Self-injury, aggression, challenging temper tantrums, and per-

sistent sleep disturbances are frequently observed in children with severe TSC-related disabilities. As individuals with TSC transition into adolescence and adulthood, anxiety and mood disorders become increasingly prevalent. These symptoms significantly impact the quality of life for both higher-functioning youth and adults [23]. Sleep disorders, such as nighttime awakenings, extended sleep onset, and sleep issues related to seizures, are among the most common behavioral manifestations in children with TSC [24].

Clinical management

To monitor the development of SGCA, it's recommended to conduct surveillance MRI scans of the brain with and without contrast every 1 to 3 years until the age of 25. Beyond this age, MRI surveillance is only necessary if there is an asymptomatic tumor [10]. Surgical resection or the use of mTOR inhibitors are considered the most effective treatment options. Vigabatrin is strongly supported as the first-line treatment for epileptic spasms in these patients. Most antiseizure medications are suitable for epilepsy in TSC. Additionally, alternative or complementary therapies like surgery, the ketogenic low glycemic index diet, and vagal nerve stimulation can be considered [9].

For specific skin lesions, options such as topical mTOR inhibitors, laser treatment, or surgical intervention may be considered [25]. If the skin lesions are not causing disfigurement or discomfort, intervention may not be required, and regular clinical monitoring could be adequate.

In most cases, ocular hamartomas are non-progressive and do not impair vision. However, if they exhibit increased aggressiveness or become fluid-filled, they can lead to retinal detachment, necessitating treatment with laser photocoagulation. Typically, these ocular lesions are observed clinically without intervention [1].

CONCLUSION

Tuberous Sclerosis Complex is a rare genetic disease, affecting multiple organs by the appearance of hamartomas, overall altering the function of the brain, heart, eyes, kidneys, and the skin. In addition to organ damage, TSC also causes mental and cognitive disfunction, further worsening the patients' quality of life. Behind the pathophysiological cause of this syndrome lies the hyperactivity of the mTOR pathway, caused by the mutation of its suppressor genes, TSC1 and TSC2. The first symptoms that usually lead to diagnosis are epileptic seizures, visual disturbances, mental retardation, and the appearance of specific skin changes. Treatment of the disease can include mTOR inhibitors (ex. Everolimus), but it is mostly based on symptomatic management, consisting of antiepileptic medication to control the seizures, surgical treatment of the tumors and psychotherapy.

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writing - original draft preparation, H.S;
writing - review and editing H.S, R.B.B;
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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
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