rcfmc Revista Científica da Faculdade de Medicina de Campos
ISSN 2965-6575

Rev. Cient. Fac. Med. Campos, v. 20, n. 1, p. 66-71, jan./jun. 2025
doi: 10.29184/1980-7813.rcfmc.999.vol.20.n1.2025
Faculdade de Medicina de Campos
https://revista.fmc.br/ojs/index.php/RCFMC

Case Report

Tuberous sclerosis diagnosed in adulthood: a case report

Esclerose tuberosa diagnosticada em idade adulta: um relato de caso

Phatryck Lhoran Pinheiro Ferreira[1], Iara Salvador Pecemilis[1], Eduarda Queiroz Amorim[1], Ramon Gonçalves Romano Cruz Ribeiro[2]

1. Medical Student, Faculdade de Medicina de Campos (FMC), Campos dos Goytacazes, RJ, Brazil.
2. Professor, Faculdade de Medicina de Campos (FMC), Campos dos Goytacazes, RJ, Brazil.
Corresponding Author: Phatryck Lhoran Pinheiro Ferreira
Contact: phatryck007@gmail.com

Keywords:
Hamartomas.
Seizure.
Tuberous sclerosis.

Palavras-chave:
Convulsão.
Esclerose Tuberosa.
Hamartomas.

Received on:
10/01/2023

Accepted on:
04/08/2025

Published on:
06/26/2025

ABSTRACT

Tuberous sclerosis complex (TSC) or simply tuberous sclerosis (TS), also known as Bourneville-Pringle disease, is a rare autosomal dominant genetic disease that alters the mechanisms of cell proliferation, generating hamartomas in several organs. Among the systems affected, the central nervous system (CNS), skin and skin appendages, kidney, respiratory, cardiac and ophthalmological systems stand out. The definitive diagnosis of tuberous sclerosis requires the identification of a pathogenic mutation in one of the genes associated with the disease, *TSC1* or *TSC2*, through molecular genetic testing; 2 major clinical criteria or 1 major clinical criterion and 2 minor clinical criteria. The treatment of tuberous sclerosis is closely related to the systems affected, considering that the disease can affect multiple organs simultaneously. Therefore, monitoring by a multidisciplinary team is essential in order to ensure a comprehensive and individualized therapeutic approach. Regarding therapeutic strategies, it is also worth highlighting that the use of targeted therapy with mTORC1 inhibitors is currently an excellent alternative.

RESUMO

O Complexo Esclerose Tuberosa (CET) ou simplesmente Esclerose Tuberosa (ET), também conhecida como doença de Bourneville-Pringle, é uma doença genética autossômica dominante de rara incidência, que modifica os mecanismos de proliferação celular, gerando hamartomas em diversos órgãos. Dentre os sistemas afetados, destacam-se o Sistema Nervoso Central (SNC), pele e anexos cutâneos, renal, respiratório, cardíaco e oftalmológico. O diagnóstico definitivo da esclerose tuberosa requer a identificação de uma mutação patogênica em um dos genes associados à doença, TSC1 ou TSC2, por meio de teste genético molecular; 2 critérios clínicos maiores ou 1 critério clínico maior e 2 critérios clínicos menores. O tratamento da esclerose tuberosa está intimamente relacionado aos sistemas acometidos, considerando-se que a doença pode afetar múltiplos órgãos simultaneamente. Dessa forma, torna-se imprescindível o acompanhamento por uma equipe multidisciplinar, a fim de garantir uma abordagem terapêutica abrangente e individualizada. No que tange às estratégias terapêuticas, destaca-se ainda que, atualmente, o uso de terapia alvo com inibidores da mTORC1 é uma ótima alternativa.

INTRODUCTION

Tuberous Sclerosis (TS) is a multisystem neurocutaneous syndrome with an autosomal dominant genetic inheritance pattern that can manifest at any age. It was first discovered in 1862 by Virchow and Von Recklinghausen during the autopsy of an infant who presented with seizures. The condition is characterized by altered mechanisms of cell proliferation and migration, leading to the development of hamartomas—benign or malignant tumors that primarily affect the central nervous system (CNS) and the skin, as well as various other organs[1–4].

TS has a rare incidence—approximately 1 in every 6,000–10,000 live births per year—and affects both sexes and all ethnic groups equally. However, some studies have shown that symptoms may manifest more intensely in females. From an epidemiological standpoint, approximately 50% of TS cases are associated with inactivating mutations, deletions, or rearrangements in the tumor suppressor genes *TSC1* or *TSC2*. These genetic alterations result in the dysfunction of the hamartin and tuberin proteins, disrupting cell cycle regulation and promoting cellular hyperplasia. Consequently, hamartomas form in various organs, including the brain, heart, skin, eyes, kidneys, and lungs[1,5,6].

This case report was approved by the Ethics Committee of the Faculdade de Medicina de Campos, under CAAE 74811023.5.0000.5244. The approval number corresponding to this submission is 6.648.377.

CASE DESCRIPTION

A 40-year-old male patient of mixed race presented to the outpatient clinic with a seizure episode that had begun approximately five months prior and was difficult to control. He denied any other symptoms. The patient was on Levetiracetam 1500 mg/day and Alprazolam 0.5 mg. He had no comorbidities. Regarding family history, he reported that his father died in his fifth decade of life and also had a history of seizures.

Physical examination revealed hypopigmented macules on both arms and back, as well as typical cutaneous manifestations such as fibrous plaques on the forehead and periungual or subungual hyperkeratotic lesions on the hands. The remainder of the physical and neurological examination was unremarkable. Brain Magnetic Resonance Imaging (MRI) was performed and showed two subependymal nodules located in the region of the right interventricular foramen, as well as a tuber in the paracentral lobule, cortico-subcortical region, and the left middle frontal gyrus (**Figure 1A e 1B**). Based on the imaging findings and clinical presentation, the patient was referred for genetic evaluation, which identified a pathogenic variant in the *TSC1* gene, enabling a definitive diagnosis. He is currently under follow-up and has achieved seizure control with the combination of Levetiracetam 1500 mg/day and Sodium Valproate 500 mg/day.

DISCUSSION

Patients with Tuberous Sclerosis (TS) commonly seek medical attention primarily due to neurological manifestations, with seizures being the most frequently reported symptom. In addition, characteristic cutaneous lesions often prompt medical consultations. The diagnosis is generally established within the first 15 months of life; however, in cases diagnosed later, symptoms that had previously been present were often found to have gone unrecognized or underappreciated during earlier medical evaluations[5–7].

Cutaneous and skin appendage manifestations represent the most frequent clinical findings in TS and can be identified across all age groups. Although present in the majority

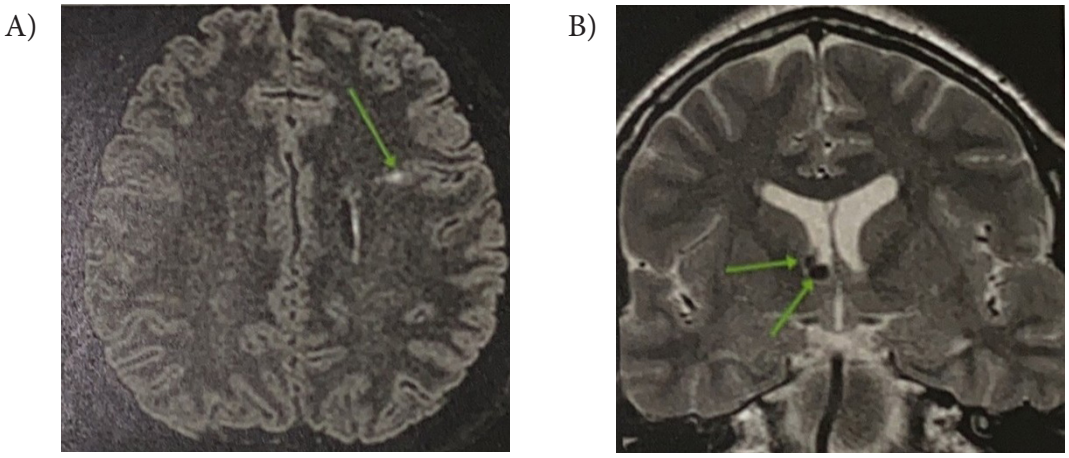

Figure 1. A: Axial FLAIR Magnetic Resonance Imaging showing a cortical tuber in the left frontal region. B: Coronal T2-weighted Magnetic Resonance Imaging revealing a subependymal nodule in the right interventricular foramen.

of patients, some lesions may be difficult to detect, particularly in the early stages of life. It is estimated that up to 90% of cases exhibit some form of cutaneous manifestation. Among the most characteristic dermatological findings are hypopigmented macules, often described as "ash leaf" spots, typically larger than 5 millimeters in diameter and potentially extending to several centimeters. These lesions are present in approximately 90% of patients, frequently since birth, although new macules may emerge over time, while pre-existing lesions may darken or regress spontaneously[6,8].

Another common cutaneous manifestation of TS is the presence of facial angiofibromas, hamartomatous nodules composed of connective and vascular tissue, which occur in approximately 83% to 90% of cases. These lesions usually appear during the first decade of life, with a marked increase in incidence during adolescence, and tend to stabilize in adulthood. Their distribution is predominantly centrofacial[6,8].

The primary neurological manifestation of Tuberous Sclerosis (TS) is epilepsy, which is present in approximately 95% of cases, making it the clinical condition most frequently associated with the diagnosis of the disease. Seizure onset typically occurs within the first three years of life and may present in any seizure type. However, in about two-thirds of patients, the condition initially manifests as refractory focal epilepsy. In addition to seizures, these patients may exhibit symptoms within the autism spectrum, intellectual disability, and mood disorders, which affect approximately 40% to 50% of cases. Compared to renal complications, neurological manifestations are the leading contributors to the highest morbidity and mortality rates associated with Tuberous Sclerosis[1,8–11].

In the renal system, angiomyolipomas—benign tumors—are frequently observed, being identified in approximately 80% of TS cases. Most of these lesions are asymptomatic; however, they can present clinically with hematuria or progressive loss of renal function. Furthermore, patients with TS have a higher prevalence of renal cysts compared to the general population. In the pulmonary system, Lymphangioleiomyomatosis (LAM) stands out as a condition characterized by the replacement of normal alveolar tissue with cysts and by abnormal proliferation of smooth muscle. Although asymptomatic LAM is the most common form, in some cases, the disease may progress to serious complications such as pneumothorax, chylothorax, and respiratory failure. In the cardiovascular system, rhabdomyoma is the cardiac tumor most frequently associat-

ed with TS. It may remain asymptomatic or, in more severe cases, lead to complications such as cardiomegaly, heart murmurs, altered blood flow, arrhythmias, non-immune hydrops fetalis, and, in extreme cases, death. Regarding ophthalmologic manifestations, retinal hamartomas are present in approximately 30% to 50% of patients, typically bilaterally and in multiple locations. Despite their high prevalence, these lesions rarely cause significant impairment of visual acuity[8,11,12].

The diagnostic criteria for TS were updated during the Second International Tuberous Sclerosis Complex Consensus Conference held in 2012. This revision incorporated advances in diagnostic methods, including the introduction of genetic testing as a definitive criterion, the refinement of previously established clinical criteria, and the elimination of the "probable diagnosis" category. The identification of a pathogenic mutation in the *TSC1* or *TSC2* genes through molecular analysis is sufficient to confirm the diagnosis of Tuberous Sclerosis and constitutes the only independently conclusive criterion. However, although genetic testing yields positive results in 75% to 90% of cases, a negative result does not exclude the disease, underscoring the importance of careful clinical evaluation[13,14].

Using clinical criteria, a definitive diagnosis is made by the presence of two major criteria or one major and two minor criteria. A possible diagnosis is considered when one major and one minor criterion are present, as summarized in the table below[14].

Further investigation is essential and should include brain MRI to assess for cortical tubers, subependymal nodules, or other cranial lesions, as well as electroencephalography to characterize cerebral electrical activity and define seizure type. Imaging studies should also include abdominal MRI for detection of

Table 1 . Clinical criteria for the diagnosis of Tuberous Sclerosis. Adapted from reference [14]

Major Criteria	Minor Criteria
≥ 3 hypomelanotic macules (at least 5 mm in diameter)	"Confetti" skin lesions
≥ 3 angiofibromas or presence of a fibrous cephalic plaque	≥ 3 dental enamel pits
≥ 2 ungual fibromas	≥ 2 intraoral fibromas
Shagreen patch (thickened, leathery, and rough-textured skin lesion, typically located in the lumbosacral region)	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Cortical dysplasia	Nonrenal hamartomas
Subependymal nodules	
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Pulmonary lymphangioleiomyomatosis	
≥ 2 angiomyolipomas	

renal angiomyolipomas and cysts, transthoracic echocardiography and electrocardiogram to evaluate for cardiac rhabdomyomas and conduction system abnormalities. In addition, pulmonary function tests and high-resolution chest computed tomography are indicated to investigate LAM[14].

The primary focus of treatment is the control of symptoms caused by hamartomas and the prevention of functional loss in affected organs. Therefore, it is crucial that patients be followed by a multidisciplinary team. As such, there is no single, specific treatment for TS, and medications must be tailored to the patient's individual symptomatology[16].

Currently, TS patients who present with cutaneous lesions that carry a risk of complications—such as hemorrhagic angiofibromas—and who are not candidates for surgical treatment, may benefit from targeted therapy with oral mTORC1 inhibitors. Rapamycin and its derivative, everolimus, have shown high efficacy in controlling various tumor-related manifestations of the disease, including renal angiomyolipomas, subependymal giant cell astrocytomas, and LAM[8,15].

Tuberous Sclerosis is a rare genetic disease characterized by the formation of hamartomas in multiple organs and systems, with clinical manifestations potentially present as early as the neonatal period. The case reported in this paper highlights the complexity and phenotypic diversity of the condition, emphasizing the importance of early recognition of clinical signs—particularly dermatological and neurological changes—which are often underestimated during initial medical encounters. As seen in this case, delayed diagnosis may lead to the silent progression of lesions with significant functional consequences.

In this context, a multidisciplinary and individualized approach is indispensable, grounded in thorough diagnostic investigation to enable early identification of affected sites and implementation of appropriate therapeutic interventions. This underscores the importance of broad clinical knowledge of the disease and continuous surveillance as essential strategies to improve prognosis and the quality of life of patients with Tuberous Sclerosis.

AUTHOR CONTRIBUTIONS:

PLPF was responsible for the conception and design of the study, data analysis, and manuscript writing. PLPF carried out data collection, statistical analysis, and critical revision of the manuscript. ISP, EQA, RGRCR provided technical support, conducted the literature review, and performed the final revision of the text. All authors read and approved the final manuscript version and agree to take responsibility for its content.

ACKNOWLEDGEMENTS:

The authors would like to thank the Hospital Escola Álvaro Alvim (HEAA) for its support and contribution to this study.

CONFLICT OF INTEREST:

We wish to confirm that there are no known conflicts of interest associated with this publication and that no significant financial support has influenced its results.

DECLARATION REGARDING THE USE OF GENERATIVE AI:

The authors declare that they used generative artificial intelligence, ChatGPT, for the language revision of the manuscript. The editorial board made the decision to utilize ChatGPT, an AI language model developed by OpenAI, for the translation of this manuscript from the original language, Portuguese, to English.

REFERENCES

1. Sá EGCD, Mota Júnior AAD, Gomes AS, Vieira RV. MANIFESTAÇÕES RADIOLÓGICAS NA ESCLEROSE TUBEROSA: UMA REVISÃO DE LITERATURA. REASE [Internet]. 31 de maio de

2023 [citado 22 de abril de 2025];9(5):841–50. Disponível em: https://periodicorease.pro.br/rease/article/view/9658

2. Oliveira I, Lopes R, Cruz I, Bragança B, Azevedo J, Andrade A. Esclerose Tuberosa: Achados Incomuns em Contexto de uma Doença Rara. Arquivos Brasileiros de Cardiologia [Internet]. 31 de janeiro de 2023 [citado 22 de abril de 2025];120(1):e20220147. Disponível em:https://abccardiol.org/article/esclerose-tuberosa-achados-incomuns-em-contexto-de-uma-doenca-rara/
3. Pereira CCDS, Dantas FDG, Manreza MLGD. Clinical profile of tuberous sclerosis complex patients with and without epilepsy: a need for awareness for early diagnosis. Arq Neuropsiquiatr [Internet]. outubro de 2022 [citado 22 de abril de 2025];80(10):1004–10. Disponível em: http://www.thieme-connect.de/DOI/DOI?10.1055/s-0042-1758456
4. Portocarrero LKL, Quental KN, Samorano LP, Oliveira ZNPD, Rivitti-Machado MCDM. Tuberous sclerosis complex: review based on new diagnostic criteria. An Bras Dermatol [Internet]. junho de 2018 [citado 22 de abril de 2025];93(3):323–31. Disponível em: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0365-05962018000300323&lng=en&tlng=en
5. Sadowski K, Kotulska K, Schwartz RA, Jóźwiak S. Systemic effects of treatment with MTOR inhibitors in tuberous sclerosis complex: a comprehensive review. Acad Dermatol Venereol [Internet]. abril de 2016 [citado 22 de abril de 2025];30(4):586–94. Disponível em: https://onlinelibrary.wiley.com/doi/10.1111/jdv.13356
6. Jacks SK, Witman PM. Tuberous Sclerosis Complex: An Update for Dermatologists. Pediatric Dermatology [Internet]. setembro de 2015 [citado 22 de abril de 2025];32(5):563–70. Disponível em: https://onlinelibrary.wiley.com/doi/10.1111/pde.12567
7. Ebrahimi-Fakhari D, Meyer S, Vogt T, Pföhler C, Müller CSL. Dermatological manifestations of tuberous sclerosis complex (TSC). J Deutsche Derma Gesell [Internet]. julho de 2017 [citado 22 de abril de 2025];15(7):695–700. Disponível em: https://onlinelibrary.wiley.com/doi/10.1111/ddg.13264
8. DiMario FJ, Sahin M, Ebrahimi-Fakhari D. Tuberous Sclerosis Complex. Pediatric Clinics of North America [Internet]. junho de 2015 [citado 22 de abril de 2025];62(3):633–48. Disponível em: https://linkinghub.elsevier.com/retrieve/pii/S0031395515000255
9. Fasolo L, Do Rocio Valenga Baroni E, Esperidião Ramos C, Benassi G. RELATO DE CASO: ESCLEROSE TUBEROSA DIAGNOSTICADA NA INFÂNCIA. SalusVita [Internet]. 9 de maio de 2023 [citado 22 de abril de 2025];41(02). Disponível em: https://revistas.unisagrado.edu.br/index.php/salusvita/article/view/293
10. De Waele L, Lagae L, Mekahli D. Tuberous sclerosis complex: the past and the future. Pediatr Nephrol [Internet]. outubro de 2015 [citado 22 de abril de 2025];30(10):1771–80. Disponível em: http://link.springer.com/10.1007/s00467-014-3027-9
11. Kingswood JC, Bruzzi P, Curatolo P, De Vries PJ, Fladrowski C, Hertzberg C, et al. TOSCA – first international registry to address knowledge gaps in the natural history and management of tuberous sclerosis complex. Orphanet J Rare Dis [Internet]. dezembro de 2014 [citado 22 de abril de 2025];9(1):182. Disponível em: http://ojrd.biomedcentral.com/articles/10.1186/s13023-014-0182-9
12. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature [Internet]. abril de 2013 [citado 24 de fevereiro de 2025];496(7446):504–7. Disponível em: https://www.nature.com/articles/nature12060
13. Curatolo P, Moavero R, De Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. The Lancet Neurology [Internet]. julho de 2015 [citado 22 de abril de 2025];14(7):733–45. Disponível em: https://linkinghub.elsevier.com/retrieve/pii/S1474442215000691
14. Northrup H, Krueger DA, Northrup H, Krueger DA, Roberds S, Smith K, et al. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatric Neurology [Internet]. outubro de 2013 [citado 22 de abril de 2025];49(4):243–54. Disponível em: https://linkinghub.elsevier.com/retrieve/pii/S0887899413004906
15. French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. The Lancet [Internet]. outubro de 2016 [citado 22 de abril de 2025];388(10056):2153–63. Disponível em: https://linkinghub.elsevier.com/retrieve/pii/S0140673616314192