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Radiological Case Report / Caso Clínico

Tuberous Sclerosis Complex Associated with Multiple Sclerosis: A Case Report with a Possible Pathophysiological Explanation

Complexo de Esclerose Tuberosa Associado à Esclerose Múltipla: Um Relato de Caso com uma Possível Explicação Fisiopatológica

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Abstract

Tuberous sclerosis complex is a neurocutaneous syndrome caused by an autosomal dominant mutation in TSC1 or TSC2 genes. Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system. In this article, we describe the case of a 29-year-old man previously diagnosed with tuberous sclerosis complex presenting with new neurological symptoms. Brain magnetic resonance imaging (MRI) demonstrated cortical tubers, with associated radial extensions into the subcortical white matter and subependymal nodules, due to tuberous sclerosis, as well as a periventricular ovoid lesion, two infratentorial lesions, and a spinal cord lesion, due to multiple sclerosis. One lesion also presented the central vein sign. Cerebrospinal fluid analysis was positive for oligoclonal bands. We hypothesize that the mammalian target of rapamycin (mTOR) signaling pathway can be a possible explanation for this association.

Keywords

Tuberous sclerosis complex; Multiple sclerosis; mTOR signaling pathway; MRI.

Resumo

A esclerose tuberosa é uma síndrome neurocutânea causada por uma mutação autossômica dominante nos genes TSC1 ou TSC2. A esclerose múltipla é uma doença inflamatória desmielinizante crônica do sistema nervoso central. Neste artigo, descrevemos o caso de um homem de 29 anos com diagnóstico prévio de esclerose tuberosa que apresentou novos sintomas neurológicos. A ressonância magnética (RM) cerebral demonstrou túberes corticais, com extensões radiais associadas na substância branca subcortical e nódulos subependimários, devido à esclerose tuberosa, bem como uma lesão ovoide periventricular, duas lesões infratentoriais e uma lesão na medula espinhal, devido à esclerose múltipla. Uma das lesões também apresentou o sinal da veia central. A análise do líquido cefalorraquidiano foi positiva para bandas oligoclonais. Nossa hipótese é que a via de sinalização do alvo da rapamicina em mamíferos (mTOR) possa ser uma possível explicação para essa associação.

Palavras-chave

Complexo de esclerose tuberosa; Esclerose múltipla; via de sinalização mTOR; Ressonância magnética.

Introduction

Tuberous sclerosis complex is a neurocutaneous syndrome caused by an autosomal dominant mutation in TSC1 or TSC2 genes.[1] Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system, characterized by symptomatic episodes that occur months or years apart and affect different anatomic locations.[2]

In this article, we present a rarely reported case of concurrent tuberous sclerosis and multiple sclerosis, highlighting the imaging aspects of both diseases and propose a pathophysiological mechanism for this association. Although these diseases present different pathophysiological mechanisms, the mammalian target of rapamycin (mTOR) signaling pathway can be a possible explanation for this association.

Case Report

A 29-year-old man, with a previous diagnosis of tuberous sclerosis, with delayed neurological development and generalized tonic-clonic seizures, since 3 years old, presented with progressive paresis in the legs, over two weeks, which worsened in the last 4 days. On physical examination, the patient exhibited reduced leg strength (grade 4 in both legs). He presented with a tabetic gait. There was reduced vibratory sensation and epicritic touch sensation up to the level of the axillae. There was no reduction in arms strength. The patient was using valproic acid and levetiracetam. He did not use mTOR inhibitors.

Brain magnetic resonance imaging (MRI) showed multiple areas of cortical thickening, with hyperintense signal on T2-weighted imaging and fluid-attenuated inversion recovery (FLAIR), due to cortical tubers, some with associated radial extensions into the subcortical white matter, as well as subependymal calcified nodules in the lateral ventricles, confirming the diagnosis of tuberous sclerosis. A few

subependymal nodules showed gadolinium-enhancement. One subependymal nodule was located in the right thalamic-caudate sulcus, next to the interventricular foramen, measuring 1 cm, with no hydrocephalus.

Furthermore, brain MRI also revealed a periventricular lesion, adjacent to the left ventricle, two lesions in the brainstem, with hyperintense signal on T2-weighted imaging and FLAIR (Figure 1) and a lesion in the left corona radiata with a central vein sign, better seen on susceptibility-weighted imaging (SWI), with a paramagnetic rim, which was better seen on SWI phase map (Figure 2), which were suspected for a demyelinating disease. Spine MRI demonstrated lesions extending over less than 2 vertebral levels, with hyperintense signal on T2-weighted imaging, affecting the right posterior and lateral funiculi of the spinal cord, at the level of C2-C3 and C5-C6, respectively (Figure 1). None of these lesions presented gadolinium-enhancement.

Cerebrospinal fluid (CSF) analysis demonstrated mild lymphocytic pleocytosis (30 cells/mm^3) and hyperproteinorrachia, with a normal glucose level. CSF film array was negative for enterovirus, herpes simplex virus types 1, 2 and 6, varicella-zoster virus, cytomegalovirus,

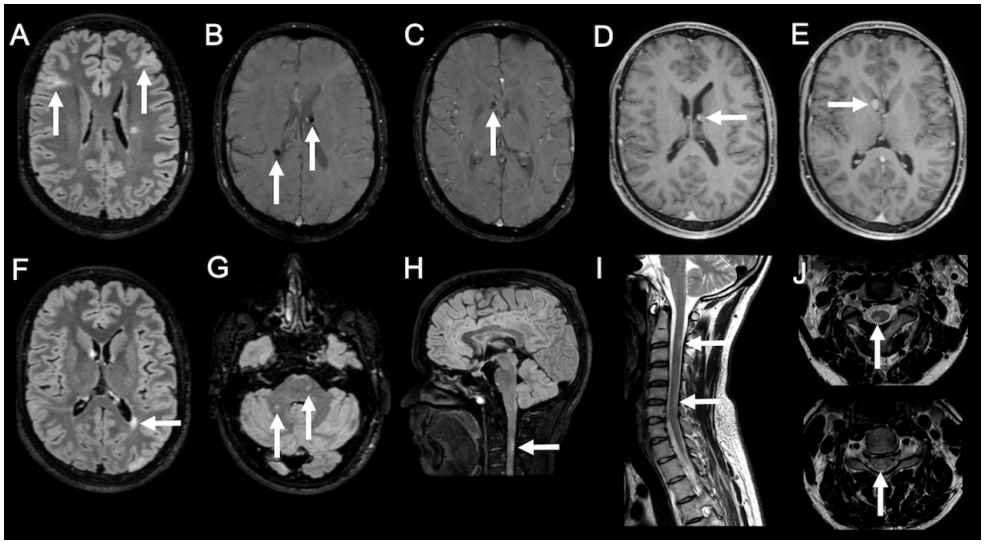


Figure 1 – Concurrent tuberous sclerosis complex and multiple sclerosis. Brain MRI demonstrated areas of cortical thickening, with hyperintense signal on FLAIR, due to cortical tubers, some with associated radial extensions into the subcortical white matter (arrows in A). SWI demonstrated calcified subependymal nodule as periventricular hypointense foci (arrows in B and C). Some of the subependymal periventricular nodules presented gadolinium-enhancement (arrows in D and E). The largest subependymal nodule was located in the right thalamic-caudate sulcus, next to the interventricular foramen, measuring 1 cm, without determining hydrocephalus (arrow in E). Brain MRI also demonstrated a periventricular ovoid lesion (arrow in F), two infratentorial lesions (arrows in G), and a spinal cord lesion (arrow in H), with hyperintense signal on FLAIR. Also note the left occipital cortical tuber in F. Cervical spine MRI showed hyperintense lesions on T2-weighted imaging, extending over less than 2 vertebral levels, at C2-C3 and C5-C6, affecting the right posterior and lateral funiculus, in the sagittal (arrows in I) and axial planes (arrows in J).

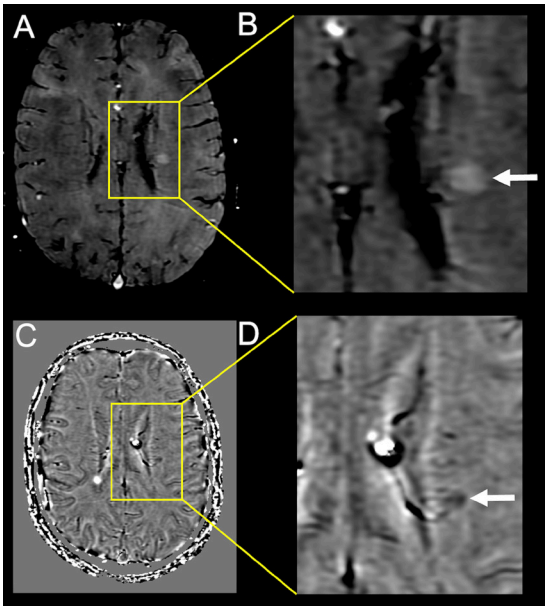


Figure 2 – Concurrent tuberous sclerosis complex and multiple sclerosis. Brain MRI also demonstrated a lesion in the left corona radiata with the central vein sign, on SWI (A), better seen on the augmented image (arrow in B). The lesion also presented a paramagnetic rim, seen on SWI phase map (C), also better seen on the augmented image (arrow in D).

parechovirus, *Escherichia coli, Heamophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, and Streptococcus pneumoniae*. Oligoclonal bands were positive in the CSF. Anti-aquaporin-4 and anti-myelin oligodendrocyte glycoprotein antibodies were negative in the CSF and in the serum. Therefore, in addition to the diagnosis of tuberous sclerosis complex, the presence of periventricular, infratentorial, and spinal cord lesions on MRI fulfills the dissemination in space criteria for multiple sclerosis. Although there was no gadolinium-enhancement, presence of oligoclonal bands in the CSF confirms dissemination in time. Exclusion of other diagnoses confirmed multiple sclerosis diagnosis.

There was no family history of tuberous sclerosis or multiple sclerosis. However, there was no investigation of first-degree relatives. The patient had no siblings. Patient was treated with intravenous methylprednisolone, followed for natalizumab. Six months after the diagnosis of multiple sclerosis, the patient showed partial improvement in strength and sensation in the legs and continues to receive outpatient follow-up. He has not experienced any new relapses. The 1 cm subependymal nodule on the right will be monitored in subsequent MRIs.

Discussion

Tuberous sclerosis complex is an autosomal dominant disorder caused by an inactivating mutation in one of two genes: TSC1 (on chromosome 9), which encodes hamartin, or TSC2 (on chromosome 16), which encodes tuberin. Hamartin and tuberin work together to inhibit the mTOR signaling pathway. Mutations in hamartin or tuberin cause hyperactivation of the mTOR pathway, which stimulates protein formation, cell growth, and proliferation.[1] The diagnostic criteria for tuberous sclerosis complex are well-established and the presence of multiple cerebral cortical tubers and/or radial migration lines and 2 or more subependymal nodules, fulfills 2 major criteria and confirms the diagnosis of tuberous sclerosis, even without the investigation of mutations, as in our case.[3] Although the largest subependymal nodule measured was located in the typical site for a subependymal giant cell astrocytoma, it was not causing hydrocephalus and measuring only 1 cm. Therefore, the decision was made to monitor the nodule with follow-up imaging rather than proceed with surgery at this time.

According to the diagnostic criteria for multiple sclerosis, MRI is decisive in the diagnosis. Fulfillment of the criteria of dissemination in space (at least one characteristic lesion, in at least two of five regions: optic nerve, periventricular, juxtacortical/intracortical, infratentorial and spinal cord) associated with a positive CSF finding, such as oligoclonal bands or kappa free light chain index) are sufficient to diagnose multiple sclerosis.[2] Therefore, the detection of oligoclonal bands in the CSF, as evidence of chronic intrathecal inflammation, completes the criterion of dissemination in time.[4]

The central vein sign is a MRI biomarker for multiple sclerosis, characterized as a hypointense dot or line running centrally through a demyelinating lesion, better seen on SWI.[5] The paramagnetic rim lesion is a marker of chronic active multiple sclerosis lesion, characterized by a T2-hyperintense core without gadolinium-enhancement, surrounded by a paramagnetic rim on SWI along at least two-thirds of its perimeter.[6] Although the presence of the central vein sign and the paramagnetic rim lesion are not required for diagnosis, these findings increase the specificity for multiple sclerosis diagnosis.[2] Both characteristics were seen in one lesion in the present case.

mTOR is a protein kinase that controls cellular metabolism, catabolism, immune responses, autophagy, survival, proliferation, and migration, in order to maintain cellular homeostasis, being activated during various processes, such as tumor formation, angiogenesis, insulin resistance, adipogenesis and T-lymphocyte activation. mTOR generates two different functional complexes, named mTORC1, which integrates signals from growth factors and nutrients to reinforce cellular proliferation, when there is adequate energy; and mTORC2, which regulates cells proliferation and survival. mTOR signaling pathway is closely related to autophagy mechanisms in various cells, including neurons, glial cells and immune cells of innate and adaptive immunity, which participate in multiple sclerosis pathophysiology. Also, mTOR inhibitors ameliorate experimental autoimmune encephalomyelitis.[7] Salehi et al.,[8] in a small trial with six patients with multiple sclerosis who received rapamycin for 6 months, reported a post-treatment reduction in the pro-inflammatory IFN-γ and an increase in the regulatory TGF-β. To the best of our knowledge, this is only the fourth published case with this association. Quigleya et al.[9] reported two patients with a known diagnosis of tuberous sclerosis who presented with new neurological signs and symptoms and imaging features suggestive of the association of tuberous sclerosis and multiple sclerosis. Sforza et al.[10] reported the case of a 10-year-old boy diagnosed with radiologically isolated syndrome during a follow-up MRI due to an already diagnosed tuberous sclerosis.

This article has some limitations. We report only one case of the association between multiple sclerosis and tuberous sclerosis complex. Then, the pathophysiological association between these diseases cannot be proven. Although mTOR signaling pathway activation is a possible pathophysiological explanation for this association, future prospective studies should be conducted to prove this hypothesis. Finally, we did not perform genetic testing on the patient to search for a TSC1 or TSC2 mutation, but the patient met the clinical diagnostic criteria for both diseases.

Conclusion

Therefore, the association of multiple sclerosis with tuberous sclerosis complex is possible and may explain new neurological symptoms in patients with tuberous sclerosis complex. Activation of the mTOR signaling pathway is a possible pathophysiological hypothesis.

Ethical Disclosures / Divulgações Éticas

Conflicts of interest: The authors have no conflicts of interest to declare.

Conflitos de interesse: Os autores declaram não possuir conflitos de interesse.

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Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Confidencialidade dos dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.

Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Protecção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

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