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Tumefactive multiple sclerosis. A rare but serious variable in multiple sclerosis

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ABSTRACT

Tumefactive multiple sclerosis is a rare variant of multiple sclerosis, characterized by the presence of brain lesions that may be solitary or multiple. Considering that these lesions have a pseudotumoral appearance, it is a challenge to differentiate them from central nervous system neoplasms through neuroimaging. Many cases are associated with the administration of monoclonal antibodies, and due to an increase in the incidence of cancer globally, it is expected that secondary to chemotherapeutic treatments, more and more cases may appear. Taking into account the above, the objective of this review is to review aspects of usefulness in clinical practice, on the diagnosis and approach of this pathological condition

Keywords
tumefactive multiple sclerosis, multiple sclerosis, demyelinating diseases, rare disease, neurosurgical disease

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Introduction

Tumefactive multiple sclerosis (TMS) is a rare variant of multiple sclerosis (MS) characterized by the presence of brain lesions that may be solitary or multiple with a diameter greater than or equal to 2 cm (1-5) These lesions are observed with a pseudotumoral appearance (6), larger than the typical MS plaques mimicking an intracranial neoplasm, infection or a non-demyelinating brain pathology (7). TMS accounts for approximately 2.8-7% of all MS cases (1,7). Magnetic resonance imaging (MRI) shows ring enhancement (4,5) and perifocal edema (2,3,5), in addition, the presence of decreased cerebral blood volume (3), hypervascularity, increased vascular permeability and mass effect, make it difficult to make a differential diagnosis with abscesses and brain tumors (2, 8). The brain lesions present in this entity are known as "tumefactive demyelinating lesions (TDL) (9), which are best described in MS (10) and are mainly located in the cerebral white matter, specifically in the frontal and parietal lobe, but can appear in any part of the central nervous system (CNS). Rare tumefactive variants of MS are Schilder's disease, acute Marburg MS and concentric Balo sclerosis (9).

TDLs in MS when presented as solitary lesions complicate the diagnosis due to their similarity to intracranial neoplasms, leading to misdiagnosis and therefore unnecessary intervention and treatments that put the patient's health at risk (5,10). To avoid misdiagnosis, better imaging techniques such as diffusion-weighted imaging (DWI), magnetic resonance spectroscopy (MRS), fluorodeoxyglucose positron emission tomography (FDGPET) (10), CSF examination (8) and brain biopsy have been sought, the latter being the one that establishes definitive diagnosis (10).

Epidemiology

The prevalence of TME is approximately 1 to 2 per 1000 cases diagnosed with MS (9-12) and a prevalence of tumor-type TDLs of 3 cases per 1,000,000 inhabitants, with the female sex being the most affected. The presentation of MS at older ages is rare with approximately 0.6-0.75 of cases diagnosed after the sixth decade of life, increasing the difficulty in distinguishing TDLs from brain tumors (11).

TDLs occur more frequently in Asian countries with an incidence between 6.3-11.76%, probably due to ethnic differences with heterogeneous immunological backgrounds (10). Kuan et al. in 2013 conducted a study in Taiwan with 190 patients with MS diagnoses between the years 1985 and 2010, of which 12 were confirmed with TMS, representing approximately 6.3% of MS patients, but this percentage does not represent the prevalence of the country because only patients who from a single medical center in Tapei City were included (13).

Aetiology

The causes that generate the appearance of TDL are not yet elucidated. However, a relationship has been found between the immature isoform of myelin basic protein (MBP) and the occurrence of extensive atypical demyelinating lesions in acute Marburg MS and probably the role of this protein in the development of TDL. Several isoforms may be involved in normal functioning and exposed to the process of protein degradation, leading to an increased likelihood of recurrence of TDLs (10).

Localization

TDLs occur most frequently in the cerebral hemispheres (especially in the frontal and parietal lobe) (5), but can be observed in different components of the CNS, such as segments of the cervical spine and the cervical spine (3). Kuan et al. reported that 80% of the lesions were found at the supratentorial level, mainly in the periventricular and juxtacortical area and 40% in the spinal cord (13,14).

Clinical manifestations

The clinical presentation of patients with TME can be polysymptomatic when the lesions are large and multiple (9). The symptoms originated by TDL can have an acute or subacute presentation (3) which depends on the location, size of the lesion and its mass effect (6,9). The clinical manifestations of TMS include headache, cognitive abnormalities, mental confusion, seizures, apraxia, aphasia (1,3,4), increased intracranial pressure, vomiting, behavioral disturbances, visual disturbances, optic neuritis and hemiparesis (3,15,16). TDL often causes memory dysfunction, Gerstmann's syndrome and in some patients, encephalopathies are observed (9). Visual and somatosensory potentials with abnormalities can be observed in 33-60% of cases diagnosed with TMS (1).

Generally, the signs and symptoms are not

associated with MS, which means that this entity is not considered in the differential diagnoses and a neoplasm or infection is suspected. However, even if there is a pre-existing diagnosis of MS, the probability of presenting a neoplasm or non-myelinating pathology is not ruled out, which leads to suggest a biopsy to diagnose the pathology (11,17,18).

Diagnosis

Histologically, TDLs show similarity to neoplasms by hypercellularity, gliosis, atypical reactive astrocytes, mitosis, permeabilized lymphocytes (6,11) necrosis, cystic changes (11) and Creutzfeldt cells (9). In addition, abundant foamy macrophages containing myelin debris and relative axonal preservation are observed (11,18,19).

Although the biopsy allows a definitive diagnosis to be made, it has been reported that the trauma produced by the intervention for taking the sample generates neurological deficit and even death (11). However, in patients with uncertain diagnosis and who present a complex clinical picture, a biopsy is justified in order to generate a definitive diagnosis. Misdiagnosis of TDL is estimated to be approximately 31% (9), leading to unnecessary interventions and treatment. It is important to distinguish LDT from a neoplasm in order not to expose the brain to inadvertent irradiation that aggravates TMS (11).

Hamed, in the published case report of a patient with TMS made the diagnosis based on: acute onset of the condition, cognitive impairment, multiple bilateral lesions on imaging studies, absence of cortical involvement, absence of mass effect, gadolinium enhancement, regression with corticosteroid, and lack of MRI evidence of new lesions on follow-up (1,18,19).

Differential diagnosis

The diagnosis of TDL in MS is a challenge due to its similarity with neoplasms, abscesses, acquired demyelinating disorders and vascular lesions (3). In order to achieve an adequate differentiation, imaging techniques have been used to avoid unnecessary biopsies that affect the patient's condition. MRS is a non-invasive imaging method that is useful for understanding biochemical alterations in various intracranial pathologies and according to studies is an important tool for the differential diagnosis of TMS with brain tumors. MRS focuses on the metabolites N-acetyl aspartate (NAA), choline, creatine, Lp and Lac; finding that when there is neuronal and axonal loss and impaired mitochondrial function, NAA levels are low. The detection of elevated levels of choline, Lp and Lac are related to myelin degradation or cell renewal processes. Kobayashi et al. found that in 2 of the 3 cases diagnosed with TMS, decreased NAA was observed and all 3 cases had in common that choline/creatine ratios were elevated in the peripheral areas associated with myelin degradation (2).

It is important to take into account that gliomas can develop in patients with MS, which makes it impossible to determine that the lesions that appear in this pathology are LDT without performing studies that support the diagnosis, because TMS can coexist with gliomas, which generates difficulties in making a differential diagnosis (9). Butteriss et al. in a study diagnosed TMS patients by using preoperative MRI, who after surgery were found to be oligodendroglioma (8). A positive response to steroids (6) and the reduction of the size of the lesions in serial neuroimaging allows distinguishing the demyelinating nature of a tumefactive lesion from an abscess or neoplasm (3). However, challenges have been reported in diagnosing TMS by MRS and PET, without biopsy and careful follow-up by serial MRI with or without steroid treatment is usually sufficient to establish a diagnosis (8,20,21).

On the other hand, although CSF analysis has not shown statistical significance as a support for the diagnosis of TMS, it has been observed that the presence of oligoclonal bands and elevated immunoglobulin G has allowed determining demyelinating processes (9,20,21).

Tumefactive variants of multiple sclerosis

Among the rare tumefactive variants of MS we find: Acute Marburg MS, Schilder's disease and concentric balloon sclerosis. Acute Marburg multiple sclerosis was described in 1906 by Otto Marburg as an idiopathic inflammatory demyelinating disease of the CNS characterized by large lesions of the CNS. Histologically, macrophage infiltration, generalized demyelination, axonal loss and areas of necrosis are observed. Mutations have been observed in MBP leading to structural instability of myelin (9). It is a pathology caused by severe axonal loss that leads to

rapid disability and can lead to death of the patient (1). Myelinoclastic sclerosis, also called Schilder's disease, was introduced in 1912 as a demyelinating disease with large lesions. However, this entity has not yet been fully elucidated and in some cases the term is used to refer to X-linked adrenoleukodystrophy. Finally, concentric Baló disease is an entity characterized by a pattern of concentric layers formed by damaged myelin tissue (1) and is known as an entity that presents rings of demyelination corresponding to areas of T2 hyperintensity on MRI alternating with rings of normal myelination or partial remyelination corresponding to areas of T2 isointensity. These lesions can be located in the basal ganglia, cerebellum and in some cases spinal cord and optic nerve (9).

Imaging

Among the imaging techniques proposed for the diagnosis of TME are: MRS, DWI, perfusion-weighted imaging (PWI), apparent diffusion coefficient (ADC) (6). TMS poses multiple challenges in imaging studies, since the mass effect and perilesional edema do not allow differentiation from a brain tumor or infection, but observing a ring enhancement after gadolinium administration suggests an TDL (7). Furthermore, it has been shown that when comparing MRI enhancement regions with the respective areas on CT, hypoattenuation was specific to make an adequate distinction of TDL from glioma or lymphoma, but this differentiation was only applicable for these two tumor subtypes. In relation to brain abscesses, lesions in TMS are centrally homogeneous on T2-w (6). Furthermore, relative to brain abscesses and tumors the mass effect along with edema in TMS are proportionally smaller relative to plaque size. It has been suggested that the lack of mass effect differentiates MS plaques from other space-occupying lesions (11,22,23).

Although there are no pathognomonic features for the diagnosis of LDT by imaging studies, features such as the presence of a hypointense ring in T2 around the lesion and the presence of white matter lesions typical of MS allow the diagnosis to be adequately directed (9). Some of the lesions on TMS are frequently enhanced on MRI, but cases have been found where this pattern is not observed, suggesting that a lack of enhancement does not rule out TDL (12). In addition, within the characteristics of the lesions on MRI are vascular structures crossing the center of the lesions in T2-w and marked reduction in blood flow perfusion compared to normal white matter (6,24,25).

DWI is an imaging method for the measurement of water molecules. Most lesions show variable ADC values on DWI as a result of the pathological heterogeneity of MS lesions (2). Most TDL demonstrate increased DWI and ADC signals on MRI, allowing differentiation of lymphomas with a water diffusivity restriction that makes them hyperintense on DWI and hypointense on ADC maps. Occasionally, acute demyelinating lesions may have areas of diffusion restriction with reduced ADC values at the periphery of the lesion (6,23,25).

MRS is an imaging method for the detection of biochemical alterations at the brain level, thus allowing improvements in the specificity of pathologies. When an increase in choline is observed due to elevated cell membrane turnover in MS during demyelination and inflammation processes, MRS is a method for the detection of biochemical alterations at the brain level, allowing for improved pathology specificity. NAA is an important brain marker because it is found only in neurons (4). A relationship of TDLs in MS and abnormal levels of choline, glutamate-glutamine and lactate has been found. In addition, an elevated choline/creatine ratio, increased lactate and an abnormal NAA/creatine ratio allow suspicion of inflammatory processes or demyelination (5,7). However, MRS is of limited utility, because TDLs present a similar pattern of increased choline/creatine and reduced NAA/creatine as in brain tumors. On the other hand, fluorodeoxyglucose positron emission tomography may provide diagnostic clues (9).

Treatment

There is still no standardized immunomodulatory treatment for TMS. Although within the pharmacological treatments we find methylprednisolone, beta interferons, plasma exchange, rituximab and natalizumab (1,9); the literature reports as first line treatment the use of high doses of steroids (9), due to the fact that in the majority of cases a positive response is obtained (6) and in some cases they are accompanied by surgical intervention (14). When patients do not respond to this, plasma exchange therapy is used. In cases

where an adequate response is not obtained, the use of rituximab or cyclosfamide is suggested (9).

On the other hand, some studies have recommended avoiding the use of fingolimod because of reports of cases of TDL occurring with the use of this drug (9).

Prognosis and neurosurgical education

The long-term prognosis depends largely on whether the patient has recurrent neurological disease. Most patients who relapse will have lesions typical of MS, with a minority recurring in a tumefactive form. Patients who develop MS after LDTs have similar long-term disability as those with prototypical MS (9). In low- and middle-income countries, where there are limitations with respect to the availability of high-cost technology and access to specialized health services, it is necessary to design strategies to facilitate the early diagnosis and management of these patients (26-28). The theoretical training of primary care physicians and medical students is a low-cost strategy that allows those who, due to policies and agreements, must go to provide health care in marginalized areas, to suspect this condition and refer the patient to high complexity hospitals (29,30). The implementation of robotic neurosurgery and translational research are other aspects that would improve patient prognosis (31). Neurosurgical education should be mainly focused on the physician, who is the one who should make the differential diagnosis.

Conclusions

Tumefactive multiple sclerosis is an infrequent disease, but it has a substantial negative impact on the functional capacity and quality of life of the affected person. It is necessary to have high quality imaging tools and suspicious clinical criteria to be able to suspect and differentiate this condition from other differential diagnoses, such as neoplasms of the central nervous system. More prospective multicenter studies are needed to more accurately characterize this condition.

References

1. Hamed SA. Variant of multiple sclerosis with dementia and tumefactive demyelinating brain lesions. World J Clin Cases. 2015; 3(6):525-32.
2. Kobayashi M, Ono Y, Shibata N, Kobayashi M, Shimizu Y, Ohta K, et al. Correlation between Magnetic Resonance Imaging Findings and Pathological Observations in Tumefactive Multiple Sclerosis. The Neuroradiology Journal. 2009; 22:155-63.
3. Ashrafi MR, Tavasoli AR, Alizadeh H, Zare Noghabi J, Parvaneh N. Tumefactive Multiple Sclerosis Variants Report of Two Cases of Schilder and Balo Diseases. Iran J Child Neurol. 2017; 11(2):69-77.
4. Kaeser MA, Scali F, Lanzisera FP, Bub GA, Kettner NW. Tumefactive multiple sclerosis: an uncommon diagnostic challenge. J Chiropr Med. 2011; 10(1):29-35.
5. Kilic AK, Kurne AT, Oguz KK, Soylemezoglu F, Karabudak R. Mass lesions in the brain: tumor or multiple sclerosis? Clinical and imaging characteristics and course from a single reference center. Turk Neurosurg. 2013; 23(6):728-35.
6. Conforti R, Capasso R, Galasso R, Cirillo M, Taglialatela G, Galasso L. A challenging diagnosis of late-onset tumefactive multiple sclerosis associated to cervicodorsal syringomyelia: doubtful CT, MRI, and bioptic findings: Case report and literature review. Medicine (Baltimore). 2016; 95(36):e4585.
7. Koppula R, Degnan AJ, Ghassibi M, Duggan P, Jones R, Levy LM. Neuroimaging of tumefactive multiple sclerosis with atypical features. Radiol Case Rep. 2012; 7(4):752.
8. Yamada S, Yamada SM, Nakaguchi H, Murakami M, Hoya K, Matsuno A, et al. Tumefactive multiple sclerosis requiring emergent biopsy and histological investigation to confirm the diagnosis: a case report. J Med Case Rep. 2012; 6:104.
9. Frederick MC, Cameron MH. Tumefactive Demyelinating Lesions in Multiple Sclerosis and Associated Disorders. Curr Neurol Neurosci Rep. 2016; 16(3):26.
10. Totaro R, Di Carmine C, Splendiani A, Torlone S, Patriarca L, Carrocci C, et al. Occurrence and long-term outcome of tumefactive demyelinating lesions in multiple sclerosis. Neurol Sci. 2016; 37(7):1113-7.
11. Lucchinetti CF, Gavrilova RH, Metz I, Parisi JE, Scheithauer BW, Weigand S, et al. Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis. Brain. 2008; 131(Pt 7):1759-75.
12. Yacoub H, Al-Qudahl Z, Lee H-J, Baisre A, Souayah N. Tumefactive Multiple Sclerosis presenting as Acute Ischemic Stroke. Journal of Vascular and Interventional Neurology. 2011; 4(2):21-3.
13. Kuan YC, Wang KC, Yuan WH, Tsai CP. Tumefactive multiple sclerosis in Taiwan. PLoS One. 2013; 8(7):e69919.
14. Munarriz PM, Castano-Leon AM, Martinez-Perez R, Hernandez-Lain A, Ramos A, Lagares A. Tumefactive multiple sclerosis requiring emergency craniotomy: case report and literature review. Neurocirugia (Astur). 2013; 24(5):220-4.
15. French HD. Tumefactive multiple sclerosis versus high-grade glioma: A diagnostic dilemma. Surg Neurol Int. 2021; 12:199.

16. Kumar S, Datta AK, Chakraborty U, Pandit A, Ray BK. Tumefactive demyelination: a clinico-radiological dilemma. J R Coll Physicians Edinb. 2021; 51(3):278-280.
17. Sánchez P, Chan F, Hardy TA. Tumefactive demyelination: updated perspectives on diagnosis and management. Expert Rev Neurother. 2021; 21(9):1005-1017.
18. Plowman RS, Varma H. Prognostic factors in Tumefactive demyelinating lesions: A retrospective study. J Neurol Sci. 2021; 428:117591.
19. Garcia JR, Baquero M, Bassa P, Compte A, Mourelo S, Riera E. A false-positive case on brain 18F-Choline PET/MR due to tumefactive multiple sclerosis. A case report. Rev Esp Med Nucl Imagen Mol (Engl Ed). 2021; S2253-654X(21)00055-X.
20. Villarreal JV, Abraham MJ, Acevedo JAG, Rai PK, Thottempudi N, Fang X, et al. Tumefactive multiple sclerosis (TMS): A case series of this challenging variant of MS. Mult Scler Relat Disord. 2021; 48:102699.
21. Di Gregorio M, Torri Clerici VLA, Fenu G, Gaetani L, Gallo A, Cavalla P, et al. Defining the course of tumefactive multiple sclerosis: A large retrospective multicentre study. Eur J Neurol. 2021; 28(4):1299-1307.
22. Fereidan-Esfahani M, Tobin WO. Cyclophosphamide in treatment of tumefactive multiple sclerosis. Mult Scler Relat Disord. 2021; 47:102627.
23. Mamilly A, Aslan A, Adeeb N, Al Asfari A, Cuellar H. Tumefactive Multiple Sclerosis of the Cervical Spinal Cord: A Rare Case Report. Cureus. 2020; 12(1):e6754.
24. Mitsutake A, Sato T, Katsumata J, Nakamoto FK, Seki T, Maekawa R, et al. Tumefactive multiple sclerosis which initially presented with brainstem encephalitis with a long-term follow-up. Mult Scler Relat Disord. 2019; 32:23-26.
25. Zaheer K, Ajmeri AN, Singh M, Suliman MS, Teka S. Tumefactive Multiple Sclerosis, A Rare Variant Presenting as Multiple Ring-enhancing Lesions in an Immunocompetent Patient: A Case Report. Cureus. 2018; 10(12):e3738.
26. Ortega-Sierra MG, Prado-Grajales V, Martinez-Imbett R, Unás-Perea K, Lozada Martinez ID. Research career in neurosurgery: a challenge for future neurosurgeons. J Neurosurg Sci. 2021 Aug 3.
27. Blanco-Teherán C, Quintana-Pájaro L, Narvaez-Rojas A, Martínez-Pérez R, García-Ballestas E, Moscote Salazar L, et al. Evidence-based medicine in neurosurgery: why and how? J Neurosurg Sci. 2021 Aug 3.
28. Ortega-Sierra MG, Durán-Daza RM, Carrera-Patiño SA, Rojas-Nuñez AX, Charry-Caicedo JI, Lozada-Martínez ID. Neuroeducation and neurorehabilitation in the neurosurgical patient: programs to be developed in Latin America and the Caribbean. J Neurosurg Sci. 2021 Jun 10.
29. Gaitan-Herrera G, Lozada-MartÍnez I, Acevedo-Aguilar L, Bohorquez-Caballero A, Moscote-Salazar L. Simulation as a tool to educate the patient about neurosurgical pathology. J Neurosurg Sci. 2021 Jan 22
30. Herrera-Martinez MP, García-Ballestas E, Lozada-Martinez I, Torres-Llinás D, Moscote-Salazar L. Letter to the Editor. Creating the conditions for gender equality to end sexual harassment in neurosurgery. J Neurosurg. 2021 Feb 5:1-2.
31. Lozada-Martínez I, Maiguel-Lapeira J, Torres-Llinás D, Moscote-Salazar L, Rahman MM, Pacheco-Hernández A. Letter: Need and Impact of the Development of Robotic Neurosurgery in Latin America. Neurosurgery. 2021; 88(6):E580-E581.