

# Lymphomatosis Cerebri associated with Movement Disorders: rare disease with uncommon presentation

*Linfomatose Cerebri associada a Desordens do Movimento: doença rara com uma apresentação atípica*

*Linfomatosis Cerebri asociada a Trastornos del Movimiento: enfermedad rara con presentación atípica*

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## Resumo

Este estudo aborda um caso de Linfomatose Cerebri (LC), ressaltando as dificuldades em alcançar o seu diagnóstico. **Relato de caso.** Mulher, 64 anos, dois meses com movimentos involuntários de membros esquerdos e tontura. Apresentava hemicoreia, mioclonia em braço esquerdo e ambas pernas, ataxia de marcha e piscaduras excessivas. Mini-mental score era 23. Na investigação ressonância nuclear magnética estava anormal. Foi tratada para encefalite autoimune e infecciosa, sem melhora. Biópsia cerebral confirmou diagnóstico de LC, tratamento foi iniciado com bons resultados. **Conclusão.** LC é uma doença rara e devastadora. Conhece-la é importante porque diagnóstico precoce pode melhorar o prognóstico desses pacientes.

**Unitermos.** Linfoma; Sistema Nervoso Central; Doenças raras

## Abstract

This study is about a case of lymphomatosis cerebri (LC), reporting the difficulties to reach the diagnosis. **Case report.** woman, 64-year-old, two months of involuntary movements of the left limbs and dizziness. Had hemichorea, myoclonus in left upper and lower limbs, excessive blinking and gait ataxia. Mini-mental score was 23. At investigation, nuclear magnetic resonance was abnormal. Patient was treated for auto-immune and infectious encephalitis, without improvements. Brain biopsy confirmed the diagnosis of LC, therapy was started with good results. **Conclusion.** LC is a rare and devastating disease. Knowledge about it is important because faster diagnosis could improve prognosis.

**Keywords.** Lymphoma; Central Nervous System; Rare diseases

## Resumen

Este estudio aborda un caso de Linfomatosis Cerebri (LC), destacando las dificultades para hacer su diagnóstico. **Caso.** mujer, 64 años, dos meses con movimientos involuntarios de las extremidades izquierdas y mareos. Tenía hemichorea, mioclono en algunos miembros, ataxia de la marcha y parpadeo excesivo. Mini-mental puntuación fue 23. En la investigación se alteró

la resonancia magnética. Fue tratada por encefalites autoinmune e infecciosa, sin mejoría. La biopsia cerebral confirmó LC, el tratamiento se inició con buenos resultados. **Conclusion.** la LC es una enfermedad rara y devastadora. Saberlo es importante porque el diagnóstico temprano puede mejorar el pronóstico.

**Palabras clave:** linfoma; Sistema Nervioso Central; Enfermedades raras

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## INTRODUCTION

Lymphomatosis cerebri (LC) is an uncommon variant of lymphoma of central nervous system (CNS), its clinical findings are variable, but ataxia, personality changes, weight loss and dementia (as cognitive decline and memory disturbance) are the most common. Gait disturbance, focal weakness, anorexia, hypotension orthostatic and paraparesis still can occur<sup>1,2</sup>.

Unlike the others CNS lymphomas that are typically present as single or multiples lesions, LC is characterized by a brain diffusely infiltrated with tumor cells, without a mass formation or parenchyma architecture destruction<sup>1,2</sup>. Magnetic resonance (MRI) findings of LC are nonspecific and reveal a diffuse leukoencephalopathy involving bilateral cerebral hemispheres, predominating at white matter, without contrast enhancement (reflecting intact blood-brain barrier)<sup>2,4</sup>. Thus, LC can be easily misdiagnosed. So that pathological examination is essential for differential diagnosis. LC is characterized by perivascular lymphocyte

infiltration by both lymphoma cells and normal reactive lymphocytes and almost all cases are diffuse large B-cell lymphomas<sup>2,4</sup>.

For these reasons, LC is a tricky disease to diagnose and can be considered a real challenging at neurological practice.

The objective is to describe a case of LC, an exceedingly uncommon disease, with the target to expand the experience in dealing with such rare condition in neurological practice.

## **METHOD**

A descriptive study was elaborated with the presentation of the clinical, imaging, and histological data of the patient. For the development of the study, the Regulatory Guidelines and Norms for Research involving human beings and the resolution number 510 of the National Health Council (BRAZIL, 2015) was respected. The study was approved by the Ethics and Research Committee (number: 3.736.999, 11/30/2019).

## **CASE REPORT**

The case report is about a 64-year-old white woman with a 2 months history of involuntary movements of the left limbs with dizziness and gait disorder. Neurologic exam disclosed chorea and myoclonus in left upper and lower limbs, with excessive blinking and gait ataxia. Her minimal mental score was 23.

MRI disclosed digitiform infiltrative non-enhancing lesions, prominent in white matter, located in right frontal, insular and temporal lobes, right thalamus and part of mesencephalus. Cerebrospinal fluid (CSF) analysis was normal, except for the presence of oligoclonal band and slight increment of protein level. CSF anti-NMDA, anti-GABA-A<sub>R</sub>, anti-IGL1 and anti-GAD were negatives. Electroencephalogram (EEG) disclosed temporal intermittent rhythmic delta activity and rare epileptiform discharges in right temporal lobe with a disorganized background activity.

All other diagnostic workup was unremarkable. A rapid deterioration occurred and, despite of no other evidence of autoimmune or infectious encephalitis, high-dose methylprednisolone and acyclovir both intravenous were started. A transient improvement was observed, but subsequently, a trial of immunoglobulin therapy was necessary, without improvements. A brain biopsy was performed, and the histological study revealed diffuse brain tissue infiltration by large lymphoid cells with preservation of the architecture (Figure 1).

Immunohistochemistry disclosed MUM1, CD20, CD45, BCL6 and CD20 positive cells and were negative for BCL1, cyclin D1 and Tdt, compatible to Lymphomatosis cerebri (Figures 2 and 3).

Therapy with high-dose methotrexate, vincristine and rituximab-procarbazine was started, with subsequent good improvement on her clinical condition and imaging features (Figure 4).



Figure 1. Brain biopsy - Hematoxylin-eosin: Cerebral parenchyma with atypical lymphoid proliferation, characterized by anomalous lymphocytes, large size, irregular nuclei and sometimes evident nucleoli. These lymphocytes are spreads, with predominant aggregates at perivascular spaces and submeningeal portion.

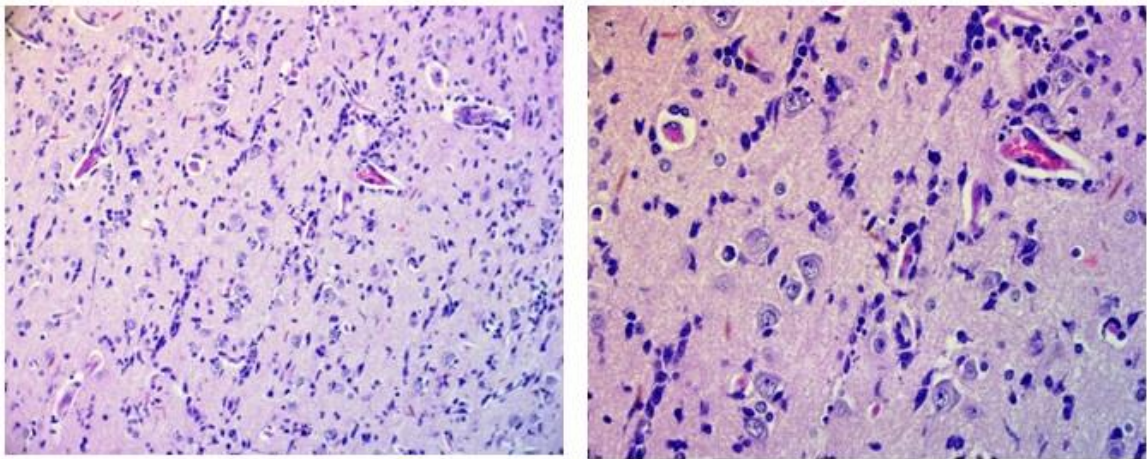


Figure 2. Immunohistochemistry.

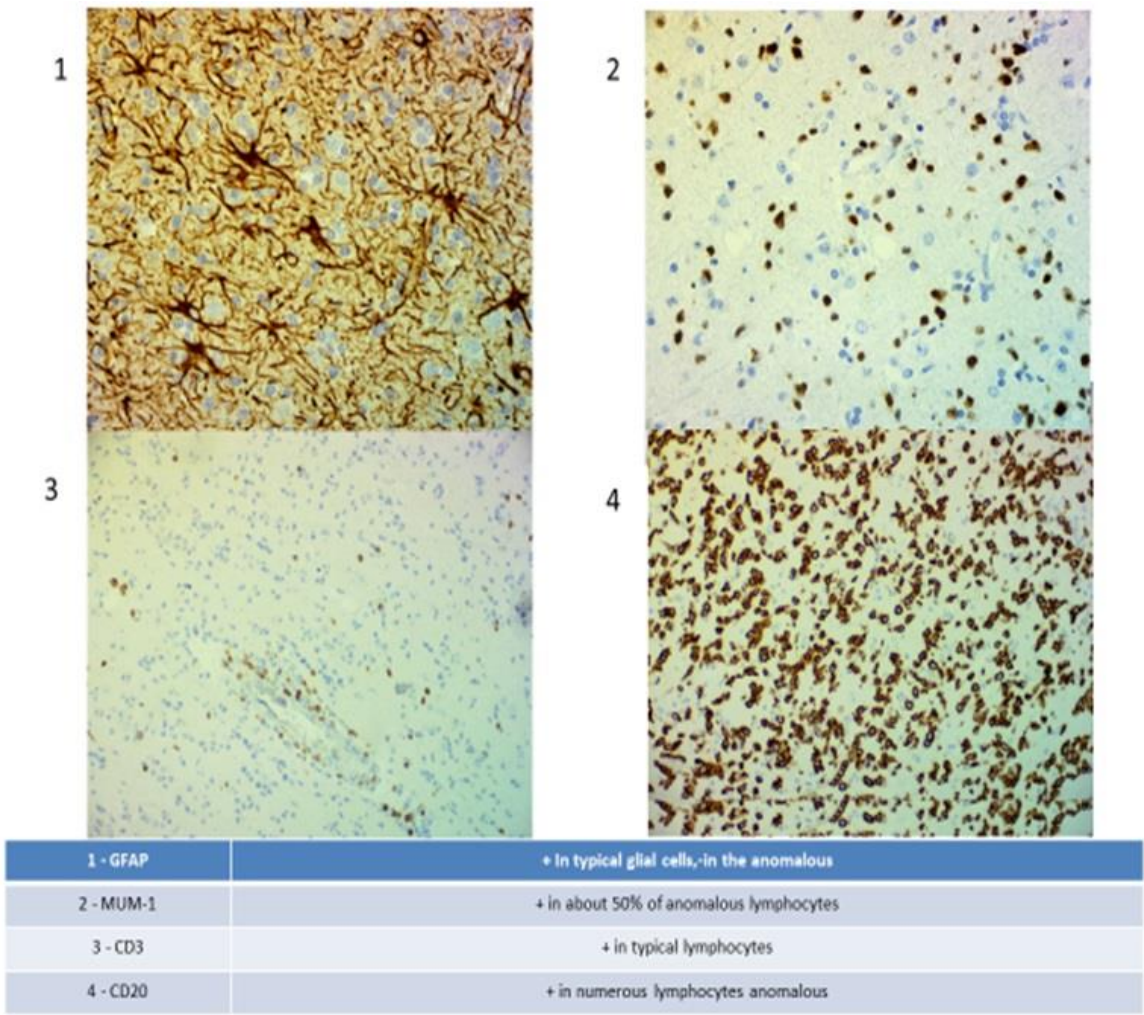




Figure 3. Immunohistochemistry.

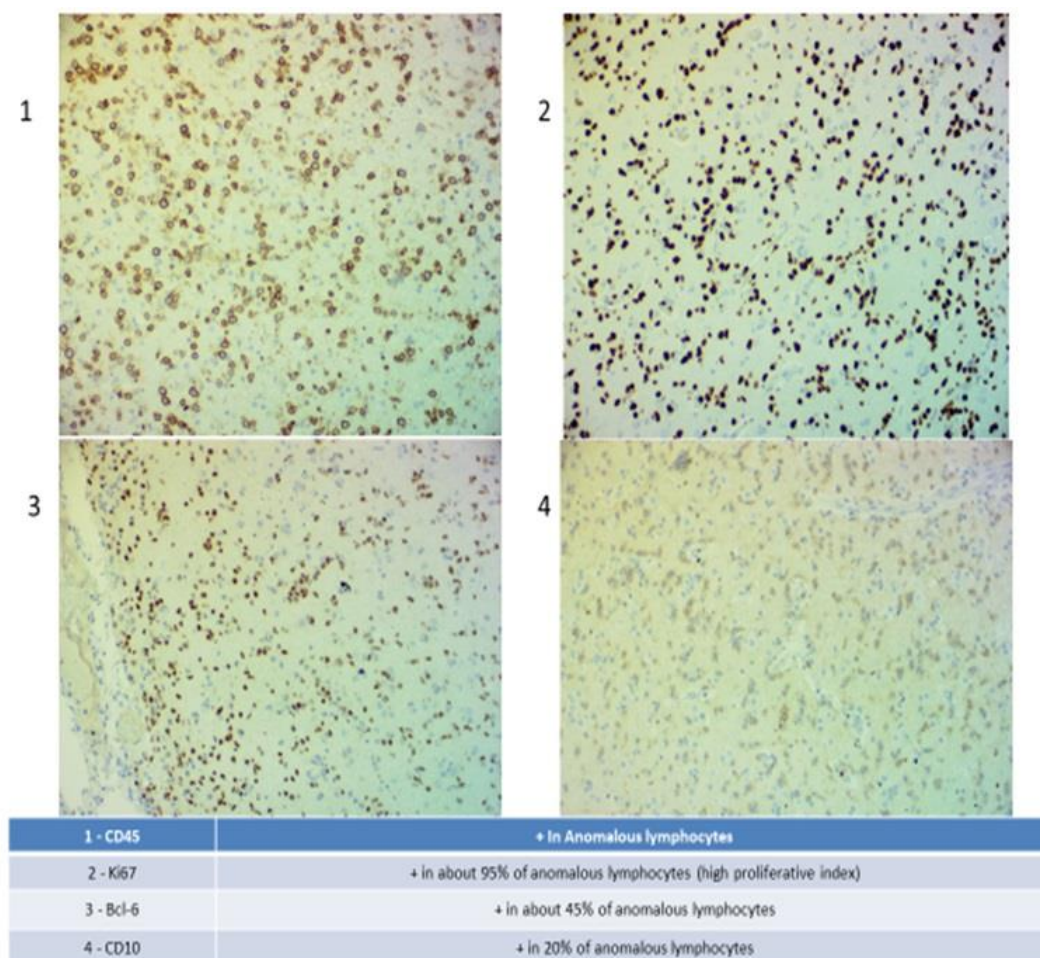
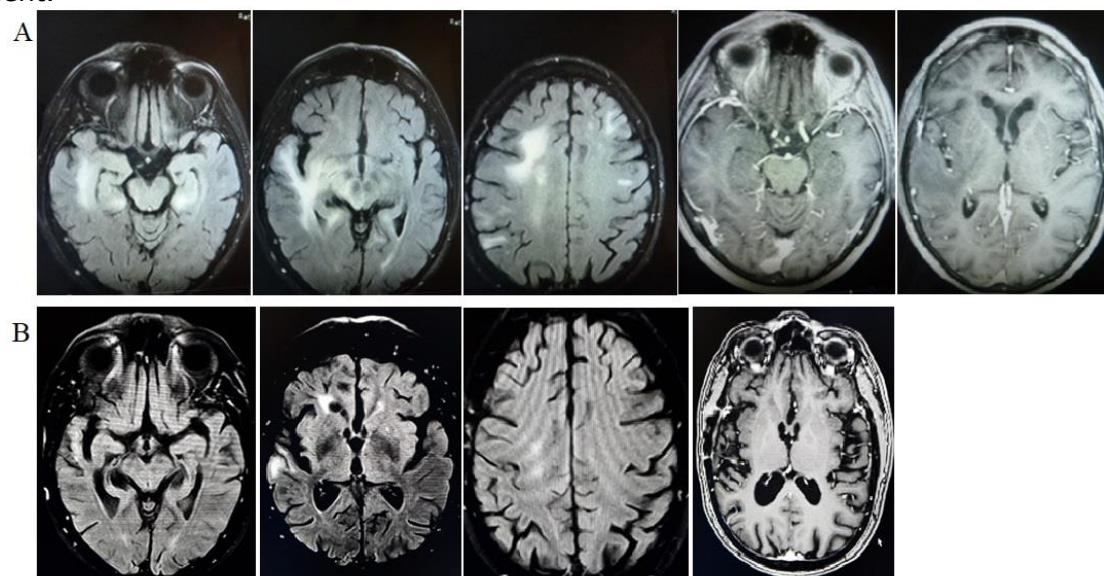


Figure 4. Magnetic resonance imaging. Figure 4-A: Magnetic resonance imaging T1 and Flair before treatment. Figure 4-B: Magnetic resonance imaging T1 and Flair after treatment.



## DISCUSSION

The diagnosis of LC is a challenge because the imaging findings are atypical and can be quite unspecific. Most CNS lymphomas are characterized by nodular lesions with homogeneous or ring contrast enhancement<sup>3</sup>. LC tumor cells infiltrates diffusely the parenchyma without mass effect. The MRI typical finding is non-contrast enhancing lesions involving predominantly white matter of both hemispheres, including in some cases supra-tentorial and infra-tentorial regions can be concurrent affected<sup>2</sup>. The most common affected areas are both hemispheres and the basal ganglia<sup>1,3</sup>. In accordance to the literature, the present patient had frontal, insular, temporal lobes and at thalamus and mesencephalus lesions.

LC clinical presentation is quite variable, but, gait disturbance, cognitive decline and behavioral changes are the most common<sup>2,3</sup>. Our patient had two of the three main manifestations. Cognitive decline noted at the mini-mental score and gait ataxia. Just involuntary movements presented at this case have not yet been cited like a clinical manifestation of LC.

Differential diagnoses include many diseases, mainly autoimmune and infectious encephalitis. Because of the relatively long evolution and not improvement with acyclovir, Herpes virus encephalitis was an improbable diagnosis in our case. However, the group of autoimmune encephalitis (AE) was a stronger hypothesis, including one, more remote, which is the adult form of Rasmussen's encephalitis (RE).

Rasmussen first described in 1958 as a progressive epileptic disorder in children due to chronic unilateral encephalitis. Nowadays we recognize that RE is not exclusively a childhood pathology and the revised Bien criteria no longer contain age at onset as a diagnostic criterion<sup>4</sup>. However, our patient had not presented a typical focal status epilepticus and EEG did not disclose a clear continuous focal epileptic activity and progressive MRI hemispheric atrophic changes were not observed. Lastly, histopathology which is a final diagnostic criterion for RE, with the presence of T-cell dominant encephalitis and activated microglia as inclusion criteria with the presence of numerous parenchymal macrophages, B cells, plasma cells, or viral inclusion bodies as exclusion criteria<sup>4</sup>. None of these abnormalities was observed in the brain tissue of our patient.

Noteworthy, movement disorders are extremely common in other AE and paraneoplastic neurological syndromes (PNS)<sup>6</sup>. Considering this and the fact that AE is one of the most common causes of noninfectious acute encephalitis<sup>5</sup>, one of the unsuccessful initial treatments of our patient, previously done to her brain tissue biopsy, had been immunological. Both chorea and myoclonus can be observed in cell surface antibodies associated encephalitis and with PNS intracellular antibodies associated encephalitis. The most common reported of cell surface antibodies associated with chorea are anti-NMDA<sub>R</sub>, anti-Dopamine D<sub>2</sub> receptor and anti-LGI1<sup>6</sup>. Myoclonus can occur in anti-NMDA<sub>R</sub>, anti-DPPX (in association with hyperekplexia) and anti-



CASP<sub>R2</sub><sup>6</sup>. PNS associated with chorea are anti-HU, Anti-CV<sub>2</sub>/CRMP<sub>5</sub> and anti-IGLON<sub>5</sub><sup>6</sup>. In the present case report, only CSF anti-NMDA, anti-GABA-A<sub>R</sub>, anti-IGL1 and anti-GAD were obtained, and they are all negatives. However, the histological immune reactions of the brain tissue had defined the diagnosis.

The prognosis of LC is poor, recent study evidenced a median overall survival of 2.95 month<sup>3</sup>. Multivariate analysis demonstrated that good clinical initial conditions and treatment with methotrexate were independent favorable survival prognostic factors<sup>1,3</sup>. The present patient was treated with methotrexate, vincristine and rituximab-procarbazine and nowadays patient has almost a full neurologic recovery, with just some visual symptoms, after two years of the onset.

## **CONCLUSION**

In conclusion, it is important for physicians, including clinicians and radiologists, be aware about the findings of LC because a faster diagnosis could accelerate the beginning of treatment and improve the prognosis of this rare form of CNS lymphoma.

## REFERENCES

- 1.Lee PJ, Berrios I, Ionete C, Smith T. Lymphomatosis cerebri: diagnostic challenges and review of the literature. *BMJ Case Rep* 2016;2016:1-5. <http://dx.doi.org/10.1136/bcr-2016-216591>
- 2.Yu H, Gao B, Liu J, Yu Y, Shiroishi MS, Huang M, *et al*. Lymphomatosis cerebri: a rare variant of primary central nervous system lymphoma and MR imaging features. *Cancer Imaging* 2017;17:1-9. <http://dx.doi.org/10.1186/s40644-017-0128-2>
- 3.Izquierdo C, Velasco R, Vidal N, Sánchez JJ, Argyriou AA, Besora S, *et al*. Lymphomatosis cerebri: a rare form of primary central nervous system lymphoma. Analysis of 7 cases and systematic review of the literature. *Neuro-Oncology* 2016;18:707-15. <http://dx.doi.org/10.1093/neuonc/nov197>
- 4.Bien CG, Granata T, Antozzi C, Cross JH, Dulac O, Kurthen M, *et al*. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain* 2005;128:454-71. <http://dx.doi.org/10.1093/brain/awh415>
- 5.Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, *et al*. Causes of encephalitis and differences in their clinical presentations in England: A multicentre, population-based prospective study. *Lancet Infect Dis* 2010;10:835-44. [https://doi.org/10.1016/S1473-3099\(10\)70222-X](https://doi.org/10.1016/S1473-3099(10)70222-X)
- 6.Honnorat J, Joubert B. Movement disorders in autoimmune encephalitis and paraneoplastic neurological syndromes. *Revue Neurologique* 2018;174:597-607. <http://dx.doi.org/10.1016/j.neurol.2018.07.006>