Epilepsy Secondary to Occipital Cobblestone Malformation in an Adult Patient with Merosin-Deficient Congenital Muscular Dystrophy Type 1A

Epilepsia Secundária a Malformações do Desenvolvimento Cortical num Doente Adulto com Distrofia Muscular Congénita do Tipo 1A

Keywords: Epilepsy/etiology; Laminin/genetics; Muscular Dystrophies/congenital; Nervous System Malformations/genetics
Palavras-chave: Distrofias Musculares/congénitas; Epilepsia/etiologia; Laminina/genética; Malformações do Sistema Nervoso/genética

Dear Editor,

We report the case of a 41-year-old male, whose first symptoms appeared at the age of four and consisted of impairment while walking on toes due to contractures of both Achilles tendons. At 11 years old, he began experiencing brief episodes of sudden loss of awareness, lasting less than a minute, with post-ictal amnesia. Carbamazepine 400 mg daily was initiated and maintained over three decades without seizure recurrence. During adolescence, he developed a severe rigid spine and multiple contractures of the elbows, knees, and interphalangeal joints. Later, at 40 years old, he mentioned the onset of transient episodes of flashing lights in his visual field, lasting a few seconds, without loss of awareness or associated headache.

At the age of 41, the neurological examination disclosed symmetric proximal muscle weakness and atrophy in the upper (4/5 on MRC scale) and lower limbs (4/5 on MRC scale). Biceps and Achilles reflexes were absent. He had an unaided waddling/myopathic gait ("duck-like" walk).

Creatine kinase levels were mildly elevated (922 IU/L – reference 26-192 U/L). Cardiopulmonary functions were unaffected. Right deltoid muscle biopsy revealed a severe dystrophic pattern with extensive fatty tissue replacement and fibrosis. Next-generation sequencing gene panel customized for congenital muscular dystrophies revealed a previously reported compound heterozygous mutation in the *LAMA2* gene. Brain magnetic resonance imaging (MRI) showed a cortical malformation pattern, described as cobblestone lissencephaly (Fig. 1A). Electroencephalogram recording showed periodic epileptiform discharges in the left posterior temporal area (Fig. 1B).

Following an increase in seizure frequency, the patient's carbamazepine dosage was incrementally raised to 800 mg daily, resulting in a two-year seizure-free period.

This case underscores the association between merosin-deficient congenital muscular dystrophy type 1A (MDC1A) and epilepsy secondary to cortical malformations. The onset of seizures in adolescence aligns with previous observations in MDC1A patients with an epilepsy phenotype, typically presenting with middle childhood-onset focal seizures.[1] The change in seizure presentation after several years in our case was also observed in some patients from the largest cohort of patients with epilepsy.[1] Although our patient exhibited interictal epileptiform activity and cortical malformations consistent with previous reports, their response to low-dose monotherapy contrasts with the typically refractory epilepsy described in this phenotype.[1-3] The benign evolution observed in this case may be attributed to the reduced extent of cortical malformations compared to previous cohorts.[1] Some case reports suggest that the severity of central nervous system (CNS) involvement and muscular phenotypes do not necessarily correlate. It remains to be elucidated which seizure-free patients should be screened for central nervous system abnormalities.

AUTHOR CONTRIBUTIONS

MS: Literature review and writing of the manuscript.

CB, CM, MOS: Literature review, writing and critical review of the manuscript.

All authors approved the final version to be published.

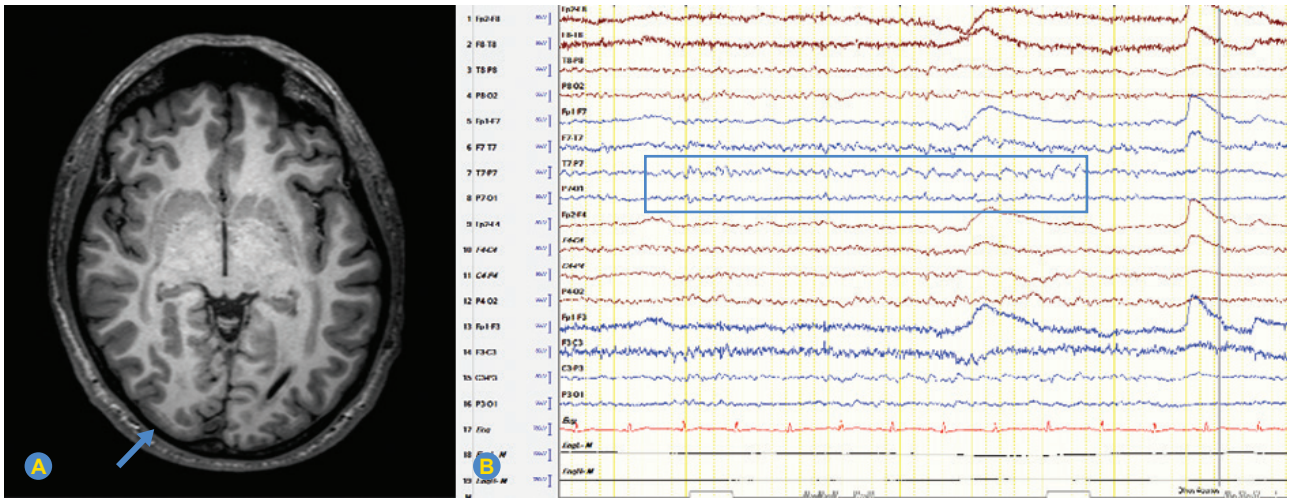

Figure 1 – Axial T1-weighted brain MRI of our patient illustrating bilateral occipital cobblestone malformation, characterized by reduction in normal sulcation, associated with a bumpy or pebbly cortical surface and streaks of discontinuous subcortical heterotopia just beneath the occipital cortex (arrow) (A). Routine EEG: slow activity in the left temporal and posterior regions. Periodic activity (sharp waves at 2 - 3 Hz) in the left posterior temporal region (rectangle).(B).

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

CB has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Angelini and Eisae; received support for attending meetings and/or travel from Angelini and Eisae; participated in a Data Safety Monitoring Board or Advisory Board for Angelini; is the president of Liga Portuguesa Contra a Epilepsia.

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REFERENCES

1. Natera-de Benito D, Muchart J, Itzep D, Ortez C, González-Quereda L, Gallano P, et al. Epilepsy in LAMA2-related muscular dystrophy: an electro-clinico-radiological characterization. Epilepsia. 2020;61:971-83.
2. Jayakody H, Zarei S, Nguyen H, Dalton J, Chen K, Hudgins L, et al. Cobblestone malformation in LAMA2 congenital muscular dystrophy (MDC1A). J Neuropathol Exp Neurol. 2020;79:998-1010.
3. Salvati A, Bonaventura E, Sesso G, Pasquariello R, Sicca F. Epilepsy in LAMA2-related muscular dystrophy: a systematic review of the literature. Seizure, 2021;91:425-36.

Miguel SCHÖN✉[1], Carla BENTES[1,2,3], Carlos MORGADO[4,5], Miguel OLIVEIRA SANTOS[1,3]
1. Department of Neurosciences and Mental Health (Neurology). Unidade Local de Saúde de Santa Maria. Lisbon. Portugal.
2. EEG/Sleep Laboratory/Stroke Unit Department of Neurosciences and Mental Health. Unidade Local de Saúde de Santa Maria. Lisbon. Portugal.
3. Centro de Estudos Egas Moniz. Faculty of Medicine. Universidade de Lisboa. Lisbon. Portugal.
4. Department of Neuroradiology. Unidade Local de Saúde de Santa Maria. Lisbon. Portugal.
5. Faculty of Medicine. Universidade de Lisboa. Lisbon. Portugal.
✉ **Autor correspondente:** Miguel Schön. miguelcbschon@gmail.com
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