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Case Report

Tumefactive demyelination after covid-19 successfully treated with betainterferon 1A ☆

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ABSTRACT

The Marburg variant of MS is a rare variant that leads to a severe clinical course, with a high rate of mortality or severe residual deficits and unclear pathophysiology. A 20-year-old female patient, presented at the hospital emergency with left inferior limb paresis and visual blurring. The neurologic exam showed complete and proportionate left hemiparesis with pyramidal signs and clonus, loss of proprioception and vibration in lower limbs, tactile, and painful hypoesthesia on the left side. This report describes a rare case of Marburg variant associated with COVID-19 infection.

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Introduction

Multiple sclerosis (MS) is an autoimmune disorder with a broad spectrum of clinical manifestations. It is one of the main causes of neurological disabilities in young adults. Most patients present the relapsing-remitting type and about 60%-80% of cases evolve to progressive phenotype with cognitive decline and accumulation of disabilities [1,2]. There is a minority of these patients that develop atypical variants of the disease, such as Balo's concentric sclerosis, Marburg variant or Schilder's disease [3]. Nearly 7% of the patients with MS show a fulminant clinical condition. The Marburg variant is a demyelinating, inflammatory, idiopathic, and high morbid-

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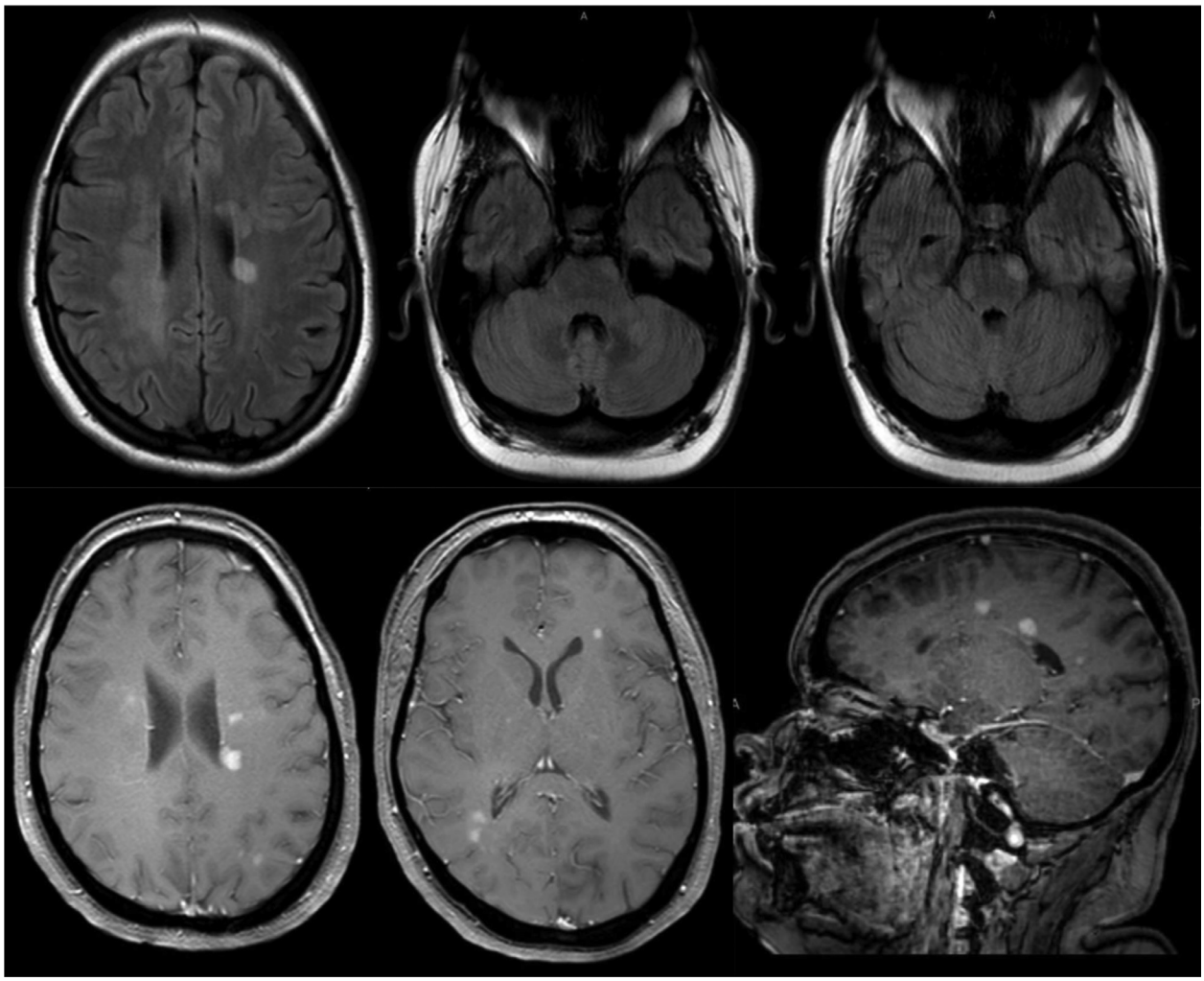

Fig. 1 – First MRI. Hyperintense lesions on T2/FLAIR sequence, involving periventricular white matter (a), left cerebellar hemisphere (b) and left pontine base (c). Diffuse hyperintense lesions on T1 sequence, involving periventricular white matter in the parietal (d), frontal and occipital lobe (e), and ovoid high signals perpendicular to the lateral ventricle, also known as Dawson fingers (f).

ity and mortality rate disease [2,4–6]. It was first reported by Otto Marburg in 1906, who described 3 cases of severe presentation of MS with widespread acute and subacute demyelinating in the central nervous system [5]. Since then, there is not a very clear pathophysiological mechanism, nor a specific and disease-modifying therapeutic approach. Meanwhile, it is recognized that a high level of suspicion is obligated in front of a rapidly progressive course with severe frequent relapses, and a fast approach may avoid fatal outcomes [7]. This article delineates the case of a patient with a Marburg variant of MS, who presents fast and progressive neurological deficits, evolving with clinical improvement after immunomodulatory therapy with betainterferon 1a.

Case report

A 20-year-old female patient previously healthy had a history of mild Covid-19, confirmed by PCR test, 1 month before neurological symptoms. At that time, the prevalence of positive Covid cases was 44,599 with 988 deaths. Total habitants were around 400,000. Total of first dose: 670,542. Second dose: 250,103. It is important to highlight that the patient didn‘t receive any dose of vaccine, because the doses were not available for this age at that time. Four days before admission she started with paresthesia in the inferior left limb, which evolved with paresis and visual blurring. There was no fever, dysphagia, or sphincters disturbance. The neurological examination showed complete and proportionate left hemiparesis with pyramidal signs and clonus, loss of proprioception and vibration in lower limbs, tactile, and painful hypoesthesia on the left side. It was observed also impaired smooth pursuit on right gaze, slightly scanning speech and hemiparetic gait. The patient was hospitalized for a neurological investigation. The differential diagnosis was made with infectious, inflammatory, and rheumatologic tests and all of them were negative. She was submitted to a brain magnetic resonance imaging (MRI) that evidenced diffuse hyperintense subcortical lesions on T2/FLAIR and hypointense on T1, involving periventricular white matter and brainstem (Fig. 1).

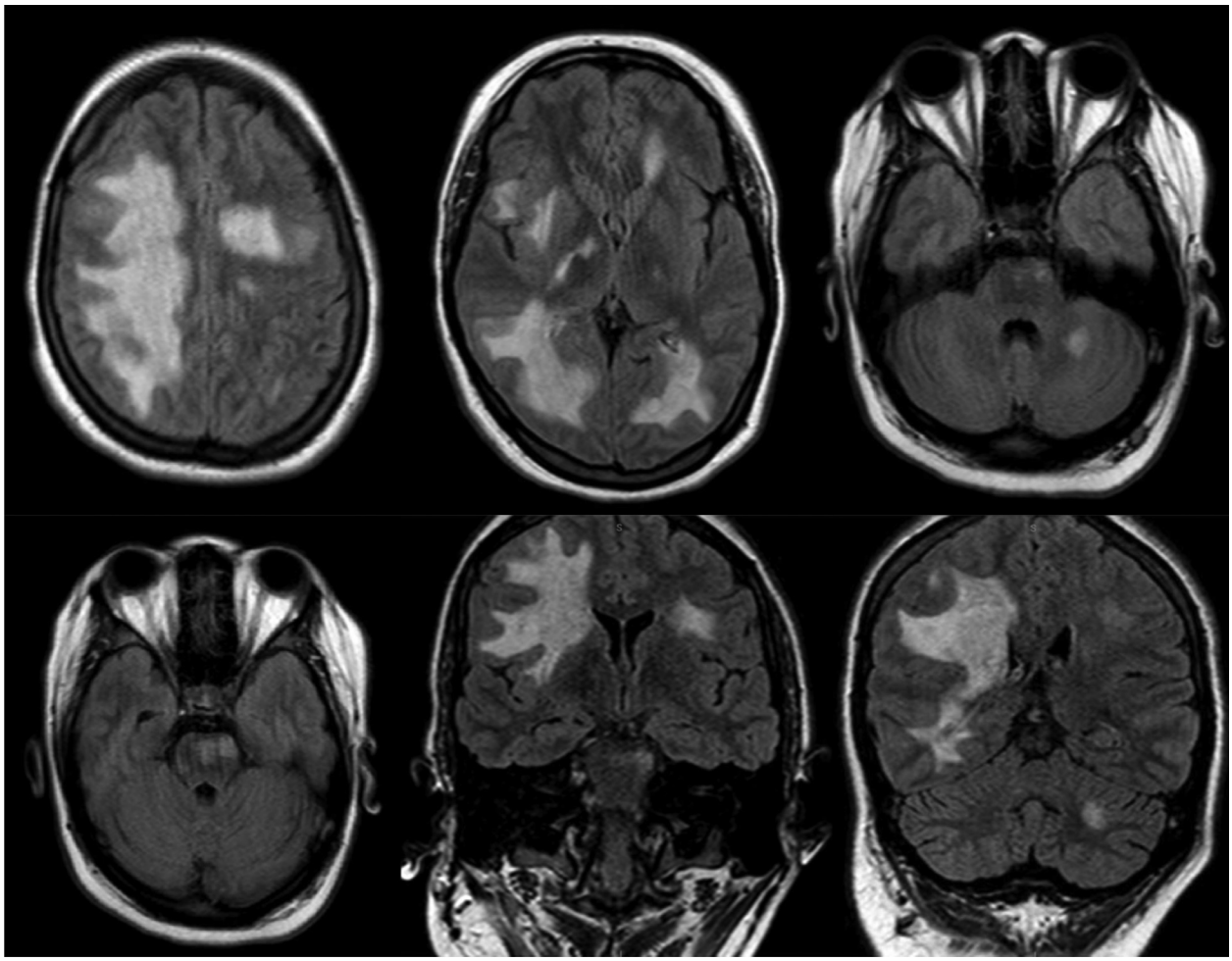

Fig. 2 – Second MRI (taken almost 2 months after the first MRI). Hyperintense axial T2/FLAIR lesions on the right frontotemporal and parietal lobes (a, b), pons (c, d), and cerebellar (c) regions with heterogeneous gadolinium enhancement. Coronal T2/FLAIR sequence revealing the large extension of lesions, affecting subcortical white matter bilaterally, greater in the right side (e, f), and also the left side of pontine base (e) and left cerebellar hemisphere.

The cerebrospinal fluid showed mild pleocytosis and hyperproteinorrhachia. She received a 5-day course of methylprednisolone 1 g with partial improvement of the symptoms and she was discharged to ambulatorial following. After 1 month, the patient had focal seizures in the face and worsening of left hemiparesis and a new MRI revealed an important increase of hyperintense T2/FLAIR lesions on the right frontotemporal and parietal lobes, pons and cerebellar regions with heterogeneous gadolinium enhancement (Fig. 2). At that moment, the main differential diagnosis was tumecfative demyelination or tumor. A brain biopsy was proposed, but the family did not agree about the invasive procedure. Due to the fast and aggressive presentation with neurological deterioration and failure of initial therapy, the possibility of Marburg's variant of MS was suggested. It was decided to start a disease-modifying therapy, with interferon beta 1a with 44 mcg 3 times a week. After one month of beginning the therapy, the patient presented an important improvement of symptoms, reduction of lesions in new MRI, and absence of contrast-enhancing lesions (Fig. 3). Along with following months the patient keeps progressive improvement with mild residual deficits.

Discussion

The Marburg variant is a particular form of MS that, generally, has a single-phase course and can lead to death in weeks to months after the initial presentation, an uncommon outcome in the general multiple sclerosis patients, who have an overall average time to death of 35 years since the onset [6,8]. Until now, there isn't quite defined which specific etiological mechanisms start the disease. However, it is known that there are biochemical changes at the myelin basic protein isoform, increasing your molecular weight and decreasing your cationic properties. This results in myelin sheath instability that contributes to the formation of demyelinating plates located at supra and infratentorial regions [5]. Also, studies have been suggesting reduction on neurogenesis markers, such as

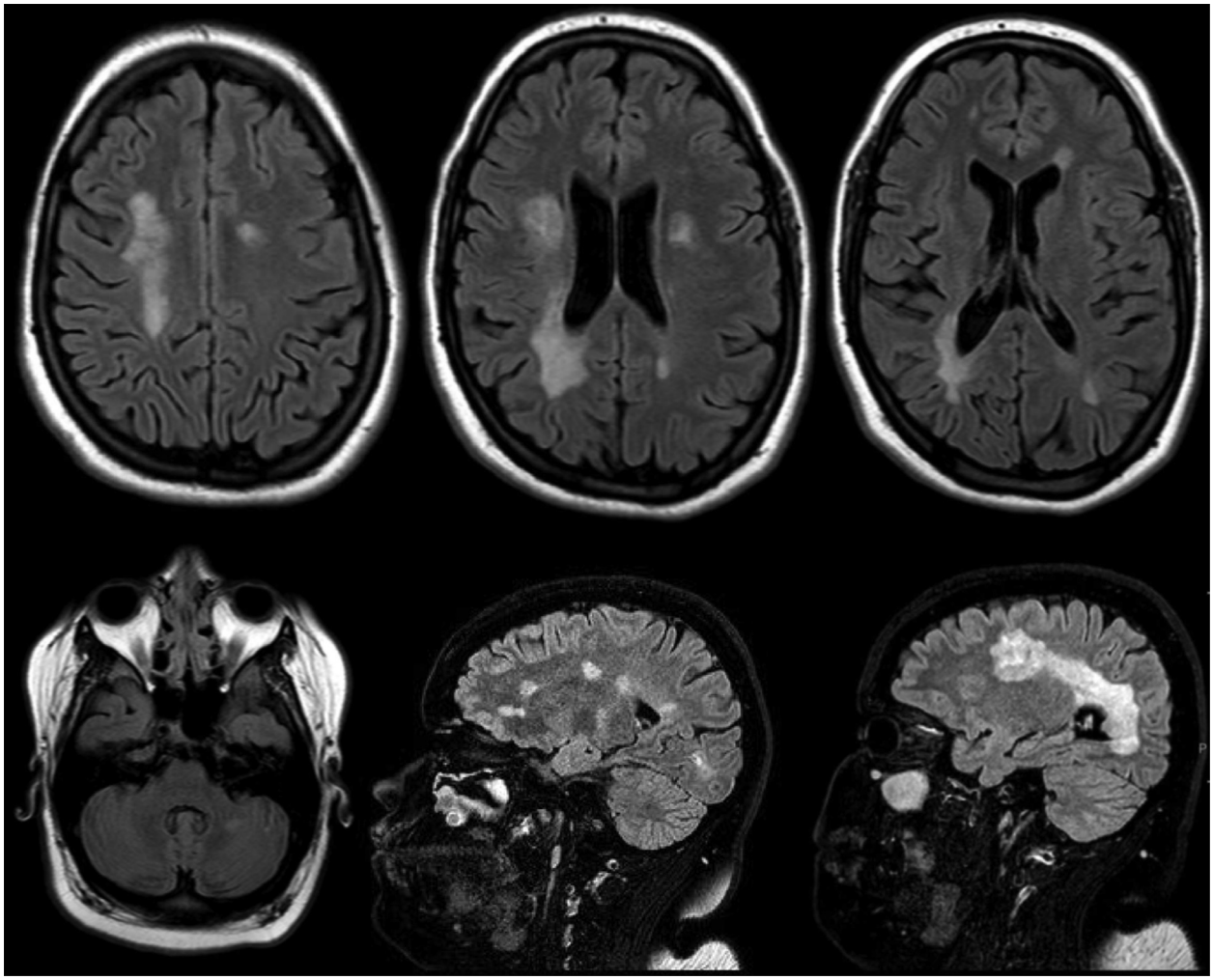

Fig. 3 – Third MRI (taken 4 months after the second MRI). Axial T2/FLAIR sequences showing improvement of the lesions in frontal and parietal lobes (a–c), pons and cerebellum (d), and absence of contrast-enhancing lesions. Residual hyperintense periventricular lesions on sagittal T2/FLAIR, maintaining Dawson fingers aspect (e) and still a wide extension on frontal, parietal and occipital lobes (f).

GFAPδ, SOX2, and PAX6, as well as some markers of proliferation, such as Ki-67 and intermediate precursors (NG2) [9]. The distribution of the lesions can be exactly as MS, though, in the variant in question, they usually spread simultaneously to diverse brain areas, and can even include the brainstem [10]. Nunes et al [11] described a Marburg variant case affecting midbrain, pons, superior cerebellar peduncles, hypothalamus, thalamus, caudate nuclei, the internal and external capsules, anterior portion of the corpus callosum, and the orbicular frontal lobe. The diagnosis can be hard, involving clinical and radiographic features. The presentation consists of neurological manifestations that will depend on the areas of the brain involved. Generally, the injuries show a widespread and inflammatory aspect, often indistinguishable from neoplastic lesions [3,10]. For the early recognition of the injuries is important the exclusion of possible differential diagnoses, such as tumor, infectious, granulomatous, and vasculitic lesions. Among the neuropathological findings of the disease, there are extensive plaques with recent demyelination, associated with severe axonal injury and necrosis with dense cellular infiltrates and giant reactive astrocytes [12]. The neuroimaging alterations are not specific, so they generally reveal multiple extensive lesions, unifocal or multifocal, confluent, involving the white matter of the hemispheres and brainstem, being able to be enhanced by contrast and perilesional edema [3,4]. The cerebrospinal fluid alterations are nonspecific and oligoclonal bands are present at 11%-33% of the cases [4]. Our case report showed a progressive evolution of neurological injuries in a young patient with no previous conditions, except history of covid-19, possibly a trigger of this catastrophic demyelinating disease. The first-line therapy in these cases is the use of glucocorticoids in high doses, and the second-line is intravenous immunoglobulin and plasmapheresis [1]. In general, there is a bad response to conventional therapies for MS and some studies have been reporting the use of mitoxantrone, ocrelizumab, and cyclophosphamide [5,13–15]. The patient described was first treated with high doses of steroids with partial response. After the progression of deficits, we de-

cided to treat with betainterferon 1a, which interrupted the progression of deficits, improved all neurological symptoms and promoted regression of brain lesions. This therapy is characterized by modulating the production of inflammatory cytokines, inhibiting the proliferation of leukocytes and antigen-presenting cells. Although this medication is not commonly indicated for this form of demyelinating disease, it shows the immune factor in the Marburg variant and its potential to respond to immunomodulatory drugs [16].

Conclusion

The Marburg variant of MS is a diagnostic and therapeutic challenge, requiring a high level of clinical suspicion and knowledge about different MS presentations. After being identified, the approach must be fast and aggressive. We present a peculiar case because a chronologic correlation with covid-19 made this a possible trigger and the good response with betainterferon 1a showed a possible drug to consider in management of this complex neurological disease.

Patient consent

Patient consent statement has been obtained.

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