

Neurophysiological assessment in a patient affected by Marfan syndrome

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Abstract

Background: Marfan syndrome (MS) is a hereditary connective tissue disorder characterized by different multiorgan patterns. The guidelines for MS diagnosis do not highlight the usefulness—or even the use—of any neurophysiological techniques for diagnosing this disease. Moreover, few neurophysiological studies assessing the central and peripheral nervous systems in MS subjects have been reported to date.

Case presentation: We describe a male patient affected by MS. To assess sensory and nociceptive pathways in this patient, a neurophysiological assessment was performed using electroencephalogram, nerve conduction studies, and somatosensory and laser-evoked potentials. To the best of our knowledge, this is the first published case report to evaluate the role of evoked potential assessments for the study of sensory and nociceptive pathways in MS.

Conclusion: Future studies should investigate the use of a complete neurophysiological approach for the clinical and therapeutic management of MS patients in a large sample.

Keywords

Marfan syndrome, evoked potentials, nociception, somatosensory, laser-evoked potentials, neurophysiological assessment

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Introduction

Marfan syndrome (MS) is an autosomal dominant connective tissue disorder that is characterized by multiorgan involvement, with impairments in the cardiovascular, renal, musculoskeletal, central nervous

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(CNS), and peripheral nervous (PNS) systems.¹ Patients present a typical phenotype, with tall and thin stature, arachnodactyly, flexible joints, and elastic skin. Dural ectasia is also often present in MS.^{2,3} The principal symptoms of dural ectasia are back, abdominal, and leg pain; sensory or motor deficits; headache; gait abnormalities; and sphincter disturbance.⁴

The current international standard for MS diagnosis is the revised Ghent criteria,⁵⁻⁷ which characterize the disease using several clinical manifestations. Moreover, a mutation in the *FBNI* gene, which encodes the microfibrillar protein fibrillin-1, has been indicated as an additional main requirement for MS diagnosis.⁸ However, the revised Ghent criteria for MS diagnosis do not highlight the usefulness—or even the use—of neurophysiological techniques for diagnosing this disease. Furthermore, few neurophysiological studies assessing the CNS and PNS in MS subjects have been reported.

Voermans et al.⁹ conducted nerve conduction studies (NCS) and needle electromyography (EMG) in 10 MS patients. Their results revealed neuromuscular involvement, consisting of myopathy and polyneuropathy with signs of polyradiculopathy. In 1992, Honda et al.¹⁰ demonstrated a polyphasic action, but not denervation potentials, in MS. Additionally, other authors have reported patients with MS symptoms related to nerve compression caused by a spinal deformity.¹¹

The incidence of epilepsy in MS patients remains unclear. Some studies using electroencephalogram (EEG) recordings have reported epilepsy in MS in patients with different manifestations: ocular findings,¹² intellectual disability,¹³ or cardiovascular and skeletal abnormalities.¹⁴ The neurological manifestations of MS are often secondary, and are characterized by cerebrovascular disease caused by compromised cardiac function, or by compressive

pathology resulting from skeletal alterations that may involve the spinal cord and nerves.

Although the medical complications, genetic etiologies, and medical management of MS have been extensively researched, the neurophysiological assessment of pain, which greatly affects quality of life and disability, has only been superficially investigated in this disease. We therefore performed a neurophysiological evaluation in a patient with MS. Specifically, we used somatosensory evoked potentials (SEPs) and laser-evoked potentials (LEPs) to a) assess sensory and nociceptive pathways; and b) investigate whether MS can be characterized by primary, direct neurological manifestations. These findings may allow for the more accurate clinical and therapeutic management of MS.

Case report

Subject and methods

We report the case of a 41-year-old man affected by MS, chronic renal failure, and sarcoidosis. He arrived at our institute for motor and speech rehabilitation after a cerebral hemorrhage, which had occurred 1 month previously. A neurological examination highlighted marked hypotrophy in the lower limbs, motor aphasia, and left hemiplegia, which have been previously described.¹⁵ The patient satisfied the revised Ghent criteria for a diagnosis of MS (aortic root dilatation Z score >2 and the presence of an *FBNI* mutation). No neurological involvement related to sarcoidosis was noted. Before the study began, the patient signed their informed consent for the use of their personal data.

We performed a neurophysiological evaluation of the patient using standard EEG, NCS, SEP, and LEP examinations, as well as magnetic resonance imaging (MRI). Motor NCS was performed on

median and peroneal nerves, while sensory NCS was performed on median and sural nerves. EEG was recorded using 20 surface Ag–AgCl electrodes (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, T7, T8, P3, P4, O1, O2, Fz, Cz, and Pz) in accordance with the International 10-20 system, and the earlobes were linked with a forehead grounding electrode. Brain and spinal MRI acquisition was performed using a 3 T MRI scanner.

Upper limb SEPs were recorded by two surface Ag–AgCl electrodes placed along the midline (C3 and C4; referred to as Fz), two electrodes placed on the cervical vertebrae (Cv7), and two electrodes placed on Erb's point (brachial plexus). Lower limb SEPs were recorded by two electrodes placed on Fz and Cz, two electrodes placed on the L3–L5 vertebrae, and two electrodes placed on the popliteal fossa of the knee. The electrical stimulus was applied to the median nerve for the upper limbs and the tibial nerve for the lower limbs. The LEPs were recorded by two surface Ag–AgCl electrodes, placed along the midline (Fz and Cz), and one electrode in the left or right temporal region (T3 and T4), contralateral to the stimulated site. The reference electrode was placed on the nose, and the ground electrode on the forehead (Fpz). The Nd:Y–Al–perovskite (Nd:YAP) laser stimuli were applied to the dorsal feet and hands.¹⁶

Results

The EEG recordings demonstrated theta rhythm in the right hemisphere, without epileptogenic patterns. The NCS results were normal in the upper limbs, while reduced motor and sensory nerve conduction was observed in the lower limbs. SEPs of the upper limbs revealed normal latency of the cortical N20 wave (21.5 ms) on the right side, but an absence of the N20 component on the left side. Increased latencies of the N11 (14.0–14.0 ms) and N13 (16.2–

15.7 ms) components were also observed bilaterally. SEPs of the lower limbs highlighted an increased cortical P40 wave latency (45.8 ms) on the right side and its absence on the left side. LEPs of the upper limbs showed bilateral increased latencies (400–474 ms) and reduced amplitudes (13.1 μ V) of the vertex complex N2/P2. LEPs of the lower limbs did not show the vertex complex N2/P2 on either side (Figure 1). Brain MRI revealed a lesion in the right frontal area and basal ganglia involving the pyramidal tracts. In addition, an arachnoid cyst was detected in the left hemisphere. Spinal MRI did not show any bone alterations, vertebral collapse, or nerve root/spinal compression.

Discussion

MS is a hereditary disorder of the connective tissue. Its symptoms are varied, but are essentially represented by flexible joints, long fingers and hands, and renal and cardiac impairments. In this case report, we described the neurophysiological evaluation of a subject affected by MS. We evaluated the patient's cortical activity and sensory and nociceptive pathways using a complete neurophysiological approach. He did not show epileptogenic patterns in his EEG recordings, although they have been reported in other studies,^{12–14} and the theta rhythm present in his right hemisphere was likely caused by the cerebral hemorrhage. However, relevant findings were noted in the patient's evoked potential responses. We observed greater alterations in the SEPs of the left limbs compared with the limbs contralateral to the cerebral hemorrhage. Furthermore, we identified a delay in the SEP latencies of the lower right limb. We hypothesize that the results obtained in the left limbs may be a consequence of the cerebral hemorrhage, whereas the SEP alterations in the lower right limb can be attributed to MS.

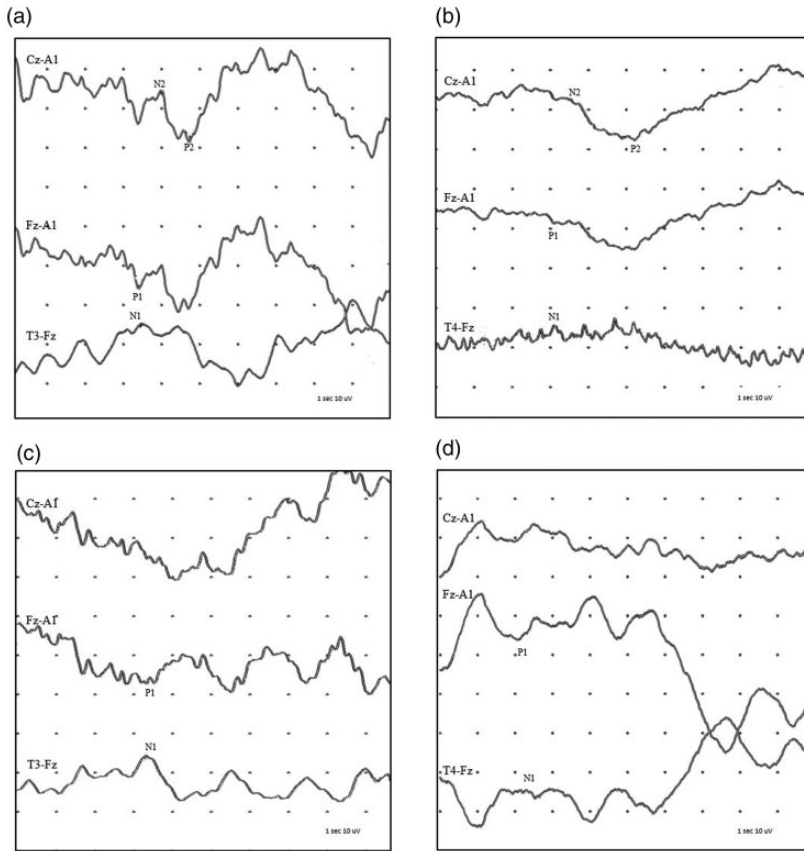


Figure 1. Averaged laser-evoked potential (LEP) traces after dorsal hand and foot stimulation with a Nd:Y-Al-perovskite (Nd:YAP) laser. a) LEPs of right upper limbs; b) LEPs of left upper limbs; c) LEPs of right lower limbs; d) LEPs of left lower limbs.

The LEP recordings in the upper limbs showed increased latencies in the cortical components on both sides. Substantial alterations were also found in the LEPs of the lower limbs; the N2/P2 vertex complex was absent on both sides. We propose that the alterations present in the sensory and nociceptive pathways in our patient may be connected to intrinsic functional alterations in the nerves, caused by structural variations as a result of the connective tissue disorder that characterizes MS. Supporting this idea, the spinal MRI examination of our patient was normal. Some authors have reported that alterations in muscle

connective tissue can influence force transmission between muscle cells and their environment, contributing to muscle weakness.¹⁷ Moreover, Voermans et al.¹⁸ demonstrated that abnormal packing of the peripheral nerves, caused by fibrillin deficiency, may increase the susceptibility to pressure or stretch, as reported in other hereditary connective tissue disorders.

A recent study by von Kodolitsch et al. reported pain as a feature of MS that is not listed in the Ghent nosology.¹⁹ The reported prevalence of pain in MS ranges from 47% to 91%,¹⁹ and mean values of reported pain are higher than those in the

general population. Pain symptoms include pain in the neck, back, chest, knee, and head, and can lead to marked disability and a considerable psychological burden.^{20,21} Although the related studies did not use the same recruitment and methodological criteria, it is probable that the prevalence of pain in MS is high, and that it interferes with daily life.²² Our SEP results also showed delays in medullar components on the right side. Therefore, our SEP and LEP findings highlighted that there may be alterations in both the sensory and nociceptive pathways in MS.

To date, the present case report is the first to investigate EPs in a subject with MS. Unfortunately, these results are from just one subject with MS. Nevertheless, we propose that a neurophysiological approach to MS research should be explored to better understand the changes that occur in this disease, and pain assessments should be included in the clinical assessment of MS patients. In addition, although our study was limited to a single case study, and a larger sample size is necessary, our case suggests that the clinical use of neurophysiological techniques—especially LEPs—is appropriate to support the neurorehabilitation and therapeutic management of MS patients. We believe that pain management and neurophysiological examinations are important considerations for the care of patients with MS, and should be included in a multidisciplinary approach for this patient population.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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