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Nabiximols in Multiple Sclerosis-Related Spasticity

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ABSTRACT

Multiple sclerosis (MS) is a chronic, autoimmune disease caused by inflammation and neurodegeneration, which is associated with a wide spectrum of central nervous system symptoms. Spasticity, defined as abnormally increased muscular tone, is 1 of the most common disabling symptoms in MS, occurring in up to 80% of MS patients and showing increased severity as the disease progresses over time. The approval of nabiximols for the management of MS spasticity opened up a new treatment opportunity to many patients. Here, we report a case of a 43-year-old man with a primary progressive MS diagnosis and spasticity-associated symptoms. Nabiximols had significant benefits with respect to spasticity symptoms.

KEYWORDS

Multiple sclerosis, spasticity, Sativex®

LEARNING POINTS

- The use of common tools for tele-neurology and -rehabilitation could improve the quality of care for people with MS and reduce the consequences related to therapy interruption.
- Nabiximols and tele-rehabilitation do not seem to have a relevant effect on disability-related spasticity.
- The addition of tele-rehabilitation seems to have strengthened the benefits of nabiximols, reducing the symptom severity perceived by the patient.

INTRODUCTION

Multiple sclerosis (MS) is a chronic disease of the central nervous system with inflammatory and neurodegenerative immunopathological characteristics. Interactions between genetic and environmental factors seem to be causative. It is the most common non-traumatic disabling neurological disease of young adults in developed nations. Up to 85% of MS patients develop the relapsing-remitting course of MS, and some relapsing-remitting MS subjects eventually evolve to secondary progressive MS, where worsening of neurologic function occurs in the absence of recognizable relapses. Approximately 15% of MS patients develop primary progressive MS from the onset of the disease. Spasticity, defined as abnormally increased muscular tone, is 1 of the most common disabling symptoms of MS, occurring in up to 80% of MS patients, and shows increased severity as the disease progresses over time[1]. Frequently, other symptoms related to spasticity, such as painful spasms, contractures and poor sleep quality, are also present. Because of its complexity, spasticity is not adequately managed with conventional antispastic therapies. The current recommended oral therapies for mild to moderate spasticity include baclofen, tizanidine, benzodiazepines (diazepam, clonazepam), dantrolene sodium, gabapentin and pregabalin. However, these therapeutic options are not completely effective in managing such complex symptoms and their prolonged use is also associated with numerous adverse reactions[2]. The approval of a delta-9-tetrahydrocannabinol:cannabidiol (THC:CBD) oromucosal spray (nabiximols, Sativex®), provides a new opportunity for use as an add-on medication in the management of moderate to severe generalized spasticity and related symptoms in patients with MS who are resistant to common oral antispastic drugs[3]. Nabiximols is an endocannabinoid system modulator containing THC and CBD in a near 1:1 ratio. THC interacts with human cannabinoid receptors that play a key role in the modulation of muscle tone, whereas CBD at higher than natural concentrations may limit the psychoactive effects of THC[4]. The efficacy of nabiximols oromucosal spray as an add-on therapy for symptom improvement in patients with MS with moderate to severe MS spasticity has been demonstrated in several clinical trials.

CASE DESCRIPTION

Here, we describe a case of a 43-year-old man with a 2-year history of worsening paraparesis. In September 2017, the patient experienced the appearance of walking impairment. For this reason, spinal cord MRI was performed (February 2018) showing cervical and dorsal demyelinating lesions, non-contrast-enhancing (*Figs. 1A and 1B*). In addition, brain MRI was performed showing lesions that were compatible with demyelinating/inflammatory disease (*Figs. 1C and 1D*).

The patient was admitted to the neurology department and subjected to: neurological examination, blood tests, anti-MOG and Aq4 antibody testing, cerebrospinal fluid examination, brain and spinal cord MRI, visual and auditory evoked potentials and somatosensory and motor evoked potentials (*Table 1*).

A diagnosis of primary progressive MS was made. The patient refused to start disease-modifying therapy (ocrelizumab). Oral antispastic

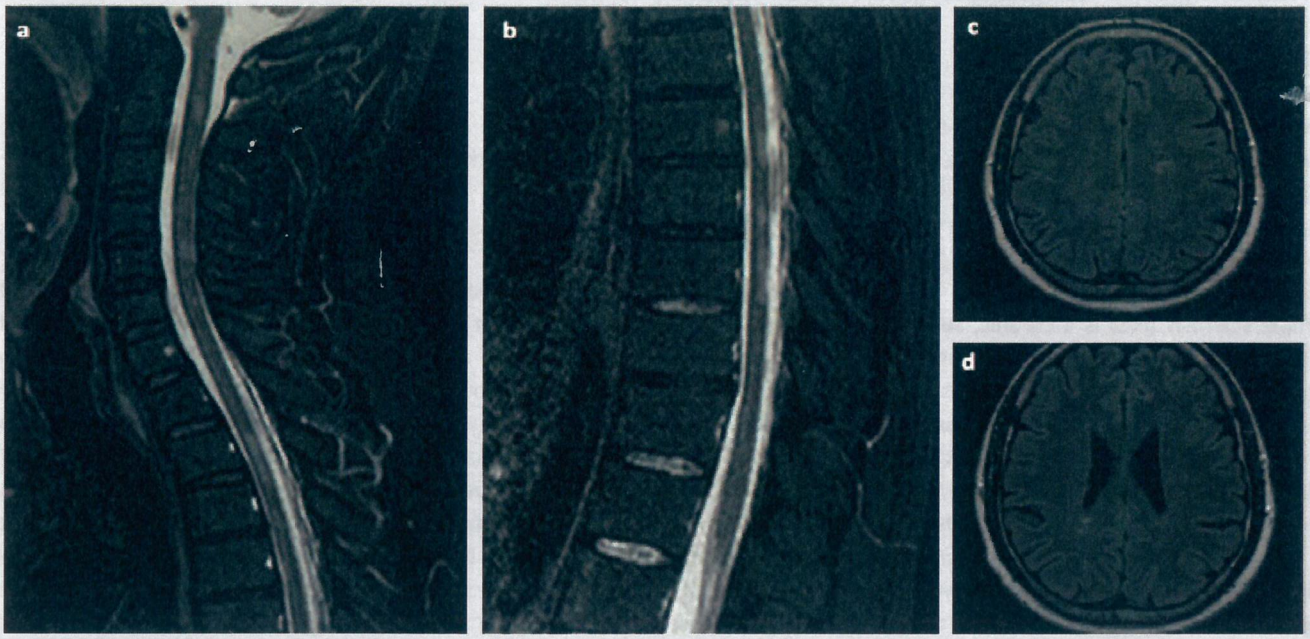

Figure 1. Spinal cord MRI showing cervical (a) and dorsal (b) demyelinating lesions and brain MRI showing lesions compatible with demyelinating/inflammatory disease (c, d)

Test	Results
Blood tests: blood count, ANA, lupus anticoagulant, ENA, anti-DNA antibodies	Normal
Anti-MOG and Aq4 antibodies	Negative
Examination of cerebrospinal fluid (CSF)	Positive oligoclonal bands
Brain MRI (February 2018)	Demyelinating lesions
Spinal cord MRI (February 2018)	Cervical and dorsal demyelinating lesions C1-C2, C4-C5, C7-D1, D2-D3, D7-D9, non-contrast-enhancing
Visual and auditory evoked potentials	Normal
Motor evoked potentials	Conduction along the central motor pathways altered to the 4 limbs
Somatosensory evoked potentials (SEP)	Right and left tibial SEP with a slight increase in latency
Brain and spinal cord MRI (December 2019)	Stable

Table 1. Tests and results during hospitalization

treatment (baclofen 50 mg/day and pregabalin 150 mg/day) led to partial symptom control. Despite antispastic oral treatment, in 2019, the patient exhibited gradual worsening of spasticity, with severe spasticity in both legs and the right arm, stiffening of the lower limbs and left calf twitching appearing at rest. Neurological examination and brain and spinal cord MRI were conducted in December 2019 (*Table 2*). Nabiximols was prescribed in January 2020 for the persistence of calf twitching and cramps up to the dosage of 8 puffs/day with significant benefits; no adverse drug reactions occurred. This patient was eligible for starting nabiximols treatment according to the AIFA registration inclusion criteria. The MS spasticity evolution was evaluated by the validated 0–10 Numerical Rating Scale (NRS) patient-rated scale (0=none, 10=maximal spasticity). The effectiveness of nabiximols was evaluated through the initial response threshold, defined as ≥20% NRS spasticity score improvement versus the baseline value, and the clinically relevant response threshold, defined as ≥30% NRS spasticity score improvement versus the baseline value.

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Neurological examination	Score
Neurological examination (April 2018): weakness of the right limbs, mild hypoaesthesia of the right limbs, mild spastic paraparesis at predominantly right side, mild urinary hesitancy and constipation, walking without assistance unrestricted, barely increased muscle tone, bilateral Babinski	***Ambulation score:*** 0 ***Expanded disability status scale (EDSS):*** 3.0 (P3, Sf1, S1) ***Numerical rating scale (NRS):*** 5
Neurological examination (December 2019): weakness of the right limbs, mild hypoaesthesia of the right limbs, moderate spastic paraparesis at predominantly right side, mild urinary hesitancy and constipation, walking without assistance for 500 metres, moderately increased muscle tone in both legs and the right arm, bilateral Babinski	***Ambulation score:*** 1 ***EDSS:*** 4.0 (P4, Sf1, S1) ***NRS:*** 7
Neurological examination (March 2020, June 2020, September 2020) weakness of the right limbs, mild hypoaesthesia of the right limbs, mild spastic paraparesis at predominantly right side, mild urinary hesitancy and constipation, walking without assistance for 500 metres, mild increased muscle tone in both legs and the right arm, bilateral Babinski	***Ambulation score:*** 1 ***EDSS:*** 4.0 (P4, Sf1, S1) ***NRS:*** 5

Table 2. Neurological examination and score

DISCUSSION

MS generally arises in the young, and has a significant negative impact on the patient's quality of life compared with the general population. Spasticity is a common symptom in MS patients. Spasms, pain, poor sleep quality and urinary dysfunction are symptoms frequently associated with spasticity in MS. To date, nabiximols, an oromucosal spray containing THC and CBD in an approximate 1:1 ratio, is the only commercially available formulation containing cannabinoids to be used as add-on therapy for treatment of spasticity in adult MS patients who are not responding to conventional antispastic therapies[4]. Patients with moderate disability on the EDSS scale but who have fully ambulatory abilities, with notable painful symptoms and spasms that affected their quality of life, benefitted from nabiximols therapy. The drug resolved the symptoms that accentuated the patient's disability and improved his quality of life. The description of this clinical case can be a prompt to consider an early start with Sativex® therapy in patients for whom there is a short-term history of the disease, although progressive, and an EDSS with a score that still indicates autonomy in walking, to ensure for the patient a better quality of life and adequate adherence to therapy without early dropout. Adherence and persistence are better in patients with less marked disability and preserved cognitive functions. The conclusion of the clinical case is to focus on an early start with the therapy to fully maximize its benefits. In MS patients suffering from spasticity, nabiximols should be started earlier to decrease the likelihood of treatment discontinuation over time[5].

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