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An Effective Treatment for Multiple Sclerosis Urinary Disorders Through a Formulation of Delta-9-Tetrahydrocannabinol and Cannabidiol

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ABSTRACT

Spasticity represents an important cause of disability for patients with multiple sclerosis. Even more, dysfunction of the bladder greatly aggravates the patient's burden and is responsible for their poor quality of life. Here, the case of a 35-year-old woman suffering from relapsing-remitting multiple sclerosis, with a slight spastic paraparesis associated with significant urinary urge incontinence, is reported. First-line antispastic treatments, physiotherapy and symptomatic drugs for urinary disorders did not bring any benefit, for ineffectiveness or side effects. However, nabiximols relieved the urinary symptoms, improving the patient's sleep and quality of life without side effects.

KEYWORDS

Nabiximols, spasticity, management of neurogenic bladder, multiple sclerosis, case report

LEARNING POINTS

- Spasticity and related symptoms, such as urinary disorders, occur in up to 80% of MS patients.
- If symptoms related to spasticity improve, the quality of life of patients with MS benefits.
- The delta-9-tetrahydrocannabinol and cannabidiol spray formulation improved symptoms related to spasticity, including urinary disorders of MS.

INTRODUCTION

Spasticity is one of the most common symptoms in multiple sclerosis (MS) occurring in up to 80% of patients and it can heavily compromise the quality of life of MS patients, independent of disease duration and other associated symptoms[1].

Spasticity is characterized by a broad spectrum of manifestations, such as skeletal muscle spasticity (which interferes with passive joint motion and impairs voluntary control of movements), stiffness, involuntary spasms, muscle pain and disturbance of normal urinary function. The most common urinary dysfunction, frequently reported in MS patients, is the neurogenic overactive bladder (OAB), defined as a condition characterized by micturition, urgency, with or without urge incontinence, usually associated with high void frequency and nocturia[2,3].

CASE DESCRIPTION

Here, a case of a 35-year-old female suffering from relapsing-remitting MS (RRMS) is reported. The patient's mother, who also suffered from MS with de Quervain's thyroiditis, died at the age of 55 years from complications of MS. In the patient's medical history, it was reported that she was treated with a modest dose of thyroxine for Hashimoto's thyroiditis. The onset of demyelinating disease dated to 2006, following an episode of paraesthesia, such as tingling in the left foot. In 2013, after 7 years of clinical and radiological stabilization with glatiramer acetate immunomodulatory therapy, the patient autonomously discontinued therapy because of persistent injection site reactions and the desire for pregnancy. After 15 months, the patient gave birth to a baby girl (who was breastfed) and did not resume any therapy, as advised by her trusted doctor. In October 2015, 8 months after giving birth, the patient had a clinical and radiological reactivation of the pathology, which was treated with intravenous steroids. After screening for second-line therapies, she began treatment with fingolimod, with the disease stabilizing to date.

With the relapse in 2015, the patient presented new neurological outcomes, a slight spastic paraparesis associated with gait ataxia, with the possibility of walking without aid, painful nocturnal spasms, with related sleep disturbances, bowel and, in particular, severe bladder dysfunction with urge incontinence, associated with high void frequency, treated with oxybutynin (5 mg twice a day). For her spasticity-related symptoms, the patient was treated with baclofen (25 mg/day), which was soon discontinued for weakness and tizanidine (2 mg/day) was suspended due to orthostatic hypotension. In recent years, she had undertaken and continues a rehabilitation programme, with only partial improvement. In addition, she did not benefit from taking gabapentin 400 mg 3/day. The patient profile is summarized in *Table 1*.

For the urinary disorders, the patient was referred to a urologist. After the specialist evaluation, including urodynamic examination and electromyography of the sphincter, she was diagnosed with a bladder dysfunction related to a dyssynergy of the detrusor sphincter[2,3]. The doctor and the patient agreed to treat the spasticity and related symptoms with cannabinoids. After starting Sativex® oromucosal spray treatment (nabiximols), a formulation of delta-9-tetrahydrocannabinol and cannabidiol, at a medium

Sex	Female
Age	35 years
Years with MS	12
Years with MS spasticity	5
Affected area(s) (pre-nabiximols)	Slight spastic paraparesis
Previous MS spasticity treatments	Baclofen, tizanidine, gapapentin, physiotherapy
Present disease modifiers	Fingolimod

Table 1. Patient profile and features

dose of 6 sprays/day, she reported an improvement of spasticity-related symptoms with a reduction in urinary frequency, especially during the night with an overall improvement in her sleep. Urinary incontinence accidents have decreased from 5 to 1 per night. The spasticity numerical rating scale was reduced from 7 to 5. The patient also reported a reduction in painful nocturnal spasms (from 3 to 1 per night) and nocturnal awakenings (from 4 to 1 per night). *Table 2* shows the trend in the disorders related to spasticity in the patient, before and after the start of treatment with nabiximols.

	Pre-nabiximols	Post-nabiximols
Severity of MS spasticity		
Modified Ashworth Scale	2	1
Spasticity Numerical Rating Scale	7	5
Mobility impairment	Yes	Slightly improved
Expanded Disability Status Scale	2.5	2.5
MS spasticity-associated symptoms		
Urinary incontinence accidents	5	1
Overactive Bladder Symptom Score	7	4
Pain	No	No
Painful nocturnal spasms	Yes, 3	Yes, 1
Nocturnal awakenings	Yes, 4	Yes, 1
Quality of Life	EuroQol5D-QoL=7	EuroQol5D-QoL=4
Instrumental Activities of Daily Living	iADL:4/6	iADL:5/6

Table 2. Course of disorders related to the patient's spasticity

DISCUSSION

Muscle spasticity guidelines recommend first-line antispastic treatment with baclofen or tizanidine, in addition to physiotherapy and exercise, medication, change in daily activities or combinations of these methods. For other agents (gabapentin, vigabatrin, tolperisone), efficacy is even less certain or potential serious adverse reactions must be considered (dantrolene, benzodiazepines). More invasive and partly off-label treatment options are intrathecal baclofen, intrathecal triamcinolone acetonide and intramuscular botulinum toxin. Among the available drugs, baclofen produces an effect only by activating the gamma-aminobutyric acid B (GABAB) receptors[4].

The case presented here demonstrates a possible therapeutic benefit of nabiximols in MS, not only on spasticity, but also on related symptoms, such as urinary disorders, poorly responsive to other pharmacological treatments. Surprisingly, the goal of improving the patient's quality of life was achieved, without significant side effects: bladder disorders, daytime frequency and, in particular nocturia and urinary incontinence accidents, were alleviated, as demonstrated by an improvement in the Overactive Bladder Symptom Score (OABSS) from 7 to 4. A final aspect concerning the oromucosal formulation of cannabinoids is the personalization of the dosage, depending on the individual response; this allows the best cost–benefit dose to be found, tailoring it to every MS patient[5–7]. It should be pointed out, however, that a review supported an improvement in bladder symptoms with the THC:CBD oral mucosal spray, while oral cannabinoid extracts and THC alone did not yield the same results in terms of efficacy[8].

The cannabinoid system is widespread in the nervous system, including the cannabinoid receptors, CB1 and CB2, together with their ligands, the endocannabinoids. A consistent accumulation of receptors is then found in the brain stem, where important functions/symptoms such as spasticity, sleep, bladder control and pain are mediated. CBD is a cannabinoid devoid of psychotropic activity, able to modulate the actions of THC on the central nervous system. It attenuates the euphoric effects, increasing the relaxation effects, but above all it reduces the harmful effects. The mechanism underlying this association of manifestations could be the increase in tone of various muscles located in different parts of the body, considering the typological duplicity of cannabinoid receptors[8-11]. Particularly for the lower urinary tract, it can be assumed that treatment with nabiximols works by improving the dysfunction in the smooth muscle of the bladder[7].

A group of researchers, opening up a promising area of research, have hypothesized the concept of a "Spasticity-Plus Syndrome" to unify the various symptoms related to spasticity. Treatment with nabiximols alone can simplify the treatment of this extensive

symptom process, one of the most unmet needs in MS treatment. The treatment of these manifestations of the disease can otherwise be particularly complex because the few available drugs, often used in polypharmacy, can determine with their adverse effects the appearance of further problems that weigh on the patient[12].

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