European Journal of Case Reports in Internal Medicine

Urinary Dysfunction Improvement after Treatment with Sativex® in a Multiple Sclerosis Patient

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Conflicts of Interests: AB and MM have received speaker's honoraria and/or compensation for consulting service and/or speaking activities from Biogen, Novartis, Roche, Mylan, Merck, Almirall and Genzyme. LM, MM and GP have no relevant conflicts of interests to report.

Acknowledgements: We thank the patient. Editorial assistance was provided by Francesca Cappellini, PhD and Aashni Shah (Polistudium SRL, Milan, Italy). This assistance was supported by Almirall.

ABSTRACT

Nabiximols has been approved to treat multiple sclerosis-related spasticity symptoms; it also improves symptoms such as pain, urinary dysfunction and sleep disturbance. We report the case of a 43-year-old patient with multiple sclerosis who started add-on treatment with nabiximols for moderate spasticity (self-reported discomfort by the Numeric Rating Scale 6/10); she experienced a remarkable improvement in pre-existing urinary dysfunction. Nabiximols enables treatment of more spasticity-related symptoms, reducing the need for symptomatic medications and avoiding the unnecessary adverse effects produced by polytherapy.

KEYWORDS

Multiple sclerosis, spasticity, urinary dysfunction, nabiximols, Sativex®

LEARNING POINTS

- Multiple sclerosis pathology affects multiple areas of the central nervous system, producing a multiplicity of symptoms. Management of symptoms is a complex task requiring a multidisciplinary approach.
- Pharmacological interventions are often considered necessary, but any pharmacological intervention has a risk of side effects and this risk is accentuated by drug–drug interactions.
- Nabiximols is effective in symptomatic treatment of bladder dysfunction, mainly on symptoms associated with detrusor overactivity. Pretreatment characterization of patients based on lesion sites can be useful to predict the nabiximols response.

INTRODUCTION

Multiple sclerosis (MS) is a common and often disabling disease of the central nervous system (CNS), which affects approximately 2.8 million people worldwide[1]. Due to the wide spectrum of spasticity manifestations, treatment of spasticity is a complex task requiring a multidisciplinary approach and a global partnership between the patient and other health professionals. Non-pharmacological interventions may be beneficial but may have a limited time effect so pharmacological interventions are often considered necessary[2]. Different classes of medications are used to manage spasticity-related symptoms, but they are only partially effective and are associated with adverse effects[3].

Nabiximols (Sativex®) is a cannabinoid compound consisting of delta-9-tetrahydrocannabinol and cannabidiol in a 1:1 ratio, which is approved as an oromucosal spray for the treatment of MS-related spasticity based on its efficacy on patient-reported outcomes[4]. The precise mechanism of action is not fully understood[5].

CASE DESCRIPTION

We report the case of a 43-year-old woman suffering from relapsing-remitting MS diagnosed in 2012. The patient was treated from 2014 to 2015 with glatiramer acetate because of her desire for pregnancy, without disease activity during first-line treatment. Her Expanded Disability Status Scale (EDSS) was 1.5 during this period. In 2016, the patient gave birth to a child with a good course of the disease during pregnancy. In the post-partum period, she presented a clinical relapse characterized by urinary retention and sensory disturbance in the lower limbs. She was treated with high-dose methylprednisolone with incomplete recovery of the sensory disturbance and overactive bladder symptoms. Brain and spinal cord magnetic resonance imaging (MRI) revealed multiple new T2 lesions in the brain, 4 of these with gadolinium enhancement, and a new T2 lesion in the dorsal spinal cord (*Fig. 1*). Neurological evaluation showed ataxic spastic walking on the right side, slight hypertonus in the right lower limb, urinary urgency and hesitation and painful hyperaesthesia in the abdominal region. Neurological evaluation showed an EDSS 3.5. Because of radiological and clinical activity, the patient started fingolimod 0.5 mg/day from January 2017 with clinical and radiological stability of the disease. Due to the persistence of bladder symptoms, the patient was evaluated using a multidisciplinary approach by the urogynaecologist and a physiatrist. Her symptoms included hesitancy, straining, slow and interrupted stream and incomplete bladder emptying. The patient completed the International Prostatic Symptom Score (IPSS) assessment[6]. The IPSS is a 7-question screening tool with each question scoring from 1 to 5 for a maximum total of 35 points, with 3 different levels of dysfunction severity: 0–7: minor; 8–19: moderate and 20–35: severe.

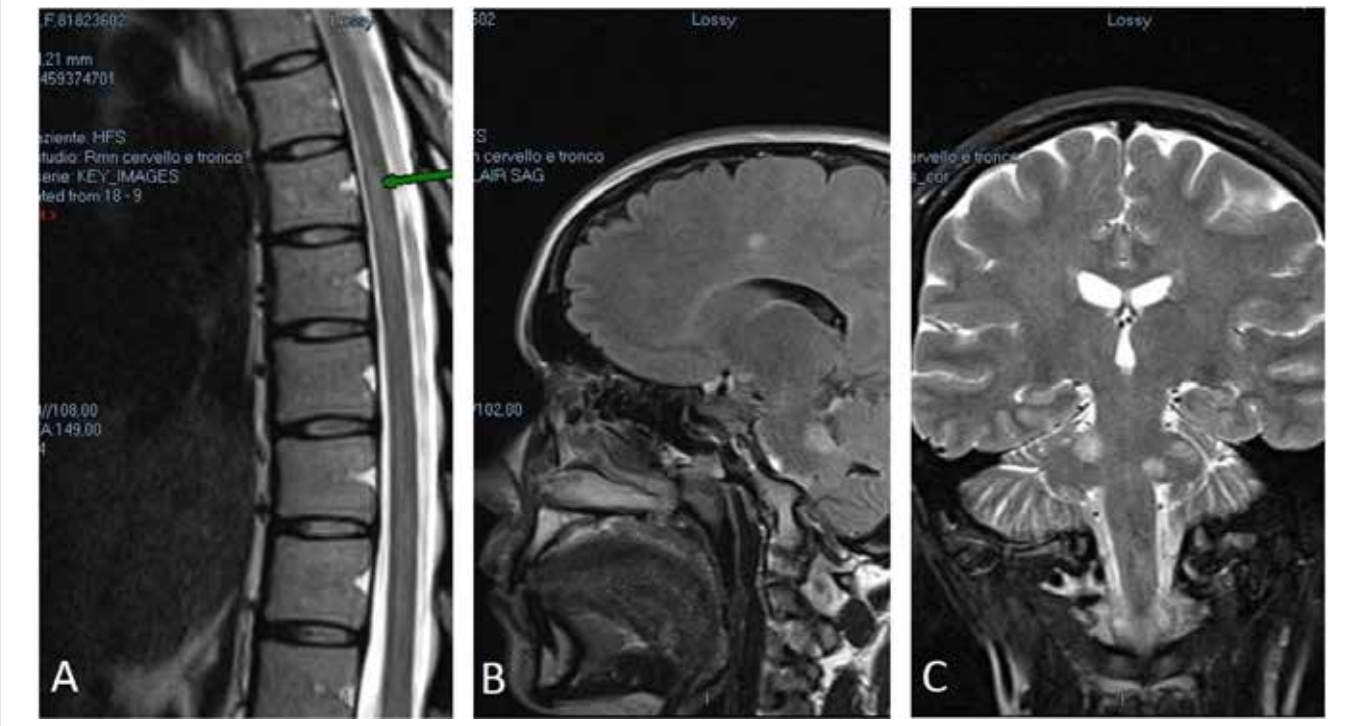

Figure 1. Magnetic resonance imaging during post-partum relapse. (A) New T2 lesions on D2–3. (B and C) New pericallosal and brainstem T2 lesions

Her IPSS score was 27. She underwent measurement of the post-void residual (PVR) volume which was 160 ml (normal value <100 ml). She was treated with oral tamsulosin 0.4 mg/day for 3 months with only partial improvement. Urodynamic studies demonstrated detrusor overactivity. She added solifenacin 5 mg/day with limited effectiveness.

The patient also began first-line treatment with baclofen 25 mg, half a tablet 3 times a day. She also started pelvic floor muscle training and physical exercise for spasticity in the lower limbs. Unfortunately, the patient had no improvement in spasticity and painful paraesthesia.

The patient was also discouraged by polytherapy, which was complex while she was caring for a young daughter. In the meantime, her bladder symptoms worsened, from a mild urinary urgency to a frequent urinary incontinence, with a high recurrence of nocturia episodes. On the bases of the failure of first-line spasticity oral treatment, nabiximols was added, with gradual titration. Initial dizziness resolved 2 days after the first drug administration and no other side effects were reported. The patient reached the dosage of 6 puffs/day after 21 days.

After 1 month, we observed a general improvement in the patient's condition. Spasticity was improved according to both the Numeric Rating Scale, which was reduced from 6 to 2, and the Modified Ashworth Scale, which was reduced from 2 to 1. The EDSS remained stable. Analyzing the bladder diary, we observed a reduction in both the total number of voids and nocturia episodes at the first month of follow-up. The IPSS score improved from 27 to 16 and the PVR decreased from 160 to 76 ml. The patient also reported a marked improvement in painful sensory symptoms.

After 12 months of nabiximols treatment, with consideration of long-term improvement in both spasticity disorders and bladder symptoms, she sequentially halted solifenacin and tamsulosin. After discontinuation of symptomatic bladder therapy, the IPSS score was 18 and the PVR was 70 ml. The long-term efficacy of nabiximols remained stable and the Numeric Rating Scale was 2 and the Modified Ashworth Scale remained at 1 (*Table 1*).

The patient's quality of life was evaluated using the EuroQol-5D tool and, more specifically, by the Patient Global Impression of Change Scale, in which the patient expressed an evaluation of 5 ("moderately better and a slight but noticeable change") and a score of 2 (which underlines a significant improvement). Both simplification of polytherapy and relief of different symptoms have driven the marked improvement in the quality of life.

DISCUSSION

This case describes a patient with MS and moderate spasticity who experienced a remarkable improvement of lower urinary tract (LUT) dysfunction after starting treatment with nabiximols.

The site of the lesion in the neurological axis determines the general pattern of LUT dysfunction, which is reflected in the patient's symptoms (*Table 2*). Lesions of the relevant suprapontine or spinal

DOI: 10.12890/2021_V8Sup2

	Pre-nabiximols	After 1 month of nabiximols	After 1 year of nabiximols
Expanded Disability Status Scale	3.5	3.5	3.5
Ambulation index	2	1	1
Numeric Rating Scale	6	2	2
Modified Ashworth Scale	2	1	1
International Prostatic Symptom Score	27	16	18
Post-void residual volume	160 ml	76 ml	70 ml

Table 1. Clinical course during nabiximols treatment

Neurological lesion	Anatomical localization	Bladder dysfunction	Clinical manifestations
Suprapontine lesion	Between encephalon and pontine centre	Hyperactivity of the neurogenic detrusor	Filling symptoms: urgency and frequency of urination, which may be associated with urinary incontinence
Spinal lesion (infrapontine–suprasacral)	Between the medullary cone and pontine centre of urination	Vesico-sphincteric dyssynergia	Difficult in starting urination, urgency, urination in two-times Coexistence of filling and emptying symptoms
Sacral/ infrasacral lesion	Medullary cone, compromising the nerve fibres corresponding to S2–S4	Hypoactivity of the neurogenic detrusor	Symptoms of emptying, difficulty urinating, weak stream or stream interruption

Table 2. Probable vesico-sphincteric involvement according to the location of the MS lesion. (Modified from Panicker et al., Lancet Neurol 2015;14:720)

pathways regulating LUT functions affect the storage phase, resulting in reduced bladder capacity and detrusor overactivity. The patient may report varying degrees of urinary urgency, frequency, nocturia and incontinence (collectively known as overactive bladder symptoms)[6,7].

The scientific basis for the effect of nabiximols on the bladder lies with the fact that this organ expresses CB1 receptors. The effect of nabiximols is mediated also by interacting with transient receptor potential vanilloid 1 (TRPV1), resulting in the release of calcitonin gene-related peptide. The interaction between TRPV1 and cannabinoid receptors is not well understood, but the bladder is rich in TRPV1 receptors and these are increased in conditions of inflammation and overactive bladder, particularly in neurogenic cases. There may also be an effect at CNS receptors, since the presence of CB1 receptors has been demonstrated in the vicinity of the periaqueductal grey, pons, hypothalamus and basal ganglia, as well as the lumbar spinal cord all regions known to be involved in bladder control[8].

Although none of the studies on nabiximols in bladder dysfunction characterized patients by the site of lesion, a response was observed mainly with symptoms associated with detrusor overactivity, and less with incontinence disturbance[8,9]. Our patient showed a spinal (infrapontine–suprasacral) pattern lesion that was associated with detrusor overactivity and was poorly responsive to combination therapy with tamsulosin and solifenacin. In this pattern, which is the most common in MS patients, nabiximols has been effective and enabled the halting of both symptomatic drugs. We believe that a pretreatment characterization of patients with urinary dysfunction based on lesion sites, alongside multidisciplinary evaluation, can be useful to predict the nabiximols response.

In responder patients, nabiximols treats spasticity-related symptoms, reducing the need for symptomatic medications and avoiding the unnecessary adverse effects produced by polytherapy.

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