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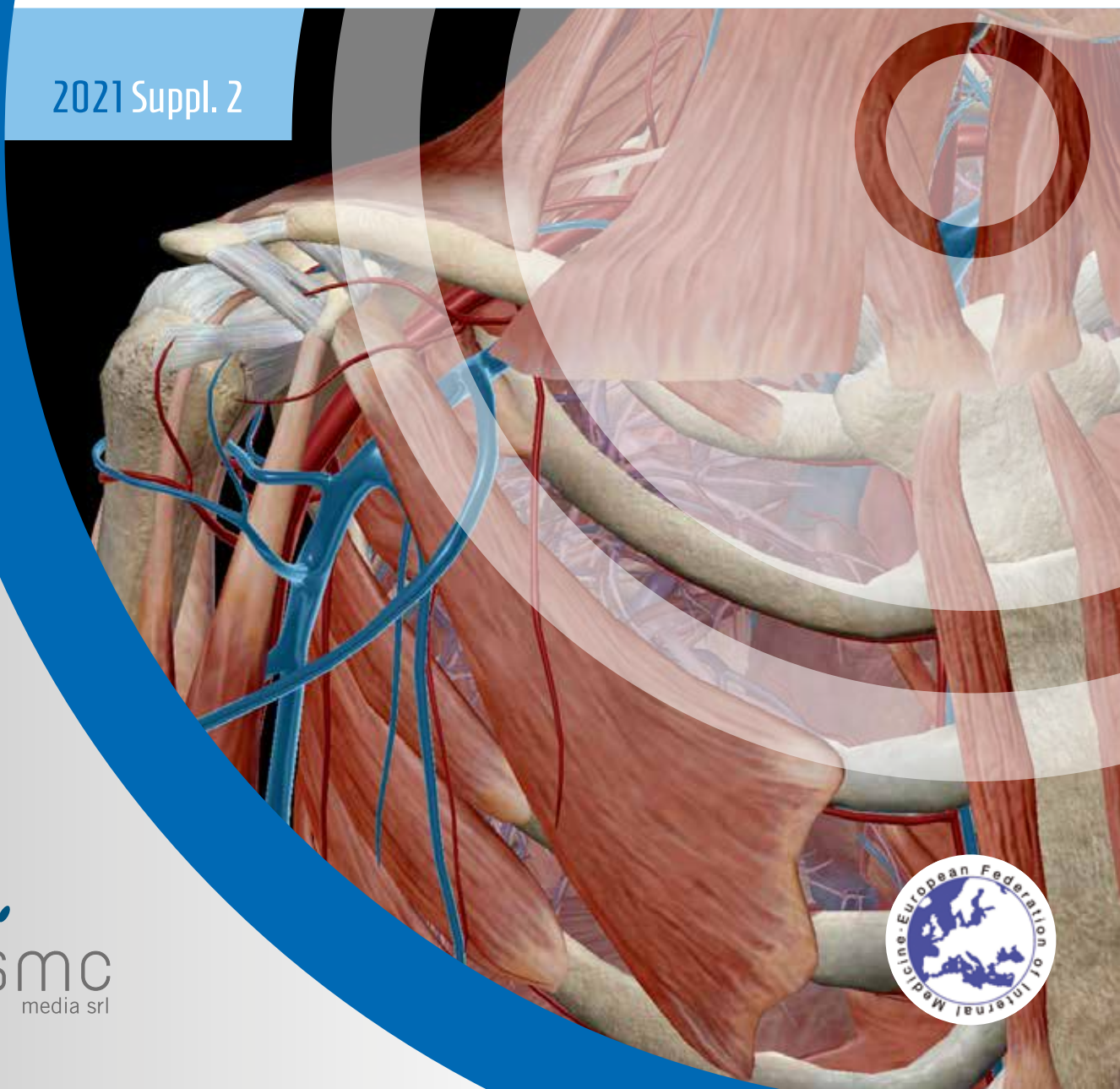

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Focus Sclerosi Multipla e Nabiximols ai tempi del COVID-19

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The Utility of Delta-9-Tetrahydrocannibinol Therapy in a Multiple Sclerosis Patient with a Neoplastic Brain Lesion

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ABSTRACT

Multiple sclerosis (MS) can sometimes cause uncommon pseudotumoural lesions that produce atypical symptoms, such as motor epileptic seizures which are often pharmacoresistant. In these cases, accurate diagnosis is essential for correct therapy, even if unconventional. We present the case of a brain tumour in a 40-year-old relapsing-remitting MS patient who presented with pharmacoresistant seizures which eventually responded to nabiximols. After various therapeutic approaches, delta-9-tetrahydrocannabinol therapy was introduced with good results. Spasticity improved, pain decreased and we observed a reduction in the number of daily seizures. It is possible that delta-9-tetrahydrocannabinol can enhance the efficacy of anti-epilepsy therapy.

LEARNING POINTS

- The patient experienced fewer daily focal motor crises after the administration of nabiximols in the morning.
- The correct combination of symptomatic drugs can optimize a specific multiple sclerosis (MS) therapy even if the real cause of symptoms is a primary brain tumour and not MS.
- The addition of nabiximols to the therapeutic program allowed anti-epilepsy drug doses to be reduced and improved the patient's cognitive impairment.

KEYWORDS

Multiple sclerosis, delta-9-tetrahydrocannabinol, brain tumour, epileptic seizure

INTRODUCTION

Multiple sclerosis (MS) is characterized by chronic central nervous system demyelination. Patients are usually young. Rarely, magnetic resonance imaging (MRI) shows pseudotumoural lesions that produce uncommon symptoms such as epileptic seizures. In such cases, a correct and timely diagnosis is particularly important, the best combination of drugs must be chosen, and other therapeutic strategies, even unconventional ones, should be considered [1, 2]. However, combining different drugs can lead to serious side effects. To avoid all risk and improve treatment efficacy [3], we must be aware of the mechanism of action of every single drug, their interactions, and potential adverse events.

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CASE DESCRIPTION

We describe the case of a 40-year-old woman who has had relapsing-remitting MS since 2015. Clinical and radiological data show low disease activity and the patient is treated with glatiramer acetate (40 mg thrice a week, subcutaneous). The patient presented after experiencing some sudden movements of the left arm and loss of conscience for a few seconds.

MRI revealed a very large right fronto-parietal brain lesion that originated inside the right frontal lobe and reached the homolateral corpus callosum and centrum semi vale with enhancement after gadolinium administration (*Fig. 1*). The electroencephalogram showed homolateral focal epileptic waves.

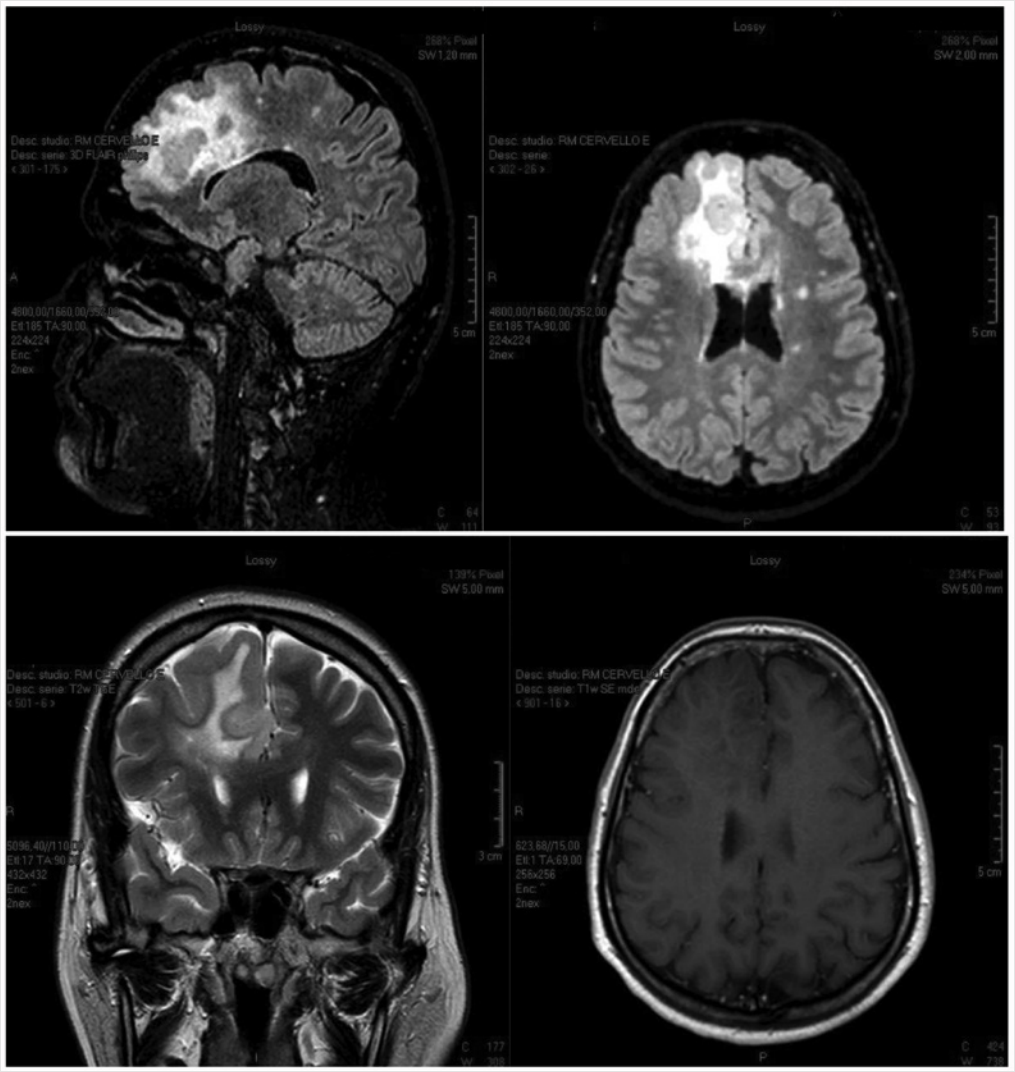

Figure 1. MRI shows a large pseudotumoural fronto-parietal lesion before treatment. This type of lesion can be caused by multiple sclerosis or a cerebral tumour

Sometimes, large MS lesions cause epileptic seizures that can regress after perilesional oedema is reduced with steroid therapy (such symptoms were originally considered due to MS relapse). Our patient started specific therapy with methylprednisolone 1 g intravenous (5 days) and lamotrigine 200 mg twice a day as symptomatic therapy. A second MRI showed unchanged results after steroid administration. After 3 weeks without seizures, the patient's clinical symptoms worsened with left arm dysaesthesia and impairment of sensitivity to touch and pain. She started symptomatic therapy with pregabalin 75 mg twice a day. After 8 weeks, she presented a new epileptic seizure, so lacosamide 100 mg twice a day was also added.

There was a possibility that the large right frontal-parietal brain lesion was caused by a primitive brain tumour. So, after neurosurgical advice, the lesion was excised with histological diagnosis of oligodendroglioma (*Fig. 2*).

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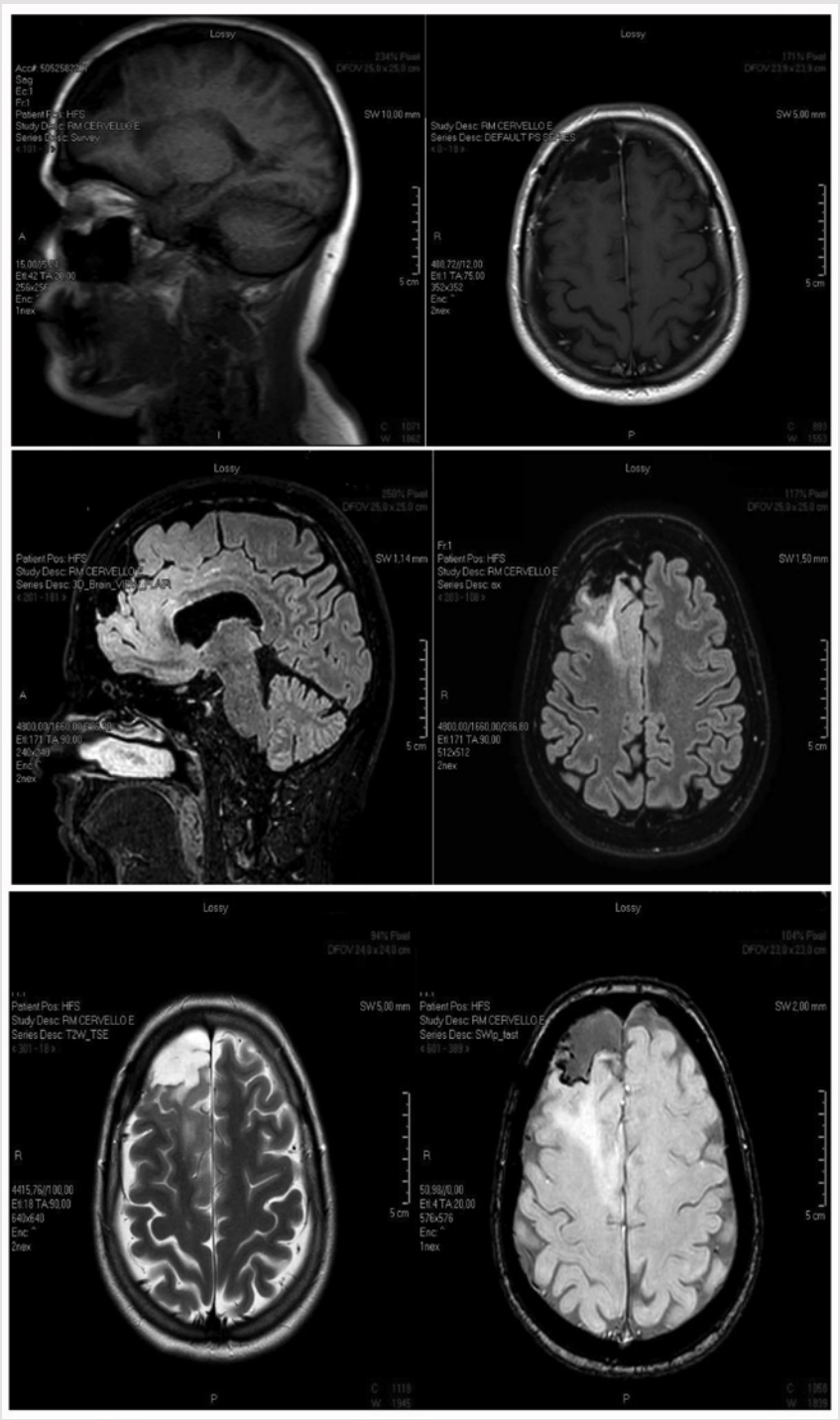

Figure 2. MRI after surgical removal of part of a large fronto-parietal lesion, which caused pharmacoresistent epilepsy because of the affected area, extent, anatomical ratios and tissue oedema

After the operation, we observed paresis of the left arm with spasticity and pain on mobilization, impairment of left arm sensitivity to touch, frequent daily motor seizures of the left arm, and side effects due to the anti-epileptic drugs, such as cognitive mpairment, weakness and drowsiness. Steroids were necessary for 1 week (dexamethasone 4 mg, twice a day) and osmotic diuretics (Mannitol 18% 100 ml, 6 times a day).

Our patient reported a high level of diffuse pain and subjective lack of concentration, which significantly affected her work and daily activities. A test battery including the TAP (Test of Attentional Performance), TMT (Trail Making Test), SDT (Symbol Digit Test) and MFCT (Multiple Feature Cancellation Target) was normal but the patient felt slower and sleepy.

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We introduced nabiximols (an endocannabinoid system modulator consisting of two active ingredients (THC, CBD) in an oromucosal spray formulation) as symptomatic therapy to decrease the spasticity of the left arm, to lower the required dose of symptomatic drugs (pregabalin 75 mg twice a day to pregabalin 75 mg once a day), and finally to reduce side effects.

After about 4 weeks of treatment with seven sprays a day, spasticity had improved, pain had decreased and the patient was able to start a rehabilitation program. She also observed a reduction in the number of daily focal motor seizures after administering nabiximols in the morning, so it was possible to reduce anti-epilepsy treatment (lamotrigine 200 mg twice a day and lacosamide 100 mg twice a day to lamotrigine 100 mg twice a day and lacosamide 100 mg once a day).

DISCUSSION

MS and primitive brain tumours can cause large cortical lesions resulting in epileptic seizures. This type of epilepsy is difficult to treat, but our data support the hypothesis that a combination of symptomatic drugs can optimize specific therapy, even if the real cause of symptoms is a brain lesion [4].

It is difficult to find a good combination of drugs to control epileptic seizures without side effects which often results in patients discontinuing therapy at follow-up [5].

Nabiximols can enhance the effect of anti-epilepsy therapy [4, 6], In fact, we successfully reduced anti-epileptic and symptomatic drug doses in our patient with an improvement in cognitive impairment [5] and decrease in seizure frequency.

In conclusion, the positive effects of combined therapy should always be investigated to improve patient welfare. Sometimes a drug combination can have an unexpected but useful interaction. It would be interesting to extend this observation to a larger number of patients to better understand our findings.

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Treatment with Delta-9-tetrahydrocannabinol/cannabidiol in Multiple Sclerosis: Influence on the Autonomy Profile according to the International Classification of Functioning, Disability and Health

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ABSTRACT

Multiple sclerosis (MS) is the most common cause of non-traumatic neurological disability in young adults. It has effects at different levels: physical, emotional, psychological, cognitive and social, with a great variety of signs and symptoms. In particular, spasticity contributes to reducing the motor performance of patients with MS, causing pain, reduction in distance walked and limitations in social life. We present the case of a 39-year-old woman with MS. She was treated with delta-9-tetrahydrocannabinol/cannabidiol and the outcome was assessed with the International Classification of Functioning Disability and Health core set framework.

LEARNING POINTS

- The clinical presentation of multiple sclerosis (MS) is heterogeneous but very often lower limb spasticity leads to severe disability.
- The use of nabiximols improved spasticity control and motor performance in walking, and also had a larger effect in improving activity and participation in personal relationships.
- Appropriate assessment of MS cases, through the ICF framework, may demonstrate further effects of nabiximols on patient capacity and performance.

KEYWORDS

Multiple sclerosis, ICF, neurorehabilitation, delta-9-tetrahydrocannabinol/cannabidiol

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INTRODUCTION

Multiple sclerosis (MS) is the most common cause of non-traumatic neurological disability in young adults [1]. The World Health Organization (WHO) defined health as 'a state of complete physical, mental and social well-being and not merely absence of disease or infirmity'. The 'bio-psycho-social' model reflects this multidimensional concept of health, which considers the person the result of a complex and dynamic interaction of physical, psychological and environmental factors [2]. Many factors can affect the degree of disability in two individuals with the same neurological disorder. Social and economic conditions have always been an obstacle for analysing outcome measures when estimating disability in relation to the surrounding environment. A particularly useful tool is the International Classification of Functioning, Disability and Health (ICF) proposed by WHO. The ICF encompasses all aspects of human health categorized in four domains: body functions (domain b), body structures (domain s), activity and participation (domain d), and environmental and personal factors (domain e)[3]. In our centre, a screening questionnaire derived from the ICF was developed for various conditions: stroke, traumatic brain injury, amyotrophic lateral sclerosis and, recently, MS [4–7].

CASE DESCRIPTION

The ICF core set profiling study was conducted on a 39-year-old woman, who is followed in our MS outpatient service and enrolled in the Italian Multiple Sclerosis Registry [8]. The patient was diagnosed with remitting-relapsing MS 12 years previously. The neurological picture is characterized by spastic paraparesis: the Medical Research Council (MRC) scale of muscle power scored 4 on lower limbs, spasticity and pain according to the Numerical Rating Scale (NRS) scored 5, and a visual assessment scale (VAS) scored 3. The woman presented with diffuse osteotendinous hyperreflexia, slight dysmetria in the limbs with left prevalence, dysuria and nocturnal cramps in the lower limbs. She can walk autonomously and for long distances with unilateral support, presenting dysarthria and modest ideomotor slowing. The patient had normal scores on the Montreal Cognitive Assessment (MoCA) and Depression Anxiety Stress Scales (DASS-21). She lives in an isolated rural area of Umbria, in central Italy, with her husband who helps her. She does not drive, and, a few years ago, also stopped horse riding. She has been treated for spasticity for over a decade with various drugs (baclofen, dantrolene and clobazam) with discomfort from side-effects and little performance improvement. She was on immunomodulatory therapy with teriflunomide 14 mg/day. The Expanded Disability Status Scale (EDSS) score wa s estimated at 4, corresponding to the best performance, as the patient was able to walk for about 300 m without aids when she was not fatigued. However, at certain times of the day, she needed unilateral support (EDSS 6), which allowed her to walk 1 km.

At the beginning of the observation period, MRI showed a pattern of multiple demyelinating supra and infra tentorial white matter damage, in the absence of active lesions.

In February 2017, treatment with delta-9-tetrahydrocannabinol/cannabidiol (nabiximols) was proposed with 6–8 puffs spread throughout the day after 15 days' titration. Other psychotropic drugs were suspended, and the patient was sent for evaluation by a physiatrist who delivered a rehabilitation program to improve gait. Before starting nabiximols treatment, the patient underwent evaluation using an edited version of the Brief ICF Core Set for MS. The assessment was divided into three sections evaluating three components: body functions (domain b), activity and participation (domain d), and environmental factors (domain e). More details are given in *Table 1*. We used this tool to investigate changes in physical symptoms and daily life functioning by comparing her condition beforetreatment with her condition after treatment with nabiximols .

Components	Examined items and corresponding ICF codes
Body functions (domain b)	Pain sensation (b280), UUrinary functions (b620), Muscle power functions (b730), Gait pattern functions (b770)
Activity and participation (domain d)	Problem solving (d175), Carrying out daily routine (d230), Walking (d450), Doing housework (d640), Complex interpersonal interactions (d720), Family relationships (d760), Economic self-sufficiency (d870), Recreational and leisure (d920)
Environmental factors (domain e)	Immediate family (e310), Extended family (e315), Friends (e320), Acquaintances, peers colleagues, neighbours and community members (e325), Health professionals (e355), Individual attitudes of immediate family members (e410), Health services, systems and policies (e580)

Table 1. Brief ICF Core Set for MS, edited version

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After 6 weeks of treatment with nabiximols, no adverse events were observed. At 12 weeks of treatment, screening scores were satisfactory (NRS: 3, VAS: 3, MoCA and DASS-21: normal) and the patient's autonomy had also increased. She went out more often, managed to take trips with her husband, had paraglided, and had expanded her circle of friends.

As regards body functions (domain b) assessed with the follow-up questionnaire at 12 weeks (*Fig. 1A*), urinary function (cumulative frequency and quality of urination), pain sensation (intensity of background and nocturnal paroxysms) and gait function (global in terms of speed and duration) had improved. muscle power remained unchanged. Regarding the activity and participation component (domain d), both capacity (what a person can do in a standardized environment, thus excluding all environmental factors) and performance (what a person actually does in her current environment with possible barriers and facilitators) showed improvement in complex interpersonal interactions (*Figs. 1B and 1C*). Regarding the environmental factors (domain e) component (*Fig. 1D*), friendships improved while individual or immediate family attitudes worsened.

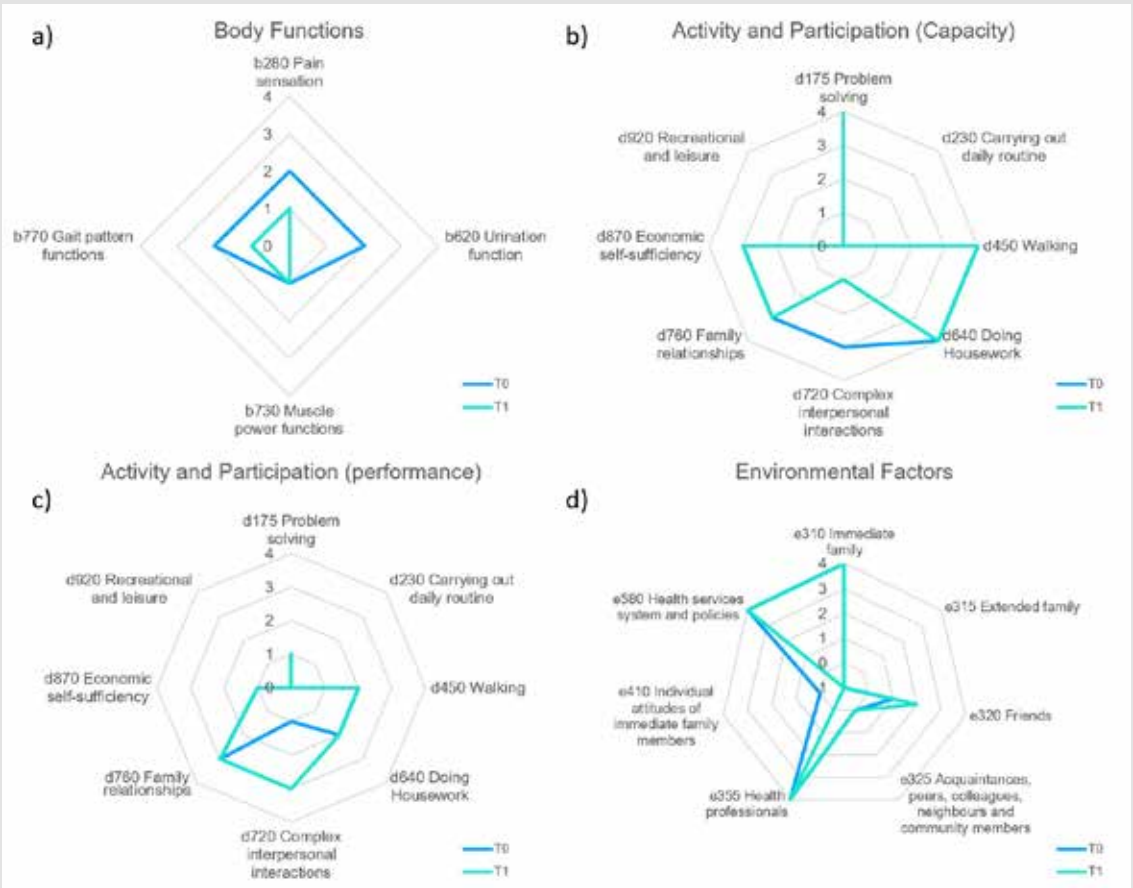

Figure1. (a) Body functions: Radar Chart with the four body functions examined at initial assessment (T0) and after 12 weeks (T1): b280 Pain sensation, b620 Urinary functions, b770 Gait pattern functions,and b730 Muscle power function .Complete integrity of these functions is scored 0, which increases to 4 with maximum impairment. It is also possible to classify not specified and not applicable (xxx.8 not specified, xxx.9 not applicable) with independent codes.

(b) Activity and participation (capacity): Radar chart of the capacity inherent in the eight activities examined at initial assessment (T0) and after 12 weeks (T1): d175 Problem solving, d230 Carrying out daily routine, d450 Walking , d640 Doing housework, d720 Complex interpersonal interactions , d760 Family relationships, d870 Economic self-sufficiency, and d920 Recreational and Leisure. Complete integrity of these activities is given a score of 0, which to 4 with maximum impairment. It is also possible to classify the not specified and not applicable (xxx.8 not specified,xxx.9 not applicable) with independent codes.

(c) Activity and participation (performance): Radar chart of the performance inherent in the eight examined at initial assessment (T0) and after 12 weeks (T1): d175 Problem solving, d230 Carrying out daily routine, d450 WalkinG, d640 Doing Housework, d720Complex interpersonal interactions, d760 Family relationships,d870 Economic self-sufficiency, and d920 Recreational and Leisure. Complete integrity of these activities is given a score of 0, which increases to 4 with maximum impairment. It is also possible to classify the not specified and not applicable (xxx.8 not specified, xxx.9 not applicable) with independent codes.

(d) Environmental factors: Radar chart of the seven environmental factors examined at initial assessment (T0) and after 12 weeks (T1): e310 Immediate family, e315 Extended family, e320 Friends, e325 Acquaintances, peers, colleagues, neighbours and community members, e355 Health professionals , e410 Individual attitudes of immediate family members, and e580 Health services system and policies. Integrity of these activities is given a score of 0 , which increases to 4 with maximum impairment.

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DISCUSSION

Spasticity control in MS may improve standardized outcome measures (e.g., walking speed). The rehabilitation treatment was delivered to our patient in an outpatient setting and limited to a few sessions to improve walking (maximum of 10 sessions twice a year). It was not possible to provide treatment in an intensive setting because the patient lived in a rural area of central Umbria with poor rehabilitation services. For these reasons, the aim of rehabilitation was to maintain residual motor quotas and autonomous walking for medium distances. Our patient had an emotional disorder with mild emotional lability (not detectable on normal rating scales). Structured evaluation of all cognitive functions was not carried out , and only the MoCA and DASS-21 scales were used. Carotenuto et al. found that higher physical and cognitive disability predicted nabiximols treatment discontinuation over 2 years in MS patients with spasticity [9]. For this reason, it would be useful to expand assessment of cognitive functions to evaluate longer treatment with nabiximols.

A broader assessment of capacity and performance may provide other benefits in daily life, activities and participation. An interview following administration of the ICF profile may offer a standardized framework for analysing overall functioning. Here, we applied the ICF profile to an MS patient, and determined the changes that took place after nabiximols treatment in body functions, activity and participation, and environmental factors. Concerning body functions (domain b), the patient reported an improvement in pain sensation (from medium to mild impairment), in urinary function (from medium to no impairment) and in gait function (from medium to mild impairment). Regarding activity and participation (domain d), she noticed an improvement in complex interpersonal interactions (from medium to mild impairment), both in capacity and in performance. Finally, with regard to environmental factors, friendships became a major facilitator, while individual or immediate family attitudes became a slight barrier. Nabiximols treatment was effective in improving some body functions and the ability to establish complex interpersonal relationships.

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Management of Spasticity in a Frail Multiple Sclerosis Patient During the COVID-19 Pandemic

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ABSTRACT

Spasticity is a common symptom in patients with multiple sclerosis, and it is associated with fatigue, anxiety, depression, pain and mobility and bladder dysfunction, negatively affecting patient quality of life. During the COVID-19 pandemic, several patients were not able to continue treatment for multiple sclerosis. Here, we present a case of a 45-year-old man who experienced symptoms that worsened after discontinuing nabiximols treatment during the lockdown. Within 2 months of treatment restoration, the patient showed a strong improvement in his overall clinical condition.

KEYWORDS

ST segment elevation, COVID-19, echocardiogram

LEARNING POINTS

- A good and constant adherence to a treatment schedule is essential to preserve its efficacy and to overcome a clinical worsening phase.
- During the COVID-19 pandemic, access to healthcare and treatments should be guaranteed to limit the consequences of reduced mobility due to social restrictions.

INTRODUCTION

Spasticity is a common symptom in patients with multiple sclerosis (MS), and it is strongly associated with symptoms that negatively affect patient quality of life[1–3]. In addition to physiotherapy, standard antispastic drugs are used in the treatment of spasticity[4]. Nabiximols (Sativex®) is an endocannabinoid system modulator consisting of 2 active ingredients, δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a ratio of 1:1, in an oromucosal spray formulation.

In Italy, during the coronavirus disease 2019 (COVID-19) pandemic declared in March 2020, disabled, elderly and frail people were advised to stay at home. Several patients could not continue treatment with nabiximols, such as in our case.

CASE DESCRIPTION

We describe the case of a 45-year-old man affected by relapsing-remitting MS, followed at the Multiple Sclerosis Center of the Tor Vergata University Hospital, Rome, Italy.

He was diagnosed with MS in 2011, after acutely developing right limb sensory and motor impairment. Over time, he progressively developed bilateral lower limb spasticity, not responding to a conventional antispastic drug (baclofen at the maximum dosage of 25 mg per day). Due to side effects (excessive weakness and mental confusion), it was not possible to increase the dosage.

In August 2019, neurological examination of the patient showed: I) Expanded Disability Status Scale (EDSS) 5.5; II) Numerical Rating Scale (NRS) 7; III) Ambulation Index (AI) 4; IV) Modified Ashworth Scale (MAS) at right lower limb 3 and at left 2 (*Table 1*).

Nabiximols treatment was started with a very slow increasing dosage of puffs up to 6 per day (2 in the morning, 2 in the middle of day and 2 before nighttime) without negative side effects. Several symptoms improved, including cramps/nocturnal spasms, pain and bladder disorders. The patient was again able to climb the stairs in his house and to walk on sandy ground after rehabilitation.

In January 2020, on neurological examination, the patient scores were: I) EDSS 5.0; II) NRS 4; III) AI 2; IV) MAS at right lower limb 2 and at left 0 (*Table 1*).

When the COVID-19 pandemic was declared in March 2020, the patient had motor and driving difficulties and lived far away from the MS Center with no caregivers.

In April 2020, the patient independently reduced the dosage to 1 puff in the morning and 2 puffs in the evening, scared of running out of treatment. Although he was advised by a phone consultation to at least continue home exercises in order to maintain good motility, we observed significant worsening of his neurological conditions when we visited him in June. He showed resumption of spasticity and the return of spasms and pain. In June, the patient scores were: I) EDSS 5.5; II) NRS 6; III) AI 3; IV) MAS at right lower limb 3 and at left 1 (*Table 1*). At this point, we suggested a new nabiximols titration scheme, with an increase in puffs in 2 weeks, up to 10 per day (at 8.00 am 2 puffs, at 11 am 2 puffs, at 2 pm 2 puffs, at 5 pm 2 puffs and at 10 pm 2 puffs). The patient had to do home exercises and stretching at least once in the morning or afternoon just after the puffs, in accordance with the closure of many rehabilitation institutes.

	T0	T1	T2	T3
EDSS	5.5	5.0	5.5	5.5
NRS	7	4	6	4
AI	4	2	4	3
MAS	Right 3 Left 2	Right 2 Left 0	Right 3 Left 1	Right 2 Left 1

Table 1. Timeline of patient's status

T0: August 2019; T2: June 2020; T3: November 2020; EDSS: Expanded disability Status Scale; NRS: Numerical Rating Scale; AI: Ambulation Index; MAS: Modified Ashworth Scale

By providing the patient with multiple packs, he had to follow this prescription until the next clinical visit. In the meantime, we were following up with the patient by periodic phone visits. After 2 months, the clinical conditions improved although he experienced adverse effects with the warm season; he experienced confusion after the after-lunch puffs. He was advised to take a nap for 30 minutes after administration, to drink more water and mineral salts and to exercise early in the morning.

In November 2020, he showed a reduction in lower limb stiffness, no painful spasms and quality of sleep improved (*Table 1*). During the same period, the patient did not feel safe to resume physiotherapy at the rehabilitation centre; he agreed to continue the mobility programme at home and maintained a dosage of 8 puffs per day. To guarantee therapeutic continuity, we have provided the patient with sufficient drug packages until the next scheduled visit.

DISCUSSION

Our patient started nabiximols for the treatment of lower limb spasticity associated with MS because he was not responding to standard antispastic drug medication. Nabiximols treatment improved the patient's quality of life and relieved his symptoms.

During the COVID-19 pandemic, the patient drastically reduced the dose of nabiximols, causing a retreat of the benefits achieved and a significant worsening of painful spasms. Our case confirms that nabiximols is a safe and effective therapy for MS-related symptoms in patients partially responding to standard approaches. It also shows the importance of a good and constant adherence to a treatment schedule to preserve efficacy and to overcome worsening of the clinical condition[5].

During the COVID-19 pandemic, access to healthcare and to symptomatic treatments, such as nabiximols, should be guaranteed to disabled people with MS to limit the consequences of reduced mobility due to social restrictions. Although partially reversible after a treatment restart, as in our case, spasticity worsening takes a long time to overcome and much effort by the patient, caregivers and the healthcare system.

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Multiple Sclerosis, Spasticity and Tele-Rehabilitation During the COVID-19 Pandemic

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ABSTRACT

Spasticity is one of the most frequently occurring symptoms of multiple sclerosis (MS) and requires a multidisciplinary team to manage it. During the COVID-19 pandemic, all non-essential elective procedures were stopped, and patients with MS discontinued physiotherapy with significant repercussions on spasticity and joint mobility. We present the case of a 56-year-old man who underwent a 30-day protocol of tele-rehabilitation in association with pharmacological therapy to manage spasticity. The use of common tools for tele-rehabilitation could improve the quality of care for people with MS during the COVID-19 pandemic.

KEYWORDS

Multiple sclerosis, spasticity, tele-rehabilitation, COVID-19, case study

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

Spasticity is one of the most frequently occurring symptoms of multiple sclerosis (MS) affecting more than 35% of patients. It is defined as a form of speed-dependent muscle hypertonia due to hyperexcitability of the tonic stretch reflex[1, 2]. The management of spasticity requires a multidisciplinary team, regular follow-ups and a combination of pharmacological and non-pharmacological interventions. Physiotherapy is the most common spasticity treatment but needs to be continuous and protracted over time[2].

During the lockdown due to the COVID-19 pandemic, all non-essential elective medical and surgical procedures were stopped. Consequently, patients with MS discontinued physiotherapy with significant repercussions on spasticity and joint mobility[3].

We developed a 30-day protocol of tele-rehabilitation consisting of physiotherapy in association with pharmacological therapy to improve the joint motility and spasticity of our patients.

CASE DESCRIPTION

We describe the case of a 56-year-old man suffering from relapsing-remitting MS since 1997, who in 2005 shifted to secondary progressive MS. From 2005 to 2007, he was on mitoxantrone, with the last administration in October 2007. In July 2013, he started glatiramer acetate.

Over the years, a progressive clinical deterioration occurred, particularly affecting walking, with an actual EDSS score of 6, compared to a stable brain and spinal magnetic resonance imaging lesion load. At the same time, the patient developed severe spasticity in the lower limbs: the Numerical Rating Scale (NRS) was 7, the Ambulation Index was 5 and the 10 m Walk Test was 45 seconds. He was treated with baclofen 25 mg and physiotherapy and remained stable until March 2020 when, due to the recent COVID-19 pandemic, Italy entered lockdown, and non-essential adult elective medical and surgical procedures were stopped. After 1 month, the patient experienced a progressive increase in spasticity due to abrupt discontinuation of physiotherapy, with a consequent reduction in autonomy, and the appearance of pain due to spasms and contractures. We then added oromucosal nabiximols (Sativex®) and started a 30-day tele-rehabilitation programme. The exercises were chosen to strengthen the functions of the trunk, namely the inclinatory, flexor, extensor and rotatory muscles. A progressive modular rebalancing approach was used, which allows the recruitment and strengthening of structures, joints and muscles to improve skills and their overall function (*Fig. 1*). The exercises were tailored to the patient's characteristics and performed twice a day. The patient was evaluated before staring the programme (T0) and after the 30-day treatment (T1) with the following scales: EDSS, NRS, Ambulation Index and 10 m Walk Test. Fatigue was evaluated using the Fatigue Severity Scale (FSS), and quality of life was evaluated using the 36-Item Short Form Survey (SF-36).

At T0, the EDSS was 6, NRS was 7, Ambulation Index was 6 and

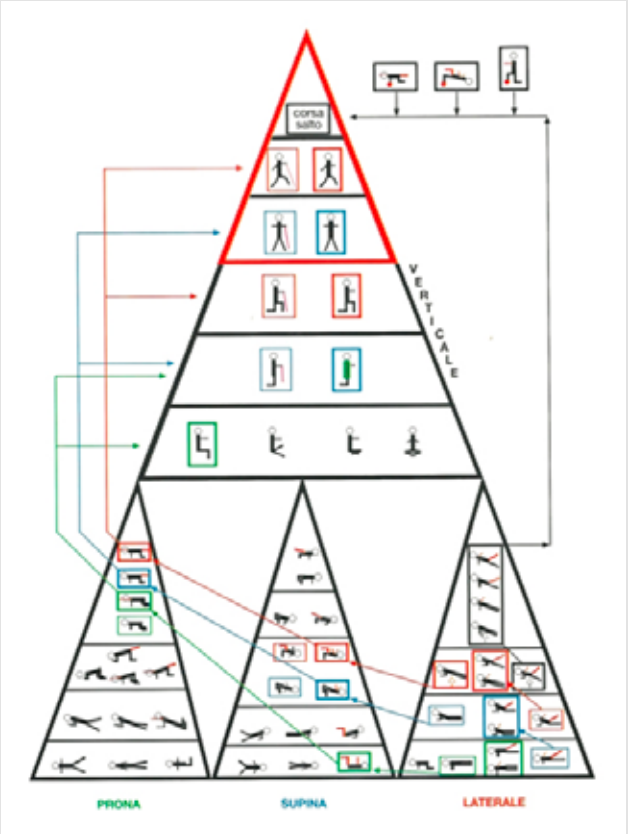

Figure 1. Example of the progressive modular rebalancing approach

the 10 m Walk Test was 45 seconds. The mean FSS was 56 and the mean SF-36 was 84. The dosage of nabiximols was increased up to 7 puffs per day with no side effects, and, after 30 days of the tele-rehabilitation programme, the NRS score was reduced by 3 points. The Ambulation Index and the 10 m Walk Test remained constant, while the mean FSS was 48, and the SF-36 was 91.

DISCUSSION

The current COVID-19 pandemic has resulted in a number of difficulties for patients with MS. Many people with MS were forced to stop their medical services with noticeable worsening of symptoms[3] For this reason, tools for tele-neurology examination (including components of neurological examination that can be assessed through video), patient-reported outcome measures and digital technology have been developed to facilitate interaction with patients[4].

Tele-rehabilitation allows real-time (or synchronous) interaction; all users (health professionals and patients) can exchange information instantaneously through media such as the telephone, virtual reality or video-conferencing platforms. The use of tele-rehabilitation can also be pragmatic and malleable, depending on the situation and needs of the patient and healthcare services alike.

Clinical studies indicate that spasticity is experienced very subjectively by patients, and individuals give different meanings to this symptom and how much it affects their lives. In addition, spasticity is associated with other symptoms, including an increase in the number of painful spasms, which can be triggered by movement, tactile stimulation or hyperventilation. Spasticity is also associated with increased frequency of sleep disorders, resulting from pain and contractions[5]. For this reason, therapy for spasticity should be personalized, combining non-pharmacological and pharmacological interventions[5]. From this viewpoint, the delta-9-tetrahydrocannabinol:cannabidiol (CBD) oromucosal spray nabiximols represented a valid add-on therapy for our patient. The ability to vary the number of puffs per day allowed us to choose the most appropriate dosage depending on the patient's needs. The best result in our patient was obtained on the NRS score for spasticity. This scale represents a completely subjective parameter for the patient, who assesses the severity of spasticity on a daily basis and according to his or her own judgment, to give a score between 0 and 10. Our patient reported a subjective improvement in muscle stiffness and an improvement in sleep quality. The addition of tele-rehabilitation seems to have strengthened the benefits of nabiximols, and the reduction in symptom severity perceived by the patient played an important role in the psychosomatic sphere and in his quality of life. Nevertheless, the effect on objective parameters, such as EDSS, was small, indicating that both nabiximols and tele-rehabilitation do not seem to have a relevant effect on disability-related spasticity.

In conclusion, the management of COVID-19 is the current healthcare priority in MS patients. The use of common tools for tele-neurology and tele-rehabilitation could improve the care quality for people with MS, because this avoids the interruption of outpatient services which could severely impact patient health assistance.

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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

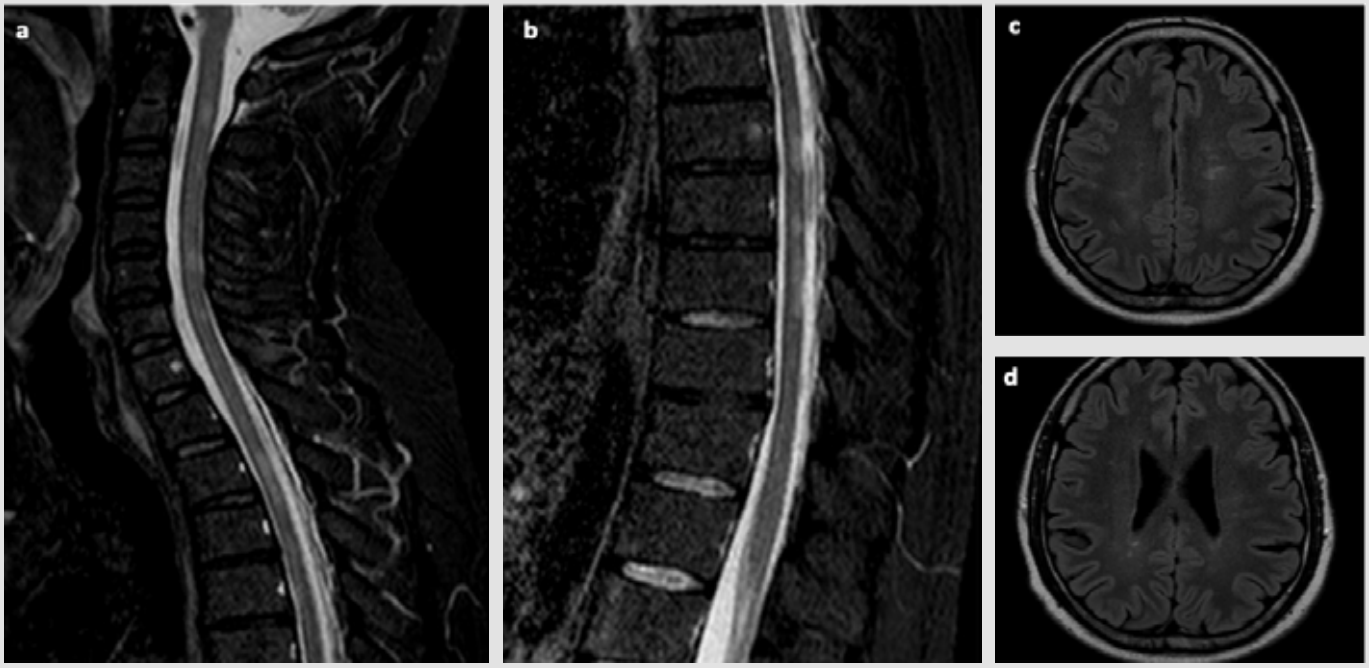

Figure 1. Spinal cord MRI showing cervical (a) and dorsal (b) demyelinating lesions and brain MRI showing lesions compatible with demyelinating/inflammatory disease (c, d)

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.

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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Improved Walking Ability in Early Treatment with Nabiximols

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ABSTRACT

We describe the case of a 46-year-old man with a 16-year history of relapsing- remitting multiple sclerosis, who, after a long period of clinical stability, manifested reduced walking ability and nocturnal painful spasm. Different therapeutic approaches were tried, such as baclofen and 4-aminopyridine, with an unsatisfactory response and a negative impact on the patient's quality of life. After introduction of nabiximols therapy, the patient showed improvement in walking with less fatigue in longer distances and a subsequent improvement in quality of life.

KEYWORDS

Multiple sclerosis, gait impairment, early treatment

LEARNING POINTS

- Efficacy of nabiximols in improving walking ability and reducing leg spasms.
- Slow titration reduces nabiximols side effects.
- Efficacy of nabiximols in improving quality of life.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, predominantly immune-mediated disease of the central nervous system (CNS), and 1 of the most common causes of neurological disability in young adults globally. MS is characterized by clinical symptoms resulting from lesions in the brain, spinal cord or optic nerves, which can affect balance, gait and fall risk. Lesions accumulate over time and occur in different areas of the CNS causing symptoms including weakness, spasticity and fatigue, as well as changes in sensation, coordination, vision, cognition and bladder function. Thus, it is not surprising that imbalance, gait dysfunction and falls are common in people with MS[1]. The majority of patients have abnormalities of postural control and gait even early in the disease course. Patients with MS represent a diverse and heterogeneous population varying in terms of disease type, its severity and progression and with regard to the wide range ofpresenting symptoms. Consequently, detailed experience with individual patients is important to provide examples of therapy to specific patient types.

CASE DESCRIPTION

A 46-year-old man with a history of relapsing-remitting MS manifested reduced walking ability and nocturnal painful spasms. The first symptoms of the disease appeared in 2004 with acute onset of dizziness and visual disturbances. A diagnosis of MS was made in 2005, when he was admitted to a neurological clinic. Magnetic resonance imaging (MRI) of the brain and spinal cord revealed multiple white matter lesions disseminated in periventricular, infratentorial, juxtacortical and spinal regions (C2-C3). Cerebrospinal fluid analysis showed the presence of oligoclonal bands. The patient started treatment with IFN-β1a therapy (3/week), and he had been treated for 8 years when he experienced a disease relapse with brain MRI demonstrating 3 new enhancing lesions. Therefore, in 2013, treatment with the monoclonal antibody natalizumab was started and clinical and neuroradiological stability was achieved. This was later suspended in 2015 due to detection of John Cunningham virus (JCV) positivity. Therapy with dimethyl fumarate was then started. Over the years, the patient presented with a progressive reduction in his walking ability, nocturnal painful spasms and he showed a mild spasticity in the right leg. Different therapeutic approaches were tried, such as baclofen 12.5 mg twice a day and 4-aminopyridine 4 mg twice a day, with a poor response.

In February 2016, his Expanded Disability Status Scale (EDSS) was 4. The Ambulation Index (AI) was 3, the Modified Ashworth Scale was 2 and the Numeric Rating Scale (NRS) was 5. Walking ability was tested by the 6-Minute Walk Test (6MWT), evaluating walking endurance: he walked for 340 metres during the 6MWT.

Due to these clinical manifestations, we decided to start treatment with the tetrahydrocannabinol (THC):cannabidiol (CBD) oromucosal spray (nabiximols, Sativex®). Nabiximols was added with gradual titration, in order to avoid side effects. After 1 month, the patient's treatment response was evaluated, and he reported an improvement in his ability to walk and a reduction of painful spasms with a dosage of 4–5 puffs a day. His EDSS was 4, AI was 2, Modified Ashworth Scale was 1, NRS was 3 and he walked for 380 metres in the 6MWT. After 6 months, the patient reported reduced fatigue, improved mobility and autonomy in walking for a longer distance without stopping.

In addition, his mood and quality of life were improved. At present, the patient is settled at a dose of 4–5 puffs daily with clinical stability.

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DISCUSSION

This case shows the efficacy of early nabiximols treatment in improving walking ability in a patient with initial gait disturbance. Sativex® 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, while CBD at higher than natural concentrations may limit the psychoactive effects of THC. Dizziness and fatigue are amongst the most common side effects; optimal up-titration strategies can, however, minimize side effects. Nabiximols is an option for use as an add-on medication for the management of moderate to severe generalized spasticity and related symptoms, such as spasms, pain, poor sleep quality and urinary dysfunction, in patients with MS resistant to common antispastic drugs.

The efficacy and safety of nabiximols is supported by data from phase III clinical trials[2] and has been further supplemented by a growing database of real-world experiences in patients with MS-related spasticity[3].

A small Italian study showed that nabiximols is able to improve stride speed, cadence and length[4].

Moreover, as observed in some clinical trials, relevant improvements in quality of life and in activities of daily living can be achieved using the THC:CBD spray in patients with MS spasticity, allowing them to engage in everyday activities.

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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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Combined Management of Multiple Sclerosis-Related Spasticity

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ABSTRACT

Spasticity is one of the most frequently occurring symptoms associated with multiple sclerosis (MS). Pharmacological therapy and interventional procedures are the main approaches to treatment of MS spasticity. Nabiximols is an oromucosal spray used as an add-on treatment for unresponsive spasticity in patients with MS. The COVID-19 pandemic has had a major impact on the management of patients with chronic neurodegenerative conditions. During this period, many people have had difficulty accessing hospitals or rehabilitation facilities.

We report a case that shows the efficacy and tolerability of the combination of pharmacological treatment and neurorehabilitation in the treatment of MS-related spasticity.

KEYWORDS

Spasticity, multiple sclerosis, nabiximols, neurorehabilitation

LEARNING POINTS

- The combination of pharmacological treatment and neurorehabilitation is effective and better tolerated in the treatment of MS-related spasticity.
- During the COVID-19 pandemic, telemedicine allowed integration of the provision of healthcare in the absence of an in-person visit.
- Nabiximols in association with an intense neurorehabilitation programme allowed improvement of the patient's neurological outlook.

INTRODUCTION

Spasticity is a common chronic symptom in patients with multiple sclerosis (MS) that increases in prevalence and severity as the disease progresses[1]. MS spasticity is associated with other symptoms, such as painful spasms, bladder dysfunction, pain, sleep disorders and depression with a severe impact on patient quality of life[2,3].

Pharmacological therapy and interventional procedures (for example, physiotherapy) are the main approaches for treating MS spasticity[1].

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, in addition, their prolonged use is associated with numerous adverse reactions[3].

Nabiximols is an oromucosal spray, containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), that is commonly used as an add-on treatment for unresponsive spasticity in MS patients. Nabiximols contains THC and CBD in a 1:1 ratio. THC binds to cannabinoid receptors, the activation of which modulates muscle tone. The high concentrations of CBD are proposed to reduce the psychoactive properties of THC. Several real-world studies have demonstrated the efficacy of nabiximols in cases of moderate to severe MS-related spasticity[2–4]. Common side effects of nabiximols include dizziness and tiredness, whereas psychiatric symptoms, such as anxiety, changes in mood and paranoid ideas, have rarely been reported[4].

Moreover, physiotherapy interventions are important non-pharmacological tools in the treatment of spasticity in MS, as neurorehabilitation is intended to maintain the muscle length, prevent contracture and change the mechanical properties of the musculoskeletal system and plasticity within the central nervous system[2].

We report our experience of one case where the management of MS-related spasticity was multidisciplinary.

CASE DESCRIPTION

A 51-year-old male, affected for 5 years with primary progressive MS, first started disease-modifying therapy with ocrelizumab in 2018. His family and personal history were unremarkable, and he was not diagnosed with any psychiatric illness, including major depression or bipolar disorders. He had never been treated with specific psychoactive drugs. Neurological examination showed moderate to severe paraparesis and hypoaesthesia prevalent on the right side, tetrahyperreflexia and urinary urgency. Walking was limited to a few steps with bilateral support and his Expanded Disability Status Scale (EDSS) score was 7.5. In addition, the patient presented a moderate to severe spasticity and intense neuropathic pain in the legs, with a Numeric Rating Scale (NRS) score for spasticity of 8 and an Ambulation Index (AI) of 7. These symptoms were partially responsive to baclofen 50 mg daily and pregabalin 150 mg daily.

In July 2018, he was prescribed nabiximols (Sativex®) to improve his severe spasticity, until reaching a daily dosage of 5 puffs (2.7 mg

of THC and 2.5 mg of CBD per single dose), gradually discontinuing baclofen. At the 3-month follow-up, he had a good response to the treatment, with the NRS score reduced to 5.

Nabiximols, in association with an intense neurorehabilitation programme, allowed improvement of the patient's neurological outlook until the national health emergency in March 2020 (COVID-19 pandemic).

During the period of national lockdown, the patient was unable to undergo rehabilitation for over 3 months. Therefore, the patient had a progressive worsening of clinical outcomes.

During telemedicine follow-up, a good response to the treatment was shown with an increase of nabiximols to 10 puffs daily. Nevertheless, at the 1-month follow-up, the patient presented behavioural changes with alternations of manic and depressive phases, and suicidal ideation, so nabiximols was reduced to the starting dosage (5 puffs daily) with remission of psychiatric symptoms within a few days. Baclofen 25 mg was reintroduced. The patient also started neuromotor rehabilitation as soon as possible.

Currently, the patient has good control of the symptoms of spasticity and neuropathic pain thanks to the integration of drug therapy and rehabilitation.

DISCUSSION

The complexity of spasticity poses several problems for its clinical management and has a strong impact on the patient's quality of life and, in particular, on normal daily activities.

In this context, nabiximols represents a valid therapeutic option when conventional therapies have been ineffective or are not tolerated. In addition, compared with existing therapies, nabiximols has the advantage of being a non-invasive treatment for patients[3].

Furthermore, recent studies have shown how patients undergoing neurorehabilitation programmes combined with nabiximols had a higher probability of having a clinically relevant response, compared to those treated only with nabiximols[2].

However, the COVID-19 pandemic is strongly impacting all domains of our healthcare systems, including neurorehabilitation. In Italy, medical activities were postponed, allowing shifting of staff and facilities to intensive care, with neurorehabilitation limited to time-dependent diseases. Hospital access to people with chronic neurodegenerative conditions, such as MS, has also been postponed. Neurorehabilitation cannot be delayed or interrupted for people with chronic disabilities and for patients with chronic progressive diseases who require constant monitoring and care[5].

During this period, the development of telemedicine platforms has made it possible to integrate the provision of healthcare in the absence of an in-person visit.

Spasticity management requires a complex approach. Our case shows how the combination of pharmacological treatment and neurorehabilitation is effective and better tolerated in the treatment of MS-related spasticity.

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When the Benefit is Unexpected: Improvement in Nystagmus During Cannabinoid Treatment

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ABSTRACT

A 40-year-old Italian man was diagnosed with multiple sclerosis through symptoms of weakness in the lower limbs, nystagmus and oscillopsia confirmed by neurological assessment. Vision disturbances progressively worsened, becoming disabling for the patient. No proven treatment was effective. However, when the patient started therapy with delta-9-tetrahydrocannabinol/cannabidiol (nabiximols), he noticed a significant improvement in nystagmus, as well as in spasticity.

KEYWORDS

Multiple sclerosis, spasticity, nystagmus, delta-9-tetrahydrocannabinol/cannabidiol

LEARNING POINTS

- Nystagmus is a frequent neurological sign and symptom in patients with multiple sclerosis; however, to date, we do not have a specific therapy for this.
- Quite unexpectedly, therapy with nabiximols resulted in an immediate improvement of nystagmus that was maintained over time.
- It would be useful to investigate the improvement of nystagmus in patients treated with nabiximols for spasticity.

INTRODUCTION

Multiple sclerosis (MS) is a chronic degenerative disease, which affects young adults. The management of a patient with MS is complex and requires a multidisciplinary approach, aimed at ensuring optimal control of the disease, but also, at improving the patient's quality of life. The latter is strongly conditioned by spasticity, urinary disorders and fatigue. Even nystagmus, although occurring less frequently, is a symptom that can affect quality of life. Spasticity is 1 of the most frequent symptoms that are subject to early intervention[1]. It requires an early and appropriate therapeutic strategy[2] as it interferes with the mobility of the lower limbs and daily activities[3].

CASE DESCRIPTION

A 40-year-old Italian man, affected by RR-MS since 2014, due to weakness in the lower limbs, nystagmus and oscillopsia, reported that the visual disturbances, described as "flicker", had progressively worsened, becoming disabling. Neurological assessment one year after the onset showed a worsening of the nystagmus, present in all directions of the gaze and in the primary position.

He underwent ophthalmologic evaluation, visual evoked potential testing, optical computed tomography and visual field assessment with normal results.

In November 2016, the patient also reported that visual disturbances related to focus and pendular nystagmus were accentuated in the evening and when he was tired. Diplopia was not reported; nevertheless, we conducted serology testing for acetylcholine receptor (ACHR) and muscle specific tyrosine kinase (MuSK) antibodies to exclude overlap with myasthenia gravis. Both gave negative results.

The patient then underwent a complete neuro-ophthalmological study and also tried prismatic lenses, without benefits.

In the summer of 2017, the patient began to complain of increased stiffness in the lower limbs often with clonus and spasms. He subsequently started therapy with oral antispastics (baclofen, 25 mg/day), which the patient took for a few months with partial benefits.

Therefore, in January 2018, we implemented therapy with a mix of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 ratio (nabiximols; Sativex®) with improvement of pain and spasticity. The patient undertook the treatment and did not report side effects. He continues the treatment with an average intake of 6 puffs per day, with dose adjustments as needed.

When the patient began therapy with nabiximols, he reported a noticeable improvement in nystagmus and spasticity.

This advantage was also confirmed by neurological assessment.

DISCUSSION

Nystagmus is an involuntary to-and-fro movement of the eyes that can result in a reduction in visual acuity and oscillopsia. The mechanisms that cause nystagmus are better understood for

acquired periodic alternating nystagmus than for acquired pendular nystagmus. Effective pharmacological treatments to reduce nystagmus are limited, as there have been very few randomized controlled trials. For this reason, most pharmacological treatment options for nystagmus remain empirical. To date, there is little scientific evidence to make firm recommendations for treatment: gabapentin or memantine for acquired pendular nystagmus, baclofen for periodic alternating nystagmus[4].

A previous study reports the use of cannabis for nystagmus in a patient with MS. *Schon et al.* noted that only by smoking the cannabis was the pendular acquired nystagmus of MS attenuated[5]. Although the beneficial effects of cannabis on congenital nystagmus have been recognized for many years by a small number of people with this condition, this latter observation raises the possibility that the drug could be used in different types of acquired nystagmus where damping the oscillations can have the beneficial effect of reducing or eliminating the debilitating effects of oscillopsia[5]. The patient with MS had tried oral nabilone and cannabis oil capsules before achieving control of his nystagmus by inhaling cannabis with the THC level exceeding 80 µg/l[5].

In a recent review, *Wang and Danesh-Meyer* reported preliminary evidence from case reports and animal studies, which have suggested that cannabinoids could be used for ocular superficial lesions and congenital and acquired nystagmus. In this work, the authors examined studies on the association between cannabis and oculomotor deficits. Several studies have found no effect on vision disorders, such as saccadic movements or nystagmus, after smoking cannabis. However, two clinical cases have documented the suppression of acquired pendular nystagmus in a patient with MS and in a patient with congenital nystagmus after inhaling cannabis[6].

Our case is the first report of nystagmus control by an oral cannabinoid formulation containing THC and CBD in a 1:1 ratio. Our view is that the muscle-relaxing effects of cannabinoids may explain their effectiveness in controlling nystagmus. However, we cannot exclude a central action involving nerve excitability.

In conclusion, to improve treatment, further research is required to understand the aetiology of different types of nystagmus, and future studies should involve standardized measurements of waveform frequency, amplitude and peak velocity in nystagmus.

To date, nabiximols is indicated for treatment of spasticity, pain and bladder urgency. Future research could help us understand more about the benefits and risks associated with cannabis, to also treat other MS symptoms.

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

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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.

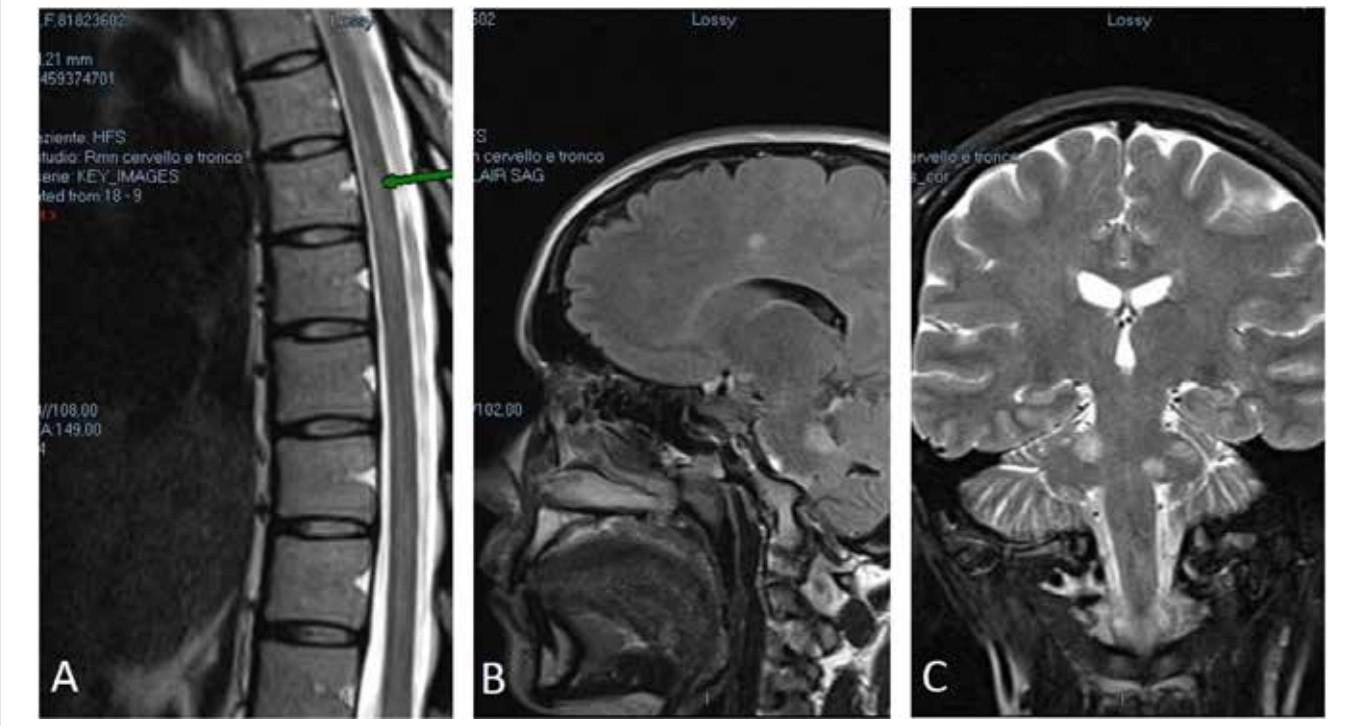

Figure 1. Magnetic resonance imaging during post-partum relapse. (A) New T2 lesions on D2–3. (B and C) New pericallosal and brainstem T2 lesions

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

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	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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Efficacy of Nabiximols in Reducing Pain and Spasticity in Primary Progressive Multiple Sclerosis

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ABSTRACT

Spasticity and its related symptoms, such as muscle stiffness, spasms and pain, are present in 60% of multiple sclerosis patients. We present the case of a 66-year-old woman with a benign form of primary progressive multiple sclerosis who had symptoms of spasticity, leg weakness and pain at disease onset. After 10 years of disease and insufficient response to antispastic and pain drugs, she was started on nabiximols oromucosal spray with good efficacy, safety and tolerability. The patient is now treated with 4 puffs per day and, after 6 years, the drug is still effective in relieving pain and improving sleep.

KEYWORDS

Nabiximols, multiple sclerosis, pain, spasticity, case report

LEARNING POINTS

- Nabiximols can represent a valid treatment option for spasticity and related pain, and is safe and well tolerated.
- Nabiximols also has a positive impact on mobility, mood, sleep and quality of life.
- The efficacy of nabiximols is maintained over time.
- The role of nabiximols in reducing pain can be extended to other clinical conditions including non-cancer pain or neuropathic pain.

INTRODUCTION

Spasticity and its related symptoms, such as muscle stiffness, spasms and pain, are present in 60% of multiple sclerosis (MS) patients, but are frequently undertreated and not properly monitored[1]. Pain was recently found to be the most common comorbidity in MS patients who are older than 60 years[2]. A recent Italian consensus study concluded that, based on available data, a strong recommendation for spasticity treatment can be given only to the use of nabiximols, intrathecal baclofen and intramuscular injection of botulinum toxin (BT)[3].

CASE DESCRIPTION

We describe the case of a 66-year-old woman with a diagnosis of primary progressive MS, which started in April 2004 at 50 years of age with the progressive onset of lower limb weakness, spasticity with muscle stiffness and systemic pain associated with back pain. In June 2005, she was admitted to the Neurological Department at Policlinico San Donato in Milan, where she underwent brain and spinal cord MRI showing the presence of T2 hyperintense lesions in periventricular and juxtacortical regions. No lesions were visible in the spinal cord, while cerebrospinal fluid examination showed the presence of specific oligoclonal bands absent in serum (pattern II), and she was diagnosed with MS.

A few months later, she experienced urinary urgency and worsening of spasticity and pain in the lower limbs, which was more evident on the right side, causing difficulty in walking and climbing stairs. She started tizanidine 1 mg daily and lorazepam 1 mg prior to bedtime. In September 2005, she also developed Lhermitte's sign; therefore, she started lamotrigine 200 mg twice a day with partial efficacy.

She was periodically readmitted to Policlinico San Donato from 2009 to 2014 for high-dose steroid treatments (methylprednisolone 1 g for 5 days) for periodic subacute worsening of the usual symptomatology. Pain was described as chronic, a sense of tightness in the lower limbs associated with occasional muscle spasms and exacerbated by physical exercise. In November 2013, gabapentin 400 mg 3 times per day was added to her prescription without efficacy. Repeated brain and spinal cord MRI results did not show any change.

Neurological examination in November 2013 showed diplopia in the bilateral extreme gaze, lower right facial nerve palsy, mild drift and difficulty in performing fine movements on the right side, drift of lower limbs with weakness more evident at proximal than distal muscles, low dysmetria in the right upper limb, difficulty in performing tandem walk, symmetric increase of reflexes in the 4 limbs, bilateral Babinski sign, Lhermitte's sign and hypoaesthesia at lower limbs (right>left). The Expanded Disability Status Scale (EDSS) was 3.5 (functional systems: pyramidal (P): 3; cerebellar (C): 2; sensory (S): 2; sphincteric (Sf): 1).

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In June 2014, the patient started treatment with nabiximols with acute improvement in pain and spasticity. In addition, sleep and mood were improved according to the patient. The drug was also safe and well tolerated by the patient. The Numerical Rating Scale (NRS) for spasticity was reduced from 8 to 1. The dosage was increased up to 8 puffs daily (times: 8, 10, 12 AM, 2, 6, 8, 10 and 12 PM). Neurological examination in September 2014 showed a reduction in spasticity in the lower limbs, weakness and reflexes, with an EDSS lowered to 2.5. The patient also suffered from spondyloarthrotic myelopathy, and spinal cord MRI demonstrated intervertebral disc herniation at C5–C6 and L3–L4. In June 2015, she had a surgical intervention for anterior and posterior vertebral arthrodesis at L3–L3 with a mild impact on pain.

In July 2019, the patient reduced nabiximols to 6 puffs and, eventually, to 4 puffs per day (1 in the morning and 3 in the afternoon/evening). From September 2020 to October 2020, she was given a daily diary on nabiximols efficacy: NRS for spasticity was 1, and clinical improvement was assigned to pain and sleep quality. She underwent new brain and spinal cord MRI in February 2020, which was also unchanged. At the last neurological visit in November 2020, she had an EDSS of 2.5.

DISCUSSION

A recent trial, SAVANT, compared nabiximols as an add-on therapy to optimized standard spasticity treatment in patients with moderate to severe MS spasticity, showing that the proportion of clinically relevant responders after 12 weeks was significantly greater with nabiximols than with placebo (77.4 vs 32.1%; $p<0.0001$)[4]. Moreover, a study on almost 2,000 MS patients found that the strongest predictors for quality of life in MS were depression, pain and walking difficulties, irrespective of MS phenotype[5], further supporting the importance of reducing pain and spasticity for quality-of-life improvement. It is worthwhile to mention that nabiximols is not the only drug that can improve spasticity; for example, a recent Italian multicentre cross-sectional study on 386 MS patients confirmed the safety of BT injections[6]. In addition, a multidisciplinary approach to spasticity and pain is warranted, combining pharmacological and non-pharmacological strategies including physiotherapy, for example.

It is difficult to assess at which level in this patient the efficacy of the drug on pain was mediated by its efficacy in reducing spasticity. This issue is particularly relevant since in most cases spasticity and pain have important implications with respect to difficulties in motion, impaired activities of daily living or problems with hygiene and daily assistance in later phases of the disease, which need to be considered as a whole.

In conclusion, the clinical case of this patient with a late-onset benign course of primary progressive MS supports the efficacy of nabiximols in reducing pain-related spasticity, weakness and impaired walking ability and in improving the sleep and quality of life of MS patients with no concerns regarding safety and tolerability. It also supports the persistence of efficacy over time, which was 6 years in this patient.

As a conclusion, it needs to be mentioned that the efficacy of nabiximols in pain relief can be extended to other clinical conditions, including chronic non-cancer pain[7] or neuropathic pain[8].

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Multiple Sclerosis, Spasticity and Nabiximols: A User Experience

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ABSTRACT

This clinical case concerns a 54-year-old woman with onset of multiple sclerosis at the age of 21 years, a long remission for 12 years and a subsequent resumption of disease activity partially contained by therapies. Not surprisingly, the increased burden of disability and impairment of quality of life is related not so much to the severity of the neurological damage as to the spasticity associated with the disease, which is responsible for severe alterations to posture control and trunk instability.

A complex therapeutic strategy pathway started combining physical and pharmacological treatment, which reached a delicate balance with the introduction of nabiximols.

KEYWORDS

Multiple sclerosis, spasticity, pain, nabiximols, case report

LEARNING POINTS

- Relevance of symptomatic treatment for quality of life in multiple sclerosis.
- Nabiximols is effective in the treatment of spasticity and pain in multiple sclerosis.
- Therapeutic introduction of nabiximols may require a careful assessment of the clinical picture and patient characteristics.

INTRODUCTION

Based on randomized, placebo-controlled, double-blind trials, nabiximols has been approved as an add-on therapy to treat symptoms of spasticity in patients with multiple sclerosis (MS). However, the occurrence of side effects, such as cognitive and psychiatric disorders, has burdened physicians with doubts and uncertainties. In this clinical case, the use of the drug within an appropriate framework led to increased physical and social activities for the patient and improved the quality of life.

CASE DESCRIPTION

A 54-year-old woman was diagnosed with relapsing-remitting MS according to the Poser criteria[1] in 1987, after her first pregnancy. The disease remained in clinical and paraclinical remission until 1999, and in 2000 the patient began therapy with interferon beta-1a. However, acute events persisted and clinical recovery between the relapses was incomplete until it stabilized on an Expanded Disability Status Scale (EDSS) of 4.0.

In 2009, after the patient's second pregnancy, she experienced a further worsening of the disease, with a partial recovery with intravenous corticosteroids (EDSS 4.5) and began therapy with natalizumab, which she had to suspend in 2011 due to a positive serology result for JC virus. Since then, she has been in therapy with fingolimod. In recent years, the patient showed mild spastic hypertonia in both legs and dysaesthesias, which were initially responsive to baclofen.

Despite extended treatment (baclofen 75 mg daily and gabapentin 1,200 mg daily), the patient experienced gradual worsening of painful spasticity of the lower limbs of a moderate/severe degree with posture control disorder. As a consequence, in 2020 the patient developed remarkable anteversion of the hips, lumbar hyperlordosis compensation, cervical lordosis flattening and then entered into a vicious cycle of exacerbation of symptoms, which led to worsening spasticity and shortening of iliopsoas, quadriceps and piriformis muscles. This in turn resulted in a severe increase in painful rigidity of paravertebral muscles with trunk instability.

The worsening of spasticity produced daily living impairment, decreased the patient's quality of life and remarkably reduced her walking ability, beyond what would be expected from an EDSS of 4.5.

Nabiximols, a phytocannabinoid combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 ratio, was added as a therapy in March 2020, but after 1 week, at a dose of 5 puffs per day, the intolerable appearance of side effects (sleepiness, dizziness, confusion and disorientation) led to suspension of this medication.

The patient complained of pain and disabling rigidity of paravertebral muscles, which could not be counteracted with intramuscular steroids. Bilateral infiltrations of the paravertebral muscles with triamcinolone and lidocaine were initially effective, but the beneficial effect had a progressively shorter duration.

Physical therapy with treatment of vertebral decompression by

the use of appropriate postures, reduction of lumbar lordosis and lumbosacral pompage and decontraction of the paravertebral masses was proposed in addition to therapy with baclofen 75 mg daily and gabapentin 1,200 mg daily.

The patient experienced quick pain relief, improved posture and gained motor movement and autonomy. However, these positive results were unstable, with unpredictable fluctuations, and gradually not lasting.

Nabiximols therapy was reintroduced at a dose of 1 puff per day with an increase in dose every 10 days up to 3 puffs per day.

With a slow titration of the drug side effects, dizziness and confusion were mild and resolved in a month. Pain and spasticity reduced in frequency and intensity and were controlled further with better fatigue management by planning of activities with day/week plans and control of energy reserves with rest breaks.

With the introduction of these articulated pharmacological, physiotherapeutic and deconditioning strategies, the patient improved her motor skills and autonomy with a considerable gain with respect to daily living and quality of life.

DISCUSSION

MS is a progressive, chronic disease with variable evolution and low predictivity of prognosis, frequently associated with even severe disability. To this broad biological spectrum of disease phenotypes, the consolidated use of immunomodulating/immunosuppressive therapies further expands the heterogeneity and stratification in the patient population, especially through the lengthening of the progression times towards disabilities.

In this scenario, for patients the degree of disability is not the only element of impairment of the quality of life and limitation of their daily activities.

Patients with mild/moderate spasticity and pain, especially if associated, experience withdrawal from social life and limitations in habitual physical activities, falling into distress and depression[2].

Extensive empirical experience suggested that Cannabis preparations have medical benefits. The characterization of products derived from Cannabis plant flowers (the psychotropic THC and the non-euphoric CBD) and the identification of the cannabinoid receptors (CB1, expressed abundantly in the brain and CB2, expressed especially in the immune system) created the conditions for the development of cannabinoid-based drugs[3,4]. Endogenous ligand lipids were subsequently identified for CB1 and CB2 receptors and for enzymes related to their metabolism. Together, the 2 receptors, the endogenous ligands and the metabolic enzymes constitute the endocannabinoid system. The discovery of this system paved the way for new therapy studies to investigate the activity, efficacy and safety of cannabinoids. In this context, the approval of nabiximols for the treatment of spasticity in MS highlights the relationship between the endocannabinoid system and neurological diseases and is an important starting point for the development of Cannabis research. In fact, the horizon is currently being further enriched with the discovery of an expanded endocannabinoid system, the endocannabinoidome, a wider endocannabinoid-related network, in overlap with other pathways and alternative metabolic processes[4,5]. This complex system projects towards the development of drugs that act selectively on the endocannabinoid system.

It is likely, from studies in animals and on patients with MS, that the modulation of endocannabinoid signalling represents an adaptive response to counteract the symptoms of the disease.

The existence of an endocannabinoidome may explain the effectiveness of reduced doses of nabiximols in this clinical case, such as a supra-additive therapeutic effect in the modulation of unidentified receptor targets and sites of action[6]. These clinical observations are a stimulus to understand the complex mechanism of action of cannabinoids. The challenge becomes the identification of specific pathways in neurological disorders within an expanded and redundant system.

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Effectiveness of Cannabinoids in Treating Symptoms of Bladder Dysfunction Associated with Spasticity in Multiple Sclerosis

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ABSTRACT

Nabiximols is an approved add-on therapy for multiple sclerosis (MS)-related spasticity for patients non-responsive to common therapies. It is also more effective in treating bladder dysfunction with more moderate side effects compared with conventional drugs. We present the case of a 48-year-old woman with secondary progressive MS who was treated with nabiximols and who showed significant improvement in bladder complaints. This case focuses on the possibility of prescribing this treatment to patients with symptoms other than spasticity. In addition, it highlights the crucial role of bladder dysfunction improvement in controlling the physiopathological mechanisms related to urinary tract infections frequently reported by patients with MS.

KEYWORDS

Case report, multiple sclerosis, nabiximols, bladder dysfunction, spasticity

LEARNING POINTS

- Nabiximols therapy can be used to treat other symptoms associated with spasticity in multiple sclerosis.
- Nabiximols therapy has a positive effect on bladder dysfunction.
- The sudden suspension of nabiximols treatment may cause worsening of bladder complaints.

INTRODUCTION

Nabiximols (Sativex®) is a Cannabis-based medicine approved in Italy by the Agenzia Italiana del Farmaco (AIFA) for adult patients with multiple sclerosis (MS) with moderate to severe spasticity. However, this treatment may be prescribed for many other symptoms as it is reported to improve bladder dysfunction caused by the reduction in muscle stiffness.

Several studies have tested the effectiveness of Cannabis in reducing some MS symptoms, and some of these analyzed its effects on bladder-related symptoms, with contrasting outcomes. A recent review reports the effects of Cannabis treatment on the bladder[1].

The use of nabiximols can reduce the dose of other oral antispastic drugs that cause urinary function worsening, controlling or avoiding their side effects.

CASE DESCRIPTION

We describe the case of a 48-year-old woman with secondary progressive MS and persistent radiological activity. She was diagnosed with MS at the age of 18 years and started different treatments, including interferon 1a/1b, natalizumab and cyclophosphamide. She is currently being treated with dimethyl fumarate (Tecfidera®), with no evidence, since starting the treatment, of clinical or radiological activity but with disability progression.

The patient presented a spastic paraparesis with a significant stiffness in the lower limbs, particularly on the left side, which caused walking difficulties with a tendency to foot drop. She could walk for a few steps without help and for approximately 20 m with assistance.

In the previous 5 years, the patient had also reported progressive bladder complaints characterized by vesical tenesmus, difficulty to urinate, urinary urgency with incomplete voiding, frequent urination and recurrent infections to the lower urinary tract.

Considering her significant stiffness, she started treatment with the oral antispastic baclofen up to 25 mg/3 times a day (75 mg/day), but she did not tolerate it. She reported 2 typical complaints of oral myorelaxant therapy: increasing sleepiness during the day together with asthenia (conditioning a progressive reduction in walking abilities) and the onset of incontinence episodes. For this reason, in November 2017, the patient started nabiximols treatment, gradually increasing the dose up to 10–12 puffs/day. A month later, the patient showed a gradual reduction in spastic symptoms in the lower limbs, followed by increasing walking abilities, such as being able to walk up to 100 m with a walker. Considering the good response to the treatment, the oral antispastic dose was reduced to half of a 25 mg pill 3 times a day. The therapy significantly reduced the side effects, with a reduction in asthenia and sleepiness during the day and increased cognitive performance. Bladder complaints were also improved thanks to the positive effects of nabiximols on an overactive bladder and to the reduction in the myorelaxant effect of baclofen on bladder muscles. The patient showed an improvement in bladder function with no incontinence episodes, vesical tenesmus improvement and complete voiding.

For 8 months, the patient received half of a 25 mg pill of baclofen 3 times a day plus nabiximols 10–12 puffs/day (6 + 6). After this time,

a sudden reduction of the nabiximols dosage to 6 puffs/day was needed due to some supply difficulties.

Several days after the therapeutic reduction, the patient presented a urinary blockage with severe urinary retention and stagnation of 800 cc of urine followed by catheterization during the hospitalization. For this reason, she started treatment with tamsulosin up to 4 mg/day. Over the following days, the patient showed a partial improvement in spontaneous voiding, but the bladder scan revealed post-void residual urine leading to more frequent post-void catheterizations.

As the supply problems were resolved, the patient continued her treatment with 12 puffs/day. From the first day of treatment, the patient rapidly registered a gradual remission of bladder function with spontaneous voiding recovery and no post-void residual urine. The treatment with tamsulosin was suspended as the patient reported severe orthostatic hypotension and tachycardia as side effects.

Currently, she takes nabiximols (12 puffs/day), and she does not need any urinary device or specific therapy for bladder dysfunction. Together with bladder dysfunction improvement, a significant reduction in urinary infections was registered, which is the most frequent problem the patient complained about.

DISCUSSION

This case presents some interesting insights into overactive bladder treatment for patients with MS. In MS centres, it is not always possible to evaluate bladder complaints carefully, although this should be normal practice for those patients with high disability and recurrent infections to the urinary tract[2].

The use of common myorelaxants is often associated with many side effects, which can cause muscle strength worsening and reduction of already impaired walking ability.

Cannabis oromucosal spray acts synergically with other antispastic drugs and, in certain cases, can reduce their daily dose and the incidence and severity of side effects[3].

Although bladder complaints result from muscle spasticity, nabiximols is not considered as a possible treatment. The regulatory authorities allow the prescribing of nabiximols only for muscle stiffness treatment.

An Italian study has tested the effectiveness of nabiximols on lower urinary tract dysfunction, showing improvement of overactive bladder symptoms due to its effects on detrusor hyperactivity[4].

As it has been presented in this case, nabiximols should be considered not only to improve bladder dysfunction symptoms and reduce antispastic therapy side effects, but also to reduce recurrent infections in the lower urinary tract. This result is particularly significant considering that drugs with a positive effect on disease progression are now available but they still have a high impact on the immune system[5].

Finally, the American Academy of Neurology document[6] concludes that the oromucosal spray is likely to be effective in terms of urinary frequency improvement (Class I), but it has no effect on incontinence episode reduction (Class I), as it has been demonstrated in randomized controlled studies on detrusor hyperactivity[7].

In conclusion, it would be interesting to conduct further studies on a more mixed and wider population to prescribe the drug more extensively so that vesical complaints could be finally included in the therapeutic criteria.

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Multiple Sclerosis-Related "Spasticity-Plus Syndrome" May Benefit from Early Nabiximols Treatment

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ABSTRACT

We present the case of a 42-year-old woman affected by relapsing-remitting multiple sclerosis who presented an extensive involvement of the spinal cord during the disease course. After a trial on first-line treatment, which she discontinued due to poor compliance, she was switched to intravenous ocrelizumab 600 mg every 6 months. At 10 years from the disease onset, as a result of the extensive spinal cord involvement, she began to complain of progressive and rapid reduction in ambulatory performance due to spasticity of the right leg, instability and severe fatigability, together with overactive bladder symptoms. The early introduction of nabiximols positively impacted on the patient's symptoms and on the neurological examination, as well as on her quality of life.

KEYWORDS

Spasticity, nabiximols, multiple sclerosis, fatigues

LEARNING POINTS

- The early introduction of nabiximols may positively impact "spasticity-plus syndrome"-related symptoms.
- Treatment with nabiximols should be considered earlier in young MS patients with low disability (EDSS <4) since it can represent a comprehensive approach to a broad spectrum of symptoms.
- Nabiximols is well tolerated in young MS patients, with a reduced risk of discontinuation.

INTRODUCTION

Spasticity is a very frequent and disabling symptom of multiple sclerosis (MS), affecting approximately 60% of patients and almost all patients with a progressive form of the disease[1]. Recently, the concept of a "spasticity-plus syndrome" has been defined to include all of the spasticity-related clinical manifestations that share common features and possibly an inclusive therapeutic approach[2]. Nabiximols treatment is safe, effective and well tolerated and it could be considered early in the disease course.

CASE DESCRIPTION

We present the case of a 42-year-old woman with relapsing-remitting MS who experienced inferior limb spasticity early in the disease course. The first clinical manifestation of MS was in 2010, when the patient presented right retrobulbar optic neuritis. She underwent brain MRI, which showed multiple inflammatory lesions disseminated in space suggestive of MS; cervical MRI disclosed an inflammatory lesion at the C2–C3 level (*Figs. 1 and 2*). Lumbar puncture revealed the presence of IgG oligoclonal bands in the cerebrospinal fluid. MS was diagnosed and the patient was started on glatiramer acetate, which was stopped after a few months due to a cutaneous reaction. The patient was therefore switched to IFN-β1a (Avonex). After 3 years, in a setting of clinical and neuroradiological stability, she decided to interrupt the treatment. In April 2014, the patient developed a spinal relapse characterized by weakness in the right leg, Lhermitte's sign, paraesthesia and allodynia of the trunk with D10 level. She was treated with high-dose steroids for 5 days with regression of symptoms and Avonex was restarted. In 2016, the patient started to complain of motor fatigability and a reduced performance in walking, still possible for more than 1 km (Expanded Disability Status Scale; EDSS 2.0). Over the following years she experienced a progressive worsening in ambulatory performance

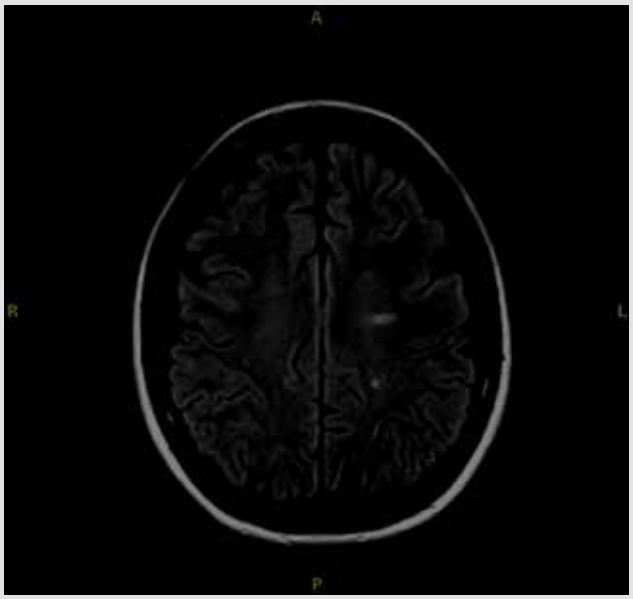

Figure 1. Brain MRI at clinical onset

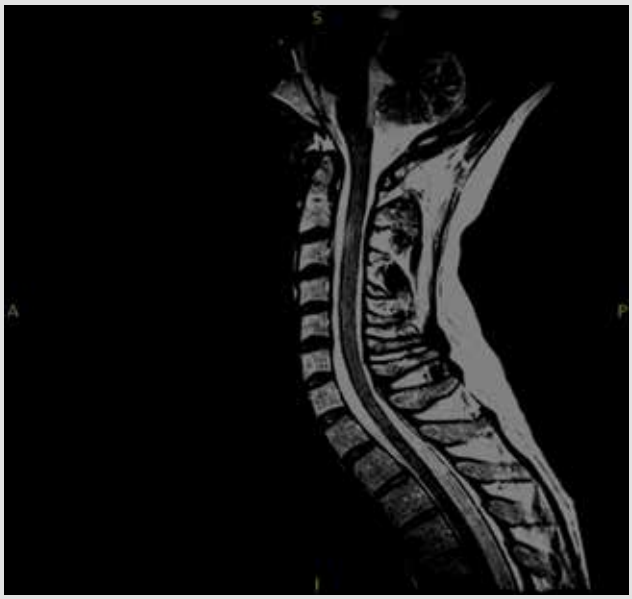

Figure 2. MRI of the cervical spinal tract at clinical onset

and in June 2019 the reported unassisted walking distance was 800 metres (EDSS 4.0). Follow-up spinal MRI disclosed multiple cervical and dorsal lesions at C1, C2, C2–C3, C4, D5, D8 and D12, showing a significantly increased spinal lesion load. A switch to a second-line treatment was suggested and, in September 2019, the patient was started on ocrelizumab 600 mg every 24 weeks, and intensive physiotherapy was recommended. In March 2020, the patient complained of increased fatigability and impaired ambulation due to muscle stiffness and spasms in the right leg, and instability in walking. She was able to walk for 400 metres without aid, then she was forced to rest. Urinary urge incontinence was associated. The neurological examination disclosed an ataxic–spastic gait with moderate spasticity in the right leg (NRS 7), increased deep tendon reflexes and non-sustained clonus in the right leg (Modified Ashworth Spasticity Scale 3). The EDSS was 4.5. The patient reported a score of 5 on the Fatigue Severity Scale (FSS), with great impact on her performance at work and consequently on the quality of life. These findings were consistent with increased muscle tone as a result of the known extensive involvement of the spinal cord, in particular the corticospinal tract. The patient was started on baclofen for spasticity and tolterodine for her overactive bladder. After a few weeks of treatment, baclofen was discontinued due to side effects and poor tolerability even at a low dosage. The patient started treatment with nabiximols in June 2020. She followed the indicated titration instructions, gradually increasing the daily number of sprays. At a dosage of 6 puffs per day, she reported an improvement in spasticity symptoms, with decreased sensation of stiffness for the right leg (NRS 5). At the end of the titration period, the neurological evaluation confirmed a decreased spasticity for the right leg (Modified Ashworth Spasticity Scale 2).

After 3 months of treatment, she reported a clear benefit for ambulatory performance due to reduced fatigability and reduced spasticity for the right leg (FSS 3.5 and NRS 4). She also reported reduced walking instability and was able to walk for 800 metres without aid (EDSS 4.0). The urinary symptoms improved as well, in terms of reduced urgency. This greatly impacted on her quality of life, affecting mood and improving her performance at work. Nabiximols was well tolerated overall and showed long-standing benefits. Variations in the EDSS, NRS and FSS scores are displayed in *Fig. 3*.

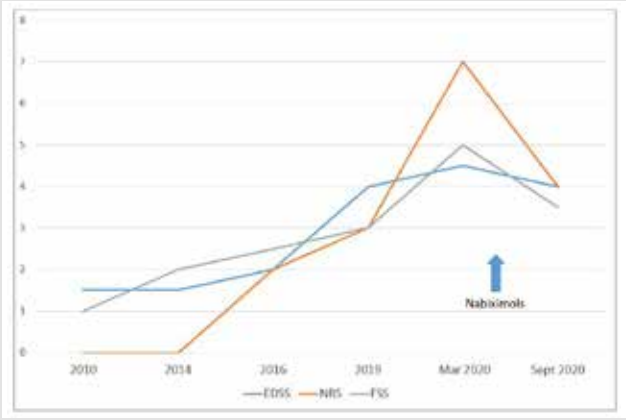

Figure 3. EDSS, NRS and FSS score variations over years. The introduction of nabiximols positively impacted both spasticity and fatigue, contributing to animprovement in ambulatory performance

DISCUSSION

Spasticity-related symptoms in young MS patients can determine long-standing disability and can have a great impact on the patient's quality of life. In a recent paper, a group of authors proposed the term "spasticity-plus syndrome" to define a new and broad concept which encompasses a cluster of symptoms sharing a common aetiology and possibly a common therapeutic approach. Spasticity and other related symptoms, namely gait disturbances, fatigue, pain, ataxia, overactive bladder, sleep and mood disorders, may all be considered as a whole, and thus, be managed with the same therapeutic approach[2]. Here, we report a real-life case of a young MS patient who developed a broad spectrum of symptoms (right leg stiffness, instability, fatigue, overactive bladder symptoms) well comprised within a "spasticity-plus syndrome", which presented early in the disease with great impact on the patient's quality of life. The early introduction of nabiximols allowed the initiation of comprehensive treatment of the patient's symptoms. This was confirmed by the noteworthy improvement both in EDSS and FSS scores. A recent Italian study retrospectively evaluated a group of MS patients treated with nabiximols in order to analyze predictors of sustained treatment persistence over long-term follow-up[3]. Carotenuto et al. found that EDSS >4 and cognitive impairment predicted treatment discontinuation at follow-up and suggested that nabiximols should be started earlier in the disease course. Our case confirms that the introduction of nabiximols in younger patients with low disability (EDSS >4) is effective and well tolerated, with a reduced risk of discontinuation. We therefore agree that nabiximols should be considered early in the disease course, since it can contribute to improving the quality of life in young MS patients.

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Management and Treatment of Late-Onset Multiple Sclerosis

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ABSTRACT

Multiple sclerosis (MS) with clinical onset after the age of 50 years is unusual and frequently misdiagnosed. Ageing is associated with diverse immune changes also known as immunosenescence, and a higher risk of comorbidities and infections, which need to be considered when planning medical treatments.

We describe the case of a 69-year-old woman with late-onset relapsing-remitting MS. Beyond the diagnostic difficulty and specific therapy for MS, we also addressed the management of symptoms, such as spasticity. Our case report confirmed the good safety profile of nabiximols in older age also. Progress in imaging and biomarker assessment has helped to distinguish MS from mimicry disease, which is important for improving disease management in the longer term.

KEYWORDS

Multiple sclerosis, late onset, disease-modifying therapy,

LEARNING POINTS

- Multiple sclerosis (MS) with clinical onset after the age of 50 years is associated with immunosenescence and higher risk of comorbidities and infections, which need to be considered when planning medical treatments.
- The onset of MS in old age also opens up new scenarios for both immunomodulatory treatments and symptom management.
- The approval of nabiximols for the management of MS spasticity opened up a new opportunity to many patients.

INTRODUCTION

Multiple sclerosis (MS) is the most common inflammatory autoimmune disease of the central nervous system (CNS). MS is usually diagnosed between the ages of 20 and 49 years[1], and MS with clinical onset after the age of 50 years (late-onset MS; LOMS) is unusual and frequently misdiagnosed. Few data are available regarding patients with very late-onset inflammatory demyelinating events. Moreover, ageing is associated with diverse immune changes also known as immunosenescence, and a higher risk of comorbidities (including vascular disease) and infections, which need to be considered when planning medical treatments. Due to previous comorbid conditions and higher odds of T2-hyperintense lesions on magnetic resonance imaging (MRI), almost 40% of LOMS patients receive a delayed diagnosis of 3–5 years. The differential diagnosis may be sometimes difficult and includes cerebrospinal vascular syndrome, hypertension-related disorders, compressive myelopathies, primary and secondary vasculitis, metabolic diseases, degenerative and nutritional syndromes[2,3].

CASE DESCRIPTION

We describe the case of a 69-year-old woman with a history of thyroiditis. In December 2017, she had fever following an onset of tremors in the left hand, which spontaneously regressed after 1 month. For this disorder, she underwent brain computed tomography (CT) in January 2018. It showed on the right parenchymal hypodensity corresponding to the corona radiata with extension to the ipsilateral external capsule compatible with non-stabilized ischaemic lesion. For an in-depth diagnostic, she underwent brain MRI with the evidence of multiple areas in the semioval centres, along the periventricular white matter. The CT hypodensity was not confirmed to be definitely ischaemic from MRI but the patient was dismissed with a cerebrovascular encephalopathy diagnosis. The patient presented a wellness period until December 2018 when she had fever followed by postural instability and eye movement deficit. She went to the ER and started therapy with intravenous (IV) methylprednisolone 500 mg for 5 days with improvement of the disorders. On 11 January 2019, she underwent brain MRI with gadolinium with evidence of numerous small focal lesions with high signal in the long TR (repetition time) sequences, some hypointense in the T1-weighted sequences, with right mesencephalic, pons, cerebellar hemispheric bilaterally and white matter both periventricular and bilateral frontoparietal juxtacortical involvement. After gadolinium administration almost all lesions showed enhancement. The findings described were compatible with the clinical suspicion of active demyelinating disease (*Fig. 1*).

The patient was admitted to our MS centre in January 2019. Neurological examination showed internuclear ophthalmoplegia, ataxic-spastic gait, urination urgency, tetrahyperreflexia and Romberg present (EDSS 4.5). The patient was treated with IV methylprednisolone 1,000 mg once daily for 5 consecutive days. In response to this therapy, her walking ability improved, and the neurological examination showed tetrahyperreflexia, urination urgency and spasticity (EDSS 1.5). The spasticity and sphincteric

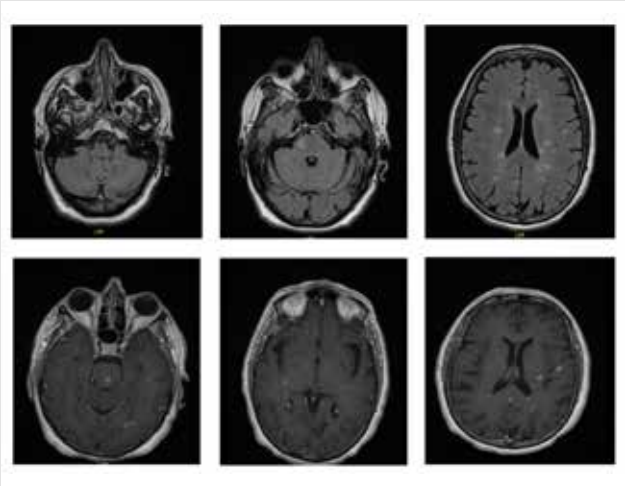

Figure 1. Brain MRI scans performed on January 2019, axial FLAIR sequences and T1-post gadolinium injection. The MRI scanner was a 1.5 T.

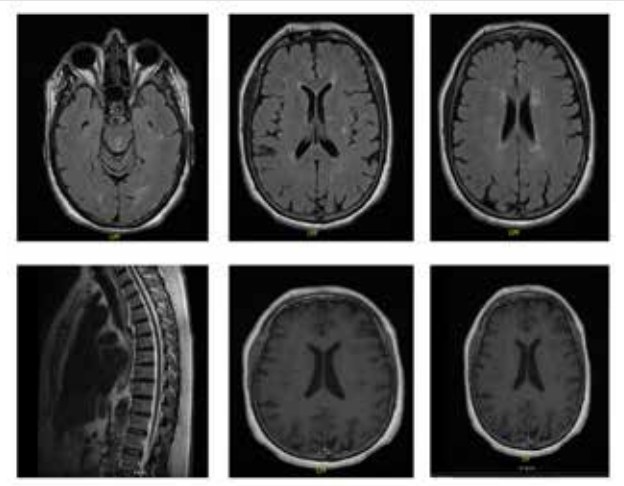

Figure 2. Brain and spinal cord MRI scans performed on April 2019, axial FLAIR sequences, sagittal T2 spinal cord and T1-post gadolinium injection. The MRI scanner was a 1.5 T.

symptoms were already present before the steroids, but after the steroids they got better. The routine blood evaluation and autoimmune pattern were both normal. Evoked potential assessment revealed bilaterally impaired tibial nerve somatosensory reactions and no evidence of bilateral affection of the visual system. The patient refused to undergo an examination of the cerebrospinal fluid.

In April 2019, she underwent follow-up brain and spinal cord MRI with gadolinium without evidence of variation of the number of brain lesions, and there were some areas of hyperintensity in the long TR sequences corresponding to demyelinating lesions at the level of D2 and D6. The administration of gadolinium does not cause accumulations of pathological contrast (*Fig. 2*). We diagnosed the patient with relapsing-remitting MS (RRMS). In June 2019, she was started on dimethyl fumarate until November 2019, when she stopped for persistent lymphopenia (500–600 mmc). Follow-up brain and spinal cord MRI performed in January 2020 showed a stable radiological picture. In January 2020, she started pegylated IFN-β1a with good tolerability. The patient did not have any relapses since. The patient also presented stiffness in the lower limbs and urinary urgency with a moderate impact on the quality of life, although this was stable from January 2019. For spasticity, she previously took baclofen 12.5 mg/day with unsatisfactory results. After 1 month we added 5–6 puffs/day of nabiximols (a mixture of delta-9-tetrahydrocannabinol and cannabidiol (THC:CBD) oromucosal spray, in a near 1:1 ratio; Sativex®) with improvement of disturbances (Numerical Rating Scale at onset was 7/10 and in the follow-up it was 4/10). 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.

DISCUSSION

LOMS shows a prevalence of approximately 4–9% in MS studies. A total of 2,707 individuals diagnosed with MS were initially identified for a recent study[4]. Of these, 84 (8.3%) were categorized as having LOMS if at the disease onset they were 50 years or older; only 7 patients from this subsample were 60 or older. At disease onset, 74.7% were diagnosed with RRMS and 25.3% were diagnosed with primary progressive MS (PPMS). Compared to young-onset patients, individuals with LOMS more often had no relapses in the first 2 years and higher EDSS scores at disease onset and at follow-up. In the study of D'Amico et al., 671 RRMS patients were recruited and of these, 143 (21.3%) had LORRMS with onset later than 40 years old[5]. The study concluded that the male population suffering from LORRMS reached severe disability faster than young-onset even if young-onset MS (YOMS) patients showed more brain inflammatory features on MRI. Delalande et al. described how in a population of 1,417 MS patients, 3.4% had their first symptoms at 50 years of age or older and 0.45% after 59 years of age. At the time of the study, patients had more frequently a progressive form: 37% had a primary progressive form and 35% a secondary progressive MS[6]. None of the patients with onset after 60 years of age had RRMS. In our case report the course is relapsing-remitting with clinical and also radiological activity[6]. A single series described the main characteristics associated with very late-onset (>70 years of age) inflammatory disease of the CNS. Only 9/25 patients eventually had an MS diagnosis.

Spasticity is a common symptom in MS patients affecting approximately 60% of patients. Spasms, pain, poor sleep quality and urinary dysfunction are symptoms frequently associated with spasticity in MS. A recent Italian consensus study on the

treatment of spasticity in MS gave a strong recommendation for the use of intrathecal baclofen, nabiximols oromucosal spray and intramuscular injection of botulinum toxin[7]. This study showed that more than 50% of patients demonstrated improvement of spasticity and only 39.5% of patients discontinued nabiximols during the entire observation period. Adverse advents occurred only in 16.3% of patients[8]. Our case report confirmed a good safety profile for nabiximols in older age also. There are a growing number of cases of individuals with MS with an onset after the age of 50 years and it is important to make a correct diagnosis. Progress in imaging and biomarker assessment has helped to distinguish MS from mimicry disease and identifying this late-onset form is important to improve disease management in the longer term.

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