The Broad Concept of “Spasticity-Plus Syndrome” in Multiple Sclerosis: A Possible New Concept in the Management of Multiple Sclerosis Symptoms

Óscar Fernández *, Lucienne Costa-Frossard 2, Marisa Martínez-Ginés 3, Paloma Montero 4, José Maria Prieto 5 and Lluis Ramió 6

Multiple sclerosis (MS) pathology progressively affects multiple central nervous system (CNS) areas. Due to this fact, MS produces a wide array of symptoms. Symptomatic therapy of one MS symptom can cause or worsen other unwanted symptoms (anticholinergics used for bladder dysfunction produce impairment of cognition, many MS drugs produce erectile dysfunction, etc.). Appropriate symptomatic therapy is an unmet need. Several important functions/symptoms (muscle tone, sleep, bladder, pain) are mediated, in great part, in the brainstem. Cannabinoid receptors are distributed throughout the CNS irregularly: There is an accumulation of CB 1 and CB 2 receptors in the brainstem. Nabiximols (a combination of THC and CBD oromucosal spray) interact with both CB 1 and CB 2 receptors. In several clinical trials with Nabiximols for MS spasticity, the investigators report improvement not only in spasticity itself, but also in several functions/symptoms mentioned before (spasms, cramps, pain, gait, sleep, bladder function, fatigue, and possibly tremor). We can conceptualize and, therefore, hypothesize, through this indirect information, that it could be considered the existence of a broad “Spasticity-Plus Syndrome” that involves, a cluster of symptoms apart from spasticity itself, the rest of the mentioned functions/symptoms, probably because they are interlinked after the increase of muscle tone and mediated, at least in part, in the same or close areas of the brainstem. If this holds true, there exists the possibility to treat several spasticity-related symptoms induced by MS pathology with a single therapy, which would permit to avoid the unnecessary adverse effects produced by polytherapy. This would result in an important advance in the symptomatic management of MS.

Keywords: multiple sclerosis, spasticity, symptomatic therapy, symptom cluster, symptomatic treatment
In the last two decades, the availability of new disease-modifying therapies has radically changed the management of multiple sclerosis (MS) and relapsing–remitting MS in particular (1), resulting in a longer life expectancy for patients with the disease (2). Nevertheless, MS currently remains incurable and, in most patients, disability will eventually progress and they must live with the very many symptoms associated with the disease. These symptoms can have a major impact on patient’s quality of life (3) and their management is considered important, although traditionally, this area has received far less attention than disease-modifying therapies (4).

A wide range of treatments are available to manage each of the MS symptoms (5–7). Given that different agents are used for different symptoms and a patient may have several symptoms present at the same time, many MS patients are multi-medicated, particularly as most patients will also be receiving disease-modifying therapies. This article will assess the current fragmented approaches to pharmacological management of spasticity muscle tone increase-related symptoms and their shortcomings. Given that the treatment of MS-associated muscle spasticity has been associated in a good number of clinical trials and also observational studies with the improvement of several other functions/symptoms present in MS (8), we will conceptualize, and subsequently hypothesize, about the clinical interest of introducing the more broad concept of “Spasticity-Plus Syndrome” to provide a unified framework for managing all these seemingly related functions/symptoms. By applying such a concept, it would be possible to simplify the management of symptoms associated with MS and reduce importantly the interactions and adverse effects associated with poly-medication.

**MS SYMPTOMS**

MS pathology affects multiple areas of the central nervous system (CNS), producing therefore a multiplicity of symptoms that can be basically classified as sensory alterations, fatigue, importantly cognitive dysfunction, pain (both paroxysmal and persistent), visual and brainstem symptoms (diplopia, oscillopsia, facial sensory symptoms, vertigo, and dizziness, nausea and vomiting, instability, etc.), those relating to mobility (spasticity, weakness, ataxia and tremor, impaired ambulation, and hand function), psychologic/psychiatric alterations (anxiety, depression, etc.), bowel, sexual and bladder dysfunctions, sleep disorders, and paroxysmal symptoms (seizures, dysarthria, etc.). All these symptoms vary along the course of the disease, being more prevalent as the disease evolves (Table 1) (9–12) (Figure 1).

Spasticity, a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes, due to the interruption of cranio-caudal pathways by MS lesions at different CNS levels, is a very frequent symptom in patients with this disease. A large survey in the United States found 84% of patients with MS with some form of spasticity, with severity ranging from minimal (31%) to total (4%) (12). Similar results were obtained in a recent survey in the United Kingdom, which reported some form of spasticity in 86% of patients with MS (13). Another survey from the United Kingdom found that 47% of randomly selected patients with MS had clinically significant spasticity, defined as modified Ashworth scale score of 2, 3, or 4 (14). Spasticity is an important symptom of MS because it has a negative effect on mobility and can be painful (15, 16), which in turn is ranked highly as a concern among patients with MS and is considered to have a large impact on quality of life (3, 17, 18). Moreover, the muscle rigidity and spasms of spasticity trigger, worsen, or are associated to other functions/symptoms in MS subjects beyond mobility impairment, such as fatigue (3), sleep disorders, and bladder dysfunction (19) (Figure 2).

Ataxia, reported in up to 80% of MS patients at some point in their disease (20), and tremor, detected in more than a half of subjects in a sample of randomly selected patients with MS in a British study (21), are also impairing symptoms that can impact mobility.

Bladder symptoms have been reported in approximately three-quarters of patients with MS (22), while sexual dysfunction was found to be present in 84% of men and 85% of women (23). Both types of dysfunction can have a marked impact on quality of life, including among patients with otherwise low disability (24). Bowel dysfunction (including both constipation and fecal incontinence) was reported in 68% of an unselected patient population with MS (25).

Fatigue, depression, and cognitive impairment are also highly prevalent among patients with MS and impact quality of life even after accounting for physical disability (26, 27). Central pain in MS can be as severe as that associated with arthritic conditions (28) and the need for treatment may be underestimated.

In summary, symptoms of MS are widespread, varied, often interlinked, and highly prevalent among patients with the disease. The impact on quality of life is substantial, and mobility is a concern for patients (16, 17). MS symptoms have been cited as

**TABLE 1 |** The percentage of symptoms present in multiple sclerosis vary along the course of the disease (adapted from [9–12]).

| Symptom                                                | % (At onset-advanced) |
|--------------------------------------------------------|------------------------|
| Sensory alterations                                    | 85–94                  |
| Fatigue                                                | 79–96                  |
| Cognitive dysfunction                                 | 63–81                  |
| Pain                                                   | 57–85                  |
| Visual and brainstem symptoms (scotoma, diplopia, oscillopsia, vertigo, dizziness, etc.) | 55–92                  |
| Motor alterations: spasticity, ataxia, tremor, impaired ambulation | 50–91                  |
| Psychologic/psychiatric alterations (anxiety, depression, etc.) | 50–79                  |
| Bowel alterations                                       | 41–82                  |
| Sexual dysfunction                                     | 40–90                  |
| Urinary dysfunction                                    | 40–87                  |
| Sleep disorders                                        | 40–60                  |
| Paroxysmal symptoms (seizures, dysarthria, etc.)       | 30–81                  |
a major barrier for employment (29). Appropriate management of these symptoms is therefore imperative.

**MANAGEMENT OF SPASTICITY SYMPTOMS**

As detailed above, the symptoms of MS are varied and substantially impact patients’ well-being. Management of symptoms is, however, a complex task requiring a multidisciplinary approach. In some cases, non-pharmacological interventions may be beneficial, e.g., physiotherapy for spasticity, but might have a limited time effect and the evidence supporting such approaches is not always strong (30), and pharmacological interventions are often considered necessary. As shown in **Table 2**, a wide variety of agents can be used (31, 32).

Any pharmacological intervention has a risk of side effects (**Table 3**) and this risk is accentuated by drug–drug interaction possibilities. In some cases, the side effects from a drug to treat one MS symptom may exacerbate another symptom produced by the disease. For example, a number of treatments used for spasticity, fatigue, pain, and depression can all cause erectile dysfunction and decreased libido (**Table 4**) (33). An approach
TABLE 2 | Commonly used pharmacological treatments for MS symptoms [adapted from (31, 32)].

| Symptom                               | Pharmacological treatment                                                                 |
|---------------------------------------|-------------------------------------------------------------------------------------------|
| MOBILITY-RELATED SYMPTOMS             |                                                                                           |
| Spasticity                            | Baclofen, tizanidine, nabixmols (THC:CBD), benzodiazepines (diazepam, clonazepam), gabapentin, dantrolene, botulinum toxin A (local treatment), intrathecal baclofen |
| Ataxia and tremor                      | Propranolol, clonazepam, levetiracetam, isoniazid, carbamazepine, ondansetron, dolasetron, cannabinoids, glutethimide |
| Impaired ambulation                    | Aminopyridines (tampridine)                                                               |
| BLADDER, BOWEL, AND SEXUAL DYSFUNCTION |                                                                                           |
| Urinary dysfunction                   | Bladder inefficiency: α1-blockers (ndoramin)                                              |
| Bowel dysfunction                      | Bulking agents, Laxatives                                                                  |
| Sexual dysfunction                     | Sildenafil, tadalafil, vardenafil, L-arginine, yohimbine, L-NAME                          |
| FATIGUE, COGNITIVE IMPAIRMENT, AND MOOD DISTURBANCE |                                                                                           |
| Fatigue                               | Amitriptyline, modafinil, pemoline, aminopyridine, carminine                               |
| Cognitive dysfunction                  | Acetycholinesterase inhibitors, memantine, amantadine, pemoline, gingko biloba, L-amphetamine sulfate |
| Mood disturbance                       | Fluoxetine, sertraline, moclobemide                                                       |
| PAIN                                  |                                                                                           |
| Paroxysmal pain                        | Carbamazepine, oxcarbazepine, lamotrigine, gabapentin, topiramate, misoprostol            |
| Persistent pain                        | Aminopyridines, pregabalina, gabapentin, lamotrigine, levetiracetam, cannabinoids         |
| VISUAL AND BRAINSTEM SYMPTOMS         |                                                                                           |
| Visual dysfunction                     | Memantine, gabapentin                                                                    |
| Brainstem-related symptoms             | Antiepileptic drugs                                                                       |
| SLEEP DISORDERS                        |                                                                                           |
| Excessive sleepiness                   | Modafinil                                                                                 |
| Restless legs syndrome                 | Dopaminergenic agonists                                                                  |

that would simplify the management of the diverse symptoms of MS-associated spasticity could potentially be beneficial for the patient.

THE BROAD CONCEPT OF “SPASTICITY-PLUS SYNDROME” IN MS

A syndrome in medicine is classically defined as a combination of signs and/or symptoms that forms a distinct clinical picture indicative of a particular disease or disorder (34). Usually, these signs and/or symptoms would be considered to have a common underlying pathophysiology, or respond to a given therapy, although the clinical manifestations could be varied. In MS, spasticity is thought ultimately to arise from damage to motor areas or pathways, at multiple possible levels, in the CNS, leading to dynamic changes in motor circuit function.

TABLE 3 | Main side effects of commonly used treatments for spasticity according to the EU Summary of Product Characteristics.

| Drug                     | Side effects                                      | Warnings                                                                 |
|--------------------------|---------------------------------------------------|--------------------------------------------------------------------------|
| Baclofen                 | Depression, fatigue, ataxia, and tremor           | Psychotic disorders, schizophrenia, depressive or manic disorders, confusional states or Parkinson's disease may be exacerbated by treatment |
| Diazepam                 | Confusion, drowsiness, ataxia, impaired motor ability, tremor, fatigue, withdrawal symptoms | Alcohol, neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, baclofen ticarcil |
| Clonazepam               | Impaired concentration, restlessness, confusional state and disorientation, somnolence, slowed reaction, muscular hypotonia, dizziness, ataxia, light-headedness, co-ordination disturbances, fatigue and muscle weakness | Alcohol, neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, baclofen ticarcil |
| Gabapentin               | Confusion and emotional lability, depression, anxiety, hypersomnia, somnolence, dizziness, ataxia, convulsions, hyperkinesia, dyssomnia, amnesia, tremor, insomnia, headache, coordination abnormal, nystagmus, increased, decreased, or absent reflexes, visual disturbances, diplopia, vertigo, arthralgia, myalgia, back pain, twitching, impotence, fatigue | Alcohol, neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, baclofen ticarcil |
| Carbamazepine            | Opioids                                           |                                                                          |
| Levetiracetam            | Depression, hostility/aggression, anxiety, insomnia, nervousness/irritability, somnolence, headache, convulsion, balance disorder, dizziness, lethargy, tremor, asthenia/fatigue | Alcohol, neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, baclofen ticarcil |
| Botulinum toxin A        | Potentially with agents with neuromuscular blocking effects | Alcohol, neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, baclofen ticarcil |
CANNABINOIDS FOR THE TREATMENT OF FUNCTIONS/SYMPTOMS BELONGING TO THE BROAD “SPASTICITY-PLUS SYNDROME”

Several randomized clinical trials have demonstrated improvement in resistant spasticity symptoms, in patients with MS following add-on treatment with an oromucosal spray containing a 1:1 mixture of 9–δ-tetrahydrocannabinol and cannabidiol (THC:CBD) (43–47).

This benefit for spasticity has also been reported in very many observational trials in the clinical practice setting (48). Studies of THC:CBD for the treatment of MS symptoms, other than spasticity itself, are fewer and often beset with design limitations, such as small number of patients. Nevertheless, large THC:CBD studies that collected evolution of pain, sleep disorders, and bladder dysfunction as secondary endpoints do point to a potential benefit for these symptoms (43–46). A study of the Cannabinoids for treatment of spasticity and other symptoms related to Multiple Sclerosis study (“CAMS”) (49)
FIGURE 3 | Areas of the CNS mediating spasticity.

FIGURE 4 | Distribution of cannabinoid receptors (CB1 and CB2) in the central nervous system (The Endocannabinoid System). Redrawn from https://www.fundacion-canna.es/en/endocannabinoid-system. Accessed April 06, 2019. With permission.
found significant benefit in the control of incontinence, although THC-only tolerability profile is less interesting than the THC and CBD combination (50, 51). In the case of MS-associated pain, a systematic review of randomized clinical trials of cannabinoid treatments concluded that these agents are effective in alleviating pain (52). There is thus evidence that THC:CBD can be used to treat a variety of MS spasticity-associated and somehow related symptoms (53). Moreover, application of the possible new broad concept of “Spasticity-Plus Syndrome” in MS would suggest an appropriate line of investigation, in patients with more than one symptom that could be amenable to a single therapy, to simplify symptom management.

As a clear limitation, we consider this as a preliminary conceptual proposal that has to be sustained in the future with new studies, not yet available, and that could give more background and support to our concept, so that the hypothesis would be testable and be a promising area of research in the field of symptomatic therapy. Another limitation is the fact that we do not know whether this concept could be applied to the spasticity present in other diseases such as spinal cord injury, stroke, etc., as it has not been surveyed yet as far as we know.

CONCLUSIONS

The numerous and varied symptoms associated with MS requires complex management with multiple drugs, all with potential side effects that may exacerbate other symptoms and with potential drug–drug interactions. Recognition that a good number of MS symptoms might have a common or close underlying pathophysiology, or respond to a single therapy, in the form of a new broad “Spastic-Plus Syndrome” in MS may help simplify treatment of these symptoms with agents such as cannabinoids that target CB1 and CB2 receptors.

AUTHOR CONTRIBUTIONS

ÔF, LC-F, MM-G, PM, JP, and LR contributed conception and design of the study. ÔF wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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