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Retrospective study on the presence of spasticity-plus syndrome in the advanced practice nurse's office in multiple sclerosis☆

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Abstract Spasticity plus syndrome (SSP) is a clinical diagnosis based on the presence of a compendium of symptoms that has been suggested recently in patients with demyelinating disease. Using this diagnosis might help to avoid polimedication and to offer a better symptomatology management in long-term patients.
Objective: The aim of this study is to retrospectively analyze the number of cases compatible with a SSP diagnostic in our nurse clinical-consultancy.
Methodology: We analyzed a time-window from 2002 till 2022 and we included cases compatible with SSP at those 2 time-points as well as the number of symptomatic treatments prescribed also in both time-points.
Results: All cases in the databased were compatible with SSP and also associated pain (90%), rigidity (83.3%), fatigue (75%) and bladder problems (43.3%). An increase in symptomatic treatments was stated (from 1.4 to 3.9 at the end of the temporal window of analysis), and THC:CBD was prescribed in 88.9% of them. There was no correlation between number of symptoms at the beginning and number of symptomatic treatments at the end of the time-window. No correlation either was found between number of symptomatic treatments and physical disability.
Conclusions: SSP is relatively easy to be diagnosed in our consultancy and it should be more frequently stated as it will offer the opportunity to individual management of symptoms and treatments for our patients that could impact their quality of life in the long-term.

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PALABRAS CLAVE
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Estudio retrospectivo sobre la presencia del síndrome de *spasticity-plus* en la consulta de la enfermera de práctica avanzada en esclerosis múltiple

Resumen El síndrome de *spasticity plus* (SSP) es un conglomerado de síntomas clínicos que se ha propuesto recientemente como una opción diagnóstica en pacientes con enfermedad desmielinizante. Su diagnóstico puede ayudar a evitar la polimedicación en estos pacientes y a mejorar la gestión de la sintomatología a largo plazo.
Objetivo: Realizar un estudio retrospectivo para identificar el número de pacientes de la consulta de enfermería que podrían ser compatibles con el SSP, analizando una ventana temporal desde el 2002 hasta el 2022.
Métodos: Se registraron los síntomas compatibles con SSP al inicio y al final de la ventana temporal, así como el número de tratamientos sintomáticos que se pautaron en ambos momentos.
Resultados: En el 100% de los casos analizados se cumplían criterios de SSP, asociando a la espasticidad el dolor (90%), rigidez (83,3%), fatiga (75%) y trastornos de vejiga (43,3%). El número de tratamientos aumentó con el tiempo, de 1,4 a 3,9 de media; el THC:CBD fue uno de los más frecuentemente utilizados (88,9% lo utilizó). No se ha encontrado correlación entre el número de síntomas registrados al inicio y el número de tratamientos sintomáticos registrados al final del periodo de análisis, ni tampoco entre el número de tratamientos y la discapacidad física.
Conclusiones: El SSP es fácilmente detectable en la consulta y debería ser más e diagnosticado con más frecuencia para proporcionar al paciente una gestión individualizada de sus síntomas, con tratamientos a medio y largo plazo que mejoren su calidad de vida.

Introduction

A clinical syndrome is defined as a combination of signs or symptoms that form a distinct clinical entity indicative of a disease or disorder. These signs or symptoms are usually considered to have a common or proximate pathophysiology, or to respond to the same treatment, directly or indirectly, even though the clinical manifestations may vary.[1]

In patients with multiple sclerosis (MS), spasticity is a common symptom, defined as a motor disorder characterised by an exaggerated speed-dependent muscle flexion reflex resulting from impaired intraspinal processing of primary afferent input.[2] Spasticity is associated with other disease-specific symptoms such as fatigue, pain, sphincter control or sleep disturbances, which negatively impact quality of life. This results in polymedicated MS patients due to the need to manage several symptoms simultaneously, in addition to receiving their disease-modifying MS treatment. This creates a difficult clinical situation to manage, with an increase in potential side effects from polymedication and more complex management of patient adherence.[1]

The symptoms of spasticity are interrelated with muscle tone and are largely mediated in the same areas of the brainstem. Treatment of spasticity with tetrahydrocannabinol (THC:CBD) has been associated with improvement of other symptoms or functions present in MS. Therefore, we propose to manage all these symptoms with as few treatments as possible, focusing on the positive effect of THC:CBD use in several of them.[1]

Spasticity plus syndrome (SPS) is defined as the existence of a set of spasticity-associated symptoms such as spasticity and/or spasm-cramps and/or pain and/or bladder dysfunction and/or sleep disturbances and/or fatigue and/or tremor, which are related to each other and may have a common aetiology in the cannabinoid system.[1] CB1 and CB2 cannabinoid receptors are unevenly distributed in the central nervous system, with a large accumulation in the brainstem, where functions such as spasticity, sleep, bladder function control and pain are mediated.[3] These concurrent symptoms may have a synergistic influence on behavioural, functional and quality of life measures, so a joint rather than individual approach and cannabinoid receptor-related treatments are proposed.[4]

The aim of this study was to identify the number of cases meeting SPS criteria in the advanced practice MS nursing practice of our hospital. In addition, we sought to identify the most frequent symptomatology in SPS, the number of symptomatic treatments and the number of cases treated with THC:CBD.

Methods

The study is a retrospective observational design in which patients with a diagnosis of MS were recruited according to the usual clinical practice of the Demyelinating Diseases Unit of our hospital.

The study was submitted to and approved by the Medical Research Ethics Committee of Area 1 of the Hospital General Universitario Gregorio Marañón. The project complies with the requirements of Royal Decree 957/2020 of 3 November, which regulates observational studies and studies with

Table 1 Percentages of symptoms present according to disease phenotypes.

	SPMS (n = 36)	PPMS (n = 14)	RRMS (n = 7)	No MS (n = 3)
Spasticity	100	100	100	100
Cramps	22.2	21.4	85.7	33.3
Stiffness	94.4	85.7	71.4	66.7
Pain	86.1	92.9	100	100
Sleep disorders	16.7	21.4	71.4	33.3
Bladder disorders	50	42.9	28.6	33.3
Fatigue	72	85.7	71.4	66.7

No MS: no multiple sclerosis; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

medicinal products for human use. The study complied with the definition of research without commercial interest as established in paragraph e) of article 2.2 of RD 1090/2015, of 4 December, which regulates clinical trials with medicinal products, ethics committees for research with medicinal products and the Spanish Clinical Studies Register. The confidentiality, processing, communication and transfer of the personal data of all participating subjects complied with the provisions of the Organic Law on Personal Data Protection 03/2018 of 5 December, including additional provision 17 of that law, and the General Data Protection Regulation 2016/679.

Information on neurological variables was collected retrospectively from patient records. The MS phenotype, the degree of physical disability as measured by the Expanded Disability Status Scale (EDSS) and the number of symptoms associated with MS were coded, namely the presence or absence of spasticity, stiffness, pain, sleep disturbances, bladder disturbances, fatigue and sexual function disturbances. The number of symptomatic treatments in use was also recorded. All this information was compiled in a database where the information was collected in a pseudoanonymised form for further analysis.

The registry included patients with a diagnosis of MS in any phenotype of the disease who belonged to the Demyelinating Diseases Unit of the Hospital General Universitario Gregorio Marañón, who presented spasticity and were receiving pharmacological treatment for it, according to the clinical criteria of the neurologist responsible for the patient, between 2002 and 2022. The exclusion criterion was not being diagnosed with a demyelinating disease, despite being diagnosed with spasticity and receiving treatment for it.

The data collected in the database were analysed statistically with the Prism 8 programme. A descriptive study of both qualitative and quantitative variables was carried out using percentages, means, medians and standard deviations. An inferential analysis of the quantitative variables was performed using Spearman's statistic to assess the correlation between these variables. The confidence level for the statistics was taken as 95%.

Results

We retrospectively recorded 68 cases of people who presented symptoms of spasticity in their evolution from 2002 to 2022. Of these, 8 cases were eliminated: 7 because they did not have a diagnosis of demyelinating disease and one due to death. Sixty patients were recruited for data analysis.

The gender distribution was well balanced (53% female). Ninety-five per cent were cases with a diagnosis of MS in its different phenotypes (12.3% relapsing-remitting [RRMS]; 63.2% secondary progressive [SPMS] and 24.5% primary progressive [PPMS]), but there were also 2 cases of neuromyelitis optica (NMO) and one longitudinally extensive myelitis. The median degree of physical disability measured with the EDSS was 6.5 (range: 2.5–8).

Only 36% of cases were on a disease-modifying drug at the time of data cut-off (13 cases with a diagnosis of SPMS, 5 with PPMS, 2 NMO and 2 RRMS); the most frequent were azathioprine (6), rituximab (5) and ocrelizumab (4).

All patients fulfilled SPS criteria and associated pain (90%), stiffness (83.3%), fatigue (75%) and bladder disorders (43.3%) as the most frequent symptoms of spasticity (Table 1). The mean number of symptoms added to spasticity was 3.5. The most frequent initial SPS symptoms were spasticity (23.3%), polysymptomatology, which included spasticity (26.7%), and pain (20%).

Regarding the different phenotypes of the disease, the data showed that in the non-progressive forms (RRMS and non-MS) the second symptom that appeared in 100% of the cases associated with spasticity was pain. For progressive phenotypes, stiffness and pain were the most commonly associated with spasticity in SPMS (94.4 and 86.1%), followed by fatigue in PPMS phenotypes (85.7, 92.9 and 85.7%, respectively) (Table 1).

In terms of symptomatic drug treatment, the mean number of symptomatic drugs recorded was 1.4 at baseline, which increased to 3.9 at data cut-off. During the evolution, 85% of the cases increased the number of symptomatic drugs and only 5 cases decreased the number of symptomatic treatments over the years. When the patients were divided according to the number of symptomatic treatments, they were receiving at the cut-off visit, it was observed that physical disability was somewhat higher in the group receiving between 5 and 9 symptomatic drugs (mode EDSS = 7) compared to those receiving fewer (between 1 and 4, with mode EDSS = 6.5) without this difference being statistically significant ($p = .1$).

When analysing the number of treatments at baseline according to phenotype, it was observed that RRMS patients had the highest number of symptomatic treatments on average (1.86) and non-MS cases the least (.33). Regarding the

Table 2 Mean number of symptomatic treatments by phenotypes at baseline and at sample data cut-off.

	At baseline	At data cutoffs
SPMS (n = 36)	1.44	3.97
PPMS (n = 14)	1.29	4.29
RRMS (n = 7)	1.86	3.57
NO MS (n = 3)	.33	2.33

No MS: no multiple sclerosis; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

number of symptomatic treatments taken at the time of the final sample cut-off, patients with progressive phenotypes had the highest mean number of treatments (4.29 for PPMS and 3.97 for SPMS) (Table 2).

Of the cases in this study, 88.3% were treated with THC:CBD at some point during follow-up and only 5% were treated at symptom onset. When spasticity was an onset symptom, treatment with THC:CBD took an average of 4 years. In 11.7% of patients, THC:CBD was withdrawn during the follow-up period of the study.

No statistically significant correlation was found between the number of symptoms presented by the patients at the start of the registry and the number of pharmacological treatments they were taking at the time of the sample cut-off ($r = .12$; $p = .38$). There was also no statistically significant relationship between the number of symptomatic treatments administered and the physical disability of the patients at the time of the sample cut-off ($r = .19$; $p = .15$).

Discussion and conclusions

The retrospective analysis of patients who presented with spasticity throughout the course of the disease showed that the existence of SPS is highly frequent in the evolution of patients diagnosed with mainly progressive demyelising diseases. These are frequently associated with symptoms of pain, spasticity and fatigue.

One conclusion of this work is the existence of polypharmacotherapy in cases of SPS. It was observed that the number of symptomatic treatments increases dramatically with the evolution of the symptoms and that there are very few cases in which the number of symptomatic treatments decreases with the evolution of the disease. THC:CBD treatment, although not prescribed at baseline, has been used very frequently in these cases. Our study does not evaluate the discontinuation of THC:CBD in relation to symptom efficacy, but rather the number of patients who, after the 20-year follow-up window, have discontinued treatment (11.7%). In this sense, we cannot replicate the 55.6% treatment drop-out rate, mainly due to ineffectiveness, reported by Italian registries.[5]

In this study, THC:CBD treatment was initiated in a very low percentage of cases at the onset of symptoms (only 5%) and it took an average of 4 years for patients with spasticity to be prescribed. This is conditioned by the drug's own label,[6] which specifies that THC:CBD is indicated for cases of moderate/severe spasticity due to MS that have not previously responded to other anti-spasticity drugs. This may result in a delay in the administration of a drug that can clinically improve SPS symptomatology in up to 33.19% of cases after 18 months of treatment.[5] This clinical efficacy coupled with the evidence of the relationship between SPS and the endocannabinoid system[7] should help earlier indication of this treatment in SPS cases.

The data show that, over a 20-year follow-up window, both the number of symptoms that make up SPS and the number of symptomatic drugs administered for its treatment increase. As we did not find a relationship between physical disability and the number of symptomatic treatments administered in patients with SPS, it could be said that these variables could be related to the evolution of the disease itself and not to a direct relationship between SPS and the evolutionary worsening of the patients. However, more research is needed to rule out the possibility of a direct relationship between SPS and the worsening of patients' outcomes.

In our sample, pain was reported as a symptom that generally formed part of the SPS, without a standardised measurement but as a clinical report by the neurologist in his examination. In the medical literature, this is the symptom most frequently associated with spasticity: 38.4% at the initial onset of symptoms[5] and 17% as reported by MS nurses on the subjective complaints of their patients in consultation.[8] This study finds that pain is associated with spasticity in up to 90% of participants, and also notes that the presence of pain is a characteristic sign in non-progressive phenotypes (RRMS and NMO), as opposed to progressive phenotypes, which more often associate fatigue in PPMS and stiffness in PPMS. This relationship could be an additional aid in the future for the differential diagnosis of MS phenotypes in the complex transitional moment from a relapsing remitting form to the secondary progressive phase.

As a symptom closely related to spasticity pain is also controversial in its specification. The original proposal[1] establishes the presence of pain as part of SPS, but other studies also specify trigeminal neuralgia as a sign to be taken into account for the possible diagnosis of SPS.[5] Up to 9 different types of pain specifically associated with MS have been proposed in the medical literature, ranging from Lhermitte's sign or headache to musculoskeletal pain.[9] Pain is an important symptom to be recorded, but further studies may validate the need to make distinctions regarding the type of pain that can help refine the diagnosis.

The main limitation of this study was a possible recruitment bias in the study sample. Case inclusion screening was performed based on patients who were on THC:CB treatment due to the presence of spasticity at some point during the analysis window proposed for this study. It is reasonable to anticipate that we may have missed cases with a possible diagnosis of SPS because they had spasticity initially but were not prescribed THC:CB, so they may not have been in our registry. This method is different from the study by Patti et al. in Italy, which included patients who started treatment with THC: CBD.[5] Similarly, the criterion of including patients according to the initial presence of spasticity as a symptom could have left out of the characterisation of SPS all those who started with another of the symptoms that make up the syndrome, such as urological problems or fatigue, both of which are very prevalent in this entity.

In our case, some symptoms such as alterations in sexual function and mood could not be included in the total number of patients included. In general, these symptoms are rarely recorded in the clinical history of the patients and could lead to an increase in the diagnostic prevalence of this syndrome if it were to be recorded in the future.

The main analysis of this retrospective study is based on the number of symptoms and symptomatic treatments administered that have been recorded in the medical records of patients who met the inclusion criteria. However, no information was collected on the efficacy of these treatments on SPS symptoms, which is of great clinical importance for the future management of these patients, as shown in the Italian registry.[5]

A limitation in the diagnosis of this syndrome is its description. The authors proposing this syndrome[1] indicate a series of symptoms that must be present to fulfil the diagnosis, but later reviews still debate the inclusion or not of some symptoms, such as tremor[10] or weakness.[11]

Another limitation of this study is the definition of spasticity used as an inclusion criterion for participants. Being a retrospective study, the presence of symptom is considered as long as the neurologist includes it in the clinical history as part of the neurological examination, but no measure of spasticity proposed in the clinical or research literature (e.g., Ashworth scale for MS-associated spasticity[12] or numerical scale for measuring spasticity[13]) has been systematically used, which may hinder the validity of the diagnosis of SPS in routine clinical practice.

We need more evidence on the effect of early symptomatic treatment of patients with spasticity to objectify the effect on the evolution of symptomatology. To this end, it is important to identify the most frequent signs to aid early diagnosis.

This study indicates that retrospective diagnosis of SPS is highly frequent and, therefore, it would be of clinical interest to perform it prospectively and early, given the repercussions on the management of polysymptomatology and its impact on the perception of people with MS on their quality of life.

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Conflict of interests

The authors have no conflict of interests to declare.

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