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Case Report

Cannabis derivatives therapy for a seronegative stiff-person syndrome: a case report

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SUMMARY

What is known and objective: **Stiff-person syndrome (SPS) is an uncommon and disabling disorder characterized by progressive rigidity and episodic painful spasms involving axial and limb musculature. SPS treatment is mostly based on benzodiazepines, baclofen, immunosuppressants and intravenous immunoglobulin. Cannabis derivatives [tetrahydrocannabinol (THC) and cannabidiol (CBD)] are available as an oromucosal spray (Sativex®), indicated as add-on treatment, for symptom improvement in patients with moderate to severe spasticity because of multiple sclerosis (MS). Our objective is to report a case of seronegative SPS successfully treated with THC-CBD oromucosal spray.**

Case summary: **We report a case of a 40-year-old man presenting with progressive muscle stiffness and intermittent spasms for 6-years. The diagnosis of stiff-person syndrome was based on the clinical features and neuroelectrophysiologic findings of continuous motor unit activity. Glutamic acid decarboxylase autoantibodies was absent in our patient, in both serum and cerebrospinal fluid (CSF). Cannabis derivatives oromucosal spray was introduced after a series of unsatisfactory traditional medical treatments. After 14 months treated with THC-CBD oromucosal spray, improvement was verified in the eight dimensions of the scale of SF-36 quality of life questionnaire.**

What is new and conclusion: **Clinical experience with cannabis derivatives in patients with multiple sclerosis is accumulating steadily, but there is no current literature about its efficacy for SPS. Because MS and SPS share some neurological symptoms such as spasticity and rigidity, it is thought that THC-CBC can be an option for SPS patient. Our case report suggests that THC-CBD oromucosal spray is an alternative treatment for patients with refractory SPS, and further validation is appropriate.**

WHAT IS KNOWN AND OBJECTIVE

Stiff-person syndrome (SPS) is an uncommon and disabling disorder characterized by progressive rigidity and episodic painful spasms involving axial and limb musculature. The first description dates from 1956 and is attributed to Moersch and Woltman.[1] An autoimmune pathogenesis is suspected because of the high prevalence of specific autoantibodies and the association with other autoimmune disorders. There are different clinical variants with different diagnostic criteria and different grades of disability. The prevalence of SPS may be underestimated. The high prevalence of specific autoantibodies against glutamic acid decarboxylase (anti-GAD), the presynaptic rate-limiting enzyme responsible for the synthesis of gamma-aminobutyric acid, in both serum and cerebrospinal fluid (CSF), was formerly considered as diagnostic features for SPS.[2] However, the absence of anti-GAD, defined as seronegative type does not exclude the diagnosis.

Stiff-person syndrome is also associated with other autoimmune disorders and endocrinopathies such as insulin-dependent diabetes mellitus, Graves' disease, vitiligo and pernicious anemia.[3,4] Many movement disorders previously considered idiopathic or degenerative are now recognized as immune-mediated. Some disorders are paraneoplastic, such as anti-CRMP5 associated chorea, anti-Ma2 hypokinesis and rigidity, anti-Yo cerebellar ataxia and tremor, and anti-Hu ataxia and pseudoathetosis. A paraneoplastic SPS variant, less well characterized, is associated with amphiphysin antibodies (anti-Amphiphysin).

Stiff-person syndrome treatment is mostly based on benzodiazepines, baclofen, immunosuppressants and intravenous immunoglobulin. Cannabis derivatives, tetrahydrocannabinol (THC) and cannabidiol (CBD), are available as an oromucosal spray (Sativex® GW Pharma Ltd., Wiltshire, UK), indicated as add-on treatment, for symptom improvement in patients with moderate to severe spasticity because of multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.[5] Our objective is to report a case of seronegative SPS successfully treated with THC-CBD oromucosal spray.

CASE SUMMARY

The 40-year-old man with SPS presented with progressive muscle stiffness and intermittent spasms for 6-years. The past medical history and related family history was unremarkable. Occasional spastic cramping of lower limbs causing continuous pain was the initial presentation, followed by easy fatigue with

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tremor-like movement after prolonged standing. At the age of 32 years, neurological examination highlighted axial and proximal stiffness with significant prevalence of lower limbs, and marked muscular tropism, hyper-reflexia and spastic gait. Sudden noise or tactile stimuli precipitated spasms of limbs, although these also occurred spontaneously. Associated symptoms included hyperthermia, insomnia, disautonia (episodes of ileus, impotence and urinary retention) and marked pruritus.

Electromyography revealed continuous activity in agonist and antagonist motor unit of both axial musculature and abdominal region, without periods of relaxation. Laboratory analyses included routine data and autoimmune profiling to exclude paraneoplastic syndromes, tumours and other autoimmune diseases. Testing that included glutamic acid decarboxylase autoantibodies (anti-GAD), paraneoplastic antibodies (anti-Hu, anti-Yo, anti-Tr, anti-Cv2, anti-Ri and anti-Amphiphysin), tumour markers and other autoantibodies (anti-nuclear antibodies, thyroid autoantibodies and anti-tyrosine phosphatase antibodies) were negative in both serum and CSF.

The patient's treatment included diazepam, levetiracetam, levomepromazine, corticosteroids, oral baclofen, mofetil mycophenolate and intravenous immunoglobulin infusion. However, these treatments offered only partial pain relief. His ambulation deteriorated progressively despite this therapy. He was wheelchair bound, and standing was only possible with support. Owing to the unsatisfactory treatment outcomes, a multidisciplinary committee decided on the off-label use of THC-CBD oromucosal spray (Sativex®) administered as an add-on to usual therapy in 2009 to reduce spasticity, relieve pain and improve quality of life. The patient's dose-titration led to the average daily two-spray dose for optimum symptom relief. Once titrated, the patient could adjust his dose according to how he felt on the day up to the maximum dose specified in the product label for the licensed indications. On stressful days, the patient required up to six sprays without reporting any adverse events. The patient was interviewed at the Outpatient Pharmaceutical Care Unit to obtain information of the patient's quality of life after obtaining informed consent. Quality of life (QoL) was evaluated before therapy with THC-CBC and over the course of 14 months of treatment using the Spanish version of health questionnaire SF-36.[6,7] Patient's QoL perception has been improving steadily (Table 1). The present is currently not wheel-chair bound and shows decreased pain and muscle spasms, as well as improvements in gait and range of motion.

Although the aetiology of SPS remains obscure, an autoimmune-mediated mechanism is suggested by the presence of specific autoantibodies, and the high prevalence of comorbidity with other autoimmune disorders and endocrinopathies.[2,3] The presence of anti-GAD helps to establish the diagnosis of SPS, and also has been described in patients with insulin-dependent diabetes mellitus, cerebellar ataxia, drug-resistant epilepsy and myoclonus. Approximately, 60–80% patients with SPS have anti-GAD in the serum or CSF.[2,3] Our patient was diagnosed with SPS according to clinical and electrophysiological findings after the insidious onset of intermittent painful spasms of the lower limbs.[8] We have rechecked the anti-GAD titre of our patient during his course of treatment with negative results.

Table 1. SF-36 questionnaire results

	Initial score	Final score	Percentage response
Physical functioning	0	80	80
Role-physical	0	100	100
Bodily pain	0	100	100
Social functioning	0	100	100
Role-emotional	0	100	100
Mental health	28	96	68
Vitality	10	50	40
General health	0	30	30

The scores for each scale of SF-36 range between 0 and 100 (100 indicating optimal health and 0 reflect a very bad state of health).

Sativex is a 1 : 1 mixture of THC-CBD. THC acts as a partial agonist at cannabinoid receptors, mimicking the effects of the endocannabinoids, which may modulate neurotransmitter release and reduce the excitatory effects. CBD antagonizes the activity associated with psychotropic cannabinoids. Evidence to date suggests that abuse or dependence on (Sativex®) is likely to occur in only a very small proportion of recipients.[9] Clinical experience with cannabis derivatives in patients with multiple sclerosis is accumulating steadily,[10] but there is no current literature about its efficacy for SPS.

WHAT IS NEW AND CONCLUSION

Stiff-person syndrome is rare and its presentation variable. Evaluate of potential treatments for SPS is difficult, and current treatments are unsatisfactory. Because MS and SPS share neurological symptoms such as spasticity and rigidity, we assessed its use for SPS patients. Our case report suggests that that THC-CBD oromucosal spray is an alternative treatment for patients with refractory SPS, and further validation is appropriate.

REFERENCES

1. Moersch FP, Woltman HW. Progressive fluctuating muscular rigidity and spasm (''stiff-man'' syndrome); report of a case and some observations in 13 other cases. *Proc Staff Meet Mayo Clin* 1956;**31**:421–427.
2. Barker RA, Revesz T, Thom M *et al*. Review of 23 patients affected by the stiff man syndrome: clinical subdivision into stiff trunk (man) syndrome, stiff limb syndrome, and progressive encephalomyelitis with rigidity. *J Neurol Neurosurg Psychiatry* 1998;**65**:633–640.
3. Meinck HM, Thompson PD. Stiff man syndrome and related conditions. *Mov Disord* 2002;**17**:853–866.
4. Solimena M, Folli F, Aparisi R *et al*. Autoantibodies to GABAergic neurons and pancreatic beta cells in stiff-man syndrome. *N Engl J Med* 1990;**322**:1555–1560.
5. *Sativex: European public assessment report*. London: Medicines and Healthcare products Regulatory Agency, 2010. Available at: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con084961.pdf (accessed 14 August 2011).
6. Alonso J, Prieto L, Antó JM. The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): an instrument for measuring clinical results. *Med Clin Barc* 1995;**104**:771–776.

7. Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36 health survey. Manual and interpretation guide*. Boston, MA: The Health Institute, New England Medical Center, 1993.
8. Espay AJ, Chen R. Rigidity and spasms from autoimmune encephalomyelopathies: stiff-person syndrome. *Muscle Nerve* 2006;**34**:677–690.
9. Robson P. Expert Abuse potential and psychoactive effects of delta-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. *Opin Drug Saf* 2011;**10**:675–685.
10. Sastre-Garriga J, Vila C, Clissold S, Montalban X. THC and CBD oromucosal spray (Sativex®) in the management of spasticity associated with multiple sclerosis. *Expert Rev Neurother* 2011;**11**:627–637.