

EFFICACY OF LEVETIRACETAM IN A CASE OF STIFF-PERSON SYNDROME - CASE REPORT

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ABSTRACT

Stiff-person syndrome (SPS) is a rare neurologic disorder characterized by severe axial and proximal limb rigidity and unexpected spasms due to continuous motor unit activity. There are several SPS variants, including stiff trunk syndrome, stiff limbs syndrome, progressive encephalomyelitis with rigidity, SPS-plus, and paraneoplastic SPS. These syndromes are often found in association with other autoimmune disorders such as diabetes mellitus in more than one thirds of all cases, and, less commonly, those caused by antithyroid, antinuclear and antiparietal cell antibodies. Glutamic acid decarboxylase autoantibodies (anti-GAD) are found in around 60 to 80 % of SPS cases. GAD is a cytoplasmic enzyme that accelerates the conversion of glutamic acid to gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter present in the brain and spinal cord. GAD is synthesized mainly in presynaptic GABAergic neurons in the central nervous system and in the beta cells in the islets of Langerhans in the pancreas. Benzodiazepines and baclofen have been used as the main therapeutic interventions addressing the muscle rigidity and spasms in these cases. Here, we described a patient with anti-GAD positive SPS with marked improvement of muscle rigidity and spasms after use of a new anticonvulsant drug (levetiracetam).

Keywords: Stiff person syndrome; Anti-GAD; Levetiracetam.

EFICÁCIA DO LEVETIRACETAM EM UM PACIENTE COM SÍNDROME DE PESSOA RÍGIDA – RELATO DE CASO

RESUMO

Síndrome de pessoa-rígida (SPR) é uma rara afecção neurológica caracterizada por uma intensa rigidez axial e proximal de membros, com espasmos inesperados, devido a uma atividade contínua das unidades motoras. Existem diversas variantes da SPR, incluindo Síndrome de tronco rígido, síndrome de membro rígido, encefalomielite progressiva com rigidez, SPR-plus e SPR paraneoplásica. Essas síndromes são frequentemente encontradas em associação com outras doenças auto-imunes, como diabetes mellitus, em mais de um terços de todos os casos, e, menos comumente, com outras associadas com os anticorpos antitireoidianos, antinucleares e anti-células parietais. Autoanticorpos contra a descarboxilase do ácido glutâmico (anti-GAD) são encontrados em cerca de 60 a 80% dos casos SPR. A GAD é uma enzima citoplasmática que acelera a conversão de ácido glutâmico a ácido gama - aminobutírico (GABA), um neurotransmissor inibitório presente no cérebro e medula espinhal. Ela é sintetizada principalmente em neurônios gabaérgicos pré-sinápticos no sistema nervoso central e nas células beta nas ilhotas de Langerhans no pâncreas. Benzodiazepínicos e baclofen têm sido utilizados como as principais intervenções terapêuticas, abordando a rigidez muscular e os espasmos nestes casos. Aqui, nós descrevemos um paciente com SPR com anti-GAD positivo que apresentou uma melhora acentuada da rigidez muscular e dos espasmos após uso de uma nova droga anticonvulsivante (levetiracetam).

Palavras-chave: Pessoa Stiff síndrome; Anti-GAD; Levetiracetam.

1 INTRODUCTION

The term “stiff-man” was first introduced by Moersch and Woltman in 1956⁽¹⁾ to describe the clinical features of “progressive fluctuating muscular rigidity” and spasm seen in 14 patients at the Mayo Clinic over a period of 32 years. Nowadays, the term “stiff person” is preferred. The best management of its muscle rigidity and spasms, which is associated with GABA system dysfunction, remains controversial.⁽²⁾ LEV is a new AED with a favorable pharmacologic profile, efficacy in different types of epilepsy, and only minor side effects.⁽³⁾ The facilitation of inhibitory GABAergic transmission is part of the mode of action of LEV. As LEV shares structural analogy with piracetam, it has been successfully used in myoclonic syndromes.^(4,5)

2 CASE PRESENTATION

The patient signed a term of consent, which allowed us to show her image and expose her clinical data in the present medical article. She was a 50-year-old woman with a three-year history of progressive painful muscular rigidity and spasms which were most severe in lumbar and abdominal muscles leading to significant hyperlordosis (Figure 1). She also had a 10-year history of breast cancer, successfully treated. Laboratory work-up was unremarkable. The ENMG disclosed spontaneous and continuous activity of normal motor units in lumbar muscles (Figure 2). Anti-GAD was positive and there was no sign of breast cancer recurrence based on a normal PET-CT scan. Initial symptomatic treatment with diazepam 30 mg/day and baclofen 40 mg/day, brought mild improvement. The clinical picture improved after use of IV immunoglobulin (IVIg) 0.4 g/kg/day for 5 days, followed by single monthly doses. Along 4 years of follow up, the patient had periods of sustained relief and followed by periods of severe spasms, generally triggered by anxiety. Recently, her symptoms became refractory to IVIg as well as high doses of tizanidine and botulinun toxin. A trial of levetiracetam up to 500 mg twice a day brought remarkable improvement.



Figure 1

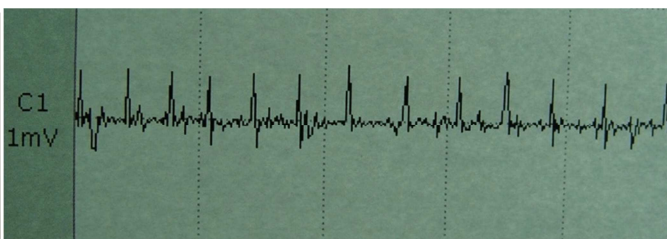


Figure 2

3 DISCUSSION

In spite of being almost impossible to forget its classical clinical features, SPS is a rare entity and it can be underdiagnosed by other medical areas. An important diagnostic criterion is the presence of continuous motor unit activity on electromyography despite attempted relaxation.⁽²⁾ Continuous motor unit activity may be recorded in many axial muscles and also in leg and proximal arm muscles. However, this activity is most evident in paraspinal muscles, particularly thoracolumbar and rectus abdominis muscles. Agonist and antagonist muscle groups are equally affected. The continuous motor unit activity gives rise to the board-like rigidity of axial muscles and produces the abnormal hyperlordotic posture of the lower trunk. Such activity subsides during sleep, peripheral nerve or spinal nerve root block, spinal anaesthesia and general anaesthesia. These findings indicate a central origin for the abnormal muscle activity. The prominence of rigidity and spasms in axial muscle groups is a universal and striking feature in the SPS.^(2,6) The morphology of the individual motor units is normal and there is no spontaneous activity such fibrillations, positive sharp waves and fasciculations.⁽³⁾ Peripheral nerve motor and sensory conduction velocities are normal.⁽²⁾ The significance of the association of insulin-dependent diabetes mellitus (DM) and SPS was enhanced by Solimena et al⁽⁷⁾ when they presented evidence for the existence of antibodies directed against glutamic acid decarboxylase (GAD), the GABA-synthesizing enzyme. GAD antibodies can be detected in serum and CSF of 60% SPS patients and can occur as a paraneoplastic disorder. Of the large number of therapies tried, benzodiazepines and baclofen have proven to be the most valuable.⁽²⁾ Other drugs reported to be of benefit include sodium valproate and tizanidine. Carbamazepine and phenytoin, in general, are not helpful, in contrast to their beneficial effects on continuous motor unit activity of peripheral nerve origin. Immunotherapy/immunosuppression can be used. Corticosteroids, azathioprine are described to be useful, but plasmapheresis and IVIg seem to achieve better results.^(2,7) Unfortunately, many SPS patients do not obtain improvement with such form of therapy. In this sense, new approaches can be tried. LEV is one of interesting drug options. LEV is a new anti-epileptic drug with a favorable pharmacologic profile, efficacious in different types of epilepsy, with only minor side effects.

4 CONCLUSION

The facilitation of inhibitory GABAergic transmission is part of LEV mechanism of action. Rüegg et al,⁽⁹⁾ Shimberg et al,⁽¹⁰⁾ and Sechi et al⁽¹¹⁾ also had observed the same improvement of SPS with this drug. SPS is exceedingly rare with many difficulties in its management. Further studies are necessary, but it is possible to speculate that the long-term management of SPS muscle spasms can, in the future, include LEV as an important drug with the aim to reduce these spasms and rigidity, with fewer adverse events.

REFERENCES

1. Moersch FP, Woltman HW. Progressive fluctuating muscular rigidity and spam ('stiff-man' syndrome): report of a case and some observations in 13 other cases. *Mayo Clin Proc.* 1956; 31:421-7.
2. Thompson PD. Stiff people. In: Marsden CD, Fahn S. *Movement Disorders 3.* Oxford: Butterworth-Heinemann; 1994. p. 373-405.
3. Welty T, Gidal BE, Ficker DM, Privitera MD. Levetiracetam: a different approach to the pharmacotherapy of epilepsy. *Ann Pharmacother.* 2002;36:296-304.
4. Frucht SJ, Louis ED, Chuang C, Fahn S. A pilot tolerability and efficacy study of levetiracetam in patients with chronic myoclonus. *Neurology.*2001;57(6):1112-1114.
5. Agarwal P, Frucht SJ. Myoclonus. *Curr Opin Neurol.*2003;16:515-521.
6. Lorish TR, Thorsteinsson G, Howard FM. Stiff-man syndrome updated. *Mayo Clin Proc.*1989;64:629-36.
7. Dalakas MC, Fujii M, Li M, Lufti B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med.*2001;345:1870-1876.
8. Solimena M, Folli F, Denis-Donini S, Comi GC, Pozza G, De Camilli et al. Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy and type 1 diabetes mellitus. *N Engl J Med,* 1988;318:1012-20.
9. Rüegg SJ, Steck AJ, Fuhr P. Levetiracetam improves paroxysmal symptoms in a patient with stiff-person syndrome. *Neurology.*2004;62:338.

10. Shimberg WR, Patel NB, Sullivan KL, Hauser RA, Zesiewicz TA. Levetiracetam for stiff-person syndrome: report of 2 patients. *Clin Neuropharmacol.* 2008;31(5):301-2.

11. Sechi G, Barrocu M, Piluzza MG, Cocco GA, Deiana GA, Sau GF. Levetiracetam in stiff-person syndrome. *J Neurol.* 2008;255(11):1721-5.