STIFF PERSON SYNDROME WITH NEGATIVE ANTI-GAD65 ANTIBODIES. CASE REPORT

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ABSTRACT

We present a case of 42-year-old woman without significant medical history, admitted in our clinic for painful neck stiffness, aggravated by emotions and stress relieved during sleep, accompanied by sweating, predominantly lower limbs weakness. The symptoms insidiously appeared one month prior presentation. On neurological examination we found painful paravertebral and laterocervical muscle contracture and spastic paraparesis. Laboratory tests included the analysis of anti-glutamic acid decarboxylase (anti-GAD65) and anti-Borrelia antibodies, carcinoma antigens (CA 125, CA 15-3) which were found negative. Cerebrospinal fluid analysis found positive oligoclonal bands with a slight increase of IgG component. Other tests including thyroid function were found normal. Brain and spinal MRI examinations showed no changes. Methylprednisolone, baclofen and carbamazepine were administered without a significant improvement. After 4 months from the first admission, the patient returns with increased symptoms for which plasma exchange achieved a slight improvement of motor deficit and rigidity. Stiff person syndrome is thought to be triggered by anti-GAD antibodies that limit the GABA receptor activity, although about 10 to 40% of the patients do not shows these antibodies in the serum.

Key words: anti-GAD antibodies; stiff person syndrome

INTRODUCTION

Stiff – person syndrome (SPS) is a rare neuroimmunologic disorder characterized by progressive muscle rigidity, spasms and continuous motor unit activity. Was first described by Moersch and Woltman in 1956 (1). Until that time patients with similar symptoms were diagnosed with psychogenic rigidity (2). The clinical presentation is usually in the adulthood with intermittent spasm that eventually become persistent and painful predominantly in the axial and proximal muscles. Quite different form spasticity and extrapyramidal rigidity, these painful muscular spasms resembles more with a tetaniform syndrome (3). This symptomatology is aided by electromyography, laboratory tests and the presence of autoantibodies. Anti-glutamic acid decarboxylase antibodies (anti GAD) are detected in 60-90% of patients with this syndrome whether is isolated, in the context of an autoimmune condition, or as a paraneoplastic syndrome.

CASE REPORT

We present a case of a 42 years old woman, admitted in the Neurology Department for painful neck stiffness, aggravated by emotions and stress relieved during sleep, accompanied by sweating, gait impairment and muscular weakness. The onset was insidious about one month prior presentation with relative rapid progression. The general examination showed an overweight patient with a body mass index of 29,1 kg/sqm. There were no other abnormal clinical features in the general examination (BP – 140/80 mmHg; HR-80 bpm, sinus rhythm). The neurological examination at admis-

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sion showed a continuous paravertebral and laterocervical muscle contracture, brisk tendon reflexes, plantar flexion, reduced segmental strength with lower limbs predominance and muscular rigidity. No sensorial, sensitive or coordination impairments were found. The laboratory findings showed a serum glucose of 76mg/dl, glycated hemoglobin (HbA1c) = 5,3%, normal oral glucose tolerance test. Serum vitamin B12 = 236 pg/ml, ESR= 34 mm/h, fibrinogen = 367,5 mg/dl, ASLO < 200, PCR < 6, RF < 8, C_3 complement = 174 mg/dl, absent ANA antibodies, creatine kinase = 25U/L, LDH= 124U/l and normal complete blood count. Further test included negative anti-GAD and anti-Borrelia antibodies. Ovarian cancer antigen CA 125, breast cancer antigen CA 15-3 and VDRL were also negative. Lumbar tap revealed oligoclonal bands with a slight increase in IgG component. Endocrine markers (TSH, FT4, anti-thyroid peroxidase antibodies) were found within normal ranges. Head and spine MRI (native and contrast) showed no brain and medullar changes. Needle EMG in repose determined a continuous tetaniform activity, very sharp on sternocleidomastoid muscle, more attenuated on trapezius muscle, with failure of relaxation (Figures 1, 2). No SPECT, PET, amphiphysin antibodies were performed due to unavailability at that moment.

We diagnosed the case with SPS and initiated the treatment with methylprednisolone 1 g daily, 7 days, oral baclofen 6 x 25 mg daily, diazepam 2 mg daily, carbamazepine 400 mg/day, sertraline 50 mg/day, tiapride 100 mg/2ml daily, potassium supplements, B1 and B6 vitamins with no considerable improvement of symptoms. L-DOPA test, to exclude other dystonias related with parkinsonian syndrome, aggravated the initial symptoms and was withdrawn. After four months from the first admission, the patient returns with painful cervicodorsal contracture and lower limb contracture and performs two sessions of plasma exchange (patient refuses the next sessions). After plasma exchange the patient's evolution is slightly improved, continuing the treatment with Baclofen 150 mg/day and carbamazepin 400 mg/day, but still requires daily personal assistance. The screening for breast, genital, pulmonary and other abdominal cancers was negative. We also found no clues for autoimmune disorders. EMG ruled out other conditions such as primary lateral sclerosis, Isaac's neuromyotonia, paramyotonia. Normal imagistic findings ruled out different types of myelopathies, spinal

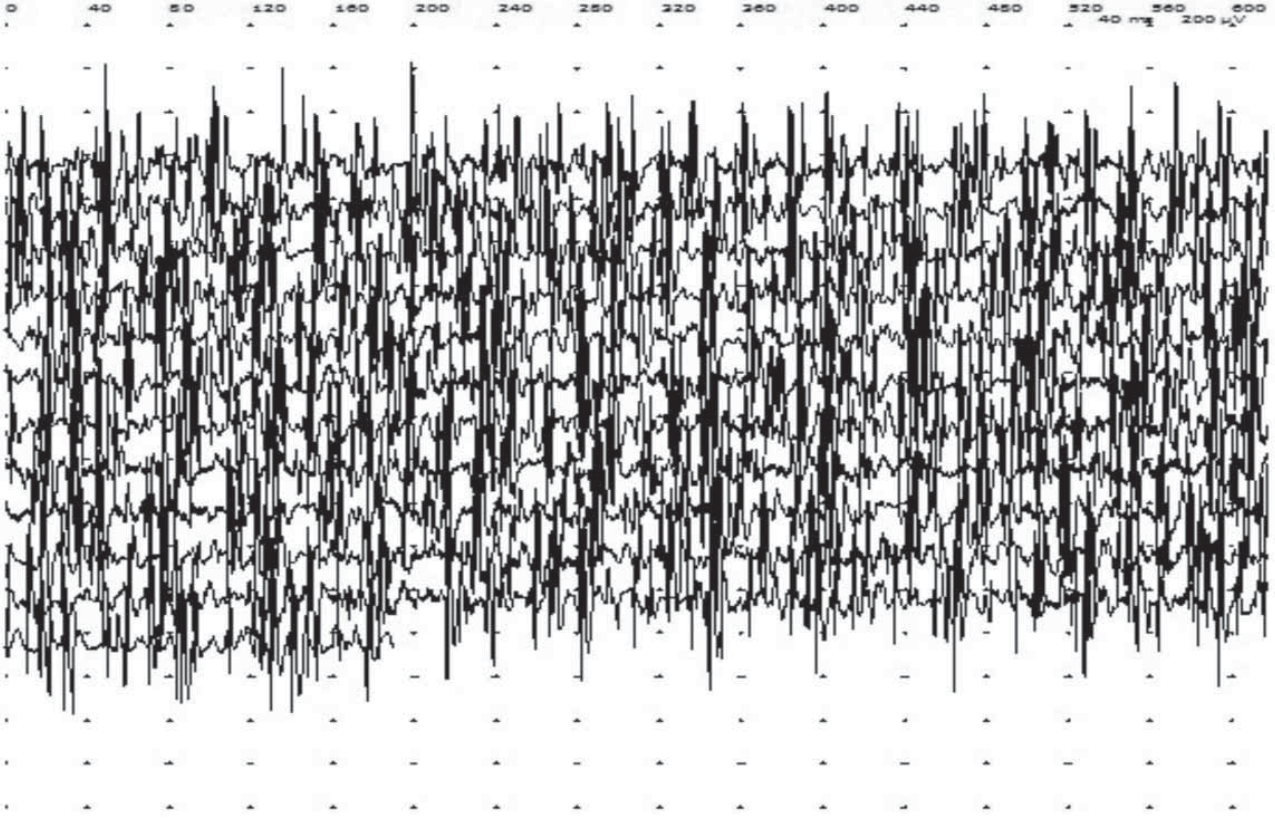

FIGURE 1. *Continuous electrical activity of tetaniform type, very sharp on SCM muscle, more attenuated on trapezius muscle, caused by failure on relaxation (in repose)*

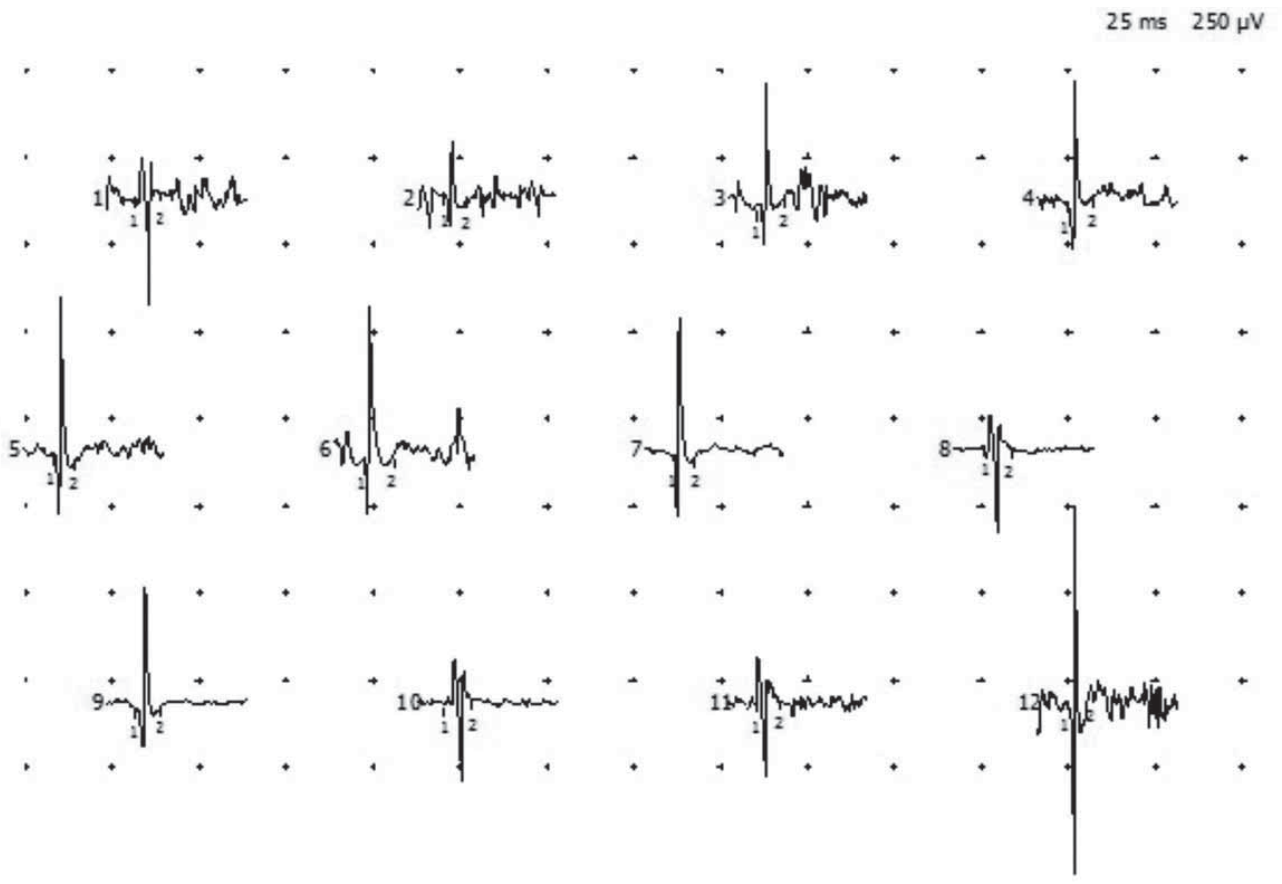

FIGURE 2. *Needle EMG showing right trapezius and sternocleidomastoid motor unit potentials with normal duration and amplitude.*

trauma sequelae. Other differential diagnosis included parkinsonian syndromes, dystonias, neuroleptic malignant syndrome and psychogenic condition, all excluded on clinical and paraclinical findings.

DISCUSSION

SPS is nowadays considered a neuroimmunologic disorder frequently associated with autoimmune diseases such as: type 1 diabetes mellitus, pernicious anemia, vitiligo, thyroiditis and myasthenia with or without thymoma (4). The association with these autoimmune diseases underlines pathogenesis of SPS, but it can be also found as a paraneoplastic syndrome especially in breast cancer, small-cell lung carcinoma, Hodgkin's disease and colon cancer (5). Other conditions resembling SPS were described as progressive encephalomyelitis with rigidity, neuromyotonia and even spinocerebellar ataxia (6,7,8). Although are not validated, the Dalakas criteria are used worldwide to diagnose SPS (9) as it follows:

1. stiffness in the axial muscles, prominently in the abdominal and thoracolumbar paraspinal muscle leading to a fixed deformity (hyperlordosis);
2. superimposed painful spasms precipitated by unexpected noises, emotional stress, tactile stimuli;
3. confirmation of the continuous motor unit activity in agonist and antagonist muscles by electromyography;
4. absence of neurological or cognitive impairments that could explain the stiffness;
5. positive serology for GAD65 (or amphiphysin) autoantibodies, assessed by immunocytochemistry, western blot or radioimmunoassay;
6. response to diazepam.

Antibody testing is very useful in the diagnosis of SPS. Anti-GAD antibodies are detected in 60-90% of patients and are strongly supportive of SPS, but the absence of these antibodies does not rule out a diagnosis of SPS (10). Other researched autoantibodies in SPS are anti-amphiphysin and anti-Ri antibodies, detected when SPS is associated with malignancy, often in breast cancer and Hodgkin lymphoma (11). Beside the immunology tests, electromyography is a very important diagnostic tool

and reveals continuous motor unit activity that disappears during sleep and general anesthesia. This is completed by the role of electromyography for differential diagnosis as is for cerebral and spine imagery.

There is no curative treatment for SPS but benzodiazepines and baclofen are the first line symptomatic therapy for SPS (12). Corticosteroids are used in high doses in patients refractory or intolerant to benzodiazepines/baclofen. The efficacy of intravenous immunoglobulin was reported in a study comparing placebo to intravenous immunoglobulin therapy where 11 of 16 patients showed improvement of functional status after intravenous immunoglobulin therapy (13). Plasma exchange has demonstrated mixed clinical efficacy and rituximab, an anti-CD-20 monoclonal antibody that attacks B lymphocytes, has been reported to lead the clinical improvement of SPS (12).

CONCLUSION

In this report, we describe a particular case of SPS with negative anti-GAD65 antibodies, and without other autoimmune or neoplastic disorders associated, with relative moderate improvement of symptoms, after plasmapheresis. We believe that our case report can provide data to the growing amount of information about SPS with negative anti-GAD antibodies.

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