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Single Case – General Neurology

Paraneoplastic Stiff Person Syndrome in Early-Stage Breast Cancer with Positive Anti-Amphiphysin Antibodies

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Keywords

Stiff person · Cancer · Anti-amphiphysin

Abstract

Stiff person syndrome (SPS) is a rare neurologic disorder, characterized by muscle rigidity and spasms. Anti-glutamic acid decarboxylase (anti-GAD) antibodies are associated with the classic form of SPS, while antibodies against amphiphysin are associated with the paraneoplastic form of the disease. We present the case of a patient with paraneoplastic SPS, presenting with muscle cramps of lower extremities that progressed to severe muscle rigidity and spasms, associated with a right breast tumor and positive anti-amphiphysin antibodies. Paraneoplastic SPS is a rare neurological disorder, challenging for the physicians both to diagnose and treat.

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Published by S. Karger AG, Basel

Introduction

Stiff person syndrome (SPS) is considered one of the rarest diseases involving the neurologic system, characterized by muscle rigidity and spasms. It was first described in 1956 by Moersch and Woltman in a study of 14 patients with back, abdominal, and thigh muscles fluctuating and progressive rigidity associated with painful spasms [1].

The true incidence of SPS is currently unknown, but it is believed to be around 1 or 2 cases per million people worldwide [2]. Cases have been described in both sexes, but with a higher prevalence in women [2].

SPS is divided into three forms: classic SPS, paraneoplastic SPS and variants [3]. The main clinical symptoms are muscle rigidity and spasms affecting predominantly truncal muscles [4]. Simultaneous activation of both agonist and antagonist paraspinal and abdominal muscles is present [3]. Therefore, lumbar hyperlordosis and postural instability are key symptoms in most patients with SPS [3]. Spasms appear intermittently, are usually spontaneous in nature but can be provoked by an unexpected noise, sudden movements or psychological stress [4]. Psychiatric involvement is quite common, including depression, anxiety, phobias, and panic attacks [3]. Imaging workup is usually with no specific findings [2], but it can help clinicians with differential diagnosis [4]. Electromyography (EMG) may show signs of continuous spontaneous discharges (continuous motor unit activity at rest) or it may be normal [2, 3].

Since the discovery of anti-glutamic acid decarboxylase (anti-GAD) antibodies in 1988, approximately 60% of the cases were diagnosed based on their presence in the serum [1]. GAD is an enzyme with a role in synthesizing the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) [2]. Anti-GAD antibodies are also found in a number of other autoimmune diseases, most predominantly in type 1 diabetes mellitus and Hashimoto's thyroiditis [2, 3, 5]. Antibodies against amphiphysin (a synaptic vesicle protein) are associated with the paraneoplastic form of the disease [2].

Diagnosis of the disease can be achieved using the criteria proposed by Dalakas [6], which include clinical presentation, EMG testing, and positive serology findings for the aforementioned antibodies [3].

Treatment of SPS is based on enhancing GABA transmission and immunomodulatory agents [3]. Administration of intravenous immunoglobulin has been used, sometimes with a favorable outcome [2]. Plasmapheresis may be of benefit to some individuals with SPS but is still under investigation in order to establish side effects and effectiveness [7]. GABA-ergic agonists used for treatment include benzodiazepines, such as diazepam, prescribed in doses up to 40–100 mg/day [1, 2], and clonazepam. Baclofen is usually used in combination with the above-mentioned drugs. Antiepileptic drugs (such as valproate, pregabalin, gabapentin, and levetiracetam) have been reported to have beneficial outcomes in a small number of individuals [1, 7]. In the paraneoplastic form of SPS, symptomology usually improves with the treatment of the underlying malignancy [2].

Case Presentation

A 68-year-old, right-handed female presented with bilateral lower-extremity stiffness and severe pain, worsened by stimuli such as light, touch, sound, and stress, associated with

urine retention. The symptoms started 5 months before admission with lower extremity cramps that worsened gradually, associated with frequent falls. Three weeks before admission, the stiffness and pain became severe, first affecting the right lower extremity, then becoming bilateral. She had thoracic vertebral column magnetic resonance imaging (MRI) after the beginning of the symptoms, showing a D10 vertebral scaling, which was also present in previous examinations before the onset of symptoms (Fig. 1). The patient had a history of osteoporosis due to an early installed menopause. She was transferred to our unit from another hospital, where she received treatment with diazepam and baclofen, with improvement of symptoms at first, and then severe worsening, receiving sedation with Propofol and treatment with intravenous Ca^{2+} and Mg^{2+} for 2 days with yield of muscle spasms, the symptoms reappearing after stopping the administration. At examination, we found lumbar hyperlordosis, bilateral lower-extremity hypertonia, and no sensitive disorders, with the impossibility to assess lower extremity deep tendon reflexes and Babinski's sign due to severe pain at stimulation. We also found a lump in her right mammary gland.

The blood workup showed high creatine kinase, a slightly increased C4 complement and carcinoembryonic antigen, low serum sodium, a slightly increased C-reactive protein, iron-deficiency anemia, leukocytosis with neutrophilia, slightly modified hepatic workup, low folic acid, low vitamin D, normal thyroid workup, no infectious disease markers present for syphilis, *Borrelia*, herpes simplex virus 1 and 2, human immunodeficiency virus and Hepatitis B and C, and no autoimmune markers present for systemic lupus erythematosus, Sjögren's syndrome, vasculitis or scleroderma. The cervical MRI showed degenerative modifications and discopathy with no evident nerve root conflicts. Cerebral MRI revealed a left bulbar ischemic lesion and a calcified superior frontal meningioma.

A lumbar puncture was impossible to perform due to the severe contraction of paraspinal lumbar muscles. The psychologic examination showed moderate anxiety and depression, with high emotional reactivity. Mammary ultrasound showed a nodular lesion of 25/24/18 mm, highly hypoechoogenic with acoustic attenuation and irregular contour, corresponding with the aspect of a mammary neoplasm, BI-RADS score 5. A biopsy was performed, and the histopathological and immunohistochemical examination revealed an invasive no special type carcinoma, Nottingham grade II with numerous apoptosis, with no ductal in situ carcinoma component and no lymphatic vascular invasion, anatomopathological classification 5, 100% estrogen receptors, 85% progesterone receptors, KI-67 of 18% and positive E cad. Computer tomography of the thorax, abdomen, and pelvis did not reveal suspicious signs of metastatic lesions. Due to the symptoms, the presence of a breast tumor, and no other changes in the blood and imaging workup we suspected a paraneoplastic SPS. Anti-GAD antibodies were negative. Anti-amphiphysin antibodies were positive. EMG examination was done with the purpose of injecting botulinum toxin, and showed no significant changes. The tibial and peroneal nerves had normal motor (Fig. 2, 3) and sensitive conduction velocity and amplitude. The sural nerve was evaluated in clinostatism due to the patient's condition. The left anterior tibial muscle and vastus lateralis muscle had no spontaneous activity present.

The patient was given high doses of benzodiazepines (diazepam and clonazepam), baclofen, anti-epileptic drugs (levetiracetam), and gabapentin (Table 1), with good outcome on the spasticity and pain at first, and reappearing of severe pain after a few days of treatment. A urinary Foley catheter was placed for the urine retention. Botulinum toxin intramuscular injection was performed in the lower extremities, under EMG guidance, for pain relief, with

slight improvement of symptoms after 8–10 days. The patient also received symptomatic treatment with fentanyl patch 25 µg/72 h and cannabidiol oil CBD 1,350 mg/100 mL, 15 mL/day, with only slight improvement on pain. During hospitalization, the physical and mental state of the patient degraded. She refused swallowing food and liquids, so a nasogastric tube was placed for feeding and hydrating the patient. The urinalysis was positive for *Escherichia coli* ESBL, and antibiotic therapy was established according to antibiogram. Because of the general state of the patient, surgery for the breast tumor was timed, and she was transferred to an oncology unit to undergo hormonal treatment and plasma exchange when the clinical condition allowed it. Two days after admission to the oncology ward, the patient showed respiratory failure, which prompted intubation and transferal to the intensive care unit. Two days later, she entered cardiac arrest and died.

Discussion

Stiff person syndrome is a rare disorder, with unknown prevalence, affecting female patients more than male [7]. It is divided into three forms: classic SPS, paraneoplastic SPS, and variants [3].

Here, we present the case of a female patient with paraneoplastic SPS. Her main clinical symptoms were muscle cramps of the lower extremities and frequent falls 5 months before admission, which progressed to severe muscle rigidity and spasms, symptoms that are characteristic for SPS [5]. Rigidity also affected the truncal muscles, lumbar hyperlordosis and postural instability being present. These are key symptoms in most patients [3, 5]. Muscle spasms appeared intermittently, spontaneously, and provoked by unexpected noise, sudden movements, psychological, and emotional stress, as in SPS [4]. The patient also had depression and anxiety, which is usually associated with SPS [3].

In SPS, the imaging testing is mostly negative [2, 8]. So was the case in our patient, whose MRI findings did not explain the symptoms. Paraneoplastic SPS is commonly associated with malignant tumors such as breast, colon, lung, and thymus cancer and lymphoma [3]. In our case, the patient had an invasive no special type breast carcinoma.

Anti-GAD antibodies are common in SPS [9], but in paraneoplastic SPS, anti-amphiphysin antibodies are more specific [3, 7]. In our case, anti-GAD antibodies were negative, and anti-amphiphysin antibodies were positive.

In most cases of SPS, EMG shows continuous unit activity in the affected muscles [9, 10]. EMG showed no significant changes, but that could have been because the patient had already been given treatment. There are also reports of cases in which EMG was normal [2, 10].

The criteria proposed by Dalakas, which include clinical presentation, EMG testing, and positive serology findings for the aforementioned antibodies, can be used for the diagnosis of SPS [6] (Table 2).

Diazepam can be used in divided doses, gradually increasing the dose up to 100 mg, and clonazepam up to 6 mg [1]. Other medications used can be levetiracetam, baclofen, and gabapentin [1]. In our case, the patient received gradually increasing doses of diazepam and clonazepam associated with levetiracetam, baclofen, and gabapentin with slight improvement of symptoms at first, and then reappearance of said symptomology. In some cases, intramuscular injection of botulinum toxin can be used for muscle relaxation [3]. We decided in favor

of this approach for the severe spasms and pain, with only a partial improvement of symptoms. In paraneoplastic SPS, specific treatment of underlying cancer is needed [3]. In our case, the patient's condition did not allow surgery at that point, but she was transferred to an oncology ward for hormonal therapy.

The prognosis in SPS is variable, depending on numerous factors, such as underlying malignancy [3]. In this case, the prognosis was not favorable due to the psychologic factor and the patient's complications. The particularity of this case was the discordance between the stage of the cancer and the severe symptoms with only partial response to treatment.

Conclusion

In this report, we described the case of a patient with severe symptoms at an early stage of malignancy, only partially responsive to therapy, and with poor prognosis. A screening for underlying malignancy could be beneficial for patients suspected of SPS. Paraneoplastic SPS is a rare neurological disorder, challenging for the physicians both to diagnose and treat.

Acknowledgements

Dr. Nicu Draghici – Imogen Institute of Medical Research, Cluj-Napoca, Romania, for the neurophysiology studies, the imaging team and oncology team for the help in the diagnostic process.

Statement of Ethics

The patient's family has given their written informed consent to publish the case (including publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There was no funding agency involved in the production of this case report.

Author Contributions

All authors made clinical and scientific contributions in writing this paper.

References

- 1 Bhatti AB, Gazali ZA. Recent Advances and Review on Treatment of Stiff Person Syndrome in Adults and Pediatric Patients. *Cureus*. 2015 Dec;7(12):e427.
- 2 Smith SR, Fu JB. Paraneoplastic stiff person syndrome: inpatient rehabilitation outcomes of a rare disease from two cancer rehabilitation programmes. *J Rehabil Med*. 2016 Jul;48(7):639–42.
- 3 Buechner S, Florio I, Capone L. Stiff Person Syndrome: A Rare Neurological Disorder, Heterogeneous in Clinical Presentation and Not Easy to Treat. *Case Rep Neurol Med*. 2015;2015:278065.
- 4 Rosin L, DeCamilli P, Butler M, Solimena M, Schmitt HP, Morgenthaler N, et al. Stiff-man syndrome in a woman with breast cancer: an uncommon central nervous system paraneoplastic syndrome. *Neurology*. 1998 Jan;50(1):94–8.
- 5 Egwuonwu S, Chedebeau F. Stiff-person syndrome: a case report and review of the literature. *J Natl Med Assoc*. 2010 Dec;102(12):1261–3.
- 6 Dalakas MC. Stiff person syndrome: advances in pathogenesis and therapeutic interventions. *Curr Treat Options Neurol*. 2009 Mar;11(2):102–10.
- 7 Newsome SD. Stiff Person Syndrome. National Organisation for Rare Disorders. <https://rarediseases.org> (Accessed on 27th October 2019).
- 8 Silverman IE. Paraneoplastic stiff limb syndrome. *J Neurol Neurosurg Psychiatry*. 1999 Jul;67(1):126–7.
- 9 Barker RA, Revesz T, Thom M, Marsden CD, Brown P. 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 Nov;65(5):633–40.
- 10 Fanous I, Dillon P. Paraneoplastic neurological complications of breast cancer. *Exp Hematol Oncol*. 2016 Oct;5(1):29.



Fig. 1. Thoracic vertebral MRI. D10 vertebral scaling and degenerative changes without spinal marrow involvement.

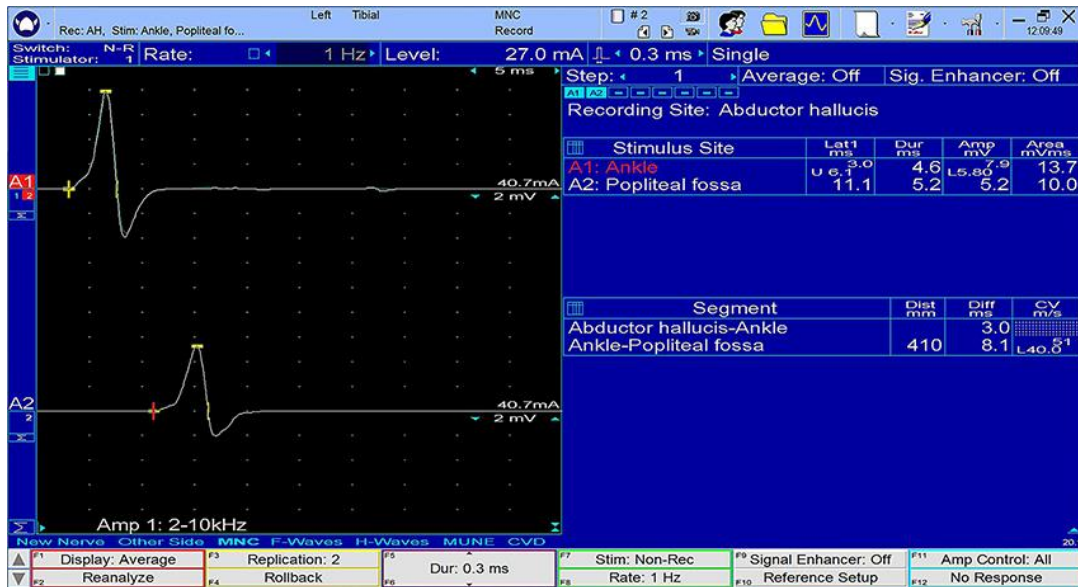


Fig. 2. Left tibial nerve motor neuron conduction (Imogen Institute of Medical Research).

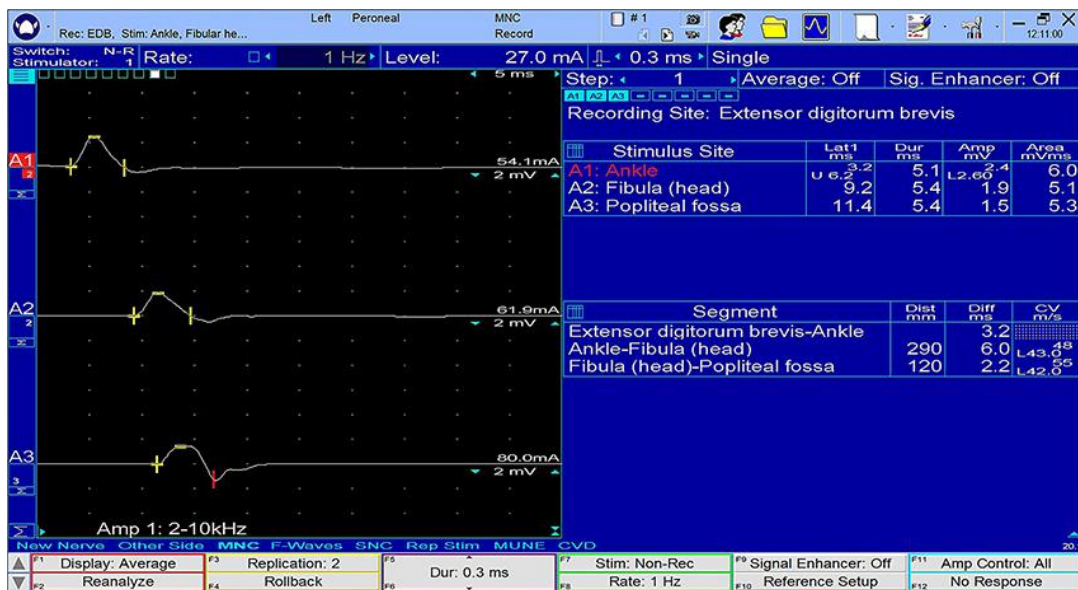


Fig. 3. Left peroneal nerve motor neuron conduction (Imogen Institute of Medical Research).

Table 1. Drug dosage administered during hospitalization in our unit

Drug	Dose (mg/day)			
	at admission	after improvement of symptoms	after worsening of symptoms	after botulinum toxin administration
Diazepam intramuscular	40	30	30	20
Clonazepam oral	1.5	1.5	2	1.25
Levetiracetam intravenous, then oral	750	750	750	750
Baclofen oral	100	100	100	100
Gabapentin oral	900	–	–	–

Table 2. Dalakas criteria of SPS present in our patient

	Dalakas criteria for SPS [6]	Our patient
1	Rigidity in limbs and trunk muscles, prominent in thoracolumbar and abdominal muscles	Rigidity in lower extremities and lumbar paraspinal muscles
2	Continuous contraction of agonist and antagonist muscles (clinically and on EMG)	Continuous contraction of agonist and antagonist muscles of lower extremities (clinically)
3	Spasms precipitated by stimuli: noise, tactile, emotional	Spasms precipitated by noise, light, touch, stress
4	Absence of other neurologic disease-explaining symptoms	MRI and bloodwork findings did not explain symptoms
5	Positive anti-GAD65/anti-amphiphysin antibodies (immunocytochemistry, western blot, radioimmunoassay)	Positive anti-amphiphysin antibodies (western blot)