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Letter to the Editor

Graves' disease as a first autoimmune manifestation of a stiff person syndrome

Une maladie de Basedow comme première manifestation auto-immune d'un syndrome de l'homme raide

1. Introduction

Stiff person syndrome (SPS) is a disabling and rare autoimmune neurological disorder characterized by progressive rigidity and paroxysmal painful spasms involving the truncal and proximal limb muscles. This syndrome can be associated with other autoimmune endocrinopathies such as diabetes mellitus or thyroiditis. Here, we report a rare case of a patient presenting with SPS and type 1 diabetes mellitus (T1DM) that appeared a few years after Graves'disease (GD).

2. Case report

A 51-year-old Caucasian woman was admitted to the department of neurology for gait disturbance. She had a thyroidectomy five years ago. At the time of surgery, no neurological evaluation was performed. She was treated for diabetes mellitus for six months. Symptoms of stasiphobia (fear to stand erect) and basophobia (morbid fear of standing or walking) started after a serious fall two years earlier. Later, she progressively developed rigidity, enlargement of the base of support and episodic painful spasms of her legs, resulting in considerable difficulty in standing up and walking. Initial evaluation, made in another institution 18 months earlier, consisted in lumbar puncture, spinal cord and brain magnetic resonance imaging, dopamine transporter SPECT imaging and electroneuromyography (EMG). All investigations were unremarkable. Nevertheless, the walking disorder and the falls got worse. On admission, she was almost unable to walk without aid. Furthermore, she presented a stiff "robotic" gait, proximal paraparesia, leg rigidity, bilateral extensor plantar response and hyperreflexia of lower limbs. Routine biological testing, thyroid function tests, antinuclear antibody and rheumatoid factor were normal as well as serologic testing for Lyme disease, syphilis, HIV and viral hepatitis B and C. Glycosylated haemoglobin (HbA1c) level was 8.3%. Autoimmune laboratory tests revealed elevated serum antibodies (Abs) level to glutamic acid decarboxylase 65 kD isoform (GAD65) (> 171 U/mL; normal < 23 ; enzyme linked immunosorbent assay (Elisa) test). The EMG recordings revealed continuous motor unit activity in the *medial gastrocnemius* and *vastus medialis* as well as in the paraspinal muscles. Cerebrospinal fluid (CSF) examination revealed unmatched oligoclonal bands and the presence of GAD65-Ab and GAD 67 kD isoform (GAD67) Ab (90 U/mL and 66 U/mL respectively; normal < 5.0 ; Elisa test) with intrathecal synthesis of Ab-specific IgG (index 9.9, based on formula from Saiz et al. [1]). The paraneoplastic Ab panel was negative in serum. There was no sign of neoplasm on positron emission tomography imaging. A diagnosis of SPS was made on this basis.

Given the uncontrolled diabetes, the patient was referred to the department of endocrinology and diabetes. At that time, she was treated with oral anti-diabetic drugs (metformin 700 mg three times/day and gliclazide 60 mg/day). She had remained obese for years with a body mass index of 32 kg/m^2 but had lost 21 kg during the last two years. A HbA1c level of 6.2% fifteen months earlier was the first evidence of prediabetes. On admission, homeostatic model assessment (HOMA) demonstrated insulin deficiency with a beta cell function at 27.6% of normal and an insulin resistance value of 1.27. The auto-Ab to protein tyrosine phosphatase-related islet antigen 2 (IA-2) and the anti-islet cell Ab were strongly positive, respectively at 12.7 UI/mL (normal < 1.4) and 1/3200 (normal < 1/12). The anti-insulin auto-Abs were negative. A diagnosis of latent autoimmune diabetes of the adult (LADA) associated with an autoimmune SPS was made. The current treatment was discontinued and replaced by a basal-prandial insulin therapy regimen. Patient past history revealed a thyroidectomy that was performed after a third relapse of GD. Hyperthyroidism started fifteen years ago. At that time, thyroid stimulating immunoglobulin (TSI) was positive. Our assessment showed that autoimmune Abs including TSI, anti-gastric parietal cell, anti-intrinsic factor, anti-21-hydroxylase, anti-transglutaminase, and anti-gliadin Abs were all negative. Only the anti-thyroid peroxidase (TPO) and anti-thyroglobulin Abs were strongly positive at 45.2 UI/mL (normal < 5.6) and 21.1 UI/mL (normal < 4.1), respectively. Adrenal function was normal.

Six months later, HbA1c level was 6.5% and thyroid function tests were normal on 175 μg L-thyroxin daily. In the meantime, the patient started oral diazepam and intravenous immunoglobulin therapy (2 g/kg, every six weeks), which significantly improved her mobility.

3. Discussion

We describe here the case of a SPS associated with LADA and GD, the latter preceding the onset of other diseases by fifteen years. A common autoimmune pathogenic process can be suspected.

Moersch and Woltman are the first who described the formerly called stiff-man syndrome in 1956 [2]. The prevalence of SPS is not well known but is estimated in one publication at approximately 1/1,250,000 [3]. This rare disorder predominantly affects women and the median age at onset is 40 years [4]. The classical presentation is characterized by progressive muscle stiffness and rigidity with superimposed episodic painful spasms involving the truncal and proximal limb muscles [3]. Symptoms are exacerbated by external stimuli like loud noise [5]. The patients end up walking slowly with a wide-based gait and tend to fall. Subsequently, they develop specific phobia such as agoraphobia, stasiphobia or basophobia [3,4].

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The pathogenesis of SPS is not yet fully understood but it is thought to be an immune-mediated movement disorder. Indeed, 60% of the SPS are associated with high GAD-Ab titers in serum and CSF [6]. In this case, the demonstration of specific intrathecal synthesis of Ab-specific IgG and the presence of GAD67-Ab in the CSF strongly support that the neurological syndrome is related to GAD autoimmunity [7]. GAD is an enzyme expressed in the central nervous system (CNS) and islet cells of the pancreas, which intervenes in gamma-amino-butyric acid (GABA) synthesis, a major inhibitory neurotransmitter [5,8,9]. Even if GAD-Ab appears not to be pathogenic, the decreased inhibition of the CNS via GABA-ergic neurons produces a characteristic continuous motor unit activity with the simultaneous contraction of agonist and antagonist muscles at rest [5,9]. The EMG showed these electrophysiological hallmarks in our patient.

Patients with T1DM also present elevated serum GAD65-Ab isoform titers but the values are up to 100 fold higher in case of the neurological disorder [4,9]. About 40% of SPS are associated with T1DM [4]. Conversely, only few patients with T1DM develop SPS. In a series of 99 SPS patients, McKeon et al. showed that T1DM preceded SPS diagnosis for years in more than two out of three cases. Furthermore, that proportion was higher when other islet auto-Abs were present [4]. Interestingly, our patient developed neurological symptoms related to GAD autoimmunity one year before the diagnosis of diabetes.

SPS can also be associated with other autoimmune disorders such as autoimmune thyroiditis, GD, pernicious anaemia, vitiligo and Addison's disease [4,5,9]. However, there are few cases reported in literature associating SPS and GD [10,11]. The association of SPS, T1DM and thyroiditis was reported in one case but no positive Abs supported the diagnosis of thyroiditis [12]. McKeon et al. found autoimmune thyroid disease in 35% of GAD65-Ab seropositive patients [4]. Unfortunately, they did not mention the kind of thyroid disease and the timing between SPS and thyroid disorder occurrence. We only found two cases associating GD and SPS. One had long-standing musculoskeletal complaints before GD onset and was ultimately diagnosed with SPS [10]. The other had signs and symptoms of hyperthyroidism a few months before stiffness [11]. In both cases, hyperthyroidism was poorly controlled until SPS was treated with immunosuppressive therapy and none required thyroidectomy. In our patient, the diagnosis of GD was made in another institution on the basis of acute hyperthyroidism, goiter, exophthalmia and high TSI titers. The three relapses of hyperthyroidism after antithyroid agent withdrawal and the requirement of curative thyroidectomy also support the diagnosis [13]. Anaesthesia and surgery for GD were uneventful in our patient.

This brings us to the peculiar situation of patients with SPS who will undergo surgery. Given the rarity of the neurological disorder, there is little experience regarding anaesthesia in patients with SPS. An increased risk of postoperative hypotonia after general anaesthesia has been highlighted when using volatile anaesthetics and neuromuscular blocking drugs [14,15]. However, contradictory data have been observed by other authors who 5reported uneventful procedures [16] and the safety of total intravenous anaesthesia [17,18]. It has also been suggested that the prolonged hypotonia following general anaesthesia is not induced by neuromuscular blockade but could result from the interaction between SPS medications (such as baclofen or diazepam) and volatile agents, owing to their effects on GABA receptors [19] . Although no anaesthetic agent or method is contraindicated, extreme caution should be used in patients with SPS treated with baclofen or diazepam in the preoperative period. The use of minimal paralytics is desirable as much as possible along with a close neuromuscular monitoring. Finally, it should be noted that exacerbation of SPS can be triggered by surgery, making continued maintenance therapy of SPS necessary during pre- and postoperative periods.

The association of T1DM and autoimmune thyroid disease is sufficient to diagnose autoimmune polyendocrine syndrome type 2 (APS-2) [20,21]. Because SPS is an autoimmune disease that can be associated with other autoimmune disorders, it would make sense to consider SPS as a component of APS-2 and screen other autoimmune disorders belonging to APS-2 in patients with SPS. However, apart from anti-GAD, anti-IA-2, anti-islet, anti-TPO and anti-thyroglobulin Abs, other organ-specific auto-Abs were negative in our patient at the time of the assessment.

4. Conclusion

In conclusion, we describe the first APS-2 associating T1DM, GD and SPS. Moreover, a latency period of fifteen years between GD and SPS occurrence has never been reported. Clinicians should be aware of a diagnosis of SPS in patients affected by autoimmune endocrine disorders combined with unusual neurologic symptoms.

Consent

Informed consent was given by the patient before submitting this case report.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Saiz A, Blanco Y, Sabater L, González F, Bataller L, et al. Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. Brain 2008;131:2553–63.
[2] 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;31:421–7.
[3] Espay AJ, Chen R. Rigidity and spasms from autoimmune encephalomyelopathies: stiff-person syndrome. Muscle Nerve 2006;34:677–90.
[4] McKeon A, Robinson MT, McEvoy KM, Matsumoto JY, Lennon VA, et al. Stiff-man syndrome and variants: clinical course, treatments and outcomes. Arch Neurol 2012;69:230–8.
[5] Rakocevic G, Floeter MK. Autoimmune stiff person syndrome and related myelopathies: understanding of electrophysiological and immunological processes. Muscle Nerve 2012;45:623–34.
[6] Solimena M, Folli F, Aparisi R, Pozza G, De Camilli P. Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. N Engl J Med 1990;322:1555–60.
[7] Gresa-Arribas N, Ariño H, Martínez-Hernández E, Petit-Pedrol M, Sabater L, et al. Antibodies to inhibitory synaptic proteins in neurological syndromes associated with glutamic acid decarboxylas autoimmunity. PLoS One 2015;10:e0121364.
[8] Balint B, Bhatia KP. Stiff person syndrome and other immune-mediated movement disorders - new insights. Curr Opin Neurol 2016;29:496–506.
[9] McKeon A, Tracy JA. GAD65 neurological autoimmunity. Muscle Nerve 2017;5:15–27.
[10] Orija IB, Gupta M, Zimmerman RS. Graves' disease and stiff-person (stiff-man) syndrome: case report and literature review. Endocr Pract 2005;11:259–64.
[11] Chia SY, Chua R, Lo YL, Wong MC, Chan LL, et al. Acute ataxia, Graves' disease, and stiff person syndrome. Mov Disord 2007;22:1969–71.
[12] Enuh H, Park M, Ghodasara A, Arsura E, Nfonoyim J. Stiff man syndrome: a diagnostic dilemma in a young female with diabetes mellitus and thyroiditis. Clin Med Insights Case Rep 2014;7:139–41.
[13] Wémeau JL, Klein M, Sadoul JL, Briet C, Vélayoudom-Céphise FL. Graves' disease: Introduction, epidemiology, endogenous and environmental pathogenic factors. Ann Endocrinol 2018;79:599–607.
[14] Johnson JO, Miller KA. Anesthetic implications in stiff-person syndrome. Anesth Analg 1995;80:612–3.

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[15] Bouw J, Leendertse K, Tijssen MA, Dzoljic M. Stiff person syndrome and anesthesia: case report. Anesth Analg 2003;97:486–7.
[16] Obara M, Sawamura S, Chinzei M, Komatsu K, Hanaoka K. Anaesthetic management of a patient with Stiff-person syndrome. Anaesthesia 2002;57:511.
[17] Ledowski T, Russell P. Anaesthesia for stiff person syndrome: successful use of total intravenous anaesthesia. Anaesthesia 2006;61:725.
[18] Yagan O, Özyilmaz K, Özmaden A, Sayin Ö, Hanci V. Anesthesia in a patient with Stiff Person Syndrome. Braz J Anesthesiol 2016;66:543–5.
[19] Cassavaugh JM, Oravitz TM. Multiple anesthetics for a patient with stiff-person syndrome. J Clin Anesth 2016;31:197–9.
[20] Barker JM, Gottlieb PA, Eisenbarth GS. In: Melmed S, et al., editors. Williams textbook of endocrinology. 12th ed. Philadelphia: Elsevier/Saunders; 2011. p. 1768–77.
[21] Husebye ES, Anderson MS, Kämpe O. Autoimmune Polyendocrine Syndromes. N Engl J Med 2018;378:2543–4.

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