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Stiff-Person syndrome and generalized anxiety disorder

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Stiff-person syndrome (SPS) also called stiff-man syndrome, is an immune-mediated CNS disorder characterized by progressive rigidity of the trunk and proximal limb muscles, associated with intermittent superimposed spasms and heightened sensitivity to external stimuli. The spasms are often triggered by emotions, such fear and unexpected tactile, auditory or emotional stimulation[1]. In most cases, SPS is associated with high levels of serum and cerebrospinal fluid autoantibodies against glutamic acid decarboxylase (GAD-65), the rate-limiting enzyme for the synthesis of a major inhibitory neurotransmitter, gamma-amino-butyric acid (GABA). The autoantibodies to GAD65, which are also produced intrathecally, can inhibit the activity of GAD65, thus impairing the synthesis of GABA, and resulting in low GABA levels in the brain and CSF. The reduction of brain GABA in patients with SPS supports the clinical symptoms and indicates that the inhibitory GABAergic pathways are involved in the disease[2].

The association between SPS and anxiety disorders has been reported. Anticipatory anxiety is common in SPS patients, occurring in situations perceived as physically unsafe, such as crossing a busy street or walking unaided in open spaces. These situations may precipitate attacks of increasing stiffness or spasms that result in falls[1,3]. Generalized anxiety disorder (GAD), panic disorder, post-traumatic stress disorder and phobic disorders have been described in patients with SPS. The pathogenesis of anxiety disorders in patients with SPS remains unknown. However, there is considerable evidence that dysfunction of GABA concentrations in central nervous system (CNS) plays an important role in the pathophysiology in these two conditions[3-5].

We report a patient with typical features of SPS and antibodies to glutamic acid decarboxylase, who also met the criteria for generalized anxiety disorder. The possible relationship between these two conditions is discussed.

CASE

A 51-year old woman presented a nine months history of progressive stiffness of the axial and leg muscles and painful spasms, which were elicited by various stimuli, particularly emotional conditions. The spasms destabilized her gait, leading to falls. The stiffness in her lower extremities became so severe that she could not walk. In addition, she reported that she had major concerns about several aspects of her life. She also had trembling, restless sleep, muscle tension and difficulties in concentrating. There was no prior history of psychiatric disease, diabetes mellitus, or other significant illness. Neurological examination showed marked stiffness of lumbar paraspinal muscles with an exaggerated lumbar lordosis. Muscle tone was increased in the lower limbs, tendon reflexes were brisk and plantar responses were flexor. She had an exaggerated startle response which resulted in painful extensor

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SÍNDROME DA PESSOA RÍGIDA E TRANSTORNO DE ANSIEDADE GENERALIZADA

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spasms. The remainder of examination was unremarkable. Electromyography (EMG) of lower limbs revealed continuous motor unit activity at rest. Peripheral nerve conduction was normal. Serum anti-glutamic acid decarboxylase autoantibodies (antiGAD-Abs) were abnormally elevated at 44 U/mL (normal values are below 1 U/L). An extensive evaluation including breast examination, chest X-ray, abdominal and pelvic ultrasonography, rheumatologic markers, anti-thyroid antibodies and fasting glucose were normal. A diagnosis of SPS was made, and the patient was treated with diazepam up to 90 mg per day. Additionally, the patient received one course of IV immunoglobulins (IVIG; 0.4 g/kg body wt/day for 5 days) and local botulinum toxin. The treatment reduced the severity of her symptoms. During her hospitalization, the anxiety symptoms became so evident that a psychiatry consultation was requested, and the diagnosis of generalized anxiety disorder was established according to DSM-IV.

One year after her SPS diagnosis, the muscle tone of lower extremities was still increased. Various anti-spasticity agents were tried, including baclofen and local botulinum toxin. Only diazepam was well tolerated and provided a subjective beneficial effect. The dose of diazepam was gradually increased up to 120 mg per day. However, at times, despite the treatment with high doses of diazepam, her anxiety symptoms became worse, resulting in a profound negative effect on her life. Treatment with paroxetine 20 mg QD was started, and during the follow up period, she presented partial remission in excessive anxiety, restlessness and sleep disturbance. The neurological symptoms showed stabilization. The patient authorized the publication of this case report by signing a consent form.

DISCUSSION

SPS was first described in 1956 by Moersch and Woltman at the Mayo Clinic. They reported few cases of "progressive fluctuating muscular rigidity and spasms". SPS affects twice as many women as men, and usually presents in the fourth to sixth decade of life. The onset is typically insidious and the disease evolution is usually progressive. Although the precise etiological mechanism is unknown, an autoimmune hypothesis has been suggested by presence of autoantibodies against GAD65, association with other autoimmune diseases, and a clinical response to immunomodulatory therapy. Variants of SPS include those with focal limb dysfunction (stiff-limb syndrome), encephalomyelitis ("SPS plus"), and paraneoplastic conditions. The paraneoplastic form of SPS has been described in association with certain types of tumors, particularly breast and small cell lung cancer. In addition to anti-GAD antibodies, antiamphiphysin antibodies, antigephyrin and anti-Ri antibodies are often present in this clinical form[6,7].

Previous communications have found significant correlations between SPS and anxiety disorders, including panic disorder (PD), post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and phobic disorders. Psychiatric symptoms (like anxiety, depression) may be prominent and, as such, may be misleading, resulting in the diagnosis of a psychiatric condition[1,3-5]. Henningsen and Meinck evaluated systematically the rate and the type of phobia in forty-three patients with SPS by anxiety disorders interview schedule, revised (ADIS-R), and a structured diagnostic interview for anxiety disorders. Surprisingly, these authors identified nineteen patients (44.2%) who developed task-specific phobia that was manifested as fear and avoidance of situations difficult to master owing to the motor symptoms of SPS (such as crossing streets). Three further patients (7%) had the same type of phobic anxiety but without behavioral avoidance. Apart from the presence of a specific phobia, the psychiatric interview revealed generalized anxiety disorder in two patients, and depression in five patients. In addition, psychosocial stressors often preceded the first manifestations of the disease, depression and alcohol abuse were co-morbid illnesses[3].

In recent years, it has been accepted that the GABA system is involved in several neuropsychiatric disorders, including epilepsy, major depression, drug addiction, SPS, and anxiety disorders[8]. Up 65% of patients with SPS have antibodies against glutamic acid decarboxylase (GAD-65), the enzyme responsible for the conversion of the excitatory amino acid glutamate to GABA, the main inhibitory neurotransmitter in the CNS. The exact mechanism involved in this disease is not entirely understood, but the circulating antibodies could impair the synthesis of GABA resulting in low GABA levels in brain. It explains the patient's symptoms of stiffness and unexpected muscle spasms, and justifies the clinical improvement observed by drugs enhancing GABAergic transmission. In addition, previous magnetic resonance spectroscopy (MRS) studies have found reduced GABA concentrations in specific brain regions of patients with SPS[2]. Recently, Galdiks et al demonstrated reduction of cerebral benzodiazepine receptor binding in a patient with SPS using positron emission tomography (PET) and flumazenil (FMZ) tagged with carbon 11. These data provided the first *in vivo* evidence of reduced postsynaptic GABA-A receptor availability, which may ultimately reflect the loss of GABAergic neuronal inhibition in SPS[9].

There is considerable evidence that the dysfunction of GABA (A) receptors or the dysregulation of GABA concentrations in CNS plays an important role in the pathophysiology of anxiety disorders. Evidence supporting this hypothesis is resulted from clinical experience with the benzodiazepines for the treatment of anxiety, which are well know to act primarily on GABA (A) re-

ceptors. Furthermore, neuroimaging studies have demonstrated reductions in GABA levels and GABA (A) receptor binding in patients with anxiety disorders[10].

This case report highlights the importance of the recognition of anxiety disorders in patients with SPS. Although the exact mechanism of such an association remains unknown, it has been postulated that it could be the result of a reduced or impaired GABAergic inhibition induced by the anti-GAD antibodies, which may predisposed the development of anxiety symptoms in these patients. This hypothesis is supported by the fact that drugs that enhance GABAergic inhibitory transmission such benzodiazepines are effective for treatment in both conditions. In conclusion, the early recognition of psychiatric symptoms in these patients is particularly important to develop treatment strategies to help them manage their disease more successfully[1,4].

REFERENCES

1. Ameli R, Snow J, Rakocevic G, Dalakas MC. A neuropsychological assessment of phobias in patients with stiff person syndrome. Neurology 2005;65: 1961-1963.
2. Levy LM, Levy-Reis I, Fujii M, Dalakas MC. Brain y-aminobutyric acid changes in stiff-person syndrome. Arch Neurol 2005;62:970-974.
3. Henningsen H, Meinck H-M. Specific phobia is a frequent non-motor feature in stiff-man syndrome. J Neurol Neurosurg Psychiatry 2003;74:462-465.
4. Culav-Sumic J, Bosnjak I,Pastar Z,Jukic V. Anxious depression and the stiff-person plus syndrome. Cog Behav Neurol 2008;21:242-245.
5. Dinnerstein E, Collins D, Berman A S. A patient with post-traumatic stress disorder developing stiff person syndrome. Is there a correlation ? Cog Behav Neurol 2007;20:136-137.
6. Lockman J, Burns TM. Stiff-person syndrome. Pract Neurol 2007;7:106-108.
7. Burns TM. A step forward for stiff-person syndrome.Lancet 2005;365:1365-1366.
8. Wong CG, Bottiglieri T, Snead OC. GABA, gamma-hydroxybutiric acid, and neurological disease. Ann Neurol 2003;54(Suppl 6):S3-S12.
9. Galldiks N,Thiel A, Haense C, FinK GR, Hilker R. (11)C-Flumazenil positron emission tomography demonstrates reduction of both global and local cerebral benzodiazepine receptor binding in a patient with Stiff Person Syndrome. J Neurol 2008;255:1361-1364.
10. Nemeroff CB. The role of GABA in the pathophysiology and treatment of anxiety disorders. Psychopharmacol Bull 2003;37:133-146.