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Case report

A case report of patient with cerebellar variant of stiff person syndrome

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ABSTRACT

Stiff person syndrome (SPS) is a rare autoimmune neurological disorder with antibodies against antigens involved in neurotransmission of gamma-aminobutyric acid (GABA). About 10% of patients with SPS may develop ataxia. This cerebellar variant is a distinct subset of SPS with more severe and complex clinical phenotype.

We report the clinical, neuropsychological and neuroradiological findings in a 39-year-old female with cerebellar variant of SPS.

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1. Introduction

Stiff person syndrome (SPS) is a rare and underdiagnosed neurological disorder characterized by the muscle rigidity and superimposed spasms. The rigidity begins insidiously at the truncal muscles and spreads to the legs. Painful spasms are precipitated by movement, emotional distress and auditory startle. Some patients do not show the classic axial distribution of stiffness. It may start focally from one lower limb, giving rise to the diagnosis of stiff limb syndrome considered as a focal form of SPS in which the symptoms are confined to a limb, although sometimes this progresses to involve the axial musculature as well. Antibodies against glutamic acid decarboxylase (anti-GAD) are diagnostic marker of the SPS, but they are also described in patients with insulin-dependent diabetes mellitus and in patients with cerebellar ataxia. Some patients with SPS may develop additional neurologic abnormalities, including ataxia (10% of patients), epilepsy (5–10% of patients), abnormal eye movements and mental disorders (phobias, anxiety, talkativeness, obsessions). Patients with ataxia (the cerebellar variant of SPS) have more severe and complex clinical phenotype of SPS with more prominent stiffness and spasms in the leg and trunk, cerebellar ataxia; dysarthria; ataxic gait, abnormal eye

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movements with impaired saccades, deficient smooth pursuit and gaze-holding nystagmus [1,11].

We report the clinical, neuropsychological and neuroradiological findings in a 39-year-old female with cerebellar variant of SPS.

2. Case report

A 39-year-old woman was referred to the department of neurology with a three-year history of cerebellar ataxia and progressive muscle rigidity of axial and limb musculature of unknown origin. In 2008, she began to complain of unsteady gait, vertigo and diplopia. Neurological examination revealed nystagmus and broad-based gait.

Six months later, she reported low back pain and stiffness in the thoracic and lumbar spine with an exaggerated upright posture. She developed cramps of thoracic and abdominal muscles and exaggerated lumbar lordosis. The stiffness has spread to the proximal limb muscles. The spasms of both legs and the low back were usually precipitated by passive and voluntary movement, as well as unexpected noise, but at times occurred spontaneously. Rigidity increased over months and patient was virtually unable to walk outdoors without a cane. Over the last several months, her back spasms had become progressively more painful with exacerbations during stressful situations resulting in frequent falls and difficulty with standing up. She was afraid to walk even with an aid. Past medical history did not reveal any neurological or psychiatric disorder or autoimmune disease. Her family history was unremarkable. She did not smoke or use illegal drugs.

On admission, neurological examination revealed symmetric paraspinal and lower extremities muscle rigidity, an exaggerated lumbar lordosis and a prominent thoracic scoliosis with vertical nystagmus, cerebellar dysarthria, mild dysmetria and dysdiadochokinesia of the upper limbs. A slightly increased tone was noted in her left upper limb, but muscle strength and range of motion were both normal. Strength of the lower limbs could not be assessed because of rigidity and spasms. Sensory examination was normal. Deep tendon reflexes were normal in upper limbs. Knee and ankle jerks were very brisk bilaterally. Pathological reflexes were absent. The gait was slow and stiff because of the rigidity in her both legs. She had problems to initiate gait and could not walk unassisted because she was afraid of falling.

In 2008, neuropsychological study including Rey Auditory Verbal Learning Test, Clock Drawing Test, Verbal Fluency Test, Trail Making Test, Stroop Test, Wisconsin Card Sorting Test, serial number subtractions (7 from 100) revealed impaired selectivity of attention and executive dysfunction. When compared with the neuropsychological assessment completed in 2011 including the same tools, the examination showed continued impairment of higher-order cognitive functions and was suggestive of involvement of frontal-subcortical regions. The assessment revealed increased executive dysfunction and language problems, impairment in short-term memory, learning disturbance, decreased verbal fluency and mental speed, reduced self-criticism, deficits of attention.

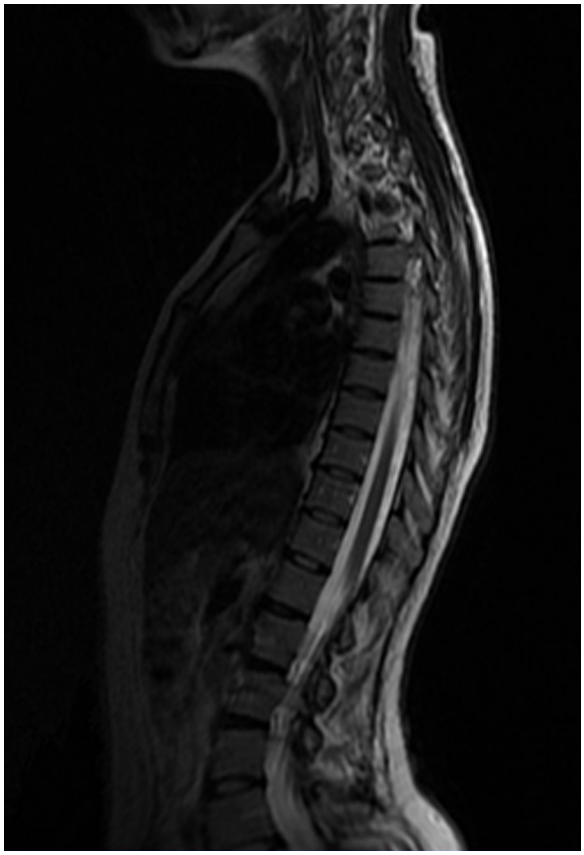

Fig. 1 – MRI of the spine shows an exaggerated lumbar lordosis.

Electromyography revealed continuous motor unit activity in agonist and antagonist muscles at rest. Magnetic resonance imaging (MRI) of the spine before and after gadolinium injection showed thoracic scoliosis and hyperlordosis (Fig. 1). MRI of the brain before and after gadolinium injection showed no evidence of atrophy of frontal lobes or medial temporal lobes (Fig. 2).

Single photon emission computed tomography (SPECT) studies showed bilateral hypoperfusion in frontal lobes, especially on the right side (Fig. 3). Visual and auditory evoked potentials were normal. Results of the routine blood biochemical analyses (including complete blood count, serum electrolytes, blood urea nitrogen, creatinine, glucose, liver enzymes, thyroid-stimulating hormone, ceruloplasmin) and urinalysis were all normal. Anti-GAD autoantibodies were found and their level was above 20000 IU/mL (normal value $<$10 IU/mL). Anti-amphiphysin and paraneoplastic antibodies were not detected. Gene analysis for spinocerebellar ataxia type 1 (SCA1) found no abnormalities. Paraneoplastic antibodies were not detected. Analysis of the cerebrospinal fluid (CSF) wasn't carried out, because the patient refused lumbar puncture.

The patient was diagnosed with SPS according to currently accepted clinical criteria [1]. Oral diazepam was administered at the dose of 30 mg daily and marked reduction of the stiffness was observed. The patient was able to walk with a walking stick. After the increase of diazepam to dose 30 mg/day, levetiracetam at 1000 mg/day was introduced. With this

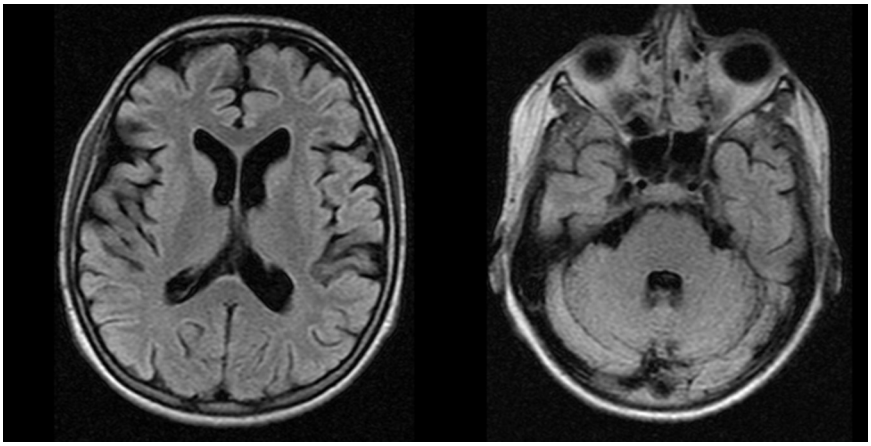

Fig. 2 – T2-weighted MRI of the brain.

treatment, her muscle cramps and stiffness diminished and her gait improved within a few days. Unfortunately, she had experienced adverse effects (sedation and nausea) and levetiracetam was discontinued. Currently, she cannot stand or walk without assistance. At a follow-up visit two months after her initial presentation, she noticed a moderate decrease in her stiffness, but loud noises and stressful situations still induced abrupt muscle spasms, primarily involving her lower back.

3. Discussion

Cerebellar variant of SPS results in a combined clinical symptomatology of SPS and cerebellar disease. Symptoms may start with cerebellar signs followed by muscle spasms and stiffness or disease begins with stiffness and spasms followed by cerebellar signs or SPS and ataxia may begin concurrently. In all patients limb ataxia, dysarthria and visual disturbances are prominent and are more disabling than axial muscle stiffness [1,11,24].

In patients with stiff person syndrome and concomitant cerebellar dysfunction increased intrathecal synthesis of anti-glutamic acid decarboxylase antibodies (anti-GAD) was found [1,11]. Intrathecal anti-GAD synthesis is suspected of inducing symptoms in the CNS, presumably by affecting the GABAergic system. It is suggested that anti-GAD antibodies may also recognize additional antigenic targets on the inhibitory cerebellar interneurons resulting in ataxia [24]. As GABAergic neurons are critical for brainstem control of eye movements, disruption of GABAergic transmission was proposed as a pathogenic mechanism of oculomotor disturbances in SPS resulting in commonly reported by patients diplopia and blurred vision [3,11,12]. Circulating anti-GAD cause a

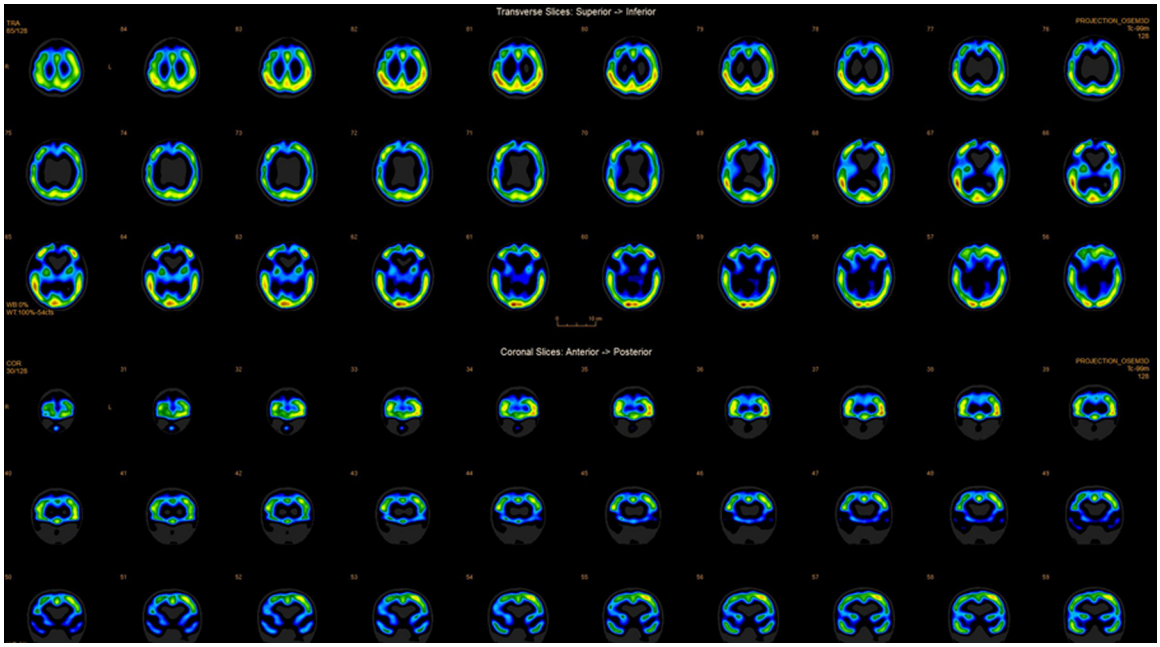

Fig. 3 – SPECT showing bilateral hypoperfusion in frontal lobes.

functional blockade of GABAergic interneurons rather than neuronal loss. On the basis of the pathogenesis drugs enhancing GABA transmission like sedative-anxiolytics (diazepam) and antiepileptic drugs (like levetiracetam) has been recommended in management of spasm and stiffness in SPS patients [1,8–10].

A number of associated neuropsychiatric symptoms of SPS including anxiety and task-specific phobias have been previously reported in SPS patients, also a slight decline in cognitive functioning in relation to premorbid levels was suggested [2]. Isolated cognitive decline in the absence of other neurological complications may be associated with anti-GAD, presumably affecting the GABAergic system which is involved in cognitive function [3]. An isolated cognitive dysfunction with bifrontal hypoperfusion in SPECT studies may develop in association with type 1A diabetes and anti-GAD autoimmunity [4].

The issue of a cerebellar contribution to cognitive functions is still under discussion. The cerebellum projects to the frontal cortex and loss of cerebellar efferents to the cortex might cause cognitive impairment. Cerebellar dysfunction may give a subtype-specific non-motor symptom described as cerebellar cognitive affective syndrome which involves mainly language, executive function and visuospatial skills [5,6].

In 5% of patients, SPS is paraneoplastic and it is associated with antibodies directed against two other components in the GABAergic synapse: amphiphysin or gephyrin and usually occurs in the presence of breast cancer, small cell lung carcinoma, thymoma and Hodgkin's lymphoma. Such patients may have more prominent stiffness in the arms and neck [1].

Diagnostic search for other conditions causing stiffness, cerebellar dysfunction and cognitive impairment did not reveal any other etiology of those symptoms in our patient. There was no evidence of associated malignancies or diabetes mellitus in our patient and she presented slowly progressive symptoms for more than three years.

In conclusion, SPS and anti-GAD autoimmunity especially with non-motor symptoms requires further systematic study to uncover its mechanism in more detail.

Conflict of interest

We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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The authors have no relevant financial interest in this article.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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