

Movement Disorders and Nonmotor Symptoms in Patient with Idiopathic Stiff Person Syndrome

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Abstract

A follow-up of a 59-year-old female patient with stiff person syndrome in combination with insulin-dependent diabetes mellitus and autoimmune thyroiditis is presented in this work. The disease was manifested by characteristic movement disorders such as stiffness and painful spasms of the abdominal muscles, back and hips, accompanied by impaired walking and frequent falls. It was noted that the erector spinae muscle was involved in the pathological process, the muscle biopsy revealed a decrease in the content of the sarcomere proteins, titin and nebulin. In the course of pathogenetic GABAergic drug therapy, movement disorders became less marked however anxiety and phobic disorders prevailed, that was manifested as gait disorder because of the fear to fall and led to diagnosis of social phobia in the patient. The therapy of nonmotor symptoms of stiff person syndrome and significance of cognitive-behavioral therapy for reducing symptoms of anxiety disorders are discussed.

Keywords: stiff person syndrome, pathogenesis, titin, nebulin, movement disorder, social anxiety disorders, cognitive-behavioral therapy

INTRODUCTION

Stiff person syndrome (SPS) is an autoimmune condition caused by deficiency of gamma-aminobutyric acid (GABA), the primary inhibitory transmitter in the central nervous system that is characterized by neurologic manifestations such as progressive rigidity of axial muscles, proximal groups of limbs muscles as well as painful muscle spasms. There are also cases of this disease described with oculomotor and cerebellar disorders considered as conditions SPS-plus [1, 2]. Electromyography (EMG) revealed constant activity of motor units in patients with SPS and SPS-plus. Blood plasma and cerebrospinal fluid (CSF) showed marked elevation of titres of antibodies to glutamine acid decarboxylase (GAD) [3, 4]. Elevation of titres of antibodies to GAD are found in the patients with various autoimmune diseases – diabetes mellitus type 1, autoimmune thyroiditis, autoimmune polyendocrinopathy and others [5,6]. In literature SPS is described mainly as movement disorder however nonmotor manifestations of this syndrome are also noted such as anxiety, depression, vegetative disorders, pathogenesis of which is not studied well [2, 8, 9]. Nonmotor manifestations of SPS have low response to psychotropic medication correction and decrease the quality of patients' life.

We represent our own observation of the case with SPS in combination with insulin-dependent diabetes mellitus and autoimmune thyroiditis.

Clinical observation

The female patient X, 59 years old was admitted into the clinic with complaints on walking impairment in open spaces, fear to fall, feeling of tension and stiffness in legs muscles intensified at motor and emotional load, increased anxiety.

9 years ago after actual psychotraumatic situation the patient noted for the first time the appearance of stiffness and painful spasms in muscles of legs and back intensifying in response to walking and anxiety. There was also sweatiness, more expressed in the upper part of the body. Soon imbalance while walking added that led to falls, the patient fell on her face, got injured. Gradually fear of falling while walking in open spaces was progressing, the patient stopped going out without an accompanying person. 3 years after the onset of the disease stable hyperglycemia was revealed and diabetes mellitus (DM) type 2 was diagnosed, 6 months later in order to compensate carbohydrate metabolism the patient was put on insulin therapy (NovoRapid 18 UI/day, Lantus 10 UI/day) which is conducted up to the present day. The patient was also diagnosed with autoimmune thyroiditis, subclinical hypothyroidism not requiring drug correction.

Family anamnesis is remarkable for cardiovascular diseases and diabetes mellitus type 2.

During 7 years the patient was examined in different medical centers with diagnosis: hereditary spastic paraplegia, multiple sclerosis, brain ischemia, anxiety-depressive disorder. Once due to suspected multiple sclerosis therapy with methylprednisolone (1000 mg intravenous infusion, №5) was conducted, with temporary positive effect. Twice she was admitted to the hospital with diagnosis anxiety-depressive disorder and received therapy with antidepressant, antipsychotic drugs with antianxiety agent without effect.

Two years ago the patient applied to the clinic of neurological diseases for the first time. Neurological status showed increased muscle tone in flexors and extensors of legs, back muscles, intensifying while walking and emotional tension. Marked lumbar hyperlordosis preserved

in the lying position on the back. Strength in all groups of muscles was preserved. Tendon reflexes on arms were normal, symmetrical, on legs – normal, symmetrical, with extension of reflexogenic zones, ankles and patellas jerks. Pathologic reflexes were absent. Walking on straighten legs with forward inclination of body, frequent falls. No sensitive disorders were found. Dynamic and static coordinative tests were performed well. Pelvic function was preserved. Hyperhidrosis of face, neck and upper part of the body intensifying at mild physical activity, emotional tension, was noted. Marked dermatography of pink colour. The patient was anxious, emotionally instable.

Clinical blood count, urine test, hormones of thyroid gland examination revealed no pathology. Biochemical blood test showed elevation of cholesterol level (up to 7,74 mmol/L). Glycemic profile – stable increase of glucose level (up to 10,0 mmol/L). Clinical analysis of CSF – no pathology, oligoclonal IgG type 1 was found. Marked lumbar hyperlordosis obstructed technically the performance of lumbar puncture, in light of this relanium (diazepamum) 10 mg was injected, it helped to decrease tension of muscles in legs and back for two days. Antibodies to glutamine acid decarboxylase were significantly increased in blood 265.00 IU/ml (norm 0-5 IU/ml) as well as in CSF 120.40 IU/ml (norm 0-5 IU/ml). The electromyographic analysis of the erector spinae muscle showed that the activity of motor units in resting muscles increased. The value ranges of motor unit action potentials are within the normal limits. No denervation spontaneous activity and spontaneous activity of motor units were detected. Results of electromyography (EMG): the value ranges of the conduction velocity of motor and sensory nerve fibres of extremities as well as the amplitudes of motor and sensory responses are within the normal limits. The induced potentials of all (visual, aural, somatosensory) modalities are within the normal limits. MRI brain scan in T1, T2 and FLAIR modes showed no pathology. An MRI of all regions of the spine demonstrates no abnormal pathologies. We carried out the morphological study of biopsy of the erector spinae muscle and SDS-gel electrophoresis of titin and nebulin, giant muscle proteins. Pro-Q Diamond phosphoprotein stain was used to measure the level of phosphorylation of titin and nebulin. No symptoms of necrosis, fibrosis development, inflammatory infiltration of muscle fibres were revealed. Analysis of electrophoregrams showed a 2-3-fold decrease in the content of titin and more significant reduction of the nebulin level (down to its lack in electrophoregrams) (Fig.). Results are indicative of the enhanced proteolysis of titin and nebulin in the erector spinae muscle. Analysis of phosphoregramms demonstrated a decreased (in 2-2.4 times) phosphorylation level of the remaining molecules of titin and nebulin in the said muscle. The level of phosphorylation was determined with the aim to elucidate if posttranslational modification has any possible impact on the change of sensitivity of the mentioned proteins to proteolysis.

A diagnosis of stiff person syndrome was made on the basis of the clinical evidence. To exclude a paraneoplastic case of the stiff person syndrome, cancer screening was performed

including CT scanning of the breast, abdominal and pelvic ultrasound exams. No pathologies were detected. It is clear that this is an idiopathic case of the stiff person syndrome in the patient with insulin-dependent diabetes mellitus type 2 and autoimmune thyroiditis

"Pulse therapy" with corticosteroids-methylprednisolone at the dose of 500 mg intravenously №5, as well as the therapy with GABAergic drugs (Baclofen, Clonazepam) has been conducted in the clinic. In the course of taking Baclofen 30 mg /day and Clonazepam 4 mg /day, a tension in the muscles of the legs and the back decreased, it became easier to walk, however the fear to fall, especially when walking in open areas, remained.

For 1.5 years, the patient does not leave home without an accompanying person, it limits significantly her social activity. At return visits to the clinic of nervous diseases - active range of motions is full; muscle strength is sufficient; an increased muscle tone in the flexors and extensors of the legs is kept. Deep reflexes from the hands are normal, symmetrical; in the legs are brisk reflexes with expansion of reflexogenic zones, symmetrical. There are no pathological hand and foot signs. The patient performs dynamic and static coordination tests satisfactorily. Walking on straightened legs is possible only with the help, but without additional support. During posturography the features of excessive tension of postural control were revealed.

A psychiatrist examined her in the clinic. Complains of fear to losing control over the muscles in the legs, losing balance when walking. In the flat and hospital room she is walking without any support from other people, however she feels increased anxiety if it is necessary to cross the open space (street, hospital hall) alone. She can leave the place only with an accompanying person or someone of her relatives or medical staff, when someone is present, she can walk without assistance. In situations when she knows that someone would accompany her in the open area, she is quite at ease. She feels no anxiety for disease forecast. Now, she agrees with the physician who properly selected efficient therapy that she does not feel anxiety of a fall during her walking. At the same time, she says that every time when she is walking alone, she recollects how she had a fall, with the face turned toward the ground and so forth. She tends to experience anxiety about her children, constantly phones them in the hospital. In spite of the fact that she feels apparent anxiety, she does not experience persistent depression, circadian rhythm in her state is absent. At home she is active: she easily cleans the apartment, prepares food, and receives guests. Appetite and sleep are good. She has no thought of suicide; psychotic symptomatology was not identified. Psychometric examination shows a high level of situational and personal anxiety-50 points by the Spielberger scale and 10 points by the Beck scale. Conclusion: the patient has secondary agoraphobia relative to the verified neurological disease with psychogenic debut. It is recommended, to add pregabalin to the therapy, as well as to conduct a course of cognitive behavioral therapy (CBT) in view of persistent avoiding behavior extended to agoraphobia.

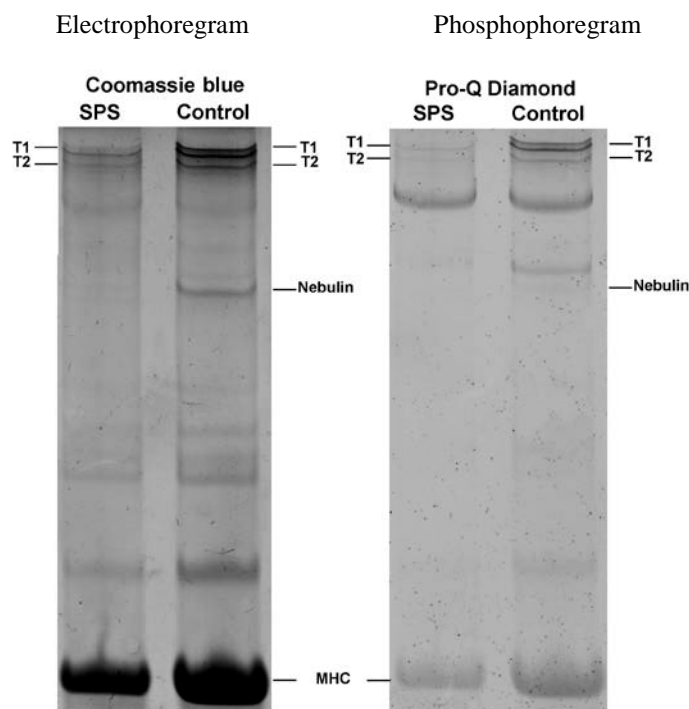
Table. Criteria of SPS [3].

Clinical:	- rigidity in the axial and abdominal muscles, leading to formation of lumbar hyperlordosis; - painful muscle spasms triggered by tactile and emotional stimuli; - absence of other neurological diseases, explaining the above symptoms;
Neurophysiological:	- constant activity of motor units according to EMG;
Auxiliary:	- detection of anti-GAD antibodies and antibodies to amphiphysin in blood plasma and CSF; - positive test with diazepam. .

Fig.1 Changes in the content and the level of phosphorylation of titin and nebulin in the erector spinae muscle (control vs. stiff person syndrome).

T1 – intact titin; T – proteolytic fragments of intact T1; MHC – heavy chains of myosin.

Changes in titin and nebulin contents were detected using agarose-strengthened polyacrylamide (2.2%) slab gels.



Thus, in the patient with SPS, who underwent treatment with the use of GABAergic drugs, under 3 year medical supervision, a severity of motor disorders in the form of rigidity and painful spasms of axial muscles reduced significantly. The main maladaptive factors the patient experienced were phobia and the increased level of anxiety, manifested as a fear of falling, that was the reason why the patient did not leave the house without an accompanying person.

DISCUSSION

A diagnosis of SPS in the patient who received treatment was made on the basis of criteria of this disease (Table). Motor disorders in the form of stiffness of the muscles of the back and lower extremities with formation of hyperlordosis, accompanied by walking disorders and frequent falls prevailed during the onset of the disease. EMG of the erector spinae muscle showed an increase in the activity of motor units at rest is typical for SPS. High titers of antibodies in GAD in blood plasma and CSF, found in the patient, refer to additional criteria of the disease, as they are not specific and may be present in other

autoimmune conditions, such as insulin-dependent diabetes mellitus, autoimmune thyroiditis, rheumatoid arthritis and others [5, 6, 7]. In healthy people, antibodies to GAD can be determined only in blood plasma and only in 1% of the cases, in CSF antibodies to GAD are revealed only in cases of CNS damage. A significant increase of the antibodies to GAD in CSF is characteristic for anti-GAD-associated neurological syndromes, which, in addition to SPS, also include sporadic ataxia, limbic encephalitis, opsoclonus-myoclonus, myasthenia gravis [5]. A combination of idiopathic SPS with insulin-dependent diabetes mellitus and autoimmune thyroiditis should be considered as the features of the observed case.

The absence of necrosis, fibrosis, inflammatory infiltration in the skeletal muscle of the patient with SPS correlates with the results of our previous morphological studies [4]. Analysis of electrophoregram and phosphophoregram of sarcomere proteins of the erector spinae muscle shows that the content and the level of phosphorylation of titin and nebulin, giant muscle proteins decreases. Titin is a component of myosin (thick) filaments in sarcomere

proteins of striated muscles [10]. It is involved in the maintenance of highly organized structure of the sarcomere thereby supporting contractile function of the muscle [11]; it also participates in regulation of actin-myosin interaction. Nebulin is a giant protein of actin (thin) filaments, which is also involved in regulation of actin-myosin interaction [12, 13]. The decreased content of titin and nebulin in the development of muscle atrophy (by ~1.5 times) [14] is a consequence of the enhanced proteolysis of these proteins, that leads to disturbance of the sarcomere structure, impairment of elastic properties and contractility of the muscles. Herewith, the increased level of phosphorylation of titin is observed. In scientific literature it has been hypothesized that hyperphosphorylation of titin may result in its increased sensitivity to proteolysis [15].

The decreased content of titin and nebulin in the erector spinae muscle, detected in the patient with SPS, is also a consequence of the enhanced proteolysis of these proteins. More significant reduction in the content of nebulin in the tested muscle may be an indicator that thin actin filaments, to which nebulin is bound, are destroyed faster in SPS than thick myosin filaments. A decrease in the level of phosphorylation in the remaining molecules of titin and nebulin in the tested muscle is probably a consequence of compensatory process directed to maintaining, though reduced, but relatively stable concentration of these proteins in the sarcomere.

In the course of treatment with GABAergic drugs and correction of the endocrinopathy, movement disorders in the patient with SPS decreased significantly, however anxiety and phobic disorders prevailed, severity of which led to diagnosis of social phobia. Pathogenesis of phobia and other non-motor symptoms of SPS are unknown. There is no data on a pathogenic role of autoantibodies against glutamic acid decarboxylase in the development of phobias [8]. Previous studies give descriptions of the patients with SPS who were mistakenly diagnosed with psychogenic motor disorder [2, 9]. There are known SPS cases when anxious-phobic symptoms advanced the motor ones for more than 5 years [8]. However, the attempts to use in those cases psychotropic drugs (typical neuroleptics, antidepressants) were inefficient that was also marked in the observed patient. The data obtained substantiates the assumption that non-motor manifestations of SPS are a consequence of dysfunction of GABAergic structures of the brain, the anterior hypothalamus and forebrain structures [1]. The literature discusses efficiency of small doses of atypical neuroleptic - clozapine [5], as well as anticonvulsants, increasing the activity of GABA – gabapentin, pregabalin [16, 17] against depression and anxiety disorders in the patients with SPS.

When assessing mental status of the patient, attention is drawn to the fact that severity of conditions is determined first by avoiding behavior that reaches agoraphobia, and not actually anxiety. According to the current standards of anxiety and phobia treatment the first-line therapy are antidepressants from the group of specific serotonin reuptake inhibitor and specific serotonin and norepinephrine reuptake inhibitors, as well as benzodiazepine tranquilizers

[18]. It should be noted that treatment with the use of antidepressants was not efficient for the patient; therefore an anti-anxiety drug with alternative mechanism of action was prescribed in combination with psychotherapy. The most preferred anti-anxiety drug in this case is pregabalin, it is efficient for treating anxiety symptoms, including those observed in the structure of SPS. Cognitive-behavioral therapy (CBT), which has maximal effect with regard to anxiety disorders, should be mentioned as an optimal method of psychotherapy [19, 20].

In the course of treatment with GABAergic drugs in combination with CBT the patients with SPS felt decreased anxiety, a decrease in fear to falls and, as a result, an improvement in walking and quality of life as a whole [8,18].

Thus, subsequent management of the patient with an idiopathic SPS showed that GABAergic drugs have long-term permanent effects. Anxiety disorder, the management of which requires both pharmacotherapy and cognitive behavioral therapy, is considered as the main maladaptive factor in the course of remedial treatment of motor disorders [21].

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