Stiff-Man Syndrome Associated with Antecedent Myasthenia Gravis and Organ-Specific Autoimmunopathy
Yoshimasa Aso, Akira Sato, Mamoru Narimatsu, Yoshiteru Takiguchi, Yoshiyuki Yamaguchi, Toshihiko Inukai and Yoshihiro Takemura

We describe a case of stiff-man syndrome accompanied by diabetes mellitus, Hashimoto’s thyroiditis and the antecedent myasthenia gravis. The diagnosis of stiff-man syndrome was made based on not only clinical findings and the characteristic electromyographic pattern but also the presence of antibodies to glutamic acid decarboxylase in the serum and cerebrospinal fluid. Stiff-man syndrome is known to be associated with organ-specific autoimmunopathy including insulin-dependent diabetes mellitus. The present case is the first one that stiff-man syndrome was preceded by myasthenia gravis of organ-specific autoimmunopathy. Stiff-man syndrome in the present case probably represents the one of fully expressed manifestations from the broad spectrum of organ-specific autoimmunopathy caused by the loss of self-tolerance. (Internal Medicine 36: 308-311, 1997)

Key words: glutamic acid decarboxylase (GAD), diabetes mellitus, Hashimoto’s thyroiditis

Introduction

Stiff-man syndrome (SMS) is a rare disorder of the central nervous system characterized by progressive spasms and stiffness of the axial skeleton (1, 2). It is hypothesized that SMS possibly represents manifestations resulting from an imbalance between catecholaminergic and γ-aminobutyric acid (GABA)-ergic systems (excitatory effect and inhibitory effect, respectively) causing a loss of inhibition of α-motoneuron fibers (2-4). In support of this hypothesis, autoantibodies against glutamic acid decarboxylase (GAD), the enzyme that catalyzes the conversion of glutamate to GABA, were recently shown to be present in 60% of patients with SMS (5). In addition, insulin-dependent diabetes mellitus (IDDM) and other organ-specific autoimmunopathies have been known to be associated with SMS (6). The autoimmune pathogenesis of SMS on the basis of these findings has been suggested (6, 7). We describe herein a case of SMS accompanied by diabetes mellitus, Hashimoto’s thyroiditis and the antecedent ocular type of myasthenia gravis, suggesting that SMS is one of the fully expressed manifestations from the broad spectrum of organ-specific autoimmunopathies.

Case Report

A 21-year-old woman was referred to the hospital in April 1995 for the investigation of muscular stiffness, rigidity and spasms. She had a history of myasthenia gravis at the age of 12; she was noticed to have drooping eyelids while staring at objects and the ocular type of myasthenia gravis was diagnosed at another institution by the positive anti-acetylcholine receptor antibody (anti-AchR Ab) 0.7 pmol/l and by the findings of electromyogram (EMG) indicating a progressive diminution in the amplitude of the action potentials evoked in the hypothenar muscle at the wrist during repetitive stimulation of 3 MHz which resulted in 10% reduction from the initial value and was reversed by edrophonium administration. Myasthenia was restricted to the ocular muscles for one year and thereafter improved spontaneously. She began to experience stiffness and rigidity of muscles of the axial skeleton at the age of 14, which gradually spread to the lower limbs with painful spasms. At the age of 19, the development of severe rigidity and spasms of the lower back muscles prevented her from standing and walking. One year later, she consulted the orthopedist at another hospital and was diagnosed as lordoscoliosis of the lumbar spine (Fig. 1), which was fixed by the posterior spinal fusion with instrumentation. Simultaneously, diabetes mellitus was diagnosed by the elevated levels of fasting plasma glucose of 449 mg/dl and

From the Department of Medicine, Koshigaya Hospital, Dokkyo University School of Medicine, Koshigaya, Saitama
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Reprint requests should be addressed to Dr. Yoshimasa Aso, the Department of Medicine, Koshigaya Hospital, Dokkyo University School of Medicine, Koshigaya, Saitama 343
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HbA1c of 11.9% without ketonuria or ketoacidosis. She was treated with insulin administration. The stiffness and rigidity of muscles persisted. She was admitted to the hospital on April 17, 1995. There was no family history of neurological disorders or diabetes mellitus. Her body weight was 41 kg and her height was 147 cm. The temperature was 36.6°C, the pulse was 72/min and the blood pressure was 120/72 mmHg. Physical examination showed pronounced lordosis despite the fixation by the previous orthopedic operation. Neither goiter nor anemia was found. Neurological examination showed slightly increased patellar and Achilles deep tendon reflexes without pathologic reflexes. Stiffness, rigidity and spasm of paraspinal and thigh muscles were observed and evoked frequently by acoustic and various somatosensory stimuli to almost all parts of the body. The muscle strength and tone were normal when she was in the stable condition without spasm. Neither sensory disturbances, autonomic nervous system disturbances, gait disturbances nor cerebellar dysfunction was found. Laboratory data showed hemoglobin 11.9 g/dl with mean corpuscular volume 94 fl, leukocyte count of 3,800/μl and erythrocyte sedimentation rate of 10 mm/h. Serum enzymes of muscle origin were as follows: creatinine kinase 128 U/l, aspartate aminotransferase 18 U/l, lactate dehydrogenase 361 U/l, and aldolase 3.1 U/l. The fasting plasma glucose concentration was 108 mg/dl and HbA1c was 5.3%. The urinary excretion of C-peptide was decreased to 35.9 μg/day. The serum level of anti-GAD antibodies measured by radioimmunoassay (Hoechst Japan) specific for 65 Kd GAD was extremely high at 316,000 U/ml (normal range: less than 4.0 U/ml). The complement-fixed cytoplasmic islet-cell antibodies were positive. The anti-thyroid peroxidase and antithyroglobulin antibodies were markedly elevated to more than 30 U/ml and 32.1 U/ml, respectively. The serum levels of free thyroxine (FT₄), free triiodothyronine (FT₃) and thyroid-stimulating hormone (TSH) were 1.07 ng/dl, 3.28 pg/ml and 12.3 μU/ml, respectively. The antinuclear antibody was positive at the titer of 1:640 and the anti-smooth muscle antibodies were positive at the titer of 1:320. The anti-AchR Ab were positive at 0.3 pmol/l (normal range: less than 0.2 pmol/l). The HLA phenotype was A2, B46, Cw1, Cw7, DR6 and DR8. Analysis of peripheral blood lymphocytes indicated that T cells, B cells, CD4⁺ T cells and CD8⁺ T cells were 85%, 6%, 32.9% and 40.5%, respectively, and the ratio of CD4⁺ T cells/CD8⁺ T cells

Figure 1. Preoperative radiograph of the spine showing marked lordoscoliosis.

Figure 2. Computed tomography of the chest showing a questionable hyperplasia of the thymus (arrow).

Figure 3. Electromyogram of the paraspinal muscle. Panel A shows the continuous motor unit activity at rest and Panel B shows the disappearance of the continuous motor unit activity after diazepam administration. Calibrations: 100 msec (horizontal) and 1 mV (vertical).
was 0.81. The computed tomography of the chest showed the questionable hyperplasia of the thymus (Fig. 2). The motor and sensory nerve conduction velocity was normal in bilateral median and peroneal nerves. EMG disclosed the continuous motor unit activity at rest in the paraspinal muscles (Fig. 3A) which was abolished by the intravenous administration of diazepam (Fig. 3B). The anti-GAD antibodies of the cerebrospinal fluid (CSF) were elevated to 315.5 U/ml despite normal CSF values in other parameters (cells 0/mm³, protein 17 mg/dl, IgG 3.5 mg/dl, negative for oligoclonal band and myelin-basic protein). She was treated with diazepam 30 mg/day, followed by a significant favorable response of a marked decrease in the magnitude and frequency of muscular stiffness, rigidity and spasm. EMG performed after treatment with diazepam did not show the decrementary response by repetitive electrical stimulation.

**Discussion**

SMS is a rare disorder characterized by intermittent spasm and stiffness occurring predominantly in the axial skeleton (1, 2). The diagnosis of SMS essentially relies on clinical findings complemented by characteristic, although nonspecific, signs such as fixed lordosis, steady firing of normal motor units on EMG, and favorable responses of both stiffness and spasm to the benzodiazepines (2–4). The present case typically illustrates the signs and symptoms of SMS such as stiffness, rigidity and spasm in axial muscles including proximal limb muscles which were frequently elicited by acoustic and various somatosensory stimuli to all parts of the body, slow progression of stiffness, a pronounced lordoscoliosis, normal findings on motor and sensory nerve examinations, normal intellect, and typical EMG findings of continuous motor unit activity which was abolished after intravenous administration of diazepam. Thus, the present case fulfills the clinical diagnostic criteria for SMS. In addition, the very high titer of GAD antibody in the serum and also in CSF were shown.

From the early reports of SMS (2–4), it has been suggested by electromyographic and pharmacological studies that the functional impairment of SMS is due to an imbalance between excitatory (catecholaminergic) and inhibitory (GABA-ergic) pathways controlling α-motoneuron activity, although the few autopsies carried out so far have failed to demonstrate the pathological lesions of specific areas of the central nervous system (7). Since Solimena et al reported that autoantibodies against GAD were found in about 60% of patients clinically diagnosed as having SMS (5–7), the diagnostic accuracy of SMS was distinctly improved. They also suggested the close linkage between SMS and autoimmune pathogenesis; one or more organ-specific autoimmune diseases were present in 58% of GAD antibodies positive SMS patients. Furthermore, they pointed that the most frequent organ-specific autoimmune disease associated with SMS was IDDM (24%). GAD antibodies from patients with SMS could detect GAD antigens of the pancreatic β-cells in Western blots or fixed tissue sections but those from patients with IDDM failed (8, 9). Moreover, the titer of GAD antibodies in patients with SMS is 10–200 times higher than that found in patients with IDDM (9). These findings suggest that GAD antibodies in patients with SMS recognize more distinct and broader epitopes than those in patients with IDDM and that GAD in pancreatic β-cells is one of the target autoantigens in the patients with SMS (8). Diabetes mellitus in the present case is not typical of IDDM but rather similar to non-insulin dependent diabetes mellitus, although the cytoplasmic islet-cell antibodies, a specific marker of IDDM, were positive. Some pancreatic β-cell activity is suggested to be left by the findings that the reduction of urinary excretion of C-peptide was not profound for IDDM and that ketonuria and ketoacidosis were not noted. Thus, the extremely increased GAD antibodies in the present case might contribute to the development of diabetes mellitus via autoimmune-mediated destructive process in a manner of partial loss of pancreatic β-cells, thereby being akin to non-insulin dependent diabetes mellitus.

Another interesting aspect of the present case is organ-specific autoimmunity. Clinically, the organ-specific autoimmunity usually affects a single organ or gland in the body, but serological evidence often indicates subclinical disturbances in other related tissues (10). In accordance with the report by Solimena et al (6), many organ-specific antibodies were found positive. Hashimoto’s thyroiditis, in particular, shown by slightly decreased levels of FT₄ and FT₃ and a mildly increased level of TSH with anti-thyroid peroxidase and antithyroglobulin autoantibodies indicates the chronic immune-mediated destructive process in the thyroid. Although in organ-specific autoimmunity a functional decrease in suppressor T cell activity is shown, no characteristic abnormality was identified in resting T cells of peripheral blood lymphocytes in the present case (11). In addition, no study of MHC linkage between SMS and organ-specific autoimmunity has been reported.

Quite interestingly, the present case had the antecedent history of the ocular type of myasthenia gravis confirmed by the waning phenomenon on EMG which was reversed by the edrophonium administration and by the positive anti-AChR antibodies which are specific markers and are also directly implicated in the pathophysiology of this disorder (10). The low titer of anti-AChR Ab is seen commonly in patients with the ocular type of myasthenia gravis (12). Furthermore, the persistent low titer of anti-AChR antibodies without the clinical findings of myasthenia gravis in this case might be an epiphenomenon induced by the broad spectrum of organ-specific autoimmunopathy. As far as we are aware, there is only one report on SMS associated with myasthenia gravis which had radiological evidence of thymoma, suggesting that SMS could have occurred as a remitting immune-mediated paraneoplastic manifestation (13). Although the hyperplasia of the thymus was suggested, there was no evidence of malignancy in this case, indicating that myasthenia gravis is one of the manifestations of the organ-specific autoimmunopathy. Thus, the present case is the first one that SMS is preceded by myasthenia gravis of organ-specific autoimmune etiology.

These findings lead us to the speculation that the production
of GAD antibodies, anti-thyroid peroxidase and anti-thyroglobulin antibodies, and anti-AchR antibodies might be attributable to a polyclonal activation of the immune system. These antibodies may simply be epiphenomena, appearing as a result of, rather than being responsible for, the primary autoimmune process (14). In other words, these autoantibodies may be involved in effecting or perpetuating tissue damage rather than initiating it. Therefore, SMS of the present case is probably one of the fully expressed manifestations from the broad spectrum of organ-specific autoimmunopathies in virtue of the loss of self-tolerance.

References