Successful Intrathecal Baclofen Therapy for Seronegative Stiff-Person Syndrome: A Case Report

Bo-Lin Ho and Pang-Ying Shih

Abstract- We reported a 27-year-old man presenting with progressive muscle rigidity and intermittent spasms for six years. The diagnosis of stiff-person syndrome was based on the clinical features and neuro-electrophysiologic findings of continuous motor unit activities. Autoantibody against glutamic acid decarboxylase in our patient was absent either in serum or in cerebrospinal fluid. The patient was successfully treated with intrathecal baclofen therapy after a series of unsatisfactory traditional medical treatments. From our experience, we propose that intrathecal baclofen could be a considerable alternative treatment for patients with refractory stiff-person syndrome.

Key Words: Stiff-person syndrome, Anti-glutamic acid decarboxylase antibodies, Intrathecal baclofen therapy

INTRODUCTION

Stiff-person syndrome (SPS) is an uncommon neurological disorder characterized by progressive rigidity and episodic painful spasms in the axial and proximal part of limb musculature. The etiology is supposed to be related to autoimmune disorders and endocrinopathies such as insulin-dependent diabetes mellitus, Graves' disease, vitiligo and pernicious anemia[1,2]. The high prevalence of specific autoantibodies against glutamic acid decarboxylase (anti-GAD), the presynaptic rate-limiting enzyme responsible for the synthesis of γ-aminobutyric acid in both serum and cerebrospinal fluid (CSF), was formerly considered as a diagnostic clue for SPS[3]. However, the absence of anti-GAD, defined as seronegative type like our patient, dose not exclude the diagnosis. Only single native case has been reported in Taiwan[4]. The actual prevalence of SPS may be underestimated due to misdiagnosis or other clinical variants. Current literatures about ITB efficacy for SPS were limited, and subsequent response was variable individually[5-7]. Herein, we report a patient with seronegative SPS successfully treated with ITB therapy.

CASE REPORT

A 27-year-old man had slowly progressive course of generalized stiffness and episodic painful spasms of four

limbs for six years. The past medical history and related family history were unremarkable despite of the fact that his aunt has systemic lupus erythematosus (SLE). The initial presentation was occasional spastic cramping of the left leg at the age of 21 years-old, and followed by easy fatigue with tremor-like movement after long-period standing. Neurological examinations revealed stiffness of the trunk and four limbs with mild lumbar hyperlordosis (Fig. 1). Attempted passive or voluntary movement, sudden noise or tactile stimuli precipitated spasms of both legs and the lower back, although spasms would occur spontaneously. He had spastic gait and needed help to turn around and to sit down. Furthermore, the mental status, cranial nerves, muscle strength, sensory and cerebellar functions were normal. Deep tendon
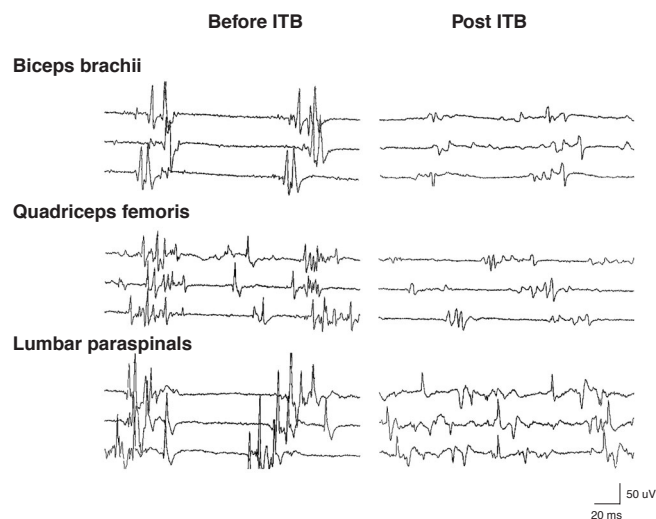
reflexes were symmetrically brisk. Sphincter functions were intact.

Laboratory data including routine hematogram, biochemistry and autoimmune profiles, serum ceruloplasmin and 24-hour copper in the urine were within normal range. Electroencephalography, nerve conduction studies and brain magnetic resonance imaging (MRI) were normal. Serial electromyographic examinations showed continuous motor unit activities (CMUA) of lumbar paraspinal muscles and lower limbs despite the manipulation to relax (Fig. 2). The CMUA disappeared during sleep, after regional nerve block by lidocaine injection, or intravenous administration of diazepam. The CSF studies revealed normal results without oligoclonal bands, and anti-GAD were absent both in his serum and CSF.

The patient received anti-parkinsonian drugs for the suspicion of early-onset parkinsonism, and initially minimal improvement was observed. However, his ambulation performance progressively deteriorated even under continuous levodopa therapy in the following years. The preliminary symptoms were unresponsive to diazepam titration (up to 50 mg/day) and several sessions of

Figure 1. The noticeable stiffness of the back and legs makes the patient flex the posture and have difficulties in bending forward.

Figure 2. Needle electromyography demonstrated decreased spontaneous firing of motor action potentials both in frequency and amplitude on attempted relaxation after intrathecal baclofen therapy.

Figure 3. Prominent hyperlordosis with rigidity of thoracolumbar paraspinal muscles. Note the pump was placed subcutaneously at the left aspect of abdomen (white arrow).

plasmapheresis. At age 26, he became wheel chair-bound, and had difficulty in turning over in bed and in getting up. According to significant effectiveness of single bolus of intrathecal baclofen (ITB, 50 µg), an intrathecal pumping device (Medtronic SynchroMed II infusion system) was implanted with catheter tip at thoracic spinal segment at the T6-T7 level for continuous ITB therapy (Fig. 3). The daily dose was titrated up gradually from 60 to 220 µg/day over eight months to reach satisfactory response. No remarkable complications developed.

Keeping ITB therapy, his muscular rigidity and episodic spasms have much diminished, and he became able to walk short distance without crutches. The improvement in his mobility continued during the two-year follow-up under oral comedication of diazepam (2 mg/day) and prednisolone (5 mg every other day) in combination with regular rehabilitation.

DISCUSSION

Our patient was diagnosed as SPS according to clinical and electrophysiological findings about three years after insidious onset of intermittent painful spasms of the left leg. Without recognized pyramidal or extrapyramidal dysfunction, symmetric stiffness and superimposed episodic spasms predominant in the axial and proximal limb muscles are typical presentations of SPS[8]. Although the definite etiology remained obscure, an autoimmune-mediated mechanism is suggested by the presence of specific autoantibodies, and the high prevalence of comorbidities with other autoimmune disorders and endocrinopathies[2,9]. Family history may be positive for SLE, insulin-dependent diabetes mellitus (IDDM), rheumatoid arthritis and thyroid disease[10].

Clinical variants of SPS may present as a variety of spectrums including ocular motor or sensory disturbance, ataxia, neuropsychological disorders (progressive encephalomyelitis with rigidity and myoclonus), or involve single one or more limbs (stiff limb syndrome), or be associated with malignancy (paraneoplastic SPS)[11,12]. Our patient presented slowly progressive symptoms over six years, without autonomic dysfunction, sensory or cerebellar deficit; hence the diagnosis of classic SPS was more favored rather than its other variants.

Although rare, there are various central and peripheral conditions causing persistent stiffness with CMUA. Tetanus is suggested by the classical symptoms of trismus, dysphagia and muscular rigidity, and the peripheral silent period is abnormal in contrast to SPS[13]. Other infective or toxic etiologies such as poliomyelitis, borreliosis, or strychnine poisoning were excluded due to absent trauma or exposure history in our patient. Focal spinal cord pathology may induce segmental stiffness with weakness, wasting, absence of tendon reflexes and denervation in the affected myotomes on electromyograms[1,13]. Clinical neuromyotonia (Isaacs' syndrome) manifests as focal stiffness, cramps and delayed relaxation predominantly involving distal limb muscles, and sleep or general anesthesia does not abolish motor hyperactivity[1,13]. Generalized dystonia is characterized by sustained muscle contractions with repetitive twisting or abnormal postures which are modifiable by sensory tricks; unlike SPS, it usually relates to positive family history or neuroleptics use[14]. The cases with encephalomyelitis are thought to be clinical variants of

SPS, namely stiff-person plus syndromes, presenting with brainstem or long tract signs, lower motor neuron signs, autonomic dysfunction or sometimes cognitive changes[5,12]. However, none of the above conditions consisted with clinical features of our patient.

The presence of anti-GAD helps to establish the diagnosis of SPS, and also has been described in patients with IDDM, cerebellar ataxia, drug-resistant epilepsy and myoclonus[9,15]. Approximately 60% to 80% patients with SPS have anti-GAD in the serum or CSF[1,2]. These antibodies can be detected by immunocytochemistry (ICC) on frozen sections of rat cerebellum, and confirmed by Western blot of recombinant human GAD. Murinson et al. proposed that marked elevations of anti-GAD on radioimmunoassay (RIA) were characteristic of ICC-confirmed SPS, while RIA was considered as a reliable substitute for anti-GAD measurement in the diagnosis of SPS[16]. We have rechecked the anti-GAD titer of our patient via ICC and RIA during treatment course, and the results were all negative.

The significance of anti-GAD in the clinical findings or in the response to medical treatment remains obscure. Some reports have indicated that there was no clear difference in the neurological manifestations of patients with and without anti-GAD[1,11]. Reviewing previous literatures to date, seronegative patients were less reported, and they may represent another clinical variant[3,12]. Shariatmadar et al. suggested that anti-GAD negative patients were less responsive to plasma exchange[17]. Present findings have indicated that in patients with SPS, the titers of anti-GAD in serum and CSF may fluctuate and do not correlate with the disease severity, duration or response to therapies[18,19].

Intrathecal baclofen, as reported to be effective in previous studies, is an alternative therapy for patients who responded poorly to or did not tolerate oral medications[5,6,11]. As compared with plasma exchange or IVIG, prolonged clinical improvement for several years will be achieved by ITB[5,6]. In a double-blind, placebo-controlled trial of ITB in three SPS patients, bolus of 50 µg ITB made rapid improvement in muscle stiffness and in reflex electromyographic activities[7]. The dramatic improvement was also found in our patient, predicting a candidate for ITB therapy. Stayer et al. have reported clinical outcomes of eight patients with SPS or progressive encephalomyelitis with rigidity and myoclonus (PERM), receiving ITB therapy[5]. Specifically among the seronegative SPS as shown in our patient, increasing doses were subsequently required within a span of several months to years. The dosage of ITB was adjusted according to both clinical response and individual tolerance to side effects. General mobilization improved significantly and long-lasting advancement was made under an acceptable dose of less than 1,000 µg/day. Due to the rarity of reported seronegative SPS patients under ITB, the present data could not demonstrate significant differences in treatment responses between seropositive and seronegative ones. Although complete remission was not achieved in our patient, we confirmed the great benefit of ITB therapy to refractory SPS.

Patients with mild or moderate severity of disease but no fixed musculoskeletal deformity most likely benefit from ITB therapy[7]. In our patient of young age, ITB therapy has successfully prevented exaggerating lumbar lordosis and preserved better prognosis of ambulation. He tolerated the increasing doses of ITB well without disabling complications. However, potentially fatal withdrawal symptoms including acute autonomic disturbance, spasmodic storm and circulatory collapse may be induced by catheter rupture or pump malfunction resulting in inaccurate administration[5,20]. Therefore, current opinions recommended ITB as a last-resort symptomatic treatment of SPS[19]. Careful screening and monitoring are indispensable for patients receiving ITB. In conclusion, ITB therapy may be a good alternative with long-term clinical improvement in refractory seronegative SPS.

REFERENCES

1. Meinck HM, Thompson PD. Stiff man syndrome and related conditions. Mov Disord 2002;17:853-66.
2. Solimena M, Folli F, Aparisi R, et al. Autoantibodies to GAB-Aergic neurons and pancreatic beta cells in stiff-man syndrome. N Engl J Med 1990;322:1555-60.
3. Barker RA, Revesz T, Thom M, et al. Review of 23

patients affected by the stiff man syndrome: clinical subdivision into stiff trunk (man) syndrome, stiff limb syndrome, and progressive encephalomyelitis with rigidity. J Neurol Neurosurg Psychiatry 1998;65:633-40.

4. Chang YJ, Wu CL, Lu CS. Stiff-man syndrome: report of a case. J Formos Med Assoc 1995;94:695-7.

5. Stayer C, Tronnier V, Dressnandt J, et al. Intrathecal baclofen therapy for stiff-man syndrome and progressive encephalomyelopathy with rigidity and myoclonus. Neurology 1997;49:1591-7.

6. Penn RD, Mangieri EA. Stiff-man syndrome treated with intrathecal baclofen. Neurology 1993;43:2412.

7. Silbert PL, Matsumoto JY, McManis PG, et al. Intrathecal baclofen therapy in stiff-man syndrome: a double-blind, placebo-controlled trial. Neurology 1995;45:1893-7.

8. Espay AJ, Chen R. Rigidity and spasms from autoimmune encephalomyelopathies: stiff-person syndrome. Muscle Nerve 2006;34:677-90.

9. Saiz A, Arpa J, Sagasta A, et al. Autoantibodies to glutamic acid decarboxylase in three patients with cerebellar ataxia, late-onset insulin-dependent diabetes mellitus, and polyendocrine autoimmunity. Neurology 1997;49:1026-30.

10. Dalakas MC, Fujii M, Li M, et al. The clinical spectrum of anti-GAD antibody-positive patients with stiff-person syndrome. Neurology 2000;55:1531-5.

11. Meinck HM, Ricker K, Hulser PJ, et al. Stiff man syndrome: clinical and laboratory findings in eight patients. J Neurol 1994;241:157-66.

12. Brown P, Marsden CD. The stiff man and stiff man plus syndromes. J Neurol 1999;246:648-52.

13. Brown P. Stiffness with continuous motor unit activity. Movement Disorders, Handbook of Clinical Neurophysiology, Vol. 1. Amsterdam: Elsevier, 2003:463-75.

14. Jankovic J, Fahn S. Dystonic disorders. Parkinson's Disease and Movement Disorders, 2nd ed. Baltimore: Williams & Wilkins, 1993:337-74.

15. Vianello M, Tavolato B, Giometto B. Glutamic acid decarboxylase autoantibodies and neurological disorders. Neurol Sci 2002;23:145-51.

16. Murinson BB, Butler M, Marfurt K, et al. Markedly elevated GAD antibodies in SPS: effects of age and illness duration. Neurology 2004;63:2146-8.

17. Shariatmadar S, Noto TA. Plasma exchange in stiff-man syndrome. Ther Apher 2001;5:64-7.

18. Rakocevic G, Raju R, Dalakas MC. Anti-glutamic acid decarboxylase antibodies in the serum and cerebrospinal fluid of patients with stiff-person syndrome: correlation with clinical severity. Arch Neurol 2004;61:902-4.

19. Meinck HM. Stiff man syndrome. CNS Drugs 2001; 15:515-26.

20. Bardutzky J, Tronnier V, Schwab S, et al. Intrathecal baclofen for stiff-person syndrome: life-threatening intermittent catheter leakage. Neurology 2003;60:1976-8.