Treatment of Stiff-Person Syndrome With Chronic Plasmapheresis

Stiff-person syndrome (SPS) is a disabling central nervous system disorder characterized by muscle stiffness, rigidity, and superimposed painful spasms affecting axial and proximal limb muscles. Electromyography shows continuous motor unit activity in axial muscles.

There is strong evidence of an autoimmune pathogenesis for SPS. High levels of antibodies against the 65-kD isoform of glutamic acid decarboxylase (anti-GAD65) are found in the serum and/or cerebrospinal fluid of 85% of patients. Paraneoplastic SPS commonly occurs in association with anti-amphiphysin antibodies.

Different immunomodulatory treatments have been tried in SPS with variable success. Plasmapheresis, usually performed in 1 cycle of 5 plasma exchange (PE) sessions over 1 or 2 weeks, has been tried in a few SPS patients with conflicting results.[1–7]

We report the clinical improvement induced by chronic plasmapheresis in 2 patients with SPS and previous poor response to symptomatic and other immunomodulatory treatments. Clinical characteristics of the patients are summarized in Table 1.

Plasmapheresis was performed using plasmaFlux PSu 2S filters (Fresenius Medical Care, Waltham, MA). A central venous catheter (subclavian) was inserted for the first sessions. Once it was confirmed that plasmapheresis was effective, a radiocephalic fistula was created. Patients underwent 1 PE per week, with 2 L of 5% albumin as replacement fluid during each procedure.

In patient 1, clinical improvement was observed after the first 4 sessions of PE and increased during the following 2 months. The spasms disappeared, face and limb stiffness subsided, and trunk stiffness was considerably reduced. The patient was able to bend at the waist and could place her fingertips at a distance of 20 cm from the floor. Lumbar pain disappeared. The patient's clinical situation remains stable after 3 years of weekly PE. Serum anti-GAD65 antibody titers (enzyme-linked immunosorbent assay), determined 1 and 2 years after the onset of chronic plasmapheresis, remained >2000 U/mL (normal values < 10 U/mL).

In patient 2, clinical improvement was observed after the first month of therapy and continued during the second month before becoming stable. After 14 months of weekly PE, the frequency of axial spasms was reduced by more than 50%, and there was marked improvement in axial stiffness. The patient is now able to bend at the waist and can place his fingertips a distance of 10 cm from the floor. He did not report falls. Anti-GAD65 antibody titers in serum after 4 months of chronic plasmapheresis remained >2000 U/mL.

We found that chronic plasmapheresis can improve spasms and axial stiffness in patients with severe SPS who did not obtain sufficient benefit from symptomatic or other immunomodulatory treatments. The improvement in the cardinal symptoms of SPS was sustained for up to 3 years of weekly PE, which, to our knowledge, is the longest reported period of effective chronic plasmapheresis in SPS.

The modulatory effect of plasmapheresis on the immune system does not persist over time, and the frequency of PE needs to be determined individually according to the underlying disease, the patient's improvement, and the rebound of pathogenic factors. Therefore, it seems plausible that patients with SPS—a chronic condition of probable autoimmune etiology—may experience sustained benefit from chronic plasmapheresis. In addition, long-term treatment with 1 PE per week was well tolerated, and no adverse effects were observed in our patients.

It is noteworthy that serum anti-GAD65 antibody titers remained high (>200-fold the normal values) despite the frequency of PE. This finding has also been observed after short cycles of PE.[1] The discrepancy between clinical improvement and high levels of anti-GAD65 antibodies calls into question the pathogenic role of these antibodies in SPS. Although clinical symptoms may be more related to intrathecal synthesis of anti-GAD65 antibodies, it is unclear whether these antibodies cause SPS directly, are markers of autoimmunity, or are an epiphenomenon of neural destruction. The therapeutic effect of plasmapheresis in our cases may be related to the elimination of other pathogenic autoantibodies, complement, or cytokines or to the modulation of other components of the immune system.

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Table 1. Clinical characteristics of the patients

	Patient 1	Patient 2
Age (y)	59	48
Sex	Female	Male
Disease duration	10 months	20 years
Stiffness	Progressive Face, trunk, limbs (proximal) Board-like rigidity Hyperlordotic posture Unable to bend at the waist Stiff and slow gait	Progressive Trunk and hips Slowness Gait blocks and falls Boardlike rigidity Hyperlordotic posture Unable to bend at the waist
Spasms	Spontaneous Abdominal and paraspinal muscles Lasting up to 20 minutes Several per month	Stimuli induced Abdominal and paraspinal muscles Short lasting Several per day
Other clinical features	Vitiligo Pernicious anemia	Vitiligo Diabetes
Electromyography	Continuous motor unit activity	Continuous motor unit activity
Anti-GAD65 antibodies	>2000 U/mL	>2000 U/mL
Antiamphiphysin antibodies	Negative	Negative
Previous treatments	Baclofen Valproic acid Diazepam Botulinum toxin IV immunoglobulin IV methylprednisolone Azathioprine	Clonazepam Diazepam Gabapentin Azathioprine IV immunoglobulin IV methylprednisolone

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First Video Report of Static Encephalopathy of Childhood With Neurodegeneration in Adulthood

Neurodegeneration with brain iron accumulation (NBIA) comprises a group of disorders characterized by abnormal iron deposition within the basal ganglia.[1–3] Eight causative genes, including *PANK2* and *PLA2G6*, have been identified.[1–4] Recently, a new NBIA subpopulation, termed static encephalopathy of childhood with neurodegeneration in adulthood (SENDA), was proposed.[1,3] These patients display early childhood nonprogressive intellectual impairment transitioning to progressive dystonia-parkinsonism and dementia in adulthood. In addition to iron deposition in the globus pallidus (GP) and substantia nigra (SN), these patients have a distinct T1-weighted MRI pattern characterized by hyperintensity in the SN with a central band of hypointensity. Cerebral atrophy also occurs. Although the features of SENDA are summarized in review articles,[1,3] here, we provide the first video presentation of this unique disorder.

The patient is a 32-year-old woman with unremarkable family and birth history. She showed psychomotor developmental delay. Although her motor functioning gradually developed, and she began to walk at 3 years, she exhibited severe mental retardation and never acquired speech. She developed epileptic seizures at age 4. Her neurological status was stable until adolescence, and when she was referred to us at age 25, she understood simple commands, ate by herself, and walked unsupported (see Video, Segment 1). She was hypotonic and did not exhibit dystonia-parkinsonism. However, akinesia and rigidity progressed from age 26. She also displayed cognitive decline. Foot dystonia and dysphagia developed after age 28. Mental and motor functioning progressively deteriorated, and she became bedridden at age 30. She has been taking carbamazepine since childhood, and there was no drug change preceding the deterioration. At age 32, she showed generalized rigidity with flexion contractures (see Video, Segment 2). She was mute and fed through a nasogastric tube. Ophthalmologic examinations revealed thinning of the retinal nerve fiber layer. Pigmentary retinopathy was not evident.

Brain CT at age 25 showed moderate frontotemporal cerebral atrophy. Calcification was observed in the bilateral GP (Fig. 1a). T2- and T2*-weighted MR images showed hypointensity in the SN and GP (Fig. 1b–e). The eye-of-the-tiger sign was not evident. Instead, T1-weighted images demonstrated hyperintensity in the SN with a central band of hypointensity (Fig. 1f). Follow-up MRI at age 32 showed marked progression of cerebral atrophy (Fig. 1i).

Serum levels of calcium, phosphate, and parathyroid hormone were normal, and there were no skeletal stigmata of pseudohypoparathyroidism. Blood and cerebrospinal fluid (CSF) lactate, urinary organic acid profile, and serum levels of ceruloplasmin, copper, iron, and ferritin were normal. Nerve

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