Case Reports in Neurology

Case Rep Neurol 2012;4:92–96
DOI: 10.1159/000339446

Published online:
May 31, 2012

ISSN 1662–680X
www.karger.com/crn

Childhood Stiff-Person Syndrome Improved with Rituximab

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Key Words
Rituximab · Stiff-person syndrome · Myoclonus

Abstract
Introduction: Stiff-person syndrome (SPS) is manifested by fluctuating rigidity of axial musculature with painful episodic spasms due to simultaneous co-contraction of agonist and antagonist muscles. We present a case report and video illustrating response to treatment with rituximab.
Materials and Methods: Case description and video are provided. A literature search for other reports of treatment with rituximab was performed.
Results: Nine cases in addition to our case were described. Substantial clinical benefit was reported in 7/9 (78%) cases. Four out of 9 (44%) cases displayed persistent anti-glutamic acid decarboxylase (GAD) antibody positivity.
Conclusion: Rituximab is an important treatment strategy in SPS. The persistence of anti-GAD antibody positivity even with clinical remission remains to be elucidated.

Introduction

Stiff-person syndrome (SPS), first described by Moersch and Woltman in 1956 [1], typically presents between the 3rd and 6th decade of life and is manifested by fluctuating rigidity of axial musculature with painful episodic simultaneous co-contraction of agonist and antagonist muscles. Episodes may be triggered by tactile, emotional, or auditory stimuli. Comorbid anxiety may be present which may raise suspicion of a psychogenic disorder and delay diagnosis [2]. Antibodies against glutamic acid decarboxylase (GAD), gamma-amino butyric acid A receptor-associated protein, and amphiphysin I have been identified in this disorder [2, 3].

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Case Report

The patient is a 12-year-old right-handed Hispanic boy who presented for evaluation of painful axial muscle contractions and exaggerated startle response.

His first symptom, stiffness of the right leg during ambulation, occurred at age 5. At age 7, he had a generalized seizure lasting 5 min with unresponsiveness and jerking movements of all extremities, but without tongue biting, bowel or bladder incontinence. He was controlled on levetiracetam until age 11. At that time, he developed episodes of nightly awakening with a prodrome of anxiety and tachycardia typically followed by up to 20 min of painful hyperlordotic posturing. Occasional episodes lasted for up to 2 h. Frequency of episodes gradually worsened from once to several times a day. Startle response to auditory and tactile stimuli triggered many of the episodes. In order to prevent falls, the patient became wheelchair bound. There is no family history of similar disorder, but there is consanguinity (the patient's paternal grandmother and grandfather are second cousins).

On examination, the patient manifested sustained right ankle clonus, markedly contracted thoracolumbar paraspinal muscles, hyperlordotic posture, and classic 'board-like' abdomen. Tactile or auditory stimulation triggered episodes with right lower extremity sustained myoclonus, diaphoresis, painful exacerbation of the hyperlordosis with thoracolumbar axial and abdominal muscle co-contraction, and rocking movements which were likely a response to the axial contraction.

Magnetic resonance imaging of the brain and video electroencephalography studies were normal. Anti-GAD antibody was positive at 4,405 nmol/l, but there were no detectable anti-amphiphysin antibodies. Muscle biopsy was normal. There was mild improvement with diazepam or clonazepam and monthly intravenous immunoglobulin treatment (IV Ig) [4]. Baclofen and gabapentin did not improve his symptoms. A course of rituximab, a monoclonal antibody which binds to B-lymphocyte CD surface antigens, consisting of two 500 mg/m^2 treatments spaced 14 days apart, markedly reduced the frequency and severity of axial contractions, diminished startle response, and abolished sustained ankle clonus. Most importantly, his gait markedly improved and he is now able to ambulate with minimal assistance, partly because of residual phobia of falling (for online suppl. video, see www.karger.com/doi/10.1159/000339446). Post-treatment anti-GAD antibody levels were not available.

Materials and Methods

A Medline search for 'stiff-person syndrome' and 'rituximab' was performed.

Results

The initial Medline search yielded 12 articles, of which 8 were relevant case reports [5–12]. The details are provided in **table 1**. Substantial clinical benefit was reported in 7/9 (78%) cases (1 report described monozygotic twins). In 4/9 (44%) of these cases, anti-GAD antibodies remained positive after treatment.

Discussion

This childhood case demonstrates the classic features of SPS and the remarkable clinical improvement with rituximab (table 1; online suppl. video). Thus, rituximab should be added to other treatments of SPS such as IV Ig, plasmapheresis, cyclophosphamide, and mycophenolate. Other antispasmodic treatments reported to be effective in patients with SPS include tizanidine, piracetam, phenobarbital, and local botulinum toxin injections [5].

Although a double-blind placebo-controlled trial of rituximab on 2 patients 'did not support a profound benefit' [7], experience with rituximab, based on open-label case

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reports, has suggested that at least 2 doses of rituximab at 350–375 mg/m^2/infusion spaced 1–2 weeks apart [5, 12] or 4 weekly infusions [9] provide clinically meaningful improvement in SPS symptoms. If a relapse occurs, a repeat dose 6–8 months later may be needed [9, 12].

Hence, rituximab should be considered as an effective and less expensive alternative in patients with SPS and other autoimmune movement disorders who fail to obtain adequate response to benzodiazepines and other conventional antispasmodic and immunologic therapies [13].

Disclosure Statement

R. Fekete has served as consultant for Lundbeck, Inc., Teva Neuroscience, Inc., and received honoraria from Medlink, Inc.

J. Jankovic: Research support from Allergan, Inc., Boehringer-Ingelheim, Inc., Ceregene, Inc., Chiltern International, EMD-Serono, Inc., Helis Foundation, Huntington's Disease Society of America, Huntington Study Group, Impax Pharmaceuticals, Ipsen Limited, Medtronic, Merz Pharmaceuticals, National Institutes of Health, National Parkinson Foundation, Neurogen, Novartis, Ortho-McNeil, St. Jude Medical, Teva, University of Rochester, and Parkinson Study Group. Consultant and/or Advisory Committee Member: Allergan, Inc., Michael J. Fox Foundation for Parkinson's Research, Merz Pharmaceuticals, Lundbeck, Inc., and Teva.

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Table 1. Summary of reported SPS cases treated with rituximab

Baker et al. [6]	41-year-old patient with full remission of SPS after a single dose of rituximab (375 mg/m^2) followed 6 weeks later by 4 weekly doses (375 mg/m^2/infusion). She had prior improvement and relapse on intravenous immunoglobulin, mycophenolate mofetil, cyclophosphamide, and intrathecal hydrocortisone treatment	Anti-GAD serum antibodies positive but decreased due to prior treatment regimens. Cerebrospinal fluid anti-GAD antibodies initially positive and disappeared 17 days after initiation of rituximab treatment
Lobo et al. [5]	41-year-old SPS patient with full remission after second infusion of rituximab, 15 days after first one. Dose: 375 mg/m^2/infusion	Anti-GAD antibodies continued to rise with treatment
Venhoff et al. [7]	Double-blind placebo-controlled trial of 34-year-old male monozygotic twins with SPS and autoimmune thyroiditis 'did not support a profound benefit', but authors concede that 'rituximab may have prevented a more severe disease course'	Anti-GAD IgG antibody decreased at the same time from 205 to 103 units/ml in both the placebo/rituximab and rituximab/placebo arms
Bacorro and Tehrani [8]	62-year-old man with diabetes mellitus and SPS achieved clinical remission with 2 doses of rituximab that were 1 week apart	Anti-GAD levels remained elevated
Dupond et al. [9]	53-year-old man with SPS and positive anti-GAD and anti-amphiphysin antibodies who had partial improvement and then relapse after thymectomy, prednisone, intravenous immunoglobulin, and mycophenolate mofetil. Rituximab was administered at a dose of 350 mg/m^2 per week, for 4 weeks. Symptoms reappeared after 8 months and were abolished after a second dose of rituximab	Serum anti-amphiphysin antibodies became undetectable. Anti-GAD antibodies remained strongly positive
Qureshi and Hennesy [10]	56-year-old man with diabetes mellitus and a 5-year history of progressive stiffness and painful spasms of his limbs and axial region successfully treated with 4 doses of rituximab over 3 months	Anti-GAD titers at 400 U/ml one year after treatment
Katoh et al. [11]	66-year-old woman with diabetes mellitus with clinical improvement of thyroid ophthalmopathy and SPS with 3 doses of rituximab treatment	Anti-GAD antibodies profoundly decreased 2 months after initiation of treatment
Sevy et al. [12]	50-year-old woman with axial and limb spasms triggered by anxiety or startle response to noise. She was treated with 1,000 mg of rituximab in 2 injections 15 days apart. She had a relapse after 6 months, treated with a third 1,000-mg rituximab injection	Anti-GAD serum antibodies increased after treatment from 51 to 75 U/ml

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