

Case Report

Chronic intestinal pseudo-obstruction with dilated biliary tract as a spectrum of stiff person syndrome in a nondiabetic patient

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Abstract

Stiff person syndrome (SPS) is a rare and challenging neuromuscular junction disorder with typical musculoskeletal manifestations associated with anti-GAD65 antibodies, extra rheumatological manifestations, including neuropsychiatric symptoms and severe dysautonomic troubles. Chronic intestinal pseudo-obstruction (CIPO) is also a rare condition corresponding to a sub-occlusive syndrome, resulting from the functional or structural impairment of smooth neuromuscular tissues of the intestinal tract. In the clinical spectrum of SPS, CIPO has rarely been described and dilated biliary tract has never been described. This present report is therefore the first in the context of anti-GAD65 antibodies with the additional involvement of the biliary tract. Here, we report the case of a 44-year-old woman hospitalized for a rapidly progressive CIPO associated with dilated biliary tract, revealing a typical SPS with slowly progressive rheumatologic complaints relegated to the background. The concomitant improvement of the neuromuscular function on skeletal, intestinal and biliary tree systems with the good outcomes of anti-GAD65 titer under immunosuppressant drugs, allowed us to link all three organic involvements to the antibody pathogenicity on the respective neuromuscular junctions. Therefore, we discussed their common pathogeny based on our patient's treatment outcome.

Keywords: Stiff Person Syndrome, Chronic Intestinal Pseudo Obstruction, Biliary Tract Dilatation, GABA, Anti GAD65

Introduction

Stiff person syndrome (SPS) is a rare and challenging neuromuscular junction disorder with a prevalence estimated in approximately 1/1 000 000. The diagnosis is evoked essentially on typical musculoskeletal manifestations, including limb and spinal muscle stiffness or spasms with enhanced lumbar or cervical lordosis. Extra rheumatological manifestations, including neuropsychiatric symptoms and severe dysautonomic troubles¹, may be in the foreground of the clinical picture and delay disease identification².

The diagnosis of SPS is supported by electromyographic abnormalities associated with the detection of antibodies against glutamic acid decarboxylase (GAD 65-antibody) in the serum or cerebrospinal fluid of more than 70% of patients. However, in addition to SPS these antibodies can be detected in other autoimmune conditions, such as Myasthenia gravis, thymoma³, type 1 diabetes mellitus, thyroiditis, adrenal insufficiency, and vitiligo, which may be isolated or associated with one another⁴. SPS may also present as a paraneoplastic condition associated with various tumoural disorders.

Chronic intestinal pseudo-obstruction (CIPO) is also a rare condition corresponding to a sub-occlusive syndrome, resulting from the functional or structural impairment of smooth neuromuscular tissues of the intestinal tract. This syndrome may be idiopathic, or it may present as the consequence of connective diseases such as systemic lupus or systemic sclerosis.

Here, we report the case of a 44-year-old woman hospitalized for a rapidly progressive CIPO associated with dilated biliary tract, which revealed a SPS with typical but slowly progressive rheumatologic complaints relegated to

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Table 1. Overview of the spinal parameters, bowel rhythm, hepatic enzymes, antiGAD-65 titres and treatment outcomes in a stiff person syndrome patient exhibiting spinal stiffness, chronic intestinal pseudo-intestinal syndrome and biliary tract dilatation.

	IgIV (2g/kg)		Cyclophosphamide (1g/month)		Rituximab (Day 1, Day 15 at M12)		
	M0	M3	M4	M8	M12	M16	M24
Anti GAD65 (mUA/mL) (Blood) N: < 5 mUA/mL	52	69	74	64	50	40	11
Anti GAD65 (mU/mL) (Cerebrospinal Fluid) N: < 5 mU/mL	68	-	74	74	-	67	-
Liver enzymes AST (U/L) N: 20 - 40 U/L	20	24	16	21	31	20	22
Liver Enzymes ALT (U/L) N: 20 - 40 U/L	21	26	20	20	25	22	14
GGT (U/L) N: < 35 U/L	167	102	80	79	98	88	100
Alkaline Phosphatase (U/L) N: 50 - 130 U/L	146	86	103	115	95	81	123
Conjugated Bilirubin (umol/L) N: 2 - 5 umol/L	14	12	8	6	10	7	8
Schober's Index (10 + X cm)	1.5	2	1.5	2	2.5	4	5
L3 To Wall Distance (cm)	10	9	10	9	8	8	7
Occiput To Wall Distance (cm)	4	3	3	3	3	1	1
Hand To Floor Distance (cm)	29	21	24	22	22	14	10
Bowel Rhythm	Rare	Rare	Rare	Few	Few	Daily	Daily

the background. In the clinical spectrum of SPS, CIPO has rarely been described and biliary tract dilatation has never been described. Therefore, we discussed their common pathogeny based on our patient's treatment outcome.

Case report

A 44-year-old woman was referred for progressive abdominal pain and weight loss consecutive to a worsening condition of chronic constipation. Her medical history included temporal epilepsy treated with lamotrigine for three years. The first symptoms began three years earlier with progressive and increasing muscle pain, stiffness in her legs and lumbar area, associated with chronic increasing constipation, abdominal bloating, occasional nausea and vomiting. Previous hospitalizations with endoscopic exams in the gastroenterology and neurology departments found no obvious anomaly, leading to functional idiopathic constipation diagnosis. At admission, clinical examination retrieved no signs of systemic sclerosis nor inflammatory rheumatism, but a clear hyperlordosis and hyper-contraction of the paraspinal muscles (Table 1, L3-wall distance 10 cm, Schober Index 1.5 cm, occiput-wall distance 9.5 cm), a swaying walk, an asymmetrical diffused and polykinetic patella hyperreflexia that was more pronounced in the right leg, a sub-occlusive digestive syndrome with major

abdominal meteorism, and rare but present hydro-air noises. Haemogram, serum electrolytes, calcium, vitamins, lipase, lipids, muscle enzymes, iron, creatinine, thyroid functions, glycaemia, and biologic inflammatory parameters were in normal range. Serum electrophoresis showed polyclonal hypergammaglobulinemia at 20 g/L and hepatic tests found only a slight persistent increase of gamma-GT (GGT), alkaline phosphatase (ALP) and conjugated bilirubin levels (1,2 to 2 times the normal values). Serum extensive tests were also negative for infectious diseases including HIV, HTLV 1 and 2, and Hepatitis B, C, and E virus. Antibody titers including antinuclear, ANCA, anti-mitochondrial, anti-LKM, ASCA, rheumatoid factor, anti-CCP, anti-smooth-muscles, and those against hu, Yo, Rhi, Ma, Ta, Peripherin G, amphiphysin, potassium channel, N-type or P/Q type calcium channel, GM1, GD1b, GQ1b, muscarinic and nicotinic acetylcholine receptor were all negative. However, anti-GAD 65 antibody was positive in blood serum and cerebrospinal fluid (52 UA/ml and 68 UA/mL, respectively; normally <5 mUA/mL). CSF remained normal for other metabolic and infectious explorations. Blood and CSF immunophenotyping were negative for clonal B, T or NK cells disease. The abdominal ultrasonography and abdominopelvic CT-scan revealed abundant stercoral stasis without any obstacles. Cerebral and spinal MRI and electromyographic exams did not reveal abnormalities, and neuromuscular stimulation showed no

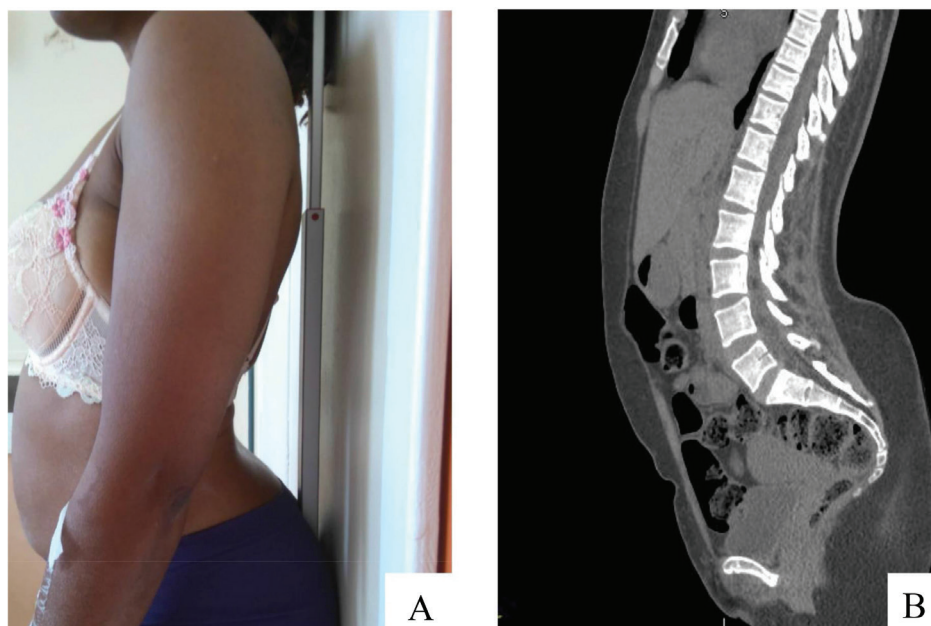


Figure 1. Clinical and CT-scan features revealing a stiff person syndrome patient suffering from lumbar pain and chronic intestinal pseudo-obstruction; **A)** Clinical hyperlordosis with bloated abdomen; **B)** Sagittal CT view showing abundant stercoral stasis and hyperlordosis.

sign of myasthenia nor Lambert-Eaton syndrome. A MR cholangiography investigating the biologic and hepatic abnormalities found a significant choledochal dilatation with slight and rare stenosis and numerous small intravesicular and accessory bile duct stones.

Collectively, the diagnoses of stiff person syndrome and CIPO, both related to the anti-GAD65 antibody, were made while the aetiology of biliary tract involvement remained uncertain. The patient denied other hepatic endoscopy and biopsy procedures while the exploration of antibodies for a coincidental sclerosing cholangitis came back negative. Finally, an 18-FDG PET scan did not find any uptake that could evoke a tumoral and related paraneoplastic syndrome, or inflammatory background.

The initial treatment combining abundant laxatives, pyridostigmine, sandostatin, bile acid chelators associated with monthly courses of intravenous immunoglobulin (IVIG), rapidly tapered oral prednisone (1 mg/kg/day) and mostly oral diazepam or other benzodiazepines showed only slight improvement on the axial muscle and digestive symptoms, respectively, while the anti-GAD65 titres were unchanged at the 4th month (74 mUA/mL in the blood and 74 mUA/mL in the CSF). Thus, IVIG cures were stopped and a second line treatment with intravenous cyclophosphamide (1 g monthly) for 6 months which allowed partial but clear improvement of all axial, digestive and biliary muscular function assessed on the clinical and biologic signs and imaging (Figure 1 and 2). This partial remission was associated with a moderate decrease of anti-GAD65 levels in serum and CSF (Table 1, 4, 8 and 12 months from diagnosis). Finally, two months after

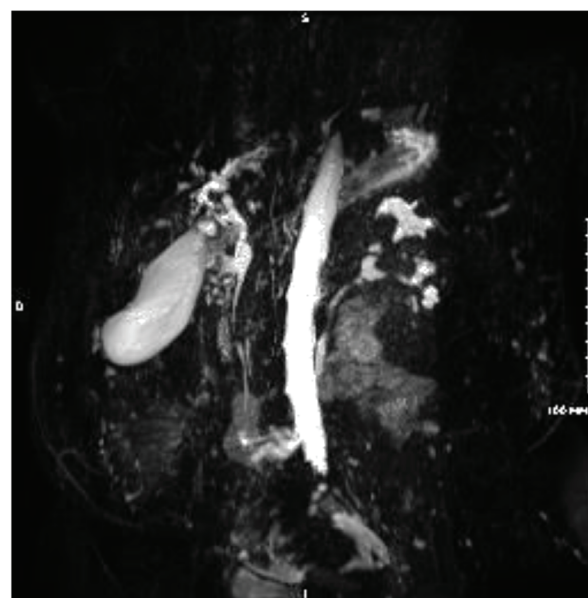


Figure 2. Biliary tract MRI showing the slight and rare stenosis of the biliary ducts and choledochal dilatation revealing stiff person syndrome with associated chronic intestinal pseudo-obstruction.

the last cyclophosphamide injection, two infusions of anti-CD20 monoclonal antibody were administered (Rituximab, intravenous 1 g at DO and D15 12 months from diagnosis)

and then renewed 12 months later (Month 24 from the diagnosis) since the clinical remission was still only moderate. This allowed a complete resolution of all rheumatologic and intestinal signs, while the GAD65 antibody dramatically decreased to the minimal threshold of its detection (Table 1; 11 mUA/mL; N<5) in the serum. As for the biliary tract dilatation, a slight improvement with attenuation of stenosis has been observed on biliary tract MRI during follow up associated with GGT, ALP and bilirubin levels decrease. This allowed us to reduce the dose of ursodeoxycholic acid to 10 mg/kg/day. The patient denied any new CSF controls. Concomitantly, both signs of anicteric cholestasis and biliary duct imaging improved.

Discussion

For the first time, this case reports CIPO and biliary tract dilatation as concomitant manifestations of anti-GAD65 antibodies in the context of SPS, which also probably includes temporal epilepsy, considering the concomitant chronology. The concomitant improvement of the neuromuscular function on skeletal, intestinal and biliary tree systems with the good outcomes of anti-GAD65 under immunosuppressant drugs, allowed us to link all three organic involvements to the antibody pathogenicity on the respective neuromuscular junctions.

Phenotypic features among patients with SPS are diverse, including clinical syndromes such as the classical pattern as described herein or more challenging clinical picture like the partial pattern and the progressive encephalomyelitis with rigidity and myoclonus (PERM). SPS also includes a large panel of symptoms, including seizures, cognitive symptoms, eye movement disorders, and myoclonus or cerebellar ataxia⁵.

CIPO is associated with various other conditions but it is sometimes thought to be idiopathic. Its pathogeny is still unclear⁶ and this syndrome is reported in various neurogenic mechanisms, such as diabetic neuropathy involving myenteric ganglia, or myogenic mechanisms and then related to connective or metabolic diseases such as hypothyroidism, ionic disorders, neoplasia, Hirschsprung disease, systemic sclerosis or systemic lupus⁷. Anti-GAD antibodies were first related to diabetes mellitus where the antibodies hindered the conversion of glutamic acid to gamma-amino butyric acid (GABA) by GAD 65⁸. In fact, beyond pancreatic beta-islet cells, GABA is also expressed in the GABAergic nerve terminals in the enteric nervous system, as well as in the central nervous system⁸⁻¹¹. On the other hand, GAD antibodies are also found in cohorts of patients with achalasia (11-fold higher than in controls, $P < 0.0001$)⁹ or in patients with predominant enteric dysmotility¹². Considering all these arguments, Maier et al described a very well documented case of SPS with limb stiffness and CIPO related to anti-GAD antibodies in a non-diabetic patient. This present report is therefore the second in this setting. However, with the additional involvement of the biliary tract, this report is the first in the context of anti-GAD65 antibodies.

At least three types of GABA receptors have been characterized, named GABA_A, GABA_B and GABA_C receptors. While GABA has an inhibitory effect on the central nervous system, it's the opposite for the activation of GABA_A receptors which has an excitatory effect on the enteric nervous system¹³. Regarding activation of GABA_B receptors, it seems to induce a reduction of the amplitude and frequency of jejunal contractions¹⁴ and to promote propulsive duodenal motor activity. Therefore, the enhanced muscular stiffness and hyperexcitability state in SPS is due to the diminution of inhibitory GABA pathways in the neuromuscular junction and central nervous system, which explains the lumbar/legs contractures as well as the epileptic manifestations and cerebellar ataxia¹⁵⁻¹⁷. Dilated biliary tract was also reported in association with CIPO in three other patients in the literature apart from anti-GAD65 antibodies, including two patients with systemic lupus and one patient with hypomotility of the sphincter of Oddi^{17,18}. Biliary stone development is therefore a possible consequence of the hypotonia of the biliary tree.

Treatment management is for the most part intended to treat the symptoms with benzodiazepines, physiotherapy and individualised care but also to treat the dysimmunity background of the syndrome. IVIg and steroids are the classical first-lines treatments for SPS and other auto immune diseases, usually show variable success, with complete failure in the present case. Other possibilities include immunosuppressants drugs such as cyclophosphamide which didn't show satisfactory result herein. Due to cyclophosphamide cumulative toxicity, rituximab was a seducing alternative to lower auto antibody production¹⁹. Regular follow up are organized to assess clinical state and surveillance of tumoral occurrence since paraneoplastic syndrome cannot be completely ruled out. Finally, the improvement and clear good outcome of patient 's general status and neuromuscular syndrome, respectively under diazepam and immunosuppressants drugs without any dopaminergic treatment, definitely excluded a Segawa 's syndrome. Moreover, even though lumbar contracture is a possible rarer manifestation of this inherited rare disease, the absence of another familial case, the late onset of the disease and the absence of typical legs dystonia and/or of associated signs of Parkinson's syndrome are all clearly in disfavour of other differential diagnosis.

To conclude, a sooner investigation of anti-GAD antibodies in patients with unclear gastrointestinal or biliary tract dysmotility, notably in the context of skeletal muscle stiffness, would enable a faster nosological diagnosis and adapted treatment, including immunosuppressants.

References

1. Ameli R, Snow J, Rakocevic G, Dalakas MC. A neuropsychological assessment of phobias in patients with stiff person syndrome. *Neurology* 2005; 64(11):1961-1963.
2. Ho CSH, Ho RCM, Wilder-Smith EP. Stiff person syndrome masquerading as panic attacks. *Lancet Lond Engl* 2014;

- 383(9917):668.
3. Mitsumoto H, Schwartzman MJ, Estes ML, Chou SM, La Franchise EF, De Camilli P, et al. Sudden death and paroxysmal autonomic dysfunction in stiff-man syndrome. *J Neurol* 1991;238(2):91-6.
 4. Nicholas AP, Chatterjee A, Arnold MM, Claussen GC, Zorn GL, Oh SJ. Stiff-persons' syndrome associated with thymoma and subsequent myasthenia gravis. *Muscle Nerve* 1997;20(4):493-8.
 5. McKeon A, Robinson MT, McEvoy KM, Matsumoto JY, Lennon VA, Ahlskog JE, et al. Stiff-man syndrome and variants: clinical course, treatments, and outcomes. *Arch Neurol* 2012;69(2):230-238.
 6. De Giorgio R, Guerrini S, Barbara G, Cremon C, Stanghellini V, Corinaldesi R. New insights into human enteric neuropathies. *Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc* 2004;16 Suppl 1:143-7.
 7. Badari A, Farolino D, Nasser E, Mehboob S, Crossland D. A novel approach to paraneoplastic intestinal pseudo-obstruction. *Support Care Cancer* 2012;20(2):425-8.
 8. Maier A, Mannartz V, Wasmuth H, Trautwein C, Neumann U-P, Weis J, et al. GAD Antibodies as Key Link Between Chronic Intestinal Pseudoobstruction, Autonomic Neuropathy, and Limb Stiffness in a Nondiabetic Patient: A CARE-Compliant Case Report and Review of the Literature. *Medicine (Baltimore)* 2015;94(31):e1265.
 9. Kraichely RE, Farrugia G, Pittock SJ, Castell DO, Lennon VA. Neural autoantibody profile of primary achalasia. *Dig Dis Sci* 2010;55(2):307-11.
 10. Auteri M, Zizzo MG, Serio R. GABA and GABA receptors in the gastrointestinal tract: from motility to inflammation. *Pharmacol Res* 2015;93:11-21.
 11. Törnblom H, Lang B, Clover L, Knowles CH, Vincent A, Lindberg G. Autoantibodies in patients with gut motility disorders and enteric neuropathy. *Scand J Gastroenterol* 2007;42(11):1289-93.
 12. Dhamija R, Tan KM, Pittock SJ, Foxx-Orenstein A, Benarroch E, Lennon VA. Serologic profiles aiding the diagnosis of autoimmune gastrointestinal dysmotility. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc* 2008;6(9):988-92.
 13. Bettler B, Kaupmann K, Mosbacher J, Gassmann M. Molecular structure and physiological functions of GABA(B) receptors. *Physiol Rev* 2004;84(3):835-67.
 14. Gentilini G, Franchi-Micheli S, Pantalone D, Cortesini C, Zilletti L. GABAB receptor-mediated mechanisms in human intestine in vitro. *Eur J Pharmacol* 1992; 217(1):9-14.
 15. Meinck H-M, Thompson PD. Stiff man syndrome and related conditions. *Mov Disord Off J Mov Disord Soc* 2002;17(5):853-66.
 16. Honnorat J. [Which role of antineural autoantibodies in central nervous system diseases?]. *Rev Neurol (Paris)* 2008;164(5):403-4.
 17. Allescher HD, Safrany L, Neuhaus H, Feussner H, Classen M. Aerobilia and hypomotility of the sphincter of Oddi in a patient with chronic intestinal pseudo-obstruction. *Gastroenterology* 1992;102(5):1782-7.
 18. Pardos-Gea J, Ordi-Ros J, Selva A, Perez-Lopez J, Balada E, Vilardell M. Chronic intestinal pseudo-obstruction associated with biliary tract dilatation in a patient with systemic lupus erythematosus. *Lupus* 2005;14(4):328-30.
 19. Sarva H, Deik A, Ullah A, Severt WL. Clinical Spectrum of Stiff Person Syndrome: A Review of Recent Reports. *Tremor Hyperkinetic Mov N Y N* 2016;6:340.