Published in final edited form as:

Eur J Gastroenterol Hepatol. 2013 November ; 25(11): 1358–1363. doi:10.1097/MEG.0b013e3283632dbc.

Detection of Anti-Conductive Tissue Autoantibodies in a Patient with Chronic Intestinal Pseudo-Obstruction and Sick Sinus Syndrome

Giacomo Caio¹, Umberto Volta¹, Enrico Cerrato², Paolo Clavenzani³, Nicolò Montali², Rosanna Cogliandro², Vincenzo Stanghellini², Pier Giorgio Golzio², Fiorenzo Gaita², Gianrico Farrugia⁴, and Roberto De Giorgio²

¹Department of Medical and Surgical Sciences / Digestive Diseases and Internal Medicine, University of Bologna and St. Orsola-Malpighi Hospital, Bologna, Italy

²Division of Cardiology, Department of Internal Medicine, San Giovanni Battista Hospital, University of Turin, Turin, Italy

³Department of Medical and Veterinary Sciences, University of Bologna, Italy

⁴Enteric NeuroScience Program, Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Abstract

A 26-year-old patient was diagnosed as suffering from chronic intestinal pseudo-obstruction with manometric and histopathologic features suggestive of a intestinal myopathy. Histology was characterized by smooth muscle degeneration without inflammatory or immune cells. The severe gut dysfunction required full parenteral nutritional support. Few months later, the patient developed symptomatic tachy-brady arrhythmia episodes with syncope. A thorough diagnostic work-up led to a diagnosis of sick sinus syndrome which was managed by pacemaker implantation and β -blockers administration. This led to a partial improvement of tachy-brady arrhythmia episodes. Nonetheless, the patient continued to experience sustained supraventricular tachyarrhythmia runs, poorly responsive to increasing β -blocker doses. To investigate the origin of the cardiologic impairment, the patient was tested for anti-conductive tissue autoantibodies, which were positive, thus supporting a possible autoimmune origin of the dysrhythmia. Other autoantibodies tested for were negative. Based on these findings, the patient was treated with high dose steroids which were then tapered. The patient responded to the steroid treatment and did not experience further episodes of syncope and tachyarrhythmias. The severe gut dysfunction remained unchanged. This case highlights an association between severe gut dysfunction and cardiac conductive tissue abnormalities with autoantibodies to conductive tissue possibly causing the dysrhythmia. The severe gut and heart (likely autoimmune-mediated) dysfunction presented in this case provide a basis to assess further a link between intestinal and cardiac abnormal rhythmicity.

Keywords

alpha-smooth muscle actin; anti-conductive tissue autoantibodies; chronic intestinal pseudo-obstruction; intestinal failure; sick sinus syndrome

Introduction

The heart and gut are electromechanical organs both designed to move content efficiently and effectively. Disruption of this process results in disease. Chronic intestinal pseudo-obstruction (CIPO) can be viewed as an insufficiency of the “intestinal pump” similarly to chronic heart failure. The lack of either coordination or propulsive forces generated by the gastrointestinal smooth muscle impairs intestinal propulsion of luminal contents. As a result, the clinical picture is characterized by recurrent episodes of nausea, bloating and vomiting that are clinically undistinguishable from true mechanical obstruction.^{1–3} CIPO is still poorly understood. It appears to be a heterogeneous disease with different underlying etiologies presenting with a similar clinical picture. Alteration in the structure or function of the key cells types involved in the control of gastrointestinal motility, including smooth muscle cells, interstitial cells of Cajal (ICCs) as well as intrinsic and extrinsic nerves, can elicit the severe motor derangement observed in patients with CIPO.^{4,5} Neuro-ICC-muscular abnormalities in CIPO may be either secondary to a number of recognized diseases^{3,5,6,7} or idiopathic.^{1,2,3,4,6} Herein we describe the case of a young male patient with a manometrically and histologically proven myopathic CIPO who developed symptomatic tachy-brady arrhythmia diagnosed as sick sinus syndrome (SSS). Notably, the patient had anti-conductive tissue autoantibodies suggesting a possible autoimmune-mediated dysrhythmia. This unusual *coincidence* between CIPO and SSS and the possible pathogenetic role of autoimmunity suggests further studies evaluating whether a link exists between intestinal and cardiac abnormal rhythmicity are *warranted*.

Case report

A 26-year-old male patient was referred for a 4-year history of progressively severe digestive symptoms including diarrhea, postprandial vomiting, abdominal pain, distension, and weight-loss. His family history was negative for major genetic and acquired diseases. The clinical picture was complicated by recurrent intestinal sub-occlusive episodes. Repeated endoscopic and radiologic tests failed to identify any organic lesion. Explorative laparoscopies performed in other hospitals did not identify a cause nor show any evidence for obstruction. Following referral, a diagnosis of CIPO was established.^{2,3,8,9} A stationary small bowel manometry showed normally propagated interdigestive activity fronts suggesting an intact neuronal system.^{2,3,5,9} However the contractile strength was reduced with decreased amplitude, suggestive of an underlying myogenic disorder (Figure 1 supplementary).^{9–11} During a decompressive ileostomy, full thickness biopsies of the ileum were obtained and analyzed by conventional histopathology and immunohistochemistry.¹² Marked abnormalities of the smooth muscle architecture characterized by degeneration and vacuolization of smooth muscle cells, along with fibrosis, were identified by hematoxylin and eosin and Masson's trichrome staining. The findings were confirmed using antibodies to

smooth muscle actin (α -SMA) and desmin^{13–15} (Figure 1). Antibodies targeting pan-neuronal markers, such as neuron-specific enolase and protein gene product 9.5, identified an apparently normal enteric innervation. Also glial cells (S-100 β) and ICC (Kit) were labeled by their respective antibodies and showed an apparently normal immunoreactive pattern. Following the gastrointestinal work up the patient was dismissed and total parenteral nutrition initiated after the patient failed tube feedings.

A few months later, the patient was admitted to a Cardiology Unit due to tachy-brady arrhythmia episodes manifesting with recurrent syncope (Figure 2). A cardiac ultrasound was normal as well as a skeletal muscle and endomyocardial biopsies, performed to rule out a systemic disease or myocarditis. An ECG Holter test showed a SSS which required a bicameral pacemaker implantation (DDDR, Medtronic Adapta, Minneapolis, Minnesota, USA). β -blocker treatment was initiated followed by a dose increase: metoprolol 25 mg b.i.d. $\rightarrow$ carvedilol 3.125 mg b.i.d. $\rightarrow$ 6.25 mg b.i.d., subsequently changed to full dose atenolol 50 mg b.i.d. (Figure 3). In spite of this treatment, the patient experienced long-lasting supraventricular tachyarrhythmia (Figure 2 supplementary). In the attempt to investigate the origin of the cardiologic impairment, autoantibodies directed against the cardiac conductive tissue were tested (see below). Due to the strong positivity to such autoantibodies, the patient was treated with steroids. He was started on methylprednisolone 1 mg/kg tapered down to maintenance dose (8 mg/day) over a period of 24 months. The patient had a progressive improvement of tachyarrhythmia episodes as documented by repeated Holter monitor tests (Figure 2 supplementary). While the patient had a significant improvement of the cardiac symptoms, the severe gut dysfunction remained unchanged continuing to require home parenteral nutrition.

Assessment of autoantibodies directed against cardiac conducting tissue

Methods

Patient's serum was tested for cardiac conducting tissue autoantibodies (CCTA) using an indirect immunofluorescence technique. Serum samples obtained at different stages of patient's clinical history (in relation to immunosuppressive treatment) were tested at the initial dilution of 1:10 and when positive were titrated up to the end-point. The secondary antibody applied was an affinity purified polyclonal rabbit anti-human IgG (DAKO, Glostrup, Denmark). Tissue substrates used were ox myocardium and conducting tissues including sinus atrial node, atrio-ventricular node and the right side of the ventricular septum, according to a previously published method.^{16,17} Ox tissues were snap frozen in isopentane pre-cooled with acetone-solid CO₂ mixture and kept at -80°C until cryostat sections were cut. Ox tissues were chosen since in ungulates the Purkinje fibres are larger than cardiac fibres and readily recognizable on microscopy, and because earlier studies also used ox heart.^{16,17} We also tested the patient's serum for other autoantibodies, i.e. anti-enterocyte, anti-neuronal, anti-nuclear and anti-smooth muscle antibodies. These were assessed by using monkey jejunum cryostat sections (routinely used to screen for anti-enterocyte antibodies), rat ileum and colon cryostat sections (used to test anti enteric nervous system antibodies) and, finally, rat kidney and liver (used to determine anti-smooth

muscle and anti-nuclear antibodies). Control sera obtained from healthy blood donors were tested simultaneously with patient's serum using the same technique.

Results

CCTA positivity was characterized by bright fluorescence of the sino-atrial node, atrio-ventricular node and bundle branches including Purkinje fibers running through the ventricular septum with no staining of myocardial tissue (Figure 3A, B, C). The immunolabeling appeared to be cytoplasmic. Sera obtained before, during and after immunosuppressive treatment (methylprednisolone 60 mg/day tapered down over a period of 24 months) did not show major differences in terms of immunofluorescence pattern and CCTA antibody titer (i.e., bright staining was observed up to a dilution of 1:200). Apart from CCTA, the patient's serum did not contain other autoantibodies (listed in the methods). Control sera were consistently negative for CCTA (Figure 3E). Histochemical analysis with Trichrome staining confirmed the location of the areas where conducting tissues were obtained (Figure 3D).

Discussion

This case represents a *coincidental* association between CIPO of myogenic origin and a life-threatening cardiologic impairment, i.e. tachy-brady arrhythmia or SSS. In addition, CCTA were detected in the patient's serum likely reflecting an autoimmune insult occurring in the conductive cardiac system.

Very little is known about the association between CIPO and heart disease but emerging evidence suggests a link. Previous studies showed cardiac changes, such as membranous interventricular septal defect, and trivial pulmonic valve stenosis, in two members of a Turkish family with a genetic form of CIPO. Notably no electrophysiological abnormalities were documented in these two patients.^{18,19} Moreover, patients with mutations in Nav1.5 showed both cardiac arrhythmias and gastrointestinal symptoms.^{20,21} In addition, a mutation in the TCAP gene, encoding for the small protein telethonin expressed both in the heart and gastrointestinal tract, has been documented in a 42-year-old male patient with CIPO. The possibility that telethonin mutation can alter Nav1.5 function represents a molecular substrate for a common involvement of gastrointestinal and cardiac tissues.²²

In our case there was no evidence of familial cluster and therefore the patient was regarded as affected by a sporadic CIPO with an unusual association between CIPO and cardiac abnormalities, predominantly characterized by conductive tissue defects leading to symptomatic tachy-brady arrhythmia / SSS. The latter condition, which is usually diagnosed in elderly patients, was further investigated by an endocardial biopsy. As a distinctive feature from elderly patients with arrhythmia / SSS, the cardiac tissue analysis in our case did not show major fibrotic ('scar-like') degeneration or inflammatory infiltrate of the cardiac muscle. This and a normal ejection fraction makes it highly unlikely that cardiac insufficiency resulted in myogenic CIPO. A link between CIPO and cardiac conductive system impairment through autoantibodies is possible, although a firm cause-effect relationship cannot be established between the two conditions from this case report.

In our immunofluorescence experiments, the CCTA recognized different portions of the ox cardiac conductive tissue (i.e., sino-atrial node, atrio-ventricular node and bundle branches including Purkinje fibers). The exact molecular targets of CCTA as well as origin remains unknown. The immunofluorescent pattern of CCTA was characterized by a bright, cytoplasmic staining of the cardiac conductive tissue. A possibility is that CCTA in this case may have arisen secondary to the profound enteric muscular abnormalities observed in this case. The enteric smooth muscle damage might have exposed / released structural proteins, triggering an inappropriate immune response.²³

Another interesting question arising from this case report is whether CCTA may have exerted a pathogenetic role in the cardiac dysrhythmias of this patient. In fact, Maisch et al.²⁴ reported autoantibodies similar to CCTA and established a 10-fold risk of developing SSS in patients carrying anti-sinus node antibodies and a 2.2-fold risk of acquiring atrio-ventricular blocks in patients with autoantibodies to atrio-ventricular node. Furthermore, CCTA have been identified in patients with autoimmune-mediated connective tissue disorders with cardiac involvement, such as scleroderma and rheumatoid arthritis.^{16,17} However, these studies, like our case report, did not clarify whether CCTA actively contributed to arrhythmias or were an immunological epiphenomenon. In favor of the first possibility is the clinical evidence that the patient's cardiac conditions improved significantly after steroid treatment (currently he is still being treated with 8 mg of methylprednisolone), whereas the second possibility might be supported by the lack of a reduced CCTA titer following the long-term steroid treatment. However, it is worth noting that persistence of detectable autoantibodies following steroid treatment can occur in other autoimmune disease, such as anti-nuclear and anti-smooth muscle antibodies in patients with autoimmune hepatitis.²⁵

In conclusion, this case showed a sporadic form of myogenic (degenerative myopathy) CIPO together with a life-threatening arrhythmias (mainly SSS). *The rarity of this coincidental association* was increased by the demonstration of circulating CCTA. The origin of CCTA as well as their potential pathogenetic role in driving cardiac arrhythmias and the possibility of a link between intestinal and cardiac abnormal rhythmicity will require further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This paper was supported by the NIH grant DK52766, USA, to G.F. and by grants from the Italian Ministry of Education, University and Research (MIUR) (PRIN2009), 'Fondazione Del Monte di Bologna e Ravenna', and funds from the University of Bologna, Italy, to R. De G.

References

1. Stanghellini V, Camilleri M, Malagelada JR. Chronic idiopathic intestinal pseudoobstruction: clinical and intestinal manometric findings. *Gut*. 1987; 28(1):5–12. [PubMed: 3817584]

2. Stanghellini V, Cogliandro RF, De Giorgio R, et al. Natural history of chronic idiopathic intestinal pseudo-obstruction in adults: a single center study. *Clin Gastroenterol Hepatol*. 2005; 3:449–458. [PubMed: 15880314]
3. Stanghellini V, Cogliandro RF, De Giorgio R, Barbara G, Salvioli B, Corinaldesi R. Chronic intestinal pseudo-obstruction: manifestations, natural history and management. *Neurogastroenterol Motil*. 2007; 19:440–452. [PubMed: 17564625]
4. De Giorgio R, Stanghellini V, Barbara G, et al. Primary enteric neuropathies underlying gastrointestinal motor dysfunctions. *Scand J Gastroenterol*. 2000; 35:114–122. [PubMed: 10720107]
5. De Giorgio R, Sarnelli G, Corinaldesi R, Stanghellini V. Advance in our understanding of the pathology of chronic intestinal pseudo-obstruction. *Gut*. 2004; 53:1549–1552. [PubMed: 15479666]
6. Stanghellini V, Corinaldesi R, Barbara L. Pseudo-obstruction syndromes. *Baillieres Clin Gastroenterol*. 1988; 2:225–254. [PubMed: 3289641]
7. Di Lorenzo C. Pseudo-obstruction: current approaches. *Gastroenterology*. 1999; 116:980–987. [PubMed: 10092321]
8. De Giorgio R, Cogliandro RF, Barbara G, Corinaldesi R, Stanghellini V. Chronic intestinal pseudo-obstruction: clinical features, diagnosis, and therapy. *Gastroenterol Clin North Am*. 2011; 40:787–807. [PubMed: 22100118]
9. Stanghellini V, Cogliandro R, Cogliandro L, et al. Clinical use of manometry for the diagnosis of intestinal motor abnormalities. *Dig Liver Dis*. 2000; 32:532–541. [PubMed: 11057929]
10. Camilleri M, Bharucha AE, di Lorenzo C, et al. American Neurogastroenterology and Motility Society consensus statement on intraluminal measurement of gastrointestinal and colonic motility in clinical practice. *Neurogastroenterol Motil*. 2008; 20:1269–1282. [PubMed: 19019032]
11. Dhanpat, J. Neuromuscular disorders of the GI tract. In: Odze, RD.; Goldblum, JR., editors. *Surgical pathology of the GI tract, liver, biliary tract and pancreas*. Philadelphia: Elsevier; 2009. p. 135–138.
12. De Giorgio R, Barbara G, Stanghellini V, et al. Clinical and morphofunctional features of idiopathic myenteric ganglionitis underlying severe intestinal motor dysfunction: a study of three cases. *Am J Gastroenterol*. 2002; 97:2454–2459. [PubMed: 12358272]
13. Knowles CH, Silk DB, Darzi A, et al. Deranged smooth muscle alpha-actin as a biomarker of intestinal pseudo-obstruction: a controlled multinational case series. *Gut*. 2004; 53:1583–1589. [PubMed: 15479676]
14. Goldfarb LG, Vicart P, Goebel HH, Dalakas MC. Desmin myopathy. *Brain*. 2004; 127(Pt 4):723–734. [PubMed: 14724127]
15. Orlandi A, Hao H, Ferlosio A, et al. Alpha actin isoforms expression in human and rat adult cardiac conduction system. *Differentiation*. 2009; 77:360–368. [PubMed: 19281784]
16. Villecco AS, de Liberali E, Bianchi FB, Pisi E. Antibodies to cardiac conducting tissue and abnormalities of cardiac conduction in rheumatoid arthritis. *Clin Exp Immunol*. 1983; 53:536–540. [PubMed: 6352096]
17. Volta U, Villecco AS, Bianchi FB, et al. Antibodies to cardiac conducting tissue in progressive systemic sclerosis. *Clin Exp Rheumatol*. 1985; 3:131–135. [PubMed: 4017310]
18. Mungan Z, Akyüz F, Bugra Z, et al. Familial visceral myopathy with pseudo-obstruction, megaduodenum, Barrett's esophagus, and cardiac abnormalities. *Am J Gastroenterol*. 2003; 98:2556–2560. [PubMed: 14638363]
19. Deglincerti A, De Giorgio R, Cefle K, et al. A novel locus for syndromic chronic idiopathic intestinal pseudo-obstruction maps to chromosome 8q23-q24. *Eur J Hum Genet*. 2007; 15:889–897. [PubMed: 17487221]
20. Saito YA, Strege PR, Tester DJ, et al. Sodium channel mutation in irritable bowel syndrome: evidence for an ion channelopathy. *Am J Physiol Gastrointest Liver Physiol*. 2009; 296:G211–G218. [PubMed: 19056759]
21. Locke GR 3rd, Ackerman MJ, Zinsmeister AR, Thapa P, Farrugia G. Gastrointestinal symptoms in families of patients with an SCN5A-encoded cardiac channelopathy: evidence of an intestinal channelopathy. *Am J Gastroenterol*. 2006; 101:1299–1304. [PubMed: 16771953]

22. Mazzone A, Strega PR, Tester DJ, et al. A mutation in telethonin alters Nav1. 5 function. *J Biol Chem.* 2008; 283:16537–16544. [PubMed: 18408010]
23. Perl A. Pathogenesis and spectrum of autoimmunity. *Methods Mol Biol.* 2012; 900:1–9. [PubMed: 22933062]
24. Maisch B, Lotze U, Schneider J, Kochsiek K. Antibodies to human sinus node in sick sinus syndrome. *Pacing Clin Electrophysiol.* 1986; 9:1101–1109. [PubMed: 2432516]
25. Volta U, De Franceschi L, Molinaro N, et al. Frequency and significance of anti-gliadin and anti-endomysial antibodies in autoimmune hepatitis. *Dig Dis Sci.* 1998; 43:2190–2195. [PubMed: 9790453]

Figure 1.

A) Representative photomicrographs showing severe smooth muscle damage with degeneration, vacuolization and fibrosis in the ileal specimen obtained from the patient during decompressive ileostomy. B) and C) show α -SMA and desmin immunoreactivities, respectively (peroxidase immunohistochemical technique). Note the marked damage to both circular and longitudinal muscle layers. Original magnification: $\times 100$.

Figure 2.

A) Fast supraventricular tachycardia (SVT), with palpitations and occasional dizziness. Electrical cardioversion was effective in restoring episodes of sinus rhythm (°). Note frequent premature atrial contractions (PAC) (*) and short runs of SVT, occasionally in conjunction with Wenckebach type atrioventricular conduction (^); junctional escape beats we also observed (°). B) "Reverse" atrial flutter. C) "Early" premature atrial contractions with "P" on "T" phenomenon (°); Wenckebach type atrioventricular conduction (*); aberrance on the second conducted atrial beat (°) and a couple of premature ventricular contractions (PVC) (^). D) "blocked" sinus beat (°) at the end of an atrial ectopic activity (*), with the occurrence of a 2.9 s pause.

Figure 3.

Representative photomicrographs showing cardiac conducting tissue autoantibodies (CCTA) of the investigated patient. Compared to control (E), the patient's serum containing CCTA evoked an intense immunolabeling of the sinus atrial node (A), atrio-ventricular node (B) and right side Purkinje fibres (C). This immunolabeling did not vary before, during and after treatment with corticosteroids. Identification of the conducting tissues was confirmed by Trichrome Masson staining of the right side Purkinje fibres (D). Original magnification: 250x for each image.