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CASE REPORT

Biliary Dyskinesia in Stiff Person Syndrome: An Association Between Reduced GABA Production and Gastroenteric Dysmotility

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Abstract

Stiff person syndrome (SPS) and biliary dyskinesia are two rare but potentially debilitating conditions that can significantly impact quality of life. SPS is a rare neurological disorder characterized by muscle stiffness, rigidity, and muscle spasms that primarily affect the trunk and limbs and is associated with extra-axial manifestations involving the gastrointestinal tract. Biliary dyskinesia is a gastrointestinal disorder characterized by abnormal gallbladder emptying, leading to symptoms of intense abdominal pain, nausea, and vomiting. Despite their distinct clinical presentations, studies have suggested a possible connection between the two disorders. This link may be due to involvement of similar neurotransmitters and autoantibodies in both conditions. In this report, we present a case of biliary dyskinesia in a 58-year-old male with prior history of chronic gastrointestinal symptoms, autoimmune disease, and SPS. Given the rarity of these conditions, there is a need for increased awareness and improved diagnostic modalities to facilitate early detection and management.

Keywords: Stiff person syndrome, Biliary dyskinesia, GAD-65 antibodies, GABA

1. Introduction

SPS is a rare autoimmune neuromuscular disease caused by a diminution in γ-amino butyric acid (GABA) mediated inhibition of excitatory pathways in the central nervous system.[1,2] The pathophysiology of this condition remains elusive but is associated with elevations in glutamic acid decarboxylase 65 (GAD-65) antibody levels.[1,2] SPS is often associated with extra-rheumatologic manifestations, including functional abdominal pain and severe dysautonomia, but there is a paucity in the literature on biliary dyskinesia corresponding with this syndrome.[2]

2. Case report

A 58-year-old man with a history of type 1 diabetes mellitus (A1c 10.2%), atrophic pancreatitis, autonomic dysfunction on fludrocortisone, stiff person syndrome on benzodiazepines (BZD), chronic abdominal pain on oxycodone, and chronic constipation on lubiprostone presents with a 24-h history of nausea and vomiting. The patient reports consuming cooked wild game meat and subsequently developing nausea, non-bloody non-bilious emesis, and epigastric pain. In the emergency department, he was found to be in diabetic ketoacidosis (DKA) with a blood glucose >600 mg/dL and was admitted to the intensive care unit (ICU) for an insulin drip. Review of the patient's history demonstrated a diagnosis of type 1 diabetes mellitus (T1DM) at the age of 46 years-old, in the setting of elevated blood glucose, non-alcoholic atrophic pancreatitis observed on CT abdomen/pelvis (A/P), and positive GAD-65 antibodies of >25,000 U/mL (normal 0.0−5.0 U/mL). The patient would later be diagnosed with stiff person syndrome in the setting of chronic pain due to axial and limb stiffness, chronic abdominal pain, and dysautonomia.

While in the ICU, the patient remained on insulin drip for a total of 8 days before being bridged to subcutaneous insulin due to persistent nausea and abdominal pain despite management with anti-

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emetics and opiates. Review of the admission CT A/P showed no evidence of abdominal or retroperitoneal abnormalities but did reveal marked gastric fluid distention with modest esophageal wall thickening. As the patient had an esophagoduodenoscopy (EGD) 3 months prior to his current admission, with negative gastric and duodenal biopsies, and a screening colonoscopy without significant abnormalities observed, endoscopy was deferred. However, gastric emptying study was performed during this admission and showed mildly delayed gastric emptying at 4 h (Table 1). After a 10-day hospital course, he was discharged on ondansetron, continued his outpatient pain regimen, provided education on gastroparesis, and given follow-up instructions to see gastroenterology in the ambulatory setting.

During his outpatient gastroenterology visit, the patient endorsed refractory nausea, vomiting, and persistent abdominal pain, with right upper quadrant involvement. He later underwent hepatobiliary iminodiacetic acid (HIDA) scan which showed impaired gallbladder contractile response with an ejection fraction of 16% (normal >35%), and mild enterogastric bile reflux status post 1.5 mcg of cholecystokinin (CCK) given 30 min prior to the procedure, which was consistent with a diagnosis of biliary dyskinesia. He subsequently underwent cholecystectomy.

3. Discussion

SPS is a rare neurologic entity, with a prevalence of 1 in 1 million.[3] The pathophysiology of SPS is characterized by reduced nerve potential inhibition as GAD-65 antibodies reduce the production of GAD, which is a rate limiting enzyme needed to produce the chief inhibitory neurotransmitter, GABA (Fig. 1). GABA is found in the mammalian central and enteric nervous systems. Due to the reduction of this neurotransmitter in the CNS, there is an occurrence of unopposed nerve firings that lead to muscle rigidity and muscle spasms.[4] In the enteric nervous system GABA is an excitatory molecule that acts on endocrine-like cells from the gastric antrum to the distal colon.[5]

The liver is the major site of GABA production and metabolism in the gastrointestinal system, and research has identified an association with its involvement in the apoptosis of large bile ducts as well as the differentiation of small into functional large cholangiocytes through the activation of adenylyl cyclase 8 via a Ca^{2+}/CaMK I mediated pathway.[3] Thus, it can be posited that an impairment in large cholangiocyte turnover and small cholangiocyte differentiation contributes to dyskinetic gallbladder motility. The liver is also responsible for the excretion of GABA into bile.[6] GABA release can be elicited by electric stimulation, substance P, neurotensin, or CCK, the latter of which is involved in gallbladder contraction, pancreatic secretion, bowel motility and satiety.[5,7] GABA has also been shown to stimulate CCK in CCK-secreting gut neuroendocrine murine STC-1 cells via $GABA_A$ receptors.[7] The diminution of GABA also leads to the accumulation of its substrate glutamate, which is involved in the enteric motility and sensory systems.[8] Increased glutamate concentrations can induce visceral pain and dysfunctions in both gastric motility and secretion, which may explain our patient's unremitting abdominal pain and gastrointestinal dysmotility (e.g., chronic constipation and delayed gastric emptying).[8] Albeit the patient's clinical picture is also confounded by his history of chronic opioid use, uncontrolled diabetes, and consequent neuropathy.

Table 1. Patient's gastric emptying study, demonstrating mildly delayed gastric emptying at 4 h.

Gastric Retention	Normal Range
At 1 h: 88%	30–90%
At 2 h: 40%	Less than 60%
At 3 h: 29%	Less than 30%
At 4 h: 18%	Less than 10%

Biliary dyskinesia is an illness characterized by impaired motility of the bile ducts and sphincter of Oddi, which can lead to bile buildup in the gallbladder without formation of gallstones.[9,10] This can in turn cause abdominal pain, nausea, vomiting, and biliary colic. Diagnosis of biliary dyskinesia can be made with the help of a radionuclide study to investigate the gallbladder ejection fraction, and findings below 35% is considered abnormal, as evidenced in our patient.[10] The disorder has two distinct types, biliary and pancreatic sphincter of Oddi dysfunction.[9] Patients with the former condition are likely to present with biliary-type pain 4–5 years on average following cholecystectomy, while the latter is associated with pre-procedural recurrent bouts of pancreatitis with limited data on post-procedural morbidity.[9] Thus, it is anticipated that our patient, notwithstanding abdominal pain related to his diabetic neuropathy and opioid dependence, can continue to present with biliary colic due to impaired GABA synthesis.

Limited articles have been published on the association between SPS and biliary dyskinesia, making it difficult to understand disease correlation.[2] Thus, more research is needed to better understand the relationship between SPS and biliary dyskinesia. Nonetheless, managing each disease

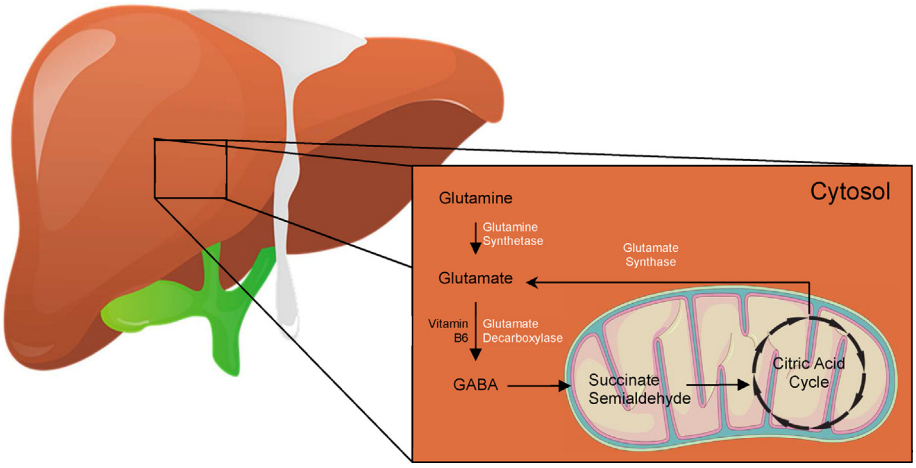

Fig. 1. A pictographic representation of the GABA synthesis pathway at the hepatocellular level.

entity is the best solution. Biliary dyskinesia is best managed with elective cholecystectomy as it eliminates the organ producing the symptoms, while patients with SPS are managed first-line with BZDs.[9,11] However, in cases such as our patient, it is unclear whether BZDs mediate biliary dyskinesia and whether cholecystectomy is curative considering impaired GABA production affects other components of gastrointestinal tract functioning.[9,11] In refractory cases of SPS, intravenous immunoglobulin or plasmapheresis can be considered.[11]

4. Conclusion

SPS and biliary dyskinesia are both complex and poorly understood conditions which are associated with severe unremitting symptoms that can impact quality of life. Though the relationship between the two conditions is poorly understood, limited literature has shown some association between the two. While the management of SPS is pharmacologic with the use of BZDs, biliary dyskinesia is managed with cholecystectomy; however, due to the continued morbidity of these conditions despite intervention, these measures may be temporizing at best. Further research is needed to better understand these individual diseases and the relationship between SPS and biliary dyskinesia.

Conflict of interest

There is no conflict of interest to disclose.

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