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Chronic atrial and intestinal dysrhythmia: A rare syndrome presenting as intestinal pseudo-obstruction

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Abstract

Chronic atrial and intestinal dysrhythmia (CAID) syndrome is a rare disorder affecting the heart and digestive systems. It results in bradycardia and arrhythmia due to sinoatrial node involvement. Concurrently, intestinal pseudo-obstruction arises from anomalies in the Cajal cells, recognized as the pacemakers of the intestine. Patients may experience dizziness, drowsiness, syncope, and palpitations attributed to the arrhythmia, while abdominal pain, distension, vomiting, and constipation can occur due to intestinal pseudo-obstruction. This report discusses the treatment management for two patients diagnosed with CAID syndrome.

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Introduction

Chronic atrial and intestinal dysrhythmia (CAID) syndrome is an autosomal recessive cohesinopathy in which SGOL1 K23E mutation leads to disruption of cardiac and intestinal pacemaker cells, leading to sick sinus syndrome (SSS) and chronic intestinal pseudo-obstruction (CIPO) [1]. CAID syndrome affects Cajal cells, leading to reduced motility and chronic intestinal pseudo-obstruction. It also impacts the sinoatrial node in the heart, causing bradycardia and arrhythmias. Patients with CAID syndrome often experience abdominal pain, vomiting, constipation, and weight loss [2,3]. Of the approximately 20 reported cases, only one required nutritional support using total parenteral nutrition (TPN) [4]. This article discusses our management approach for two patients diagnosed with CAID syndrome.

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Case Report

Case 1

A 28-year-old woman diagnosed with CAID syndrome was hospitalized due to abdominal pain, steatorrhea, and weight loss. Twelve years prior, she had a cardiac pacemaker implanted for sick sinus syndrome. Over several years, she frequently visited emergency services for obstructive symptoms and had been monitored for intestinal pseudo-obstruction. Ten months before this admission, she underwent a diagnostic laparotomy and ileostomy. Genetic testing on tissue samples revealed a homozygous mutation in the SGOL1 gene, confirming her CAID syndrome diagnosis. Post-ileostomy, her symptoms exacerbated, and her weight decreased from 43 kg to 33 kg.

Upon admission, her measurements were as follows: weight 33 kg, height 164 cm, body mass index (BMI) 11.2 kg/m^2, body temperature 36.6 ^{o}C, blood pressure 100/60 mmHg, heart rate 61 beats/min, and oxygen saturation 96%. A physical exam revealed abdominal tenderness. When she

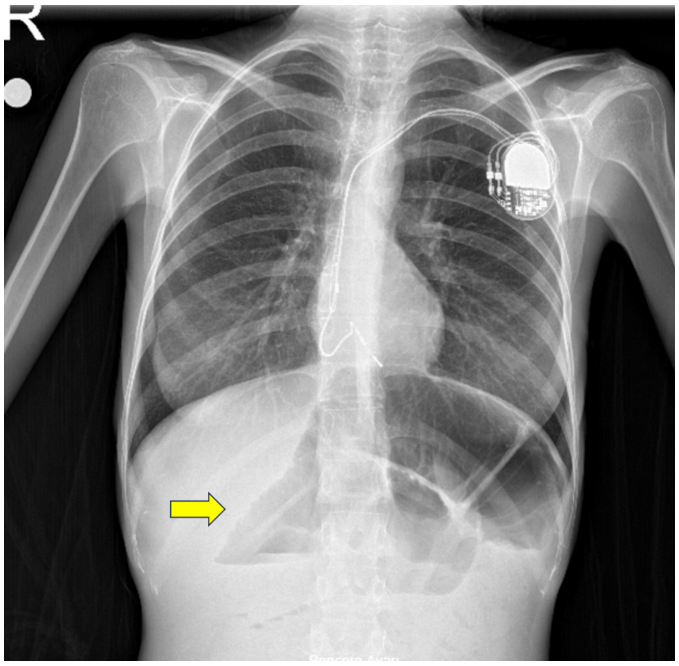

Figure 1. Air-fluid levels (arrow) in abdominal X-ray.

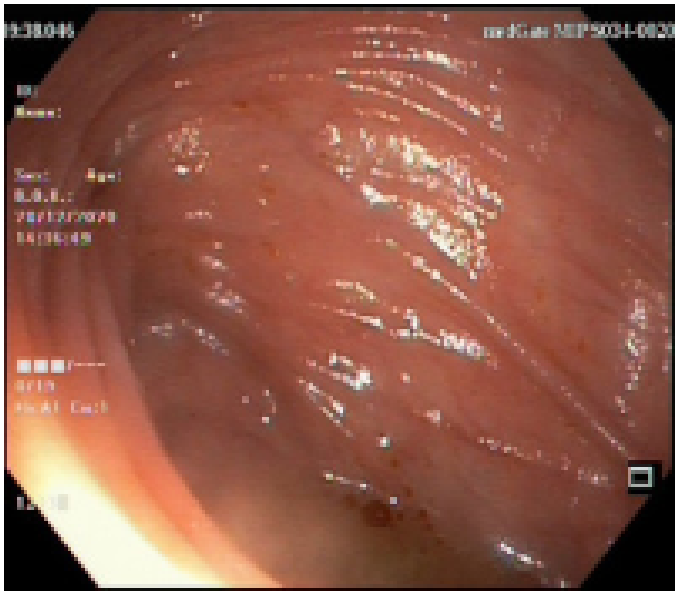

Figure 2. Colonoscopy image shows dilated intestinal loop and oily stool.

was constipated, enemas were administered through the ileostomy site, expulsing significant oily stools, amounting to 6 L daily. Laboratory tests revealed low albumin and vitamin B12 levels and elevated folic acid levels. Abdominal radiography showed air-fluid levels (Figure 1). Esophagogastroduodenoscopy (EGD) and colonoscopy were performed to rule out organic and infectious causes. The EGD revealed duodenal segment dilation and absent peristalsis. An enteroscopy through the ileostomy showed a dilated ileum filled with fluid, solid stool, and oily particles, with no visible peristalsis (Figure 2).

The patient's daily caloric requirement was established at 1500 kcal/day. A central venous catheter was inserted, and she received 1000 kcal/day via TPN and 500 kcal/day via enteral nutrition (EN). Vitamin K and D supplements were given. Over two weeks, her TPN caloric intake was increased to 1500 kcal/day. Rifaximin 600 mg/day was prescribed for small intestinal bacterial overgrowth (SIBO). As her treatment progressed, there was a noticeable reduction in stool volume and oil content. Erythromycin 500 mg three times daily was initiated for its prokinetic effects. This eliminated the need for enemas. Her weight increased to 41 kg within 25 days, after which she was discharged and continued home TPN. After two years of diligent follow-up and management with home TPN administered via a permanent catheter, the patient died due to a catheter-related infection.

Case 2

A 44-year-old woman previously diagnosed with Hashimoto's thyroiditis presented with recurrent abdominal pain. She had been experiencing these symptoms for 15 years, seeking emergency care during flare-ups. One month before this admission, she underwent a right hemicolectomy for suspected colonic subileus at another hospital. However, her postoperative concerns persisted, leading her to our hospital for malnutrition and decreased oral intake.

At admission, she presented with a fever of 35.5^{o}C, bradycardic heart rate of 52 beats/min, blood pressure of 95/60 mmHg, respiratory rate of 22, and oxygen saturation of 99%. Her weight was 38 kg, height 145 cm, and BMI 18 kg/m^2. Physical examination revealed a distended abdomen, epigastric tenderness, and absent bowel sounds. Laboratory test results were within reference ranges, including electrolytes, kidney, liver, and thyroid function tests. Abdominal radiography revealed air-fluid levels (Figure 3). Abdominal computed tomography showed dilated small bowel loops, with no mechanical obstruction

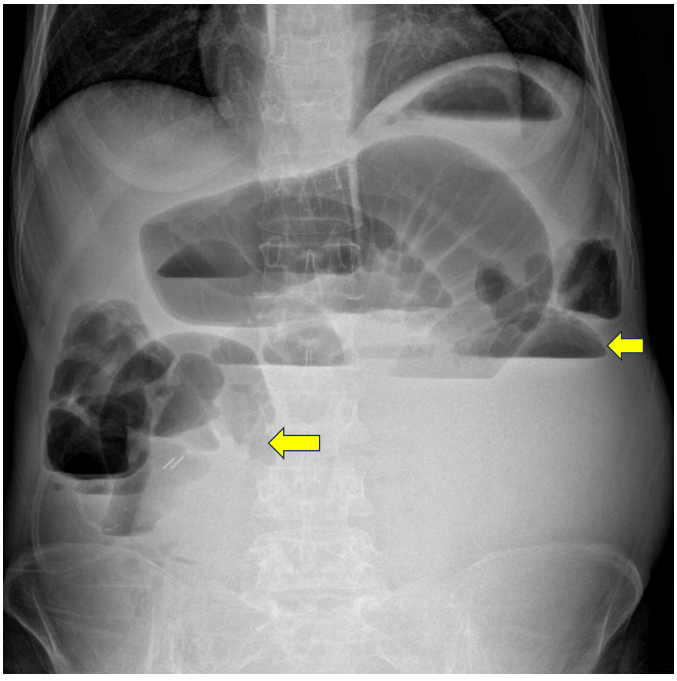

Figure 3. Abdominal X-ray image of patient 2. Diffuse air-fluid levels (arrows) are observed.

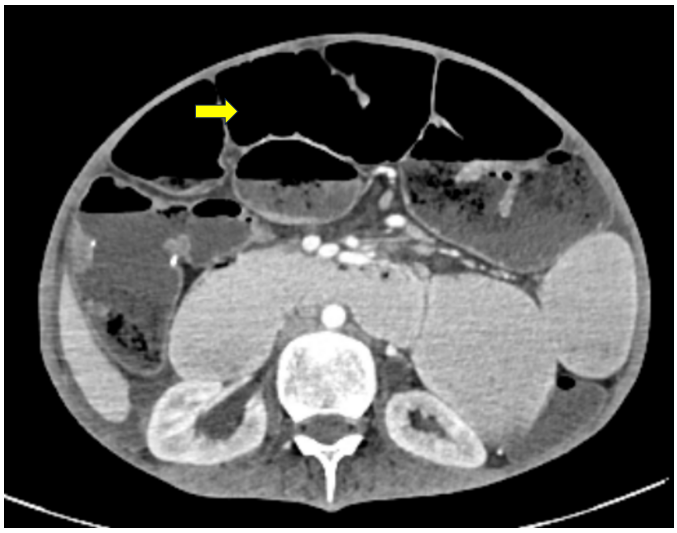

Figure 4. Computed tomography scan showing multiple dilated loops of small bowel with free fluid and air (arrow).

evident (Figure 4).

She was diagnosed with intestinal pseudo-obstruction. The pathology department evaluated a resected bowel sample from her hemicolectomy and noted reduced numbers of smooth muscle cells with decreased staining intensity. Submucosal, muscularis propria, and subserosal collagen deposition/fibrosis were also observed. Test results for secondary intestinal pseudo-obstruction causes, including antinuclear antibodies (ANA), anti-Topoisomerase I (anti-Scl-70), anticentromere antibodies (ACA), anti-RNA polymerase III, U1 Ribonucleoprotein (U1 RNP), Smith Antigen (Sm), Sjögren's syndrome A (Ro), Sjögren's syndrome B (La), and double-stranded DNA (dsDNA), were negative. Nailfold capillaroscopy results were within reference limits. Given her bradycardia consistent with SSS and episodes of intestinal pseudo-obstruction, genetic testing revealed a homozygous K23E mutation in SGOL1, thus confirming CAID syndrome.

For management, a nasogastric tube was inserted for decompression, and a central venous catheter for TPN. Her daily caloric needs were set at 1100 kcal/day, with 700 kcal/day from TPN and 400 kcal/day from EN. Erythromycin 500 mg three times daily was initiated. Her general condition improved, and she was discharged on a home TPN regimen. However, she was rehospitalized due to recurrent nausea, vomiting, and malnutrition. Tragically, she died two months post-admission from complications linked to poor absorption and severe cachexia.

Informed consent form was obtained from the patient's relatives on 20/02/2024.

Discussion

Chronic intestinal pseudo-obstruction is a syndrome marked by symptoms and findings suggestive of continuous or periodic obstruction in the absence of a mechanical obstruction. CIPO accounts for 15% of intestinal failures in pediatric patients and 20% in adults [2]. This obstruction can present acutely or chronically, with imaging revealing intestinal dilation. CIPO can stem from underlying neuropathic or myopathic disorders, which can either be primary/idiopathic or secondary. While most primary/idiopathic instances are sporadic, complicating our understanding of CIPO's causes and pathomechanisms, there are noted mutations in genes such as FLNA, ACTG2, TYMP, POLG1, and RAD21 [4]. Secondary causes include neurologic, paraneoplastic, autoimmune, metabolic, endocrine, and infectious diseases [5].

Cohesinopathies result from dysfunctions of proteins in the cohesin complex, which plays a pivotal role in gene expression and sister chromatid segregation. Some genes in the cohesin complex, such as RAD21 and SGO1, are linked to CIPO. Biallelic mutations of RAD21 lead to neurogenic CIPO, presenting with Barrett esophagus and cardiac abnormalities [2]. CAID syndrome, described by Chetaille et al., arises due to homozygous SGO1 mutations [4]. Compared to many with cohesinopathies, CAID syndrome patients do not display symptoms of premature aging or cancer. Although the exact molecular mechanisms remain unclear, CAID cases often exhibit abnormalities in the enteric nervous system, as mislocated ganglia and Cajal cells indicate. Additional research highlights damage to smooth muscles and changes in heart rate when sgol1 is reduced in zebra fish, further explaining the syndrome's unique manifestation [4].

To detect c.67A>G (K23E) hotspot mutation of the SGO1 gene that is associated with CAID, we performed Sanger sequencing using BigDye™ Terminator v3.1 Cycle Sequencing Kit (Cat No: 4337455; ThermoFisher Scientific, USA) and Applied Biosystems 3130 Genetic Analyzer (ThermoFisher Scientific, USA). Total genomic DNA was isolated from peripheral blood of the patients using a commercial kit (DNeasy Blood and Tissue Kit; Cat No: 69504; Qiagen GmbH, Germany) according to the protocol of the supplier. Exon 2 and its exon/intron boundaries up to a minimum of 20 bases in the intronic regions of the SGO1 gene were amplified using the primer sets given as GCCTGAGGAGGAAGAGAGAATATC and TTTCAGCAGTGTAGAAGTGTTGG by a standard PCR (Veriti™ Thermal Cycler; Cat No: 4375305; ThermoFischer Scientific, USA).

Typically, CAID syndrome becomes evident in the second decade of life, simultaneously affecting the heart and intestines. These patients typically appear normal at birth without other congenital anomalies. Bradycardia in CAID syndrome results from sinoatrial node dysfunction, while intestinal pseudoobstruction is due to Cajal cell anomalies [6,7]. Often, gastrointestinal symptoms emerge before cardiac ones and are the primary drivers of morbidity and mortality [2].

The current literature lacks comprehensive information on CAID syndrome's prevalence, diagnosis, and management. Nearly 20 cases have been documented, with the most extensive series by Chetaille et al., who identified an autosomal recessive inheritance of the SGOL1 gene in 17 patients [4].

Our patients underwent ileostomy for diagnostic and symptomatic relief, but the procedure increased concerns and weight loss. Several studies link surgical treatment with elevated postoperative morbidity in CIPO patients [8,9]. Our management strategy mirrored those docu-

mented for CAID and idiopathic CIPO. Prioritizing nutritional status is critical, and when patients can manage it independently, specialized treatment may not be necessary. We began TPN and gradually increased caloric intake. Based on energy requirements, patients were also given fluid, soft foods, and high-calorie enteral feeding.

In our first patient, SIBO was suspected due to steatorrhea, vitamin B deficiency, and elevated folate. Thus, 600 mg/day of rifaximin, a gastrointestinal-specific antibiotic, was initiated [10]. Prokinetics, which enhance motility, can be beneficial in acute and chronic CIPO cases [11]. Our patient responded well to short-term oral erythromycin, alleviating symptoms without long-term treatment. With an improved nutritional status and symptom relief, the patient was prepared for at-home TPN.

Conclusion

In young patients presenting with symptoms like abdominal pain, distension, nausea, and constipation, intestinal pseudo-obstruction should be a consideration, especially if imaging shows dilated intestines and air-fluid levels suggestive of obstruction. A CAID syndrome diagnosis should be considered for CIPO patients with concurrent cardiac arrhythmia. Surgical interventions in these patients elevate the risk of postoperative complications. A thorough nutritional assessment should guide TPN treatments. When SIBO is suspected, timely treatment is crucial. Healthcare professionals can consider prokinetic agents such as erythromycin to enhance motility in acute scenarios, weighing the potential benefits and risks.

Additional information

Human subjects

All authors have confirmed that this study did not involve human participants or tissue.

Conflicts of interest

In compliance with the ICMJE uniform disclosure form, all authors declare the following: The authors declare no conflicts of interest.

Payment/services info

All authors have declared that no financial support was received from any organization for the submitted work.

Financial relationships

All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other relationships

All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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