CASE REPORT

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Gastroparesis in Adolescent Patient with Type 1 Diabetes: Severe Presentation of a Rare Pediatric Complication

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What is already known on this topic?

Gastroparesis is a long-term complication of poorly controlled diabetes, which can also evolve into potentially life-threatening conditions, including dehydration, malnutrition, and electrolyte imbalance.

What this study adds?

Although gastroparesis is more frequent in adults, it may also affect pediatric patients with type 1 diabetes. The use of technology, especially of hybrid closed-loop systems, can be helpful in the management of these patients, as in the presented case.

Abstract

Gastroparesis is a long-term complication of diabetes related to autonomic neuropathy. It is characterized clinically by delayed gastric emptying and upper gastrointestinal symptoms, including early satiety, postprandial fullness, nausea, vomiting, and abdominal pain. Gastric emptying scintigraphy is the gold standard for diagnosis as it reveals delayed gastric emptying. Therapeutic strategies include dietary modifications, improvement of glycemic control, and prokinetic drugs. Case descriptions of diabetic gastroparesis in pediatric ages are very scarce. We report the case of a 16-year-old adolescent with severe presentation of diabetic gastroparesis. She presented with recurrent episodes of nausea, vomiting and abdominal pain which led progressively to reduced oral intake and weight loss. Her past glycemic control had been quite brittle, as demonstrated by several hospitalizations due to diabetic ketoacidosis and recurrent episodes of severe hypoglycemia. After the exclusion of infectious, mechanical, metabolic, and neurological causes of vomiting, a gastric emptying scintigraphy was performed, leading to the diagnosis of gastroparesis. Treatment with metoclopramide was started with progressive relief of symptoms. To improve glycemic control, insulin therapy with an advanced hybrid, closed loop system was successfully started. Pediatricians should consider diabetic gastroparesis in children and adolescents with long-standing, poorly controlled diabetes and appropriate symptomology.

Keywords: Advanced hybrid closed-loop, gastric emptying, metoclopramide, microvascular complications, scintigraphy

Introduction

Long-term complications of type 1 diabetes (T1D) include retinopathy, nephropathy, neuropathy, and macrovascular disease. Clinical manifestations of these complications are rarely observed in the pediatric population, but early alterations can be detected even in the first years of disease, among children and adolescents with poor glycemic control. Therefore, screening strategies and therapeutic optimization are fundamental in young patients to prevent progression towards advanced stages of complications (1).

Diabetic neuropathy can affect both somatic and autonomic nerves. The most common form is diabetic sensorimotor polyneuropathy, characterized by progressive damage of

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peripheral nerves, usually starting with sensory fibers and thereafter involving motor fibers (2). The first symptoms usually include numbness, prickling, paresthesia, and burning of upper and lower limbs. According to the latest ISPAD guidelines (1), screening of peripheral neuropathy should start at the age of 11 years in patients with 2 to 5 years of diabetes duration, and then should be performed every year. Screening should include a careful clinical neurological evaluation and electrophysiological tests. Therapy for neuropathy is often personalized and modified according to the effectiveness and safety for each patient. In the early stages, the most commonly used drugs to relieve diabetic neuropathic pain are pregabalin, duloxetine, and gabapentin (2).

Autonomic neuropathy can affect many nerves, including those innervating cardiovascular, urinary, and gastrointestinal systems (3). Cardiovascular autonomic neuropathy is the most prevalent form of autonomic impairment, affecting at least 20% of people with diabetes of all ages (4). Orthostatic hypotension and abnormal heart rate response are the most common manifestations of this complication, which is related to a high risk of death due to life-threatening arrhythmias and sudden cardiac death (5). Moreover, an impaired mechanism of sympathetic response to hypoglycemia has been suggested in patients with autonomic neuropathy, which may lead to the onset of unawareness of hypoglycemia (6,7). Finally, autonomic neuropathy may also result in gastrointestinal involvement, known as diabetic gastroparesis. An impaired interaction between the enteric nervous system and gut-brain axis causes the occurrence of this insidious complication (8).

Case Report

We present the case of a 16-year-old girl with T1D, diagnosed when she was two years old. Since the onset of diabetes she has been on multiple daily injection therapy and followed at a local pediatric diabetes service. Glycemic control has been quite brittle, as demonstrated by several hospitalizations due to diabetic ketoacidosis and recurrent episodes of severe hypoglycemia. Screening tests for common chronic diabetic complications had been never performed. The patient was admitted at our department due to a three year history of recurrent episodes of nausea, vomiting, and abdominal pain. Family history was negative for gastrointestinal and autoimmune diseases. Gastrointestinal symptoms were mainly associated to solid meals and had drastically worsened in the preceding months, leading to reduced oral intake and weight loss. Vomiting episodes had no stereotypical characteristics, predictable timing or associated neurovegetative symptoms. She also had constipation that was unresponsive to polyethylene glycol treatment.

At admission, she suffered from abdominal pain, which was exacerbated by palpation. On clinical examination, she had mild dehydration. No other relevant findings were present. At presentation she weighed 53.6 kg [-0.25 standard deviation score (SDS)], had a height of 160.2 cm (-0.50 SDS), and her body mass index was 20.9 kg/m^2 (+0.17 SDS). Her pubertal development was complete. Complete blood count and blood biochemistry analyses, including liver function, renal function, pancreatic enzymes, electrolytes, blood ketones, inflammatory indices, thyroid hormones, plasma ammonia concentration, toxicological tests, and β-human chorionic gonadatropin were normal or negative. Glycated hemoglobin (HbA1c) was 9.9% (85 mmol/mol). Screening for celiac disease was negative. Normal levels of adrenocorticotropic hormone, serum cortisol, and plasma renin ruled out adrenal insufficiency. Neurological causes of vomiting were excluded by performing brain magnetic resonance imaging and electroencephalogram. Plain abdominal radiography showed stool burden without any sign of intestinal obstruction or perforation. A computed tomography scan with contrast excluded extrinsic causes of gastric outlet obstruction, including superior mesenteric artery syndrome. An upper endoscopy was performed, revealing moderate, non-specific gastritis. No obstruction in the upper gastrointestinal tract was present and no esophageal or duodenal lesion was evident. Autoimmune gastritis was excluded because of normal levels of vitamin B12 and negative anti-gastric parietal cell antibodies. Treatment with proton pump inhibitor and ondansetron at the maximum dosage of 30 mg/day was started without any benefits. Oral feeding was replaced by total parenteral nutrition. To minimize the blood glucose instability continuous intravenous administration of regular insulin was started.

A gastric emptying scintigraphy after administration of a liquid meal radiolabeled with technetium-99mTc-diethylenetriaminepentaacetic acid was then performed, revealing gastric meal retention (Figure 1). On the basis of her history, characterized by prolonged poor glycemic control, and laboratory and radiographic findings, a diagnosis of diabetic gastroparesis was definitively made and treatment with metoclopramide, starting at the dose of 30 mg/day was begun.

In the following days, a progressive improvement of symptoms was recorded, and liquid and solid foods were reintroduced gradually, being well tolerated by the patient. Oral polyethylene glycol was then administered, with progressive regularization of bowel movements. To reduce

glycemic excursions, insulin therapy with an advanced hybrid closed loop (aHCL) system (Medtronic MiniMed 780G™; Medtronic Diabetes, Northridge, CA, USA) was started, achieving a prompt improvement of glycemic control, as demonstrated in Figure 2.

To evaluate the presence of other signs of early diabetic complications, nerve conduction studies were performed, revealing the presence of peripheral neuropathy affecting mainly lower limbs. Supplementation with B complex vitamins, folate and uridine was then started. An early

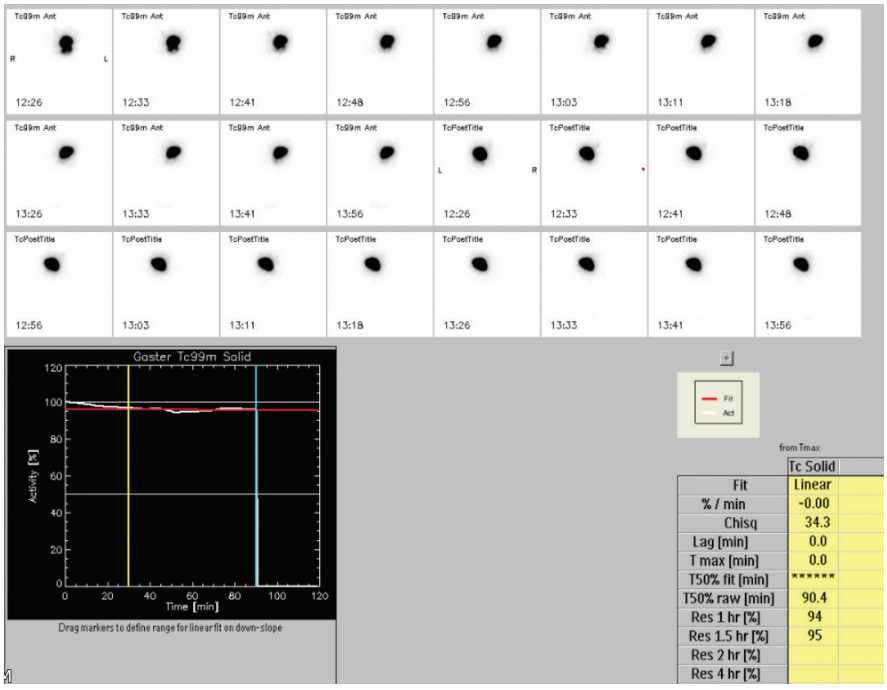

Figure 1. Upper panel: anterior and posterior planar images of the gastric contents up to 90 minutes after ingestion of the liquid bolus. Lower panel: the activity/time curve of the gastric contents shows no significant deflection

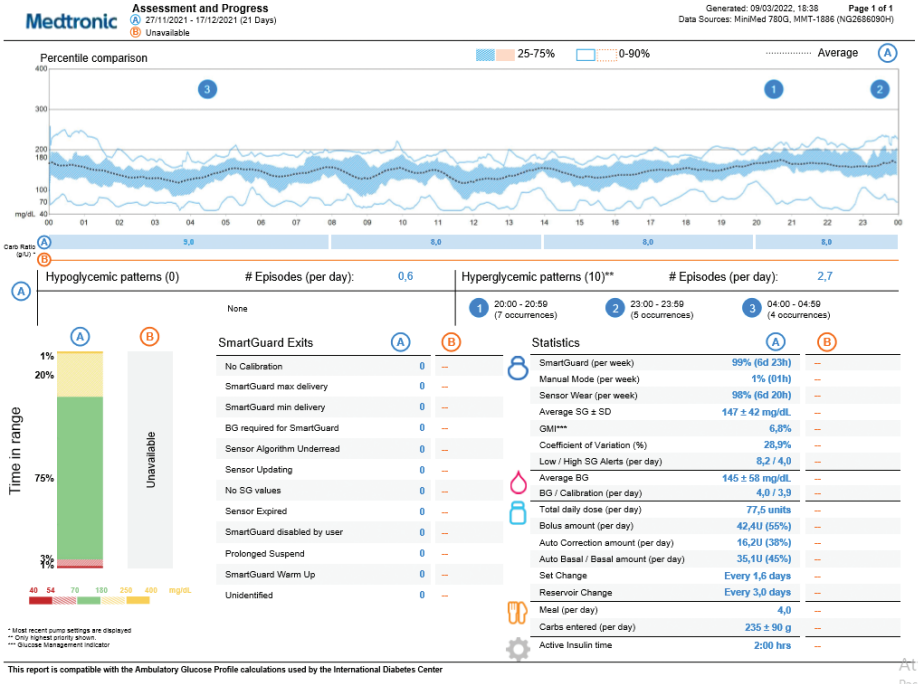

Figure 2. Assessment of glucose control during the first three weeks of advanced hybrid closed loop system use. All glucose metrics met the recommended clinical targets. Data were extracted from CareLink™ system software

stage retinopathy was also evident on fundus examination. Diabetic nephropathy was ruled out by the normality of albuminuria in a 24-hour urine collection.

The dose of metoclopramide was gradually reduced until complete withdrawal after three weeks of treatment. Therapy on demand with domperidone was then recommended in the case of relapse of symptoms.

At the three-month follow-up visit after discharge, the patient showed persistent remission of gastrointestinal symptoms, a weight gain of 5.9 kg, and improved quality of life. She is currently being followed up at an ophthalmological center for further investigations relating to her retinopathy.

Discussion

Gastroparesis is a clinical condition characterized by delayed gastric emptying and upper gastrointestinal symptoms, including early satiety, postprandial fullness, nausea, vomiting, and abdominal pain. Clinical manifestations are heterogeneous, ranging from mild symptoms to potentially life-threatening conditions such as dehydration, malnutrition, and electrolyte imbalance (9).

Pathogenesis of diabetic gastroparesis involves autonomic neuropathy and enteric neuromuscular system damage caused by different mechanisms including oxidative stress, hyperglycemia, and inflammation (8). An independent negative effect of acute hyperglycemia on gastric emptying time has been also hypothesized (10).

Diabetic gastroparesis may adversely affect the management of diabetes. Its pathogenetic mechanism is associated to glycemic control through a bidirectional causal relationship: long-term poor glycemic control and acute hyperglycemia can both cause gastric emptying delay and gastroparesis, and *vice versa* gastrointestinal dysfunction can affect glycemic variability of patients (10,11). Indeed, published data show that patients with diabetic gastroparesis present an increased risk of hypoglycemia (12), especially in the post-prandial period. This phenomenon has been named "gastric hypoglycemia" and seems to be related to a mismatch between prandial insulin absorption and postprandial increase of blood glucose, which is delayed in patients with gastroparesis (13).

There are few published data about prevalence of diabetic gastroparesis, and none of them consider the pediatric population. Within the largest adult T1D clinical registry of the United States, 4.8% of patients had a clinical diagnosis of gastroparesis (14). A community based study revealed a cumulative incidence of diabetic gastroparesis during 10 years of 5% in patients with T1D, and a greater risk in comparison to type 2 diabetes (15). Case descriptions of diabetic gastroparesis in pediatric patients are very scarce (16). To the best of our knowledge, this is the first report with such a severe presentation in an adolescent.

Gastric emptying scintigraphy is currently considered the gold standard for the diagnosis of gastroparesis in both children and adults (17,18). Gastric scintigraphy is considered diagnostic when it detects a retention of >90% of the radiolabeled meal after the first hour of exam (19). Mechanical gastric outlet obstruction should be ruled out prior to the scintigraphy by performing an upper endoscopy (20).

Therapeutic strategies for diabetic gastroparesis include dietary modifications, prokinetic drugs, and improvement of glycemic control. Modifications of diet are mandatory to facilitate gastric emptying and generally consist of the consumption of small meals and the avoidance of fibers and high-fat foods (21). Pharmacological therapy with prokinetic drugs is fundamental in the management of these patients. Dopamine agonists, including metoclopramide and domperidone, are widely used for the treatment of diabetic gastroparesis in adult patients, as they have been shown to relieve symptoms of nausea and vomiting and to accelerate gastric emptying (22,23). However, the use of metoclopramide in pediatric patients should be carefully evaluated and is not recommended for the long-term, due to the high risk of developing severe extrapyramidal side effects (24).

Optimization of glycemic control has been also demonstrated to improve symptoms of gastroparesis (10). Moreover, lower levels of HbA1c have been shown to be associated with reduced gastrointestinal symptoms and with faster gastric emptying (25). In the presented case, we decided to start continuous subcutaneous insulin infusion therapy with an aHCL system. Two studies have already demonstrated the efficacy of HCL systems in adults with T1D and gastroparesis (26,27). In particular, Daly et al. (26) recently reported significant reductions in HbA1c and mean glucose in five patients over one year of HCL use, while Kaur et al. (27) had previously shown that HCL had similar effectiveness and safety in adults with T1D and gastroparesis compared to age, sex, and diabetes duration controls.

Conclusion

The present case suggests that diabetic gastroparesis, with its wide range of possible clinical presentations, should be kept in mind by pediatricians managing children and adolescents with long-standing, poorly controlled diabetes.

Finally, detection of delayed gastric emptying should alert clinicians to the possible coexistence of other microvascular complications.

Ethics

Informed Consent: Written informed consent was obtained from the patient's parents for the publication of both clinical information and imaging.

Authorship Contributions

Surgical and Medical Practices: Stefano Costa, Mariella Valenzise, Nino Giannitto, Davide Cardile, Sergio Baldari, Writing: Fortunato Lombardo, Bruno Bombaci, Giuseppina Salzano, Stefano Passanisi.

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