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Macroamylasemia in a Two Year Old Boy as the First Manifestation of Celiac Disease: A Case Report

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Keywords: Macroamylasemia, Celiac disease, Children, Gluten-free diet

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Abstract

Introduction: Macroamylasemia is a rare biochemical disorder in which the amylase molecule binds to other macromolecules, most commonly immunoglobulin A or G. The increased molecular weight of this complex reduces renal excretion of the enzyme, resulting in chronically elevated serum amylase levels. It can be associated with various non-pancreatic conditions, including celiac disease. In some reported cases, macroamylasemia resolved with a gluten-free diet. We present a pediatric case in which macroamylasemia was the initial manifestation of celiac disease. **Case Presentation:** A two-year-old boy presented with a three-month history of abdominal pain, anemia, and, constipation. Physical examination revealed paraumbilical tenderness. Laboratory tests showed hypochromic anemia; elevated serum amylase (171 U/L); low serum iron (2.5 µmol/L); vitamin D3 deficiency (15.9 ng/mL), and low urine amylase with an amylase/creatinine clearance ratio below 1%, confirming macroamylasemia. Imaging studies were normal. HLA typing revealed the HLA-DQ2 haplotype. Celiac serology was positive for tTG-IgA (87.55 IE/mL) and EMA-IgA (1:>100). Duodenal biopsy confirmed Marsh type IIIb histology. A gluten-free diet was initiated alongside iron and vitamin D3 supplementation. Symptoms resolved within two months, accompanied by normalization of serum amylase levels and a weight gain of over 1 kg. Vitamin D3 therapy was continued until serum levels normalized. **Conclusion:** Celiac disease should be considered in patients with unexplained macroamylasemia, even in the absence of classical gastrointestinal symptoms. The primary treatment in such cases is a strict gluten-free diet, which can lead to the normalization of serum amylase levels when macroamylasemia is associated with celiac disease.

Keywords: Macroamylasemia, Celiac disease, Children, Gluten-free diet

Introduction

Macroamylasemia is a rare, benign biochemical disorder in which amylase binds to large complex molecules, most commonly immunoglobulin A or G. This binding increases the molecular weight of the enzyme, reducing its renal clearance and prolonging its half-life. The prevalence of macroamylasemia in the general population is estimated to be between 1% and 2%. It is characterized by persistent hyperamylasemia in the absence of elevated urinary amylase and without accompanying clinical signs or symptoms [1]. Macroamylasemia most commonly occurs in adults, though rare cases have also been reported in children [2–4]. Elevated serum amylase levels may be observed in various non-pancreatic conditions, including liver and renal failure, celiac disease, inflammatory bowel disease, abdominal trauma, diabetic ketoacidosis, lymphoma, systemic lupus erythematosus, rheumatoid arthritis, and head trauma [5–7]. Celiac disease (CD) is an immune-mediated systemic disorder triggered by gluten and related prolamins in genetically predisposed individuals. It is characterized by a variable combination of gluten-dependent clinical manifestations, the presence of specific antibodies—such as tissue transglutaminase [tTG], endomysial antibodies [EMA], deamidated gliadin peptides [DGP], HLA-DQ2/DQ8 haplotypes, and inflammatory damage to the small intestinal mucosa. The prevalence of CD in the general population is approximately 1%, and it is about twice as common in children. This higher prevalence is attributed to both genetic factors (HLA and non-HLA genes) and environmental influences, such as wheat exposure, age of gluten introduction, gastrointestinal infections, and early or excessive use of proton pump inhibitors and antibiotics [8]. Macroamylasemia associated with CD has been documented in a few adult cases, and even more rarely in pediatric patients. In these reports, macroamylasemia either improved or resolved following the initiation of a gluten-free diet [5, 9, 10]. We report a rare case of a two-year-old boy with macroamylasemia associated with celiac disease prepared in accordance with the CARE guidelines. The corresponding checklist completed by the authors is provided as online supplementary material in accordance with the CARE reporting checklist.

Case Presentation

A 2-year-old boy was admitted to the pediatric department due to abdominal pain lasting for the past 3 months, anemia, and constipation. The abdominal pain was cramp-like, lasted approximately five minutes occurred several times daily, and was localized to the paraumbilical region. The intensity of the pain had increased over the previous month. The anemia had been present for six months and had been treated with iron supplements, but without significant improvement. The child had dry stools every 4–5 days. On physical examination, the child was in relatively good general condition. The abdomen was soft on palpation, with tenderness in the paraumbilical area and no evidence of organomegaly. His body weight was 12 kg, corresponding to the 50th percentile, and his body height was 85 cm, corresponding to the 25th percentile. Laboratory tests revealed hypochromic anemia, with hemoglobin (Hgb) = 115 g/L, hematocrit (Hct) = 29%, mean corpuscular volume (MCV) = 65 fl, and C-reactive protein (CRP) = 0.2 mg/L. Biochemical analyses showed elevated serum amylase (171 U/L), normal serum lipase (5 U/L), low serum iron (2.5 µmol/L), alkaline phosphatase= 220 U/L, and vitamin D3 = 15.9 ng/mL. Other biochemical parameters, including immunoelectrophoresis and IgG4, were within normal limits. An abdominal ultrasound was performed on admission, and the results were normal. An ultrasound of the neck region, with special focus on the parotid glands, was also normal. Due to persistent abdominal pain and an increase in serum amylase to 188 U/L, an abdominal CT scan was additionally performed, with normal findings. A 24-hour urine test showed very low urinary amylase, and the amylase clearance/creatinine clearance ratio was below 1%, confirming macroamylasemia. A sweat test was within the normal range. Based on clinical and laboratory findings, the patient was diagnosed with macroamylasemia, anemia, and constipation—features that may indicate an underlying autoimmune condition such as celiac disease. HLA typing revealed the presence of the HLA-DQ2 haplotype. Serological testing showed positive tTG-IgA at 87.55 IE/mL (reference: >20 IE/mL), and a second serum sample was positive for EMA-IgA at a titer of >1:100. An esophagogastroduodenoscopy (EGD) was performed, with one biopsy taken from the duodenal bulb and four from the distal duodenum. Histopathological examination revealed subtotal villous atrophy and crypt hyperplasia, consistent with Marsh type IIIb (shown in Fig. **1a**, **1b**). The patient was started on a gluten-free diet, iron supplementation, vitamin D3 therapy, and polyethylene glycol for constipation, as per protocol. After one month, abdominal pain resolved. Stool frequency normalized within two months, and the child gained more than 1 kg. Serum iron levels gradually increased to 15 µmol/L, and hemoglobin rose to 127 g/L. Serum amylase returned to normal levels two months after initiating the gluten-free diet. Vitamin D3 supplementation was continued until serum levels normalized.

All procedures performed in this study were in a with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parent for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically predisposed individuals. It can present with a wide range of nonspecific signs and symptoms, making diagnosis challenging. Identifying CD is important not only in children with classic gastrointestinal manifestations but also in those with subtle or atypical features, as untreated disease can lead to significant long-term health complications. Currently, extraintestinal manifestations are more frequently observed than the traditional malabsorption symptoms. Extraintestinal manifestations include: weight loss or failure to thrive, irritability or chronic fatigue, peripheral neuropathy, chronic iron deficiency anemia, rickets, osteopenia, osteoporosis, recurrent aphthous stomatitis, dermatitis herpetiformis, dental enamel defects, abnormal liver enzymes. In untreated patients with CD, anemia is a common finding because there are significant structural changes in the mucosa of the small intestine, which reduces the absorption of iron, folic acid, and vitamin B12. The recommendations are that these children receive supplementation in addition to a gluten-free diet and that these micronutrients be regularly monitored at each follow-up until normalization [11]. Venous thromboembolism can occur in patients with CD and is associated with increased levels of homocysteine and thrombin-activatable fibrinolysis inhibitor (TAFI), which stimulate the formation of blood clots [12,13]. Vitamin K malabsorption can cause hypoprothrombinemia and bleeding. Other rare hematological abnormalities include leukopenia, thrombocytopenia, and thrombocytosis, which are likely due to micronutrient deficiencies [14]. In our case, the parents reported that the child consumed large amounts of cow's milk, which led us to believe that the hypochromic anemia was due to inadequate nutrition. Information about constipation was obtained only after the child was admitted to the hospital, which is why the initial laboratory tests did not include a diagnosis of CD. A diagnosis of CD without biopsy may be made when serum tTG-IgA levels are ≥10 times the upper limit of normal, confirmed by a positive EMA-IgA in a second serum sample. However, in patients with tTG-IgA levels below this threshold—as in the present case—or in those with

selective IgA deficiency, histological confirmation remains essential. In such cases, biopsies must be obtained from both the duodenal bulb and the distal duodenum to establish a definitive diagnosis [11].

Only a few pediatric cases of macroamylasemia have been reported in the literature [2, 4]. In most instances, macroamylasemia appears to be a benign condition, not linked to any underlying disease. In one case, a non-hemorrhagic duodenal ulcer was identified, and serum amylase levels normalized following treatment with a proton pump inhibitor [3]. The diagnosis of macroamylasemia in patients with isolated amylase elevation can be made using the amylase–creatinine clearance ratio (ACCR), which is reduced in macroamylasemia due to decreased filtration of macroamylase complexes. This ratio is calculated in 24-hour urine collection according to the formula: ACCR= Amylase (urine) x Creatinine (urine) x 100 / Amylase (serum) x Creatinine (serum). In the absence of renal insufficiency, a normal ACCR ranges between 3% and 5%, while a result below 1% is highly suggestive of macroamylasemia [15]. Further confirmatory tests include electrophoresis, polyethylene glycol precipitation, and chromatography [16]. Further confirmatory tests include electrophoresis, polyethylene glycol (PEG) precipitation, and chromatography [13]. However, since these advanced diagnostic methods are available only in specialized laboratories—which are not accessible in our country—the diagnosis of macroamylasemia was confirmed by calculating the ACCR. Velmishi et al. reported a case of macroamylasemia in a six-year-old child with celiac disease, in whom amylase levels returned to normal after the initiation of a gluten-free diet [9]. The association between macroamylasemia and celiac disease (CD) is thought to result from cross-reactivity to gluten or other antigens, leading to the formation of autoantibodies (IgA or IgG) against pancreatic serum amylase at the intestinal level [17]. Serum amylase testing is not part of the initial protocol for diagnosing CD, but if tested, elevated serum levels of pancreatic amylase are due to decreased renal elimination secondary to its binding to immunoglobulins. An alternative hypothesis for elevated serum amylase in CD is subclinical pancreatic inflammation [18]. Given the frequent association of CD with other autoimmune diseases, the possibility of subclinical autoimmune pancreatitis should also be considered [18]. In our patient, this was evaluated; however, serum IgG4 levels were within the normal range, making autoimmune pancreatitis unlikely.

In this pediatric case, we observed a clear association between CD and macroamylasemia, with complete resolution of macroamylasemia following the initiation of a gluten-free diet. Therefore, in any case of unexplained elevated serum amylase or suspected macroamylasemia, CD should be considered, even in the absence of typical gastrointestinal symptoms.The primary treatment for this condition is a strict gluten-free diet, which leads to the normalization of serum amylase levels in cases of CD associated with macroamylasemia.

Statement of Ethics

Written informed consent was obtained from the patient's parent for publication of this case report and any accompanying images. This case report of patient data did not require ethical approval in accordance with local/national guidelines. The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

M.D.I,. is the the physician directly involved in the case and edited and revised the manuscript. M.D.I, E.S.J, M.K.I initiated the study concept and design and supervised this case report. M.D.I, E.S.J, M.K.I, A.D., B.C.J., S.P.K. searched the literature and wrote and revised the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Figure Legends

Fig. 1. H & E stain shows pathohistological changes in the mucosa of the proximal duodenum. (a) Subtotal villous atrophy and crypt hyperplasia (x 10). (b) Increased number of intraepithelial lymphocytes and infiltration of the lamina propria mucosae predominantly by lymphocytes (x 40).

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