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Correspondence

A negative fallout of COVID-19 lockdown in Italy: Life-threatening delay in the diagnosis of celiac disease

Dear Editor,

The contact/movement restrictions imposed by the current COVID-19 pandemic had a deep impact on primary health care, with possible negative fallouts on even common and usually benign gastrointestinal disorders, as clearly illustrated by the clinical history we briefly summarize herein.

On COVID-19 day-19 lockdown in Italy (March 31, 2020), a 17-month-old girl presented at our pediatric academic medical center for evaluation of abdominal pain and distention, and widespread edema. During the first year of life, the patient's medical history had been unremarkable. The child had been breastfed for 4 months and then baby-led weaned with formula, cereals, meat and vegetables. Poor appetite, constipation, stunting growth and abdominal distention gradually manifested after the first 12 months. At age 15 months (end of February 2020), the parents consulted the family pediatrician by phone, but the doctor was unable to visit the child because of the first contact/movement restrictions imposed by the COVID-19 emergency in Italy. During the following weeks, clinical worsening manifested with walking refusal and progressive swelling of face and lower limbs. At this time, the child was brought to the local hospital and then immediately transferred to our academic regional Center. On admission, ileocecal intussusception and mesenteric lymphadenitis were diagnosed by abdominal ultrasound and barium enema, and laparotomy was needed for reduction of involved intestinal segments. The day after surgery, on clinical examination the child was markedly irritable and showed edema on the face, hands, abdomen and legs (Fig. 1). Vital signs were normal. A reduced lower limbs motility was noted but the neurological examination was normal. Weight and height were 8.0 Kg (below 3rd centile) and 70 cm (below 3rd centile), respectively. Congestive heart failure, as a cause of widespread edema, was first excluded by a normal echocardiography. First-level laboratory investigations were normal, including urinalysis and liver function tests, except for low serum albumin (2.8 g/dL) and total calcium (8 mg/dL).

Since the clinical history suggested celiac disease (CD), serum CD autoantibodies were checked, as recommended by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) diagnostic guidelines [1], and a gluten-free diet (GFD) was started before getting the results, due to the severity of symptoms. Diagnosis of CD was strongly suggested by high-level positivity (> 10x upper normal limit - UNL) of IgG anti-deamidated gliadin peptide (DGP) and borderline levels (1x UNL) of IgA anti-transglutaminase (TTG). The daily caloric intake was gradually increased to avoid a refeeding syndrome. After 10 days of GFD, edema had disappeared and the child lost 1 Kg of retained fluids (14% of body weight). At that time, the clinical picture of typical CD became evident (Fig. 2). CD diagnosis was definitively confirmed by an intestinal biopsy showing severe villous atrophy with increased intraepithelial lymphocyte count. After 4 weeks of treatment with the GFD, the child showed further signs of improvement (appetite and mood amelioration, weight regain, reduced abdominal distention).

CD is an immune-mediated enteropathy triggered by the ingestion of gluten-containing cereals in genetically susceptible individuals. It is a common disorder worldwide, affecting around 1% of the population. In typical CD cases, symptoms appear gradually during the first years of life, after gluten introduction at weaning, with failure to thrive, abdominal distention, chronic diarrhea (rarely constipation) and malnutrition. CD diagnosis is based on the findings of serum CD autoantibodies, particularly IgA anti-TTG and antiendomysial (EMA) antibodies, and severe villous atrophy at the intestinal biopsy [2]. In children younger than 2 yrs, IgG anti-DGP antibody may precede IgA-TTG positivity, and should be included in the serological CD screening [3,4]. Treatment of CD is based on the complete exclusion of gluten-containing products from the diet, i.e. GFD.

In young children, delayed CD diagnosis may be responsible for life-threatening manifestations, such as the celiac crisis and intestinal intussusception observed in our patient. Celiac crisis is a potentially fatal complication of CD, characterized by hypoproteinemia, edema, and profound metabolic and nutritional abnormalities [2]. During the first half of the 20th century, when pediatric CD was associated with a high mortality rate (on average 15%) in Western countries, a celiac crisis was often the precipitating cause of death [5]. Nowadays, the celiac crisis has nearly disappeared in Europe and North America, due to improved infant nutrition, decreased infection rate, and reduced lag time between CD development and diagnosis, but is still reported from developing countries [6,7]. Treatment of celiac crisis requires gradual increase of daily caloric intake (as we managed in this case) to avoid the risk of a refeeding syndrome [6]. Acute/recurrent Intestinal intussusception is another complication that can be associated with untreated CD. According to recent data from India, intussusception is frequently seen in children with newly diagnosed CD (up to 25% of cases), it is generally asymptomatic and resolves spontaneously on GFD. Interestingly, hypoalbuminemia and abdominal distention are more common in CD children with intussusception [8]. In our patient, the delay in medical referral, caused by the COVID-19 related restrictions in Italy, was clearly responsible of the previously described life-threatening presentation of CD.

Another interesting feature of our case was the pattern of CD serological markers found at diagnosis, with nearly normal values of TTG-IgA (1x) and very high values of DGP-IgG (10x). Several studies have shown that DGP-IgG may be the first positive marker of CD in children aged less than 2 yrs [3,4]. For this reason it is advisable to include DGP-IgG determination in the first-level serological screening for CD in young children. This recommendation

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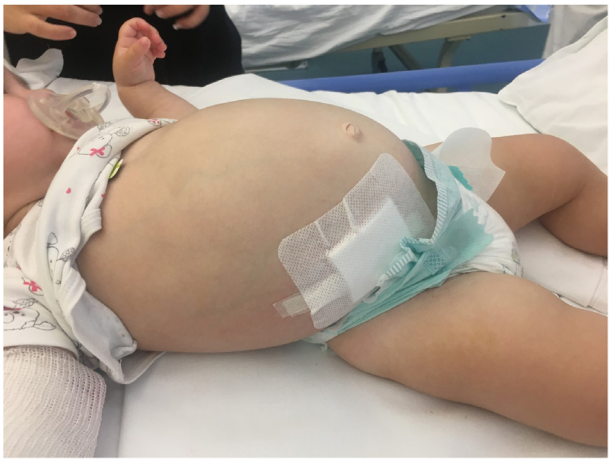

Fig. 1. On admission, abdominal distention and widespread edema was evident particularly on face, hands, and lower limbs. The laparotomy wound medication is visible on the lower right abdomen.

Fig. 2. Ten days after starting the gluten-free diet, edema had disappeared and the child clearly shows the picture of typical celiac disease with marked abdominal distention and malnutrition.

was included in the 2012 ESPGHAN Guidelines for CD diagnosis [9], but has been removed from the 2020 revision [1].

In conclusion, the history of this patient highlights a potentially life-threatening delay in the diagnosis and treatment of CD, a disorder usually characterized by a benign presentation in Europe, that was apparently related to the negative impact of COVID-19 lockdown on clinical practice in Italy.

Conflict of interest statement

Carlo Catassi has received consultancy honoraria from Dr. Schaer and Takeda. Other authors have no conflicts of interest or relevant financial activities to disclose.

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References

[1] Husby S, Koletzko S, Korponay-Szabó I, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. J Pediatr Gastroenterol Nutr 2020;70:141–56.
[2] Leonard MM, Sapone A, Catassi C, Fasano A. Celiac Disease and Nonceliac Gluten Sensitivity: A Review. JAMA 2017;318:647–56.
[3] Barbato M, Maiella G, Di Camillo C, et al. The anti-deamidated gliadin peptide antibodies unmask celiac disease in small children with chronic diarrhoea. Dig Liver Dis 2011;43:465–9.
[4] Assandri R, Montanelli A. Diagnosis of gluten-related enteropathy in a newborn: how and when? Gastroenterol Hepatol Bed Bench 2019;12:278–86.
[5] Catassi C. Celiac crisis/refeeding syndrome combination: new mechanism for an old complication. J Pediatr Gastroenterol Nutr 2012;54:442–3.
[6] Agarwal J, Poddar U, Yachha SK, et al. Refeeding syndrome in children in developing countries who have celiac disease. J Pediatr Gastroenterol Nutr 2012;54:521–4.
[7] Radlovic N, Lekovic Z, Radlovic V, et al. Celiac crisis in children in Serbia. Ital J Pediatr 2016;42:25–8.
[8] Borkar VV, Poddar U, Thakral A, et al. Intussusception in celiac disease: Is it a common feature in children? J Gastroenterol Hepatol 2018;33:380–4.
[9] Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54:136–60.

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