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CASE REPORT

COVID-19 infection as a trigger for the manifestation of celiac disease in a 4-year-old child

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ABSTRACT

The article presents the case of a girl who, after being infected with COVID-19, developed a seroconversion of anti-tissue transglutaminase antibodies as she developed symptoms from the gastrointestinal tract, which consequently allowed her to be diagnosed with celiac disease. In recent years, more and more articles describing possible autoimmune complications have been published after suffering from an infection caused by the SARS-CoV-2 virus. The aim of the work was to show how many diseases are potentially related to COVID-19 infection, pointing out that in the medical literature, the number of articles describing such cases in the paediatric population is still insufficient. We describe herein the case of a 4-year-old patient, who was diagnosed with celiac disease after suffering from COVID-19. We also aim to return attention to vigilantly observing any new symptoms that appear from various source organs after suffering an infection caused by the SARS-CoV-2 virus.

KEY WORDS:

COVID-19, coeliac disease, IgA-tTG, IgA-EmA.

INTRODUCTION

The SARS-CoV-2 virus has the ability to damage the epithelium of the gastrointestinal tract. This tropism is due to the high expression of angiotensin-converting enzyme 2 (ACE 2) and the serine proteases transmembrane serine protease 2 (TMPRSS2) in enterocyte cells, by means of which the virus enters the cell. This results in possible damage to the intestinal epithelium as a consequence of the cytokine storm and an increase in intestinal barrier permeability, e.g. for gliadin. There are reports in the world literature on the potential role of COVID-19 infection as a trigger for autoimmunity and the development of coeliac disease in genetically predisposed individuals [1, 2].

Below, we present a case report of a 4-year-old girl who was proven to have coeliac disease immediately after contracting COVID-19 infection. Based on the observed strong correlation between the severity of abdominal symptoms and the increase in the titre of celiac disease-specific autoantibodies, we suppose that COVID-19 may have been a trigger for the development of celiac disease in our patient.

CASE REPORT

The 4-year-old girl was first admitted to the Paediatric Gastroenterology Unit in July 2021 for the diagnosis of abdominal pain, flatulence, increased belching, and bad breath. The family history included psoriatic arthritis in the child's father and duodenal neoplasia of an unspecified nature in her grandmother on her mother's side. Pregnancy, delivery, and the perinatal period were without complications. The child's psychomotor develop-

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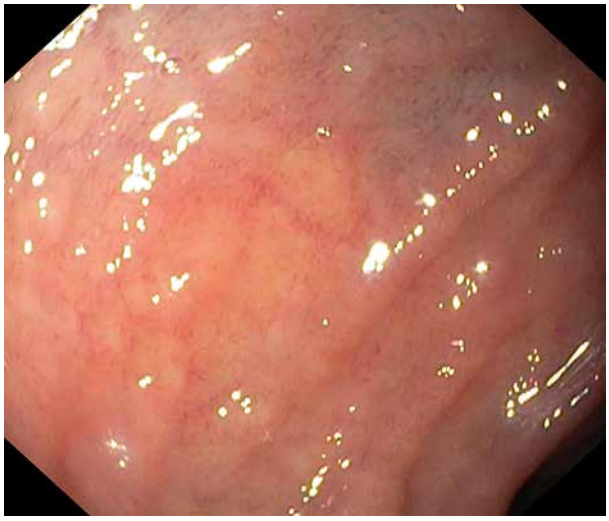

FIGURE 1. Granulated duodenal mucosa

ment was normal. In the outpatient diagnosis, the child's parents performed a genetic test for coeliac disease on their own, confirming a genetic predisposition to the disease (human leukocyte antigens HLA DQ 2.5 positive, HLA DQ 2.2 positive, HLA DQ 8 negative), but tissue transglutaminase antibodies (tTG)-IgA antibodies (enzyme-linked immunosorbent assay – ELISA) were negative at the time. The child ate gluten-containing meals.

On admission to the clinic, no abnormalities were found on physical examination apart from valgus knee joints. Serological tests (ELISA) repeated in the ward again ruled out coeliac disease (normal total IgA concentration, tTG-IgA 0.78 RU/ml; N < 20 RU/ml). Abdominal ultrasound visualised normal organs, but attention was drawn to the large amount of intestinal gas. Due to the predominant 'fermentation' symptoms, hydrogen breath tests were performed with which an overgrowth of small intestinal bacterial flora was excluded, and fructose intolerance was confirmed. Oesophageal pH-metry did not show features of pathological acid gastro-oesophageal reflux. Dietary management was recommended to limit fructose and fermentable foods ('low-FODMAP') in the child's diet, which resulted in a significant improvement in wellbeing and remission of ailments.

For the next 5 months, until December 2021, the girl felt well and did not require gastrological consultations or treatment. In December 2021, the child had a serologically confirmed COVID-19 infection. During the infection she reported abdominal pain, diarrhoea, lack of appetite, and loss of smell. In a short period of time gastrointestinal symptoms in the form of pain and flatulence increased. Despite 2 previous serological tests for coeliac disease and 2 previous negative results, due to the significant increase in symptoms that could be consistent with coeliac disease, the child's parents, after consultation with the paediatric gastroenterology clinic, performed another outpatient determination of antibodies against tissue transglutaminase (tTG-IgA) in 2 different laboratories, this time with a strongly positive result of 150 IU/ml, which was the reason for the child's readmission to the ward.

Laboratory tests performed in the unit showed mild neutropaenia. Control serological tests for coeliac disease (ELISA) were taken with an additional determination of antibodies against smooth muscle endomysium (IgA-EmA). Due to a positive tTG-IgA antibody result, but not exceeding 10 times the upper limit of normal, a gastroscopic examination was performed, which revealed a macroscopically granulated duodenal mucosa. Histopathological examination confirmed the presence of duodenal mucosa with features of crypt proliferation, villous atrophy, and increased intraepithelial lymphocytosis, which corresponded to Marsh type 3a. After several days, the results of serological tests taken during hospitalisation were also obtained. The presence of tTG-IgA in a titre of more than 200 RU/ml (more than 10 times the upper limit of normal) and a positive IgA-EmA result were found. A diagnosis of coeliac disease was made. A gluten-free diet was included with a gradual improvement in wellbeing and a reduction in complaints (Figure 1).

DISCUSSION

Celiac disease is an autoimmune disease caused by gluten, which is found in the grains of wheat, rye, and barley. It occurs in genetically predisposed individuals, and its pathophysiology is multifactorial [3–5]. In almost 100% of patients with coeliac disease, at least one of the 2 haplotypes HLA-DQ2 and/or HLA-DQ8 is detected. A positive genetic test result indicates a predisposition to the disease with a risk estimated at 5–14% depending on the genotype [3–5]. In our patient's case, the HLA DQ 2.5 and HLA DQ 2.2 haplotypes were present.

Serological diagnosis of coeliac disease uses the determination of IgA class antibodies: against tissue transglutaminase (tTG), against gastrointestinal smooth muscle endomysia (EmA), and against deamidated gliadin peptides. Current guidelines for the diagnosis and treatment of coeliac disease attribute the highest sensitivity and specificity to the first 2 of these 3 antibodies [3–5]. Patients who are found to be IgA-deficient, which is the case for approximately 2% of people with coeliac disease, should have their IgG antibody titre determined. It is possible to diagnose coeliac disease solely on the basis of serological tests, but the prerequisite is strongly positive IgA-tTG and IgA-EmA results, subject to the need for assays from 2 independent serum samples and confirmation of IgA-tTG concentrations exceeding the 10-fold positivity limit [3–5]. In cases of diagnostic doubt and/or IgA-tTG concentrations less than 10 times the upper limit of normal, an endoscopic small bowel biopsy with at least 5 mucosal sections, including at least one from the duodenal bulb and at least 4 from the distal bowel, is required [3–5].

In the patient described in our study, due to a genetic predisposition to the development of coeliac disease,

during the initial diagnosis, it was decided to perform a tTG IgA antibody titre, which was negative. False-negative IgA-tTG antibody results are possible in children under 2 years of age [5]. Our patient was 4 years old at the time of the first negative IgA-tTG results, which seems to rule out laboratory error and suggests that the first determination was a true negative result, and the child did not yet have coeliac disease at that time. The situation changed after the child underwent COVID-19 infection, when an escalation of gastrointestinal symptoms (pain and flatulence increased) was observed shortly after SARS-CoV-2 infection. For this reason, a decision was made to repeat the serological tests that were positive, which, together with the results of the histopathological examination of the samples taken during gastroscopy in the girl (endoscopic examination of the upper gastrointestinal tract was necessary because the result of tTG-IgA at that time did not exceed 10 times the upper limit of normal), authorised the diagnosis of celiac disease. It seems reasonable to treat the clinical picture described above and the sequence of test results obtained as confirmation of the 'before our eyes' manifestation of coeliac disease with a direct temporal link and probable causal relationship to fresh COVID-19 infection.

In recent years, there has been increasing interest among doctors and researchers in possible autoimmune complications after contracting an infection caused by the SARS-CoV-2 virus. An analysis published in February 2022 by Cakir *et al.* showed that during the COVID-19 pandemic, the number of celiac disease diagnoses among children increased significantly compared to previous years [2]. This is also confirmed by the work of Samasca *et al.* [6].

Coeliac disease during the pandemic was undoubtedly of interest to many researchers. Among others, there have been papers focusing on the potential protective role of the HLA DQ2 and/or DQ 8 haplotype in SARS-CoV-2 infection [7].

SARS-CoV-2 virus attacks the gastrointestinal tract by entering enterocytes via ACE 2 receptors and TMPRSS2 serine proteases. This results in damage to the intestinal epithelium through a cytokine storm and an increase in the permeability of the intestinal barrier to, inter alia, gliadin, which in genetically predisposed individuals may lead to the development of the disease [1, 2]. In June 2022, a paper was published to analyse the potential pathomechanisms for the triggering of autoimmune processes in the body by the SARS-CoV-2 virus. It noted that viruses induce autoimmunity by mechanisms such as, inter alia, molecular mimicry and T-lymphocyte activation [8]. It was concluded that infection of the respiratory epithelium by SARS-CoV-2 virus leads to dysregulation of the immune system, triggering both innate and acquired immune responses [8, 9]. This results in hyperactivation of the immune system and an excessive release of cytokines, known as a 'cytokine storm' [8, 10]. Exploring the topic of the molecular mimicry of the virus, the authors, referring to previously published papers, observed a correlation of the SARS-CoV-2 hexapeptide sequence (nucleocapsid [N], membrane [M], ORF7b, ORF7a, ORF71a, ORF71b, and especially glycoprotein S) with that of human proteins, which may cause pulmonary and cardiac complications and result in neurological disorders and autoimmune syndromes [8, 10, 11]. In addition, the potentially important role of cytokines in the pathogenesis of autoimmune diseases has been highlighted. It has been observed that SARS-CoV-2 infection stimulates the release of serum cytokines, mainly tumour necrosis factor α, interferon β-1b, interleukin (IL)-1β, IL-6, IL-17, and IL-18, resulting in loss of tolerance to autoantigens [8, 10].

The studies cited above were carried out on adult patients. There is still an insufficient amount of published work in the literature relating to the paediatric population. However, from articles written in recent years on paediatric patients, it can be seen that, in this group too, COVID-19 illness and isolation related to this infection had a significant impact on the development of various complications. During the pandemic period, the number of children with obesity increased significantly, which in turn increased the incidence and diagnosis of endocrine diseases such as thyroid disease, diabetes, and precocious puberty [12, 13].

In a May 2021 publication, Seo, citing data available at the time, wrote about the increased incidence of thyrotoxicosis and thyroiditis observed in the adult population among patients with severe forms of COVID-19. In his article, he noted that, to date, there have been no reports on COVID-19 and thyroid abnormalities in children [12]. However, there are now publications relating to the aforementioned relationship. In July 2022 Sakaleshpur Kumar *et al.* described the onset of primary hypothyroidism after COVID-19 in previously healthy twins. Laboratory tests performed after infection detected significantly elevated levels of thyrotropic hormone, reduced free thyroxine fraction levels, positive titres of thyroid peroxidase antibodies and thyroglobulin antibodies [14]. An analysis of 164 patients (including 14 children) from May/June 2021 also showed an association between thyroid disease and having SARS-CoV-2 virus infection [15].

In the adult population, cases of other autoimmune diseases temporally associated with COVID-19 transfection such as autoimmune haemolytic anaemia, immune thrombocytopaenic purpura, and Graves-Basedow disease have also been described [16, 17]. Complications such as autoimmune hepatitis have also been described after vaccination for SARS-COV-2 [18]. Data relating to the paediatric population, on the other hand, are currently insufficient and require further research.

To sum up, the case report we describe strongly supports the role of COVID-19 infection as a possible trigger for celiac disease.

CONCLUSIONS

A history of COVID-19 infection can induce the manifestation of various autoimmune diseases including coeliac disease. Any new symptoms from different organs that appear after a child has experienced COVID-19 should be vigilantly observed. Negative results of tests for autoimmune diseases performed prior to COVID-19 infection do not exclude indications for their repetition because it is possible that a fresh manifestation of the disease may be in direct temporal relation to the past SARS-CoV-2 infection.

DISCLOSURE

The authors declare no conflict of interest.

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