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COELIAC DISEASE NOT RESPONDING TO A GLUTEN-FREE DIET IN CHILDREN: CASE STUDIES AND LITERATURE REVIEW

CELIAKIA OPORNA NA LECZENIE DIETĄ BEZGLUTENOWĄ: OPIS PRZYPADKÓW ORAZ PRZEGLĄD LITERATURY

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Abstract

We presented the cases of three children with coeliac disease who despite good adherence to a gluten-free diet remained non-responsive to treatment. Two patients, one of them with IgA deficiency, were successfully treated by complete gluten exclusion with enteral nutrition. However the third child with a severe coeliac disease did not achieve clinical and histologic improvement, even on immunosuppressive treatment.

If no hidden sources of gluten can be identified, other causes of persistent villous atrophy, different from coeliac disease, have to be considered. They include e.g. inflammatory, immune and endocrine diseases of the digestive tract. In severe cases of childhood coeliac disease not responding to a gluten free diet, autoimmune enteropathy and refractory coeliac disease must be taken into account.

Key words: coeliac disease, enteropathy, gluten-free diet, enteral nutrition, refractory coeliac disease, children

Streszczenie

Przedstawiamy trzy przypadki dzieci z celiakią oporną na leczenie pomimo przestrzegania diety bezglutenowej. Dwóch pacjentów, w tym jeden z niedoborem IgA, było skutecznie leczonych żywieniem dojelitowym z wyłączeniem glutenu. Trzeci pacjent z ciężką postacią choroby trzewnej nie uzyskał poprawy klinicznej ani histologicznej mimo zastosowania leczenia immunosupresyjnego. Wśród przyczyn braku odpowiedzi na leczenie celiakii należy rozważyć przede wszystkim ekspozycję na gluten w diecie. Do innych przyczyn przewlekłego zaniku kosmków jelitowych należą m.in. choroby zapalne przewodu pokarmowego, niedobory immunologiczne oraz zaburzenia hormonalne. W celiakii o ciężkim przebiegu, niereagującej na leczenie dietą bezglutenową jako przyczynę należy rozważyć celiakię oporną na leczenie oraz enteropatię o podłożu autoimmunologicznym.

Słowa kluczowe: celiakia, enteropatia, dieta bezglutenowa, żywienie dojelitowe, celiakia oporna na leczenie, dzieci

INTRODUCTION

Coeliac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy. CD-specific antibodies comprise autoantibodies against tissue transglutaminase (TG2), anti-endomysial antibodies (EMA), and antibodies against deamidated forms of gliadin peptides (DGP) [1].

After the elimination of gluten from the diet, patients usually demonstrate clinical improvement and restoration of the intestinal architecture. However, sometimes clinical and histologic response to a gluten-free diet (GFD) cannot be achieved. In these circumstances first of all gluten contamination should be considered. If this can be ruled out, further investigations towards any concomitant pathologies that could mimic CD have to be done. They include food allergy, inflammatory bowel disease, microscopic colitis, autoimmune enteropathy, exocrine pancreatic insufficiency, bacterial overgrowth, endocrine and immune deficiency etc. In severe cases of true non-responsiveness to a GFD, refractory CD (RCD) should be considered [2-4].

In the following section we present three patients with CD, who were initially non-responsive to a GFD.

The presentations of patients

Patient 1

A 7-year-old boy was referred to our clinic for a second opinion because of CD which was not responsive to treatment with a GFD. The clinical history comprised of cerebral palsy, hemiplegia and epilepsy from the age of 13 months, caused by multiple thrombotic infarctions in the brain of an unknown origin. At the age of 16 months he presented with abdominal pain. IgA class anti-endomysial antibodies (EMA) were strongly positive and histologic examination of the duodenum showed subtotal villous atrophy, classified as Marsh class 3b. CD was diagnosed and he was treated with a GFD. However, during the 5-year follow-up, the complaints persisted and EMA remained elevated. Repeated duodenal biopsies, reviewed by two pathologists experienced in CD, revealed Marsh class 3 lesions.

On admission to our clinic the patient was in a good clinical condition, but EMA remained strongly positive (TG2 antibodies were unavailable at that time in our centre). His HLA typing was DR3-DQ2/DR7-DQ2. The GFD was re-evaluated several times by a registered dietician, but no gluten contamination could be identified. His anti-epileptic drugs were tested by the Dutch Food and Consumer Product Safety Authority for gluten, but they were found to be gluten-free (<200 ppm). To be certain that gluten was completely excluded from his diet, he was treated with exclusive enteral feeding for three months. Afterwards we repeated the duodenal biopsies. The histology showed some improvement, described as Marsh class 3a. The CD3 staining showed no refractory CD (confirmed by laboratories in Rijnstate Ziekenhuis

Hospital, Arnhem, the Netherlands and l'Hospital Necker-Enfantes Malades, Paris, France). High intraepithelial lymphocytosis on biopsy and absence of anti-enterocyte antibodies were against the diagnosis of autoimmune enteropathy. The boy was further treated with an oral GFD and during the follow-up his abdominal pain resolved, the EMA and TG2 antibodies disappeared. At the age of 9 years and 4 months, after 8 years on a GFD, duodenal histology was normal, consistent with a good response to the GFD.

Patient 2

A 7-year-old girl with an unremarkable medical history presented with abdominal pain and constipation that was not responsive to treatment with macrogol. Among other causes, CD was suspected. Examinations revealed a selective IgA-deficiency (IgA <0.05 g/l), strongly positive IgG class EMA, and markedly increased IgG-class TG2 antibodies (2510 U/ml). Duodenal biopsies showed subtotal villous atrophy consistent with Marsh class 3b. CD was diagnosed and she was treated with a GFD. The clinical symptoms resolved soon but, despite thorough dietary evaluation, after 19 months of follow-up, the IgG class EMA and IgG class TG2 antibodies remained strongly positive.

At the age of 8 years and 8 months, the girl was referred to our clinic. Repeated CD serology continued to show highly positive IgG EMA and slowly decreasing IgG TG2 antibodies. No overt sources of gluten intake were identified. Duodenal biopsies were repeated and showed Marsh-class 3a lesions in the duodenal bulbus and normal mucosa (Marsh 0) in the descending duodenum. CD3 staining did not reveal abnormalities seen in the refractory CD. T-cell flow cytometry performed on IELs isolated form duodenal biopsies showed 22% aberrant T cells (CD52+, sCDR-, cytCD3+). To guarantee complete gluten avoidance the patient was treated with exclusive enteral feeding for three months. After this period, the EMA and the IgG TG2 antibodies remained elevated, but repeated duodenal biopsies showed an almost complete restoration of the bulbus mucosa (Marsh 1) and normal mucosa in the descending duodenum. T-cell flow cytometry showed 23% IEL of aberrant phenotype (CD52+, sCDR-, cytCD3+). At present, after nearly 5 years of follow-up on a GFD, she reports no complaints. Although the levels of IgG EMA in serum are still elevated, the titers of IgG TG2 antibodies have gradually decreased and are now almost normal.

Patient 3

A male infant with provisional diagnosis of CD was referred to our clinic at the age of 12 months. His past medical record included poor weight and prolonged diarrhea that started after introduction of gluten in the 4th month of life. On admission he had positive serum IgA EMA, TG2, IgA and IgG anti-gliadin (AGA) and anti-reticulin (ARA) antibodies. Duodenal biopsy showed villous atrophy grade Marsh 3c. His HLA typing was DQ2 homozygous. Diagnosis of CD was confirmed. However, treatment with a GFD was not successful and diarrhea and malnutrition persisted throughout the 20 years of

clinical follow-up. In the meantime, the patient developed osteopenia, anemia, hypoalbuminemia, hypokalemia, and hyponatremia. Several duodenal biopsies revealed persistent villous atrophy grade Marsh 3c accompanied by crypt hyperplasia, high intraepithelial lymphocytosis (>50 IEL/100E) and lymphoplasmocytosis of lamina propria, although he strictly adhered to the GFD. Autoimmune enteropathy was ruled out based on duodenal histology suggestive for CD (as described above), absence of other autoimmune diseases, lack of anti-enterocyte and other auto-antibodies. Repeated gastroscopies and coloscopies were consistent with histology and showed lesions limited only to the duodenum. Thorough investigations made the following unlikely: food allergy, inflammatory bowel diseases, microscopic colitis, pancreatic insufficiency, bacterial overgrowth, cystic fibrosis, rheumatoid and collagen diseases, tuberculosis, endocrine disorders and immune deficiency. At the age of 4 years EMA, AGA and TG2 antibodies became negative.

GFD was maintained for over 20 years with good compliance, verified by negative TG2, EMA antibodies and evaluated by an experienced dietician and gastroenterologist. Because constant adherence to a GFD did not significantly improve either the patient's clinical condition or his severe duodenal villous atrophy, we considered the possibility of refractory CD.

At the age of 16 years, we started therapy with prednisone (2mg/kg) and within a month we observed a major clinical improvement. The patient eventually reported well being and gained weight (about 2 kg per month). After twelve months of corticosteroid treatment villous atrophy improved to Marsh 2. However, on a tapering dose of prednisone, the patient's condition deteriorated again. He also suffered from corticosteroid-related severe osteopenia. Azathioprine (2mg/kg) was started in order to withdraw prednisone but subsequent duodenal biopsy revealed reoccurrence of villous atrophy Marsh 3c. Elemental diet (amino acid-based formula) was maintained for 5 months without improvement. The patient was switched to cyclosporine, which had to be withdrawn after 4 months, because of the lack of efficacy and side effects (thrombocytopenia and musculoskeletal pain). At the age of 20, apparently after a dietetic error, the patient was urgently admitted to our unit presenting with severe diarrhea, significant weight loss (2.5kg within 3 days), muscle cramps, pruritus, urticaria and electrolytic and biochemical disturbances. He was treated with hydrocortisone, antibiotics i.v. and total parenteral nutrition (TPN). A few years after being discharged from our health centre, he remains in a stable condition, but still requires TPN.

DISCUSSION

Our paper describes three cases of children with symptomatic, non-responsive CD, who strictly adhered to GFD for a long period of time (5-20 years). In all the patients the diagnosis of CD was confirmed by duodenal histology and the presence of EMA and TG2 antibodies that are considered highly sensitive and specific for CD. In addition, patients 1 and 3 had HLA typing highly predisposing to CD.

Non-responsive CD should first of all raise questions over the strict gluten avoidance. As shown previously, exposure to even a small amount of gluten (for example nutritional preservatives) might be sufficient to maintain intestinal damage in exceptionally gluten-sensitive individuals [5,6]. Therefore, deliberate or covert gluten contamination should always be taken into account. To provide appropriate surveillance of a gluten-free diet our patients were closely monitored by experienced dieticians. Where available, food was tested for possible gluten content in specialized laboratories.

Patients 1 and 2 eventually reacted to complete gluten exclusion on enteral nutrition. As reported earlier, patients with CD not responding to a GFD may benefit from further dietary restrictions, such as elemental diet or parenteral nutrition [7, 8]. However, to the best of our knowledge, improvement of a GFD applied via enteral nutrition has not previously been described in these patients. We speculate that the use of gluten-free enteral formulas may prevent accidental gluten contamination or ingestion.

Patient 2 presented with CD and concomitant IgA deficiency. Interestingly, in this case the serologic markers of CD (EMA) remained elevated after clinical improvement and histologic restoration of the duodenal mucosa. However, it is known that in IgA-deficient patients, the IgG CD serology may be persistently elevated, despite histologic recovery [9]. Specific antibody production is dependent on T helper lymphocyte function, T cell priming and cytokine profiles and B cell responsiveness shows alterations in IgA deficiency. Therefore, the slow disappearance of IgG coeliac antibodies may be part of the immunoregulatory defect seen in IgA deficiency [10].

Patient 3 did not achieve clinical and histologic improvement, even on immunosuppressive treatment. He presented with a clinical picture of severe CD which was confirmed by duodenal histology, HLA typing and the presence of EMA and TG2 antibodies on several occasions. In addition, extensive differential diagnosis excluded potential causes of coeliac-like enteropathy, such as food allergy, inflammatory bowel disease, microscopic colitis, exocrine pancreatic insufficiency, bacterial overgrowth, endocrine and immune deficiency etc. [2-4]

The early onset of symptoms, no response to GFD, persistent villous atrophy and improvement on immunosuppressive therapy could be indicative of autoimmune enteropathy (AIE), an immune-mediated disease that may cause protracted diarrhea and malabsorption, usually with onset in infants and young children. The endoscopic and histologic lesions in AIE show similarities to these found in untreated CD. Moreover, AIE is linked to other autoimmune disorders and may present with circulating anti-enterocyte antibodies or other autoantibodies, however their pathogenic role is not clear [11]. On the contrary to the findings in our patient, villous atrophy in AIE is characterized by reduced intraepithelial lymphocytosis and AIE patients do not present with CD-specific antibodies, such as EMA and TG2 [12]. Anti-enterocyte antibodies were never found. Neither were there any coexisting autoimmune disorders or immune deficits. The family record was

negative for autoimmune disease. AIE is considered a generalized autoimmune disorder of the gastrointestinal tract [13], but in our patient repeated upper and lower GI endoscopies showed lesions limited only to the duodenum. Furthermore, our patient achieved long-term improvement on total parenteral nutrition, while patients with AIE usually do not improve on any diet restriction therapy. Immunosuppressive treatment, which is claimed beneficial for patients with AIE [14-17], was not successful in our patient in the long-term. All these facts made the diagnosis of AIE unlikely in patient 3.

In patients with non-responsive CD, after exclusion of other CD-mimicking disorders, refractory CD should be taken into account [4]. We speculate that, based on the course of the disease and no response to dietary intervention and pharmacotherapy, RCD could be the most probable diagnosis in patient 3, although specific immunochemical testing for RCD was not available at that time in our centre.

Refractory coeliac disease (RCD) should be suspected in CD patients with persistent enteropathy in spite of good adherence to treatment with a gluten-free diet for at least 12 months [2-4]. The definition of RCD also includes the occurrence of severe clinical deterioration in diagnosed CD, which requires rapid intervention independent of the duration of the GFD. RCD accounts for 7-15% of all adult-onset CD and predominantly concerns HLA-DQ2 homozygous individuals [18,19]. Two types of RCD have been recognized on the basis of immunophenotyping of intraepithelial lymphocytes: type I - without or with less that 20% aberrant CD3- CD4- T-cells and type II - with over 20% aberrant T-cells in the intestinal mucosa [20]. RCD type II is usually resistant to any conventional treatment and has a higher risk of transition into malignancies, particularly enteropathy associated T-cell lymphoma (EATL) [21].

RCD has been seen almost only in adult-onset CD, while in children it is a rare condition. Only incidental cases of RCD in the pediatric population have been described so far. Recently, Mubarak et al. reported a single case of a child with RCD type I, in whom the GFD was sufficient to achieve a good clinical but not a histologic response. Complete resolution of duodenal lesions was eventually seen after a 1-year-long treatment with azathioprine [22].

Current therapeutic guidelines in RCD include both nutritional and pharmacological therapy. The maintenance of GFD and enteral nutrition should be the primary approach in these patients. A further dietary regime, such as an elemental diet, proved to be successful in several studies [7]. Corticosteroids are the first-line pharmacological option to induce remission followed by azathioprine [21, 23, 24]. Cyclosporine was also claimed beneficial in some studies [25]. There have been reports that budesonide may reverse the clinical symptoms of RCD without the side effects associated with systemic corticosteroids, however no improvement on mucosal histology was seen in these patients [26, 27]. There is growing evidence that infliximab may induce remission in RCD patients resistant to conventional treatment (favorably RCD type I). The initial results are encouraging but the safety and efficacy of this therapy has

to be proven in longitudinal, large cohorts studies [28-30]. Interleukin 10 is generally not successful in adults with RCD and the effects of alemtuzumab are uncertain [31, 32]. Cladribine (2-chlorodeoxyadenosine), a cytotoxic purine nucleoside effective in hairy cell leukemia, showed some promising results in recent open-label studies in RCD II, as it potentially decreases the number of aberrant T-cells and may reduce transition into EATL [33]. Autologous stem cell transplantation (ASCT) remains the ultimate treatment for carefully selected patients who did not respond to any pharmacotherapy including cladribine, however its results are not satisfactory at the moment [34]. As the interleukin 15 overexpression is supposed to be responsible for intraepithelial lymphocytic expansion, IL-15 blocker-drugs may be useful in the management of clonal refractory coeliac disease in future research [35].

In conclusion, the medical records of our patients show that childhood CD which is not responsive to GFD may be managed by complete gluten exclusion with enteral nutrition. However, in the case of failure after total gluten exclusion, other diagnoses, such as autoimmune enteropathy or refractory CD should be considered. These patients may benefit from immunosuppressive treatment or total parenteral nutrition.

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