

# Refractory coeliac disease

## Choroba trzewna oporna na leczenie dietą

Anna Szafarska-Szczepanik

Department of Pediatrics, Allergology and Gastroenterology University School of Medical Sciences in Bydgoszcz, Poland

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### Abstract

In this paper we present a review of the literature concerning refractory coeliac disease (RCD). It can be expected that the prevalence of RCD is related to the general prevalence of coeliac disease (CD). The rate is estimated to be 7-8% of patients with CD, predominantly affecting adults. Before making a definitive diagnosis, a long list of possible concomitant diseases and intended or unconscious intake of gluten should be excluded. Immunohistochemical tests and DNA analyses can be very helpful in determining abnormal phenotype and changes in the TCR- $\gamma$  receptor gene, which is found in morphologically normal intraepithelial lymphocytes in the majority of refractory coeliac patients. Many studies indicate that RCD is the link between CD and small intestine T-cell lymphoma (EATL). This is why early diagnosis is of such great importance. The prognosis is unfavourable. Trials with steroid monotherapy or in combination with azathioprine or with other drugs (cyclosporin, anti-TNF- $\alpha$ , IL-10) and an elementary diet – if lacking response to steroids – have been undertaken. (*Gastroenterol. Pol.*, 2004, Vol. 11, No. 5, p. 471-475)

**Key words:** refractory coeliac disease, enteropathy – associated T-cell lymphoma, treatment

### Streszczenie

W pracy przedstawiono przegląd piśmiennictwa dotyczący choroby trzewnej odpornej na leczenie dietą. Należy się spodziewać, że wraz ze wzrostem częstości występowania celiakii, wzrośnie również częstość wykrywania choroby trzewnej odpornej na leczenie dietą. Szacuje się, że dotyczy ona 7-8% pacjentów z chorobą trzewną, głównie osób dorosłych. Przed postawieniem ostatecznego rozpoznania należy wykluczyć błędne rozpoznanie wstępne, długą listę możliwych współwystępujących chorób oraz świadome lub przypadkowe nieprzestrzeganie diety bezglutenowej. Dużą pomocą w ustaleniu rozpoznania mogą być badania immunohistochemiczne oraz metody analizy DNA umożliwiające wykrycie nieprawidłowego fenotypu oraz zmian w obrębie genu receptora TCR- $\gamma$ , które są stwierdzane w obrębie morfologicznie prawidłowych limfocytów śród nabłonkowych u większości pacjentów z chorobą trzewną oporną na leczenie dietą. Wiele danych wskazuje na to, że choroba ta jest ogniwem łączącym pomiędzy celiakią, a chłoniakiem jelita cienkiego wywodzącym się z komórek T (EATL), dlatego ważne jest wczesne ustalenie rozpoznania. Rokowanie jest złe. Podejmuje się próby leczenia steroidami w monoterapii lub skojarzeniu z azatiopryną, a w przypadku braku odpowiedzi na steroidoterapię innymi lekami (cyklosporyna, anti-TNF- $\alpha$ , IL-10), a także dietą elementarną.

**Słowa kluczowe:** choroba trzewna oporna na leczenie dietą, chłoniak jelita cienkiego, leczenie

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### Introduction

Coeliac disease (CD) is a chronic inflammation of the small intestine caused – in genetically predisposed people – by the intestinal mucosa's exposure to gluten, a plant protein contained in the seed coat of European grains. According to the modified criteria of the European Society of Gastroenterology, Hepatology and Nutrition (ESPGHAN), clinical recovery and histological improvement of

the small intestine mucosa damaged by gluten can be expected after implementation of a gluten-free diet (1). However, based on the prior literature, a gluten-free diet is ineffective in 10-20% of coeliac patients (2).

In patients with suspected CD who are resistant to dietary treatment (refractory coeliac disease, thereafter – RCD), it should first be decided whether the initial diagnosis of CD was correct. Unfortunately, CD is still diagnosed on the basis of clinical improvement after implementation

of a gluten-free diet, without performing a small intestine biopsy. This is especially common in young children, due to the ambiguous and multi-symptom clinical presentation of many diseases in this age range. In such cases, the first biopsy of the small intestine mucosa is recommended at least two years after implementation of a gluten-free diet. Subsequently, gluten introduction with monitoring of the clinical course with repeated determination of serum anti-gliadin (AGA) or anti-endomysial (EmA) antibodies and the second small intestine biopsy are recommended. It should be pointed out that other medical conditions that are unrelated to CD also show good response to a gluten-free diet. According to some authors, up to 40% of patients with irritable bowel syndrome report improvement after excluding wheat from their diets (3). Gluten elimination from the diet also leads to clinical improvement in patients with an allergy to gluten or transient gluten intolerance (4). It is worth noting that partial intestinal villous atrophy could be caused by diseases other than CD, e.g., post-infection syndromes, parasitic infections, drug syndromes and ionizing radiation effect (5).

Furthermore, in patients considered to be suffering from CD resistant to dietary treatment (RCD), gluten-free diet compliance should be verified. Accidental or intended intake of gluten-containing food or even a normal diet seem to be the most common reasons for the lack of clinical improvement after implementing the diet (5, 6). The rate for coeliac patients who consistently or periodically fail to follow medical advice is estimated at 30-70%. The non-compliance with the gluten-free diet could be related to several factors including: insufficient knowledge of the disease and its treatment, self-denial, low flavour value of gluten-free foods, difficult access to gluten-free products, and presence of gluten as technological supplement in generally used food products without including such information on their labels (7).

Several definitions of RCD appear in the literature. Although the term "refractory coeliac disease" seems contradictory because, according to the diagnostic criteria for CD, improvement after implementation of a gluten-free diet is necessary, it is frequently encountered in the medical literature. Therefore, this term has been used in this review. Based on the literature review and their own clinical assessment, Biagi and Corazza (2) proposed a new terminology. They introduced the term "refractory coeliac disease" meaning CD without complications of lymphoma, ulcerative jejunoileitis or collagenous colitis, no longer responds to a gluten-free diet. They used the term "non-coeliac refractory sprue" to mean enteropathy with no response to a gluten-free diet and no histological variation with CD, in which lack of HLA alleles or hypersensitivity to gluten excludes CD.

The prevalence of RCD is difficult to assess due to case reports in the literature in which CD is not well documented or diagnosis seems to be incorrect. According to O'Mahony et al. (5), RCD should be diagnosed in patients with villous atrophy in the small intestine mucosa consistent with CD with no histological improvement after an arbitrarily accepted term of 12 months of a strict gluten-free diet. Adhering to these criteria, RCD could be estimated to occur in 7-8% of patients with CD.

The relationship between RCD and CD is widely discussed in the medical literature. The proof of the relationship is a presence of serum anti-gliadin and/or anti-endomysial antibodies and HLA-DQw2 haplotype in patients of both groups (8). According to Isaacson (9), RCD can start both as "de novo" disease or as a complication of histopathologically proven typical CD.

The majority of patients with RCD shows so-called primary resistance. In those patients who do not respond to dietary treatment, CD could not be definitely diagnosed according to compulsory diagnostic criteria, and they would fall into a more general diagnosis of unclassified sprue. A small number of patients initially responds to a gluten-free diet, but later, despite strict compliance, they develop the so-called secondary resistance (10).

Resistance to dietary treatment could be classified as 1) clinical resistance, that is, persistence of clinical symptoms of chronic diarrhea, flatulence or abdominal pain, despite stated histological regeneration of the small intestine mucosa, or 2) histological resistance with persistent or recurrent histopathological disturbances in the small intestine (11). It should be noted that a significant clinical effect is observed after a few days of a gluten-free diet, while histological regeneration can last up to 2 years (12). Simultaneous histological improvement is characterized by a significant rise in the length of intestinal villi, decrease of intestinal crypt hyperplasia and reduction in intraepithelial lymphocyte count, and it occurs more rapidly in the distal small bowel. In many coeliac patients responding to dietary treatment despite normal intestinal villous architecture, the number of T lymphocytes with  $\gamma/\delta$  receptors remains slightly increased with the normal level of T  $\alpha/\beta$  lymphocytes T, which is in strict correlation with the rate of intestinal villi shortening (13).

No satisfactory clinical improvement with good histological response to a strict gluten-free diet most likely indicates concomitant additional disease. The diseases responsible for persistence of chronic diarrhea in coeliac patients include collagenous colitis, lymphocytic colitis, ulcerative colitis, secondary lactose intolerance, pancreatic insufficiency and rectal sphincter insufficiency (14).

The combined resistance to gluten-free diet treatment in coeliac patients requires strict exclusion of other factors, which despite a gluten-free diet can lead to no clinical improvement or histological regeneration of the small intestine mucosa. Many studies show that the most common reasons for combined resistance are small intestine lymphoma, inflammatory bowel disease, autoimmune enteritis, collagenous enteritis, other than gluten food protein intolerance (milk, soy, egg), gardiasis, Whipple's disease and bacterial overgrowth (11, 15-17). The algorithm of procedures to follow for patients suspected to suffer from RCD is presented in figure 1 (11).

Autoimmune enteropathy, in particular, should be noted. It is a chronic disease of the lower part of alimentary tract, which had originally been reported only in children, but in subsequent years some cases of incidence in adults were also presented. The diagnostic criteria of the disease comprise histopathologic signs of enteropathy without identification of a triggering food protein, persistence of chronic diarrhoea despite long-term parente-

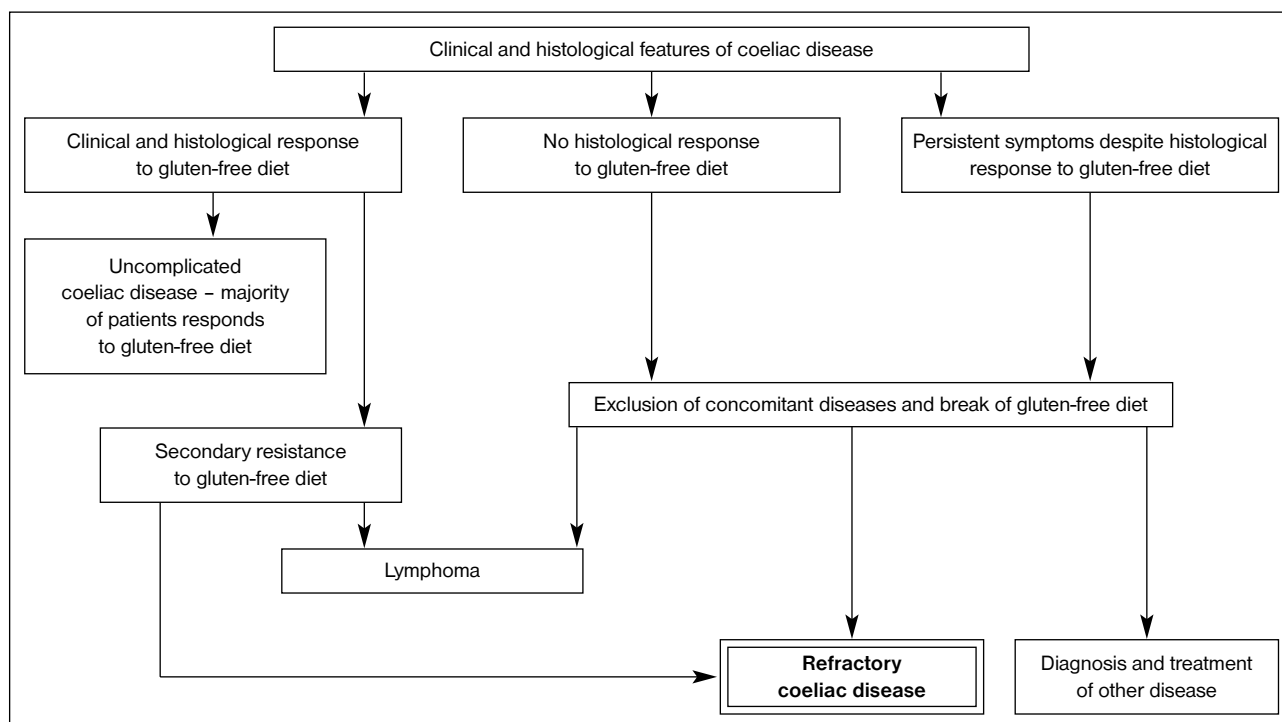


Fig. 1. Algorithm of procedures in refractory coeliac disease (27)

ral nutrition, presence of antibodies against enterocytes and concomitant autoimmune diseases. Recently, special cases of adult patients with autoimmune enteropathy who were treated as suffering from RCD have been reported (15, 18, 19). In none of the reported cases was there IgAEmA in serum; in one case IgAAGA were present. All had HLA-DQ2 alleles, which, though typical for coeliac patients, are also found in patients with other autoimmune diseases (15, 19). It seems that in all patients in whom RCD is considered the antibodies against enterocytes should be determined because proper identification of patients with autoimmune enteropathy has significant therapeutic and prognostic implications (11).

For many years the relationship of RCD and enteric lymphoma from T-cells (enteropathy - associated T-cell lymphoma - EATL) has been discussed. In coeliac patients sensitive to gluten-free diet, intraepithelial lymphocytes have a normal phenotype, and the majority are CD8+ lymphocytes and T lymphocytes with  $\alpha/\beta$ , and especially  $\gamma/\delta$  receptors. In the majority of coeliac patients not responding to dietary treatment, intraepithelial lymphocytes are morphologically normal, but they have a different phenotype when compared to the control group and patients with typical CD: the presence of intracytoplasmic CD (iCD3e), surface marker CD103+ and absence of surface markers CD3+, CD8+, CD4+ and TCR $\gamma$  receptor (TCR-CD8-CD4-CD3-), and monoclonal rearrangements in TCR $\gamma$  gene (8, 11, 20). An abnormal immunophenotype is easy to find using the immunohistochemical method on formalin fixed paraffin embedded biopsy samples from the small intestine mucosa, while the clonal population is easily detected by analysing DNA (PCR) extracted from intestinal biopsy samples (8, 21). Such phenotypically abnormal intraepithelial lymphocytes are identical as described in the small intestine mucosa of patients with ulcerative jejunitis and in the "non-lymphomatous"

and "lymphomatous" mucosa of patients with EATL, implying that both RCD and ulcerative jejunitis could be the missing link between CD and enteropathy-associated T-cell lymphoma (8, 20, 22, 23). The type of CD with phenotypically abnormal intraepithelial lymphocytes classified as type II occurs significantly more often and, according to clinical trials, sometimes shows progression in subclinical or latent form of small intestine lymphoma. It seems that identification of coeliac patients resistant to a gluten-free diet with a population of abnormal intraepithelial lymphocytes will allow to distinguish patients with an increased risk of EATL development, enabling to start chemotherapy in the early phase of the disease (11). The patients with CD resistant to a gluten-free diet and the phenotypically normal population of CD3+CD8+ intraepithelial lymphocytes classified as type I exhibit long-term clinical and histological recovery after steroid treatment in combination with a gluten-free diet, implying that the lack of such lymphocytes could be a successful prognostic factor of good treatment results (8).

The treatment of RCD patients is still one of the most often discussed problems in the medical literature focusing on gastroenterology. The analysis of the published cases still shows the prognosis to be unfavourable (2). Clearly, despite patient resistance, a strict gluten-free diet should be recommended, stressing potential consequences of accidental or sometimes intended intake of food products containing gluten (11). The general laboratory diagnostics could identify vitamin deficiencies, especially vitamin B<sub>12</sub>, folic acid and microelements such as zinc and copper, and supplementing the missing components in some patients could result in a therapeutic advantage. In patients with a considerable body weight loss, food deficiency and edema from hypoproteinemia, exclusively parenteral nutrition is recommended (11, 24). Elemental diet is still controversial although the literature contains reports of excel-

lent clinical and histopathological improvements following the implementation of such a diet in patients non-responsive to a gluten-free diet and refusing to take steroids or immunosuppressive drugs (25).

In addition to the diet, the essential therapy of RCD is immunosuppressive treatment. The justification for such a type of therapy is proven participation of abnormal intraepithelial and mucous lymphocytes and local rise in some cytokines (interferon, IL-6, TNF) production in pathogenesis of RCD (11). It is recommended that prednisone (30-40 mg) be administered daily for individualized length of time with subsequent decrease to the minimal maintenance dose, or with addition of azathioprine to decrease side effects of steroid therapy (6, 25, 26). In some patients steroids result in good clinical and histopathological response; however, they do not prevent the development of enteric lymphoma, often disguising the symptoms and delaying the diagnosis (11).

The literature also includes individual reports on efficiency of azathioprine and cyclosporin in some patients with RCD and with no response to steroids (6, 19, 27). One should remember the risk of severe opportunistic infections in patients with long malnutrition and immunosuppressive treatment as well as the risk of EATL develop-

ment in patients with enteric lymphoma in latent phase (27, 28). Gillett et al. presented the case of a 47-year-old woman with RCD resistant to steroids, who responded well to treatment with anti-TNF- $\alpha$  (Infliximab) (29). The trial to administer IL-10 product with inhibitory effect to immune response T-lymphocytes and monocytes in the group of 10 patients with RCD caused histological regeneration of the small intestine mucosa in only one patient (30).

We should expect that the prevalence of RCD is related to the general prevalence of CD. Before making a definite diagnosis a long list of possible concomitant diseases and intended or unconscious intake of gluten should be excluded. Immunohistochemical tests and DNA analyses can be very helpful in determining abnormal phenotype and TCR- $\gamma$  gene rearrangements found in morphologically normal intraepithelial lymphocytes in the majority of refractory coeliac patients. Many studies show that disease is the link between CD and enteropathy-associated T-cell lymphoma (EATL), and an early diagnosis is of great importance. The prognosis is unfavourable. Trials with steroid in monotherapy or in combination with azathioprine, other drugs (cyclosporin, anti-TNF- $\alpha$ , IL-10), and elementary diet – in case of lacking response to steroids – have been undertaken.

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**Address for correspondence:**

Anna Szaflarska-Popławska MD PhD  
Department of Pediatrics Allergology and Gastroenterology  
University School of Medical Sciences  
M. Skłodowskiej-Curie 9  
85-094 Bydgoszcz, Poland  
tel. (+48 52) 585 48 50  
e-mail: klped@amb.bydgoszcz.pl

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