CLINICAL STUDY

What can we do to promote the recognition of celiac disease: a report on diagnostic strategies

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Abstract: Searching for risk groups with celiac disease is an interdisciplinary problem, and therefore it requires the co-operation of all branches of medicine. It has been suggested that the determination of antiendomysial antibody (AEA) and tissue transglutaminase (t-TG) should be performed by doctors in the first-contact medical facilities. In diagnosed patients, and especially in paediatric practice, it the values of autoantibodies regarding the adherence to a gluten-free diet should be monitored. After reaching the adulthood, patients should be entrusted to the care of gastroenterologists. Biopsy of duodenum samples remains the golden standard for the diagnosis of celiac disease. Every histological examination of a duodenum sample must be completed by histological grading in accordance with Marsh-Oberhuber. Histochemical investigation should be an inseparable part of the malabsorption diagnostics in biopsy. In controversial biopsies, such as with minimal or mild pathological changes, application of antibodies to the intraepithelial lymphocytes is recommended. It is also useful to perform electron-microscopy of duodenum samples as well, when repeated biopsies are negative, but the patient’s troubles persist (Ref. 32). Full Text (Free, PDF) www.bmj.sk.

Key words: celiac disease, gluten, gluten-free diet, histopathology, malabsorption, small bowel.

Celiac disease (CD) is a disorder associated with a permanent intolerance of gluten, which is an ingredient of some cereals. In clinical practice there are a number of disease forms distinguished. The typical form is found in 40% of cases, and the remainder are considered atypical with varied clinical manifestation. Recent studies show that this disorder is still under-diagnosed all over the world (2, 10, 21). Symptoms of atypical disorder forms are often inconspicuous. For every patient with a typical CD, there are a number of patients with an atypical form, which remain unrecognised. The introductions of serological markers as a sensitive method of testing enable the identification of new cases of the disease. However, in spite of an increased screening intensity among children and adults, CD is still under-diagnosed. The prevalence of CD is about 1:100 to 1:550 (7, 8, 22, 29). The percentage of CD, which remains unrecognised is about 60%. This is CD with extraintestinal symptoms. Its prevalence is much higher than a previous study in Iceland showed (9). The diagnosis of CD is based on biopsy. A spectrum of mucosal abnormalities was defined in accordance to Marsh-Oberhuber (31, 32). There are several works, which show that patients with atypical CD are often diagnosed only after a long time (15, 30). This is a worldwide problem in clinical practise. With regard to this fact, many methods for detection of atypical forms of CD in the population of children and adult individuals have been proposed. The aim of this study was to compare and verify the degree of endomyssial antibody and histopathological picture of atypical CD. As the histological appearance of the mucosa is not specific, it’s necessary to distinguish the mucosal lesion of celiac sprue from the other lesions. Some methods, which are used in pathology practise, are discussed and described here. What follows is a report on diagnostic strategies of CD. Problems concerning methods of examination, such as detection of circulating autoantibodies, and histochemistry and electron-microscopy are also described.

Material and methods

Twenty-for gastroenterological patients with a newly-diagnosed atypical form of CD are presented in this study (18). This diagnosis was made after small bowel biopsies and their histopathological investigation. Adult populations with non-specific symptoms of gastrointestinal tract are frequently investigated. All patients were examined more than once in different departments. After a long time, all patients were examined at gastroenterology clinics, where blood samples were subjected to standard biochemical examinations and detection of antiendomysial antibodies (AEA). AEA IgA antibodies were tested by an indirect immunofluorescence (NIF) (EUROIMMUN-DYNEX). All serum samples were diluted by 1:20 in phosphate buffered saline (PBS). A second antibody, fluorescein-isothiocyanate-conjugated (FITZ)
an antibody against human IgA, at a dilution of 1:100 was used. The samples were assessed as positive for AEA according to their significant reactions to a typical staining pattern detected. After the determination of AEA positivity, biopsies from the duodenum were performed. The samples were fixed in formalin and embedded in paraffin wax for routine histopathology. They were cut, and the specimens were stained with haematoxylin-eosin (HE). They were then examined using Nikon Eclipse E600 microscope.

Results

Fluorescent microscopic results

A brilliant green full-area reaction, particularly in the endomysium of smooth muscle layers was observed. These layers looked almost like an artificial network. Positive reactions were also visible in the Wharton gelatine with reticular fibres.

Histopathological results

There were diffuse duodenal mucosal lesions, which are characterised by total atrophy of villi intestinalles and by crypt hyperplasia. There were visible chronic infiltrations of the lamina propria with intraepithelial lymphocytes (IEL) and damage to the surface epithelial cells. In summary, there were visible mucosal structural changes, with the absence of villi and with hyperplastic crypts. The microscopic images are accompanied by an increased number of IEL and plasma cells in the lamina propria. The results are consistent with a diagnosis of florid CD.

Discussion

Histological examination of a biopsy specimen of the small intestine remains the diagnostic “gold standard” for CD (5). This can be performed by biopsy and is an essential step in the diagnosis of celiac sprue. Many patients with minor symptoms or non-specific symptoms are not diagnosed. The severity and extent of the histological abnormalities in CD are wide. A study from the UK suggests that CD in adults may be more common than the estimated incidence of 1:3345 (26). Screening studies for CD suggest the prevalence of 1:250 (3). Our results show that CD is a frequent disease in adults (18). Divergences between typical and atypical CD were identified only in clinical practise through the manifestation of disorders. The symptoms of disease are variable and non-specific for typical CD until a relapse (17). Lurie et al (14) described a case study of CD diagnosed in patients diagnosed over the age of 60. With regard to this fact, there are significant problems in the diagnosis of CD. Therefore the question remains: What can we do so that CD does not remain unrecognised and under-diagnosed. The diagnosis of CD takes place in a routine pathology practise. There are three stages in the diagnostic process: screening programs such as autoantibody detection, followed by histochemistry and immunohistochemistry, and finally electronmicroscopy examinations.

Screening programs for detection of autoantibodies such as antigliadin antigens (AGA), antiretikulin antigens (ARA), anti-jejunal antigens (JAB), or AEA by NIF are employed in the pathology departments. Applications of screening methods in practise meet a great approval. There have been many publications which determined the utility of autoantibodies (12, 25). Our results also show that antibodies can help in the detection of atypical CD (31). However, on the other hand, autoantibody negativity is not a rare finding during the study of adults with CD. It has also been shown that sensitivity to serology varies depending on intestinal atrophy (23). In literature there also exists the proposition, that the presence of dome antibody is sufficient for the diagnosis of CD (6, 27). This is a very controversial statement. The main problem with accepting a positive serology as a final diagnosis lies in the variable tests sensitivity and specificity, but also on the activity of disease. We state that the histopathological examinations of samples from the small intestine are always necessary for the examination of the morphologic stage of the disease.

Another procedure, which is interesting for the pathologist, is histochemistry. Some data from literature state that histochemical investigation is no longer necessary for the diagnosis of CD, that it is a relic of the history (13). Good for investigation of systemic thies in the field remain. This is possible only in some specialized workplaces. Not so long ago the histochemical investigation of the small intestine was very important for distinguishing primary and secondary malabsorption syndrome. In literature, there are two contradictory opinions on histochemical investigation. The first maintains that a knowledgeable pathologist must be familiar also with HE, the height of the villi, the depth of the crypts and the stage of lamina propria infiltrations, with Marsh-Oberhuber criteria detected. The other maintains that histochemical investigation is necessary as a supportive investigation, and that the results can indicate the development of the disease (20). It is our experience that histochemical investigation can assist in the diagnosis of CD (17).

In literature there exist some recommendations for IEL detected in the diagnosis of CD. Some CD antibodies are recommended (1). Complications accompany its positive diagnosis if malignant lymphoma is observed (28). The activity of CD is coupled with diagnostic IEL (4, 11). This represents a further challenge to find a test which will detect sensitised mucosal lymphocytes (23). In accordance with this, antibodies against IEL, as demonstrated in some controversial biopsies, are recommended. Damage to the intestinal mucosa also occurs to a lesser degree, and the structure of the villi intestinales often remains the same or with minimal pathological changes.

The find point in our discussion is electron-microscopy examinations of samples from the small bowel. There exist cases in literature where CD can be associated with minimal mucosal changes not detectable by conventional light microscopy (16, 24). In this case, electron-microscopy reveals alterations of the enterocyte brush border with a significant reduction of the height of the microvilli. We believe that the use of this investigation is not necessary as a diagnostic method of CD. There is the possibility that some controversial biopsies or biopsies from patients appear normal, but where there are repeated non-specific gas-
trointestinal symptoms, these can be sent to specialized facilities for electron-microscopic examinations.

Celiac disease is more common than one might think. The more atypical CD cases remain unrecognized. The symptoms are not specific, or minor degrees of mucosal abnormalities are ignored. With regard to this fact, active search in risk populations is necessary. There are populations with non-specific gastrointestinal symptoms, with repeated problems of unknown aetiology and in families where CD has already been diagnosed.

References

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