

Clinical updates on diagnosing glutensensitive enteropathy

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In the last twenty years serology for the diagnosis of coeliac disease has improved substantially. As the result of our serological studies in 1998 we proposed a gentle, low-risk, and cost effective algorithm for diagnosing various forms of gluten sensitive enteropathy, using a combination of different antibody determinations, namely IgA Endomysium antibodies (EMA), Tissue-transglutaminase antibodies (IgA anti tTG, IgG anti tTG), IgA-and IgG antigliadin-antibodies. Performing routinely serologic testing contributes to a decreased rate of endoscopic interventions and improves the quality of the patient's life.

Key words: Coeliac disease, Antibodies, Intestinal biopsy, Diagnosis.

Coeliac disease is an immune-mediated enteropathy caused by intolerance to gluten in genetically susceptible individuals. In intolerant patients, gluten ingestion induces a variety of symptoms. Classical symptoms include diarrhoea, malabsorption and weight loss while clinically occult or atypical presentations of the disease range from growth failure in children, irritable bowel syndrome, anaemia, chronic fatigue, osteoporosis, dental defects and infertility to severe psychological alterations and/or seizures.

The diagnosis of coeliac disease has traditionally depended on intestinal biopsies; nowadays the diagnosis has been extended to include an array of serological markers (1). In 2005 the European and North American Societies for Paediatric Gastroenterology, Hepatology and Nutrition released a consensus statement that children with elevated tissue transglutaminase antibodies in their plasma should be referred to a paediatric gastroenterologist for an intestinal biopsy (2). Similar recommendations for adults and children were put forward by the US National

Institute of Health (3). The conclusion resulting from above recommendations is that coeliac disease is diagnosed when the duodenal or jejunal mucosa displays a villous atrophy, crypt hyperplasia and an increase in intraepithelial lymphocytes (Marsh 3a,b,c) (1, 2, 3).

Is the importance of small bowel biopsy overrated?

In our opinion the above recommendations overestimate the importance of small bowel biopsies:

A loss of villous height is considered to be pathognomonic for gluten sensitive enteropathy by many clinicians, thus, it is important to emphasise the *nonspecific* nature of this finding and that individual differences in villous architecture across the population can be dramatic¹

The biopsy should not be considered as the „gold standard“ because it is not pathognomonic. Different diseases not related to gluten sensitive enteropathy, such as cow's milk intolerance, gastroenteritis, giardiasis, eosinophilic gastroenteritis, bowel ischemia, severe malnutrition, diffuse lymphoma of the small intestine, autoimmune enteropathy, hypogamaglobulinemia and peptic duodenitis can induce flat mucosa mimicking coeliac disease. Importantly, patients with gluten sensitive enteropathy and normal small bowel mucosal architecture have also been described shedding doubt on the dogma of the necessity of villous atrophy and crypt hyperplasia for diagnosis of coeliac disease (4, 5).

Technical insufficiency is another disadvantage of small bowel biopsy: by grasp biopsy forceps or endoscopic procedure, the biopsy specimen was considered satisfactory in only 90% of cases (6). Finally, although the *procedure* is considered to be safe, 1.5% out of 1007 biopsies haemorrhaged with 0.3% requiring transfusion and 0.3% had a laparotomy following small bowel perforation (7).

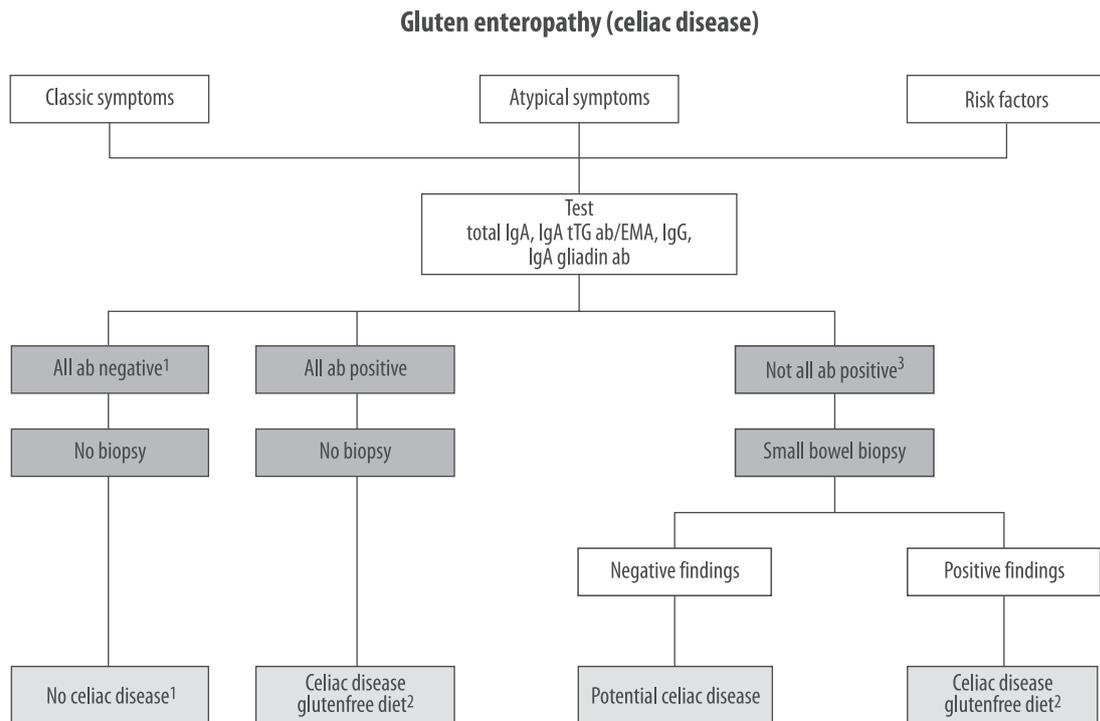
Small children have to undergo general anaesthesia with a significantly higher risk for complications if compared to no risk from obtaining blood for serological diagnosis.

The role of antibodies today in diagnosing coeliac disease

As the result of our studies we proposed in 1998 a gentle, low-risk, and cost effective algorithm for diagnosing various forms of gluten sensitive enteropathy (8). The following serological tests should be performed if coeliac disease is suspected: IgA tissue transglutaminase - (IgA tTG) and IgA endomysium antibody (EMA) determination as well as IgA and IgG gliadin antibody assessment (Figure 1). In the case of IgA deficiency IgG tTG antibody determination should be performed.

In our laboratory, the sensitivity of the IgA tTG and IgA EMA antibody test is 96%. Specificity was found for IgA EMA 97% and IgA tTG of 96% (9, 10, 11) when using human tissue transglutaminase as the antigen. In other laboratories similar values are obtained depending on the quality of the test used (12). Nevertheless, the discordance of 4% between positive IgA tTG and positive IgA EMA found in our patients is high enough to advocate both tests being used simultaneously to achieve the best possible predictive value for the active disease.

More importantly Figure 1 shows that the additional determination of IgG and especially the IgA gliadin antibody increases the diagnostic significance of antibody assessment. Following a former study (9) together with recent data, the positive predictive value of positive IgA tTG/EMA and IgA and IgG gliadin ab was 99.8% (Table 1). In 641 out of 642 patients pathological (Marsh 3a,b,c) mucosa was found. This constellation of antibodies has an extremely high positive predictive value and abrogates the necessity



1 Total IgA must be normal for age. If low total IgA, test IgG tTG ab, when positive → biopsy

2 Clinical remission after a period of gliadinfree diet is additional evidence for diagnosis of celiac disease

3 If only IgG gliadin ab are present: low evidence for celiac disease, observe the patient, repeat the tests before performing a biopsy

Figure 1 Algorithm for diagnosing coeliac disease

of small bowel biopsy. However, this is not generally accepted. ESPGHAN, NSPGHAN and NIH recommend performing a biopsy in every patient with positive IgA tTG (2, 3). Since the predicting value of combined determinations is 99.8%, these recommendations induce 58% of unnecessary biopsy procedures! Furthermore, we would miss at least 6.3% of patients with coeliac disease if we depended exclusively upon one positive tTG antibody result.

In our opinion a small bowel biopsy should be performed after discordant or equivocal serological results (Figure 1). AGA and EMA/tTG may not be present at the same time in the course of the disease (9). Patients with coeliac disease and lesser degrees of villous atrophy may have equivocal or negative serological results more of-

ten. The negative predictive value of all antibodies in combination is as high as 98% (9, 10, 11). Despite the higher predictive value of positive antibodies, the majority of gastroenterologists today insist on small bowel biopsy, while the same clinicians accept that a negative antibody result does not require small bowel biopsy. This attitude is even more astonishing because patients with undiagnosed coeliac disease left on a gluten rich diet have a higher risk of malignancy and other comorbidities, while a gluten free diet in a non-coeliac patients is certainly inconvenient but harmless for the patient. Furthermore, the consensus papers do not require gliadin antibodies to be negative. If a negative tTG result is the only exclusion parameter, as recommended, than according to our population, 6% (63/1100) coeliac

patients would have been missed (Table 1). In our cohort the chance of coeliac disease (Marsh 3a,b,c) in a seronegative patient is as low as 0.08% (9/1100 coeliac patients). The group of patients with partial villous atrophy and sero-negative results who have coeliac disease is harder to identify (13, 14) and it represents a real challenge for gastroenterologists. It is our policy to observe all our sero-negative patients in regular periods in order not to miss one of the rare cases of seronegative coeliac disease which occurs mainly in adults.

Monitoring compliance to a gluten free diet

After the introduction of a gluten free diet in a patient with newly diagnosed gluten sensitive enteropathy, the decrease in plasma antibody concentration is an excellent parameter for disease follow up (10, 11). It is important to realize that it takes up to 12 months or even more on a gluten free diet for antibodies to disappear (10, 11). IgA gliadin antibodies decrease quickly and in 6-12 weeks they are no longer detectable. IgA tTG or EMA needs 10 – 12 months and IgG gliadin antibody even longer to disappear completely.

It is a reality that although aware of coeliac disease and having no problems in obtaining a gluten free diet and with adequate support from dieticians, 30% of our patients are noncompliant to strict gluten free diet! Regular monitoring of antibodies is an important tool and an excellent indicator of compliance, helping patients to keep on the gluten free diet.

In the case of diet failure a discordant rise in antibodies takes place. AGA is the first to be detected in plasma, followed by IgA tTG/EMA. If compliance failure continues over a long time, AGA disappears in most patients, while IgA tTG/EMA is detectable over many years on a continuous diet containing gluten.

Conclusion

In conclusion, it is our experience over the past 20 years that the approach now summarized in the algorithm (Figure 1) is safe, gentle and cost effective for diagnosing and monitoring coeliac disease. In view of the diverse presentation of coeliac disease, knowledge of the limitations of both serologic testing and small bowel biopsy interpretation is important. We entirely agree that it is important to avoid the self-fulfilling prophecy, taking biopsies only from IgA EMA positive individuals (15). Those patients with all positive antibodies do not need a biopsy. Performing serologic testing routinely should not result in increased biopsy interventions. In contrast if used properly it should contribute to a decreased rate of endoscopic interventions and improve the quality of the patient's life. It is time to acknowledge adequately the importance of antibody assays.

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