

New European Recommendations for the Diagnosis of Celiac Disease in Children: Did the Experts Make it Simple?

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1. Introduction

Celiac disease (CD) is an immune-mediated systemic disease caused by the consumption of gluten. Its prevalence lies between 1 to 2 % in the general population, and can reach 20% in groups who are at risk. It was classically defined as a chronic enteropathy with secondary villous atrophy caused by inappropriate immunological response of the intestinal mucosa to prolamines of wheat (gliadine), barley and rye. Beside the typical method of diagnosis, which relies on the histological analysis of duodenal biopsy, the development of the serological markers uncovered the elevated incidence of truncated, monosymptomatic, silent and even latent forms of CD, and made CD and the non-digestive manifestations of gluten intolerance frequently encountered pathologies. Actually, CD must be comprehended as a systemic immuno-/autoimmune-pathology, stimulated by gliadine and related prolamines arising in genetically susceptible subjects (HLA group [human leukocyte antigen] DQ2 and/or DQ8), and characterized by variable combinations of diverse clinical manifestations, specific antibodies, and an enteropathy [1]. Till this day, strict gluten-free diet is the only efficient treatment known. Perfectly followed, it allows the symptoms to disappear and prevents the appearance of complications as osteoporosis, certain autoimmune diseases or cancer. On the other hand it is difficult to follow this diet daily, as it is restricting, expensive and considered as a social burden [2]. For all these reasons, the criteria for diagnosis of CD must be precise and efficient, whether for the diagnosis of an individual case, screening of patients at high risk or screening of cohorts who are not at risk. The utilized tests have to be reliable, reproducible, sensitive, and specific. For many years, the clinicians and

the researchers have worked to develop non-invasive tests, that are simple to implement, inexpensive and available even in less fortunate countries, to reduce the heavy weight of the actual diagnostic procedure which includes an upper gastrointestinal endoscopy with biopsies from the bulb and from the duodenum.

2. History of Diagnostic Criteria

In 1990, the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) revised the diagnostic criteria for children highlighting that the diagnosis can be made after a suspicious or a suggestive clinical history, if at the same time the subject had positive auto-antibodies with intestinal villous atrophy associated with an augmentation of intra-epithelial lymphocytes and a clear remission of symptoms after implementing a gluten-free diet [3]. Worldwide, this diagnostic strategy was universally known and applied [4,5]. It was validated by scientific societies who deal with CD in adults. Till this day intestinal biopsy stays, for the adult patients, an indispensable examination for confirmation of CD diagnosis and for starting a gluten free diet, even in certain cases where the realization of endoscopy and biopsy was questionable [6,7].

3. Serological Diagnosis

The serological markers constitute the first step in diagnosis. The dosage of immunoglobulins (Ig) A, antitransglutaminase (IgA-TG), or anti-endomysium (IgA-AE) must be prescribed. At the same time, an IgA deficiency must be eliminated by measuring the level of total IgA. The anti-gliadin antibodies must not be

prescribed anymore because of their weak sensitivity and specificity. The interpretation of the results of the method of immunofluorescence, used for detection of the anti-endomysium antibodies, is more difficult than the method ELISA, which is used for the detection of anti-transglutaminase. And yet the latter was more improved by the use of recombinant human antigens.

Currently the scientific societies and expert groups recommend the dosage of IgA-TG as a first line test. According to the literature, the use of human anti-transglutaminase permits the achievement of a sensibility of 85 to 98% and a specificity of 94 to 98% [8]. However, it is important to emphasize the fact that the search for IgA-TG alone, in a known population has a limited positive predictive value; between 75 and 80% for screening individuals with proven villous atrophy by intestinal biopsy.

To overcome this insufficiency, other strategies and protocols have been suggested: the coupling of IgA-TG and IgG-TG, the repetition of the tests two or three times, and the coupling of IgA-TG and IgA-AE. All these associations do not increase significantly the efficacy of these protocols. Nevertheless, the systematic study of serological markers by cohorts permitted the demonstration of the frequency of paucisymptomatic or silent forms, as well as the displacement of the age at diagnosis from 30 months, to become between 12 and 15 months of age [9].

4. Research of Susceptibility Genes: an Important Step forward

Recently, the advancing techniques of molecular biology permitted the identification of susceptibility genes for gluten intolerance. A very strong association exists with HLA- DQ2 and DQ8, as it is expressed in more than 95% of affected subjects. These genes are present in 40% of the general population. The major interest in the association between the HLA genotyping and measuring the anti-transglutaminase antibodies is that its negative predictive value is 100%, when the subject doesn't have any antibodies and doesn't have the susceptibility genes [10,11,12]. Although, this association is not very expensive and is available almost universally in the developed countries, still it has the problem of using genetics for screening, which has its heavy effect on formalities: information, authorizations, informed consent, and signing of protocol papers by the families. On the other hand, these tests cannot be realized for diagnosis and screening in less-developed countries.

5. Tests less and less Invasive

Rapid tests for detection of IgA-TG in saliva or in a spot of blood have been developed and commercialized, but their routine utilization either in consultations in clinics by physicians or in protocols of health screening of cohorts must be validated by studies done on bigger scales. The rates of false positives and false negatives are elevated [13]. Up to this moment, the criteria that characterize a good tool for screening (liability,

dispensability in all countries, non-invasive, and inexpensive) are not fulfilled in these tests.

6. New Recommendations for Riagnosis of CD

New recommendations for the procedure of diagnosis of CD have been long waited for several years [11,12]. The levels of sensitivity and specificity obtained by the anti-transglutaminase antibodies of human origin drive a lot of our colleagues to start a gluten free diet over a simple positivity of these antibodies, while the scientific societies continue to recommend a confirmation by a systematic intestinal biopsy. This situation poses a lot of problems for the specialists in following up their celiac patients due to lack of diagnostic and management protocols. In an article published in 2012, the working group on the diagnostic criteria of celiac disease of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) defined new protocols for diagnosis, which can be simplified in the form of two algorithms [13].

The aim of the two algorithms is to simplify the procedure of diagnosis and decrease the use of intestinal biopsy to confirm it. They are based on the use of IgA-TG and IgA-AE and on the search for the susceptibility genes of HLA class II, mainly DQ2 and DQ8 serotypes.

Primarily, it proposes the measurement of total levels of IgA and the search of IgA-TG. If IgA-TG was negative, and the IgA levels were normal, it can be decided with certitude that there is no CD. It suggests that another cause for the digestive symptoms should be sought. On the contrary, if IgA-TG is positive, two possibilities are advised on the basis of the levels of IgA-TG obtained: if the level is superior to 10 times of the normal, the child must be addressed to a pediatric gastroenterologist, who will search for anti-endomysium antibodies and perform a HLA-DQ2 and DQ8 typing. If the two biological tests are also positive, the diagnosis of CD can be confirmed without doing a biopsy and so a gluten-free diet is indicated and started.

When IgA-TG levels are lower than 10 times the normal, keeping in mind that HLA DQ2 and DQ8 groups are also found in 40% of the general population who doesn't have gluten intolerance, it is strongly recommended to do a duodenal biopsy with intra-epithelial lymphocyte study, as these IgA-TG levels might suggest a false positive or a gluten intolerance from the beginning. In the case of congenital IgA deficiency, the diagnosis cannot be eliminated as the cause of absence of specific antibodies; in this case IgG-TG and IgG-AE must be measured.

7. New Recommendations for Screening of CD

It is suggested that systematic screening should be performed only for CD patients' relatives. Screening of masses in all the population is very expensive and not practical [14]. The working group suggests as a first line, a search for susceptibility genes: if they were negative, this

excludes totally the presence of CD and its development in the future. However if the genotypes HLA DQ2 or DQ8 are present, the levels of total IgA and IgA-TG must be measured. If the antibodies are higher than three times the normal, an intestinal biopsy is indicated to confirm the diagnosis. If they are less than three times the normal levels of IgA-AE must be measured. If they are positive, intestinal biopsy is indicated to confirm or eliminate the diagnosis of CD; if the IgA-AE are negative, there is no indication for performing a gluten-free diet, but a close follow-up by a pediatric gastroenterologist is desirable.

In practice, the opinion of a pediatric gastroenterology is always necessary before all executions of gluten-free diet. In all the doubtful cases, digestive endoscopy with intestinal biopsy stays the ultimate test to confirm or eliminate the diagnosis. The efficacy of this protocol was validated in retrospective studies in at risk subjects [15,16], and a prospective validation study is in process.

These recommendations were the end results of multiple works that evaluated prospectively, in multicentric studies, scores to diagnose suspected CD cases on the basis of combining the most frequent symptoms of gluten enteropathy, the results of auto-antibodies and the molecular biology which searches HLA haplotypes [10,11,12].

8. Conclusion

The new recommendations for the diagnosis and screening of CD in children have been published since more than 2 years by the ESPGHAN. The objectives of these recommendations, and of the group of experts were many: to simplify the procedure of diagnosis, to preferentially use <<non-invasive>> biological techniques, to decrease the number of endoscopies done under general anesthesia, to clarify the role of intestinal biopsy, and to define the role of general pediatricians and pediatricians specialized in gastroenterology. This new diagnostic procedure is doable and efficient only when the pediatric gastroenterologist does it. On the other hand, it is certain that the reading of a 24-page document is not that easy and that the two proposed algorithms are complex and difficult to apply in practice by a general pediatrician. Finally, the role of the latter consists, essentially, in front of evocative signs, in prescribing the measurement of total plasma IgA and IgA-TG (assessment completed by IgG-TG in case of total IgA deficiency), and to ask for a specialist opinion in case that these tests show the possibility of CD being present. The new recommendation stipulates very clearly that a gluten-free diet must only be prescribed by a pediatric gastroenterologist, when the levels of antibodies are more than 10 times the normal, and they are associated with positive IgA-AE and the presence of HLA-DQ2 and/or DQ8. Yet we notice regularly that gluten-free diet is often prescribed after a

positive result of a single auto-antibody test (including sometimes anti-gliadine antibodies). Thus, some children are left with an uncertain diagnosis and an expensive and restricting diet, while others dwell under the necessity to re-introduce normal diet and eventually a realization of duodenal biopsy which inevitably in the future will lead to an increase in the number of endoscopies and biopsies performed.

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