

Serological Markers and/or Intestinal Biopsies in the Case-finding of Celiac Disease

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Abstract The new 2012 ESPGHAN guidelines for the pediatric diagnosis of celiac disease (CD) unraveled and stimulated an old/new discussion on the most efficient case-finding in pediatric CD. The fine balance between reliable serological markers and the gold diagnostic standard of small bowel histology is somewhat better understood. Due to a low diagnostic rate, changes in phenotype, increased incidence, epidemiological shifts, importance of early implementation of gluten free diet to prevent complications, the case-finding of CD should be improved. Our adult gastrointestinal colleagues did not adopt ESPGHAN diagnostic criteria and within the pediatric gastroenterology community, controversies exist. The present editorial on pediatric CD complements an adult CD one. It expands on the drawbacks, limitations and criticisms of the guidelines and calls for prudence, further research and follow-up studies. Until recent observations are implemented in the future guidelines, small bowel histology should remain the gold standard for case-finding in CD.

Keywords: celiac disease, case-finding, diagnosis, serology, intestinal biopsy, children

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1. Introduction

Why should case-finding of CD be improved?

It is generally accepted that CD affects 1% of western populations, whereby northern countries like Sweden, Finland and Ireland the incidence is higher. One exception is the Sahara desert region in North Africa with an incidence of 5.6%. Even in the Far East, where rice is the main staple food, increased incidence of CD is being reported. Currently, we are witnessing a diffused ongoing epidemic of CD of great scale. Epidemiological data provides strong evidence of a steady rise in celiac disease throughout westernized societies over the last six decades [1]. The reasons for this worldwide surge in CD incidence are debatable.

Table 1. summarizes the suggested explanation for CD incidence expansion

Potential reasons	references
Increased wheat intake:	
-Increased production and consumption of wheat	[2]
-Higher gluten content in modern wheat	[3]
Increased influence of environmental inducers of CD:	
-Infections	[4]
-Stress	[5]
-Gastrointestinal microbiome alterations=dysbiosis	[6]
Increased intestinal permeability by food industrial additives	[2,7]
Increased public and professional awareness	[8,9]
Improved tools for diagnosis	[10]
Genetic advantage and survival of CD patients	[3,11]

In addition to the increased incidence, the ratio between diagnosed/undiagnosed CD is substantial, ranging between 1-2/8-9, respectively. Key reasons for this are the epidemiological and phenotypical shifts taking place in the disease. It has been shown that the classic intestinal clinical picture of malnutrition, chronic diarrhea and nutritional deficiencies are disappearing and extraintestinal presentations are emerging. Skin, endocrine, skeletal, hepatic, hematological, thrombophilic, gynecological, fertility-related, dental, obesity and behavioral abnormalities are often described. Today, we are witnessing an epidemiological shift in the disease phenotype toward a more advanced age, and increased prevalence of latent, hyposymptomatic or asymptomatic behavior [12]. All these changes make the diagnosis of the disease more difficult and the reliance on symptomatology more remote [13]. These are some of the reasons why serological screening and diagnosis of CD have achieved prime importance. Finally, upon diagnosis, CD is a treatable disease and implementation of a GFD can prevent many complications and extraintestinal manifestations of the disease including: hematological and gastrointestinal malignancies, osteoporosis/penia, decreased height, malnutrition and nutritional deficiencies, fertility impairment, stillbirth, dysmaturity, psychosocial retardation, impairment of quality of life, increased mortality and additional autoimmune associated conditions. Thus, early diagnosis and subsequent adherence to a gluten-free diet is highly recommended.

These are the main reasons why we need to improve our case-finding strategies in CD.

2. Case-finding Strategies

There are currently three main strategies for case-finding: serology, HLA-DQ2/8 typing or intestinal biopsy histology - or any combination of these three. An additional debate is whether to screen normal/high risk asymptomatic/only symptomatic populations or to perform intestinal biopsy on each upper endoscopy.

According to the recent criteria for the diagnosis of childhood celiac disease, published by ESPGHAN in 2012, there is a definite distinction between symptomatic and asymptomatic children [14]. Only symptomatic children with positive HLA-DQ2/8, that mount anti-tTg IgA antibody levels 10 times above the upper normal limit and have positive EMA IgA, are exempt from small bowel biopsy.

These new diagnostic criteria have not been adopted by the different adult gastroenterological associations worldwide [15].

Since implementation of the new ESPGHAN diagnostic flow-charts, substantial experience has been gained and both complimentary [16] and critical [17] publications have appeared. Emerging data are continuously being generated and no doubt will impact future diagnosis algorithms [18].

3. Bias in ESPGHAN CD Diagnosis Guidelines

The main criticisms of the 2012 ESPGHAN guidelines cover the following aspects:

1. A more precise definition of “symptomatic” children is needed due to the multifaceted phenotype and the continuous clinical pattern changes [19].

2. Lack of serological markers standardization and relative definitions of the upper limit of normal cut-off levels.

3. Lack of more extended, multicenter data on the optimal multiplication times of the upper limit of normal cut-off, to be used [20,21].

4. The subjectivity and inter-observer variability of the anti-endomysial antibodies.

5. Lack of availability and insurance coverage of HLA-DQ determination, at least in the developing countries.

6. Lack of standardization of HLA-DQ determination methodology and reporting of its dosage zygosity. An improvement, was recently suggested by the Australasian group [22]

7. By omitting intestinal biopsies, considered as the gold diagnostic standard, CD research might be jeopardized.

8. Lack of adherence to and/or understanding of the guidelines, even by subspecialists [23].

9. Lack of comparison of CD additional specific autoantibodies to challenge IgA-tTg primership in the guidelines, for example with the neo-epitope tTg [24-29]. Recent observations show that the tTg neo-epitope outperformst Tg [30,31,32] and also a combination test including IgA and IgG isoforms [1]. Adding an additional

autoantibody can detect Marsh 3 intestinal damage among subjects with moderate anti-tTg levels [33].

10. Not taking into account additional HLA or the multiple non-HLA genes associated with CD. It is foreseeable that a combination of these may improve CD diagnosis, as has recently been suggested [34].

11. None of the CD associated dysbiosis or individual's microbiota, is taken into account. In fact, CD dysbiosis correlates to clinical manifestation, even with a strict GFD, and is determined by the HLA-DQ2 status [35,36,37]

12. None of the evolving epigenetic, transcriptomics, proteomics, and metabolomics of the microbiome or the intestinal compartments' data have been incorporated.

4. Conclusions

In summary, the 2012 ESPGHAN guidelines took the professional communities a step forward in CD diagnostic guidelines, but many aspects of these guidelines are incomplete and deserve further evaluation and discussion. Based on the above mentioned arguments [38], and with full respect to the honorable members of the ESPGHAN's CD interest group, it is our personal opinion, that omitting intestinal biopsy is premature. We share Freeman HJ. opinion that a case-finding of CD should, for the time being, include the most cost effective serology, substantiated by adequate small intestinal mucosal biopsies. The subject of serological mass screening of general populations or asymptomatic family members needs further large randomized trials, as suggested recently [39,40].

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