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Diagnosis Guidelines for Screening Celiac Disease – A Systematic Review

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Abstract Celiac disease (CD) is an autoimmune disorder that is expressed by chronic food sensitivity to gluten. Among the autoimmune diseases, CD is the one that has more expression, having the numbers of new cases increased steadily during the last years. In addition to the most common symptoms, such as low weight, diarrhea and abdominal pain, atypical cases, such as overweight, arise which imply the development of new approaches and diagnostic methodologies. The most obvious diagnosis involves endoscopy, an invasive and costly method that causes discomfort to the patient and overload of the health systems. The protocol methodology for CD diagnosis from WGO, NASPGHAN, ESPGHAN and BSPGHAN, the worldwide most recognized specialist 'organizations, was analyzed in order to assess if social implications were considered on their guidelines. After a detailed review of the literature, a global chart was completed in order to summarize the most referenced protocols for the screening and CD diagnosis.

Keywords: *celiac disease; diagnosis; screening; guidelines; duodenal biopsy*

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1. Introduction

Celiac disease (CD) is not an allergy or food intolerance, but a chronic autoimmune enteropathy in genetically susceptible individuals. The environmental trigger for the immunogenic response is the presence of gluten proteins consumed in common grain products. Gluten are proline- and glutamine-rich proteins in sequence combinations that render them resistant to complete proteolysis by gastric enzymes. The partial digestion produces small peptides with affinity for human leukocyte antigen (HLA) DQ2 and/or DQ8 [1,2]. The immunogenic mechanism is not totally known, however continuous presentation by major histocompatibility complex class II molecules, of these peptides to autoreactive T lymphocytes, leads to a breakdown in immunological tolerance [3].

Despite DQ2 and/or DQ8 peptides, but not other HLA molecules, being the predominant restriction elements for reactive T cells present in CD patients, the HLA-DQ2 and/or -DQ8 genotype is only relevant when combined with positive antibody results. The most commonly antibodies detected during the screening of symptomatic and non-symptomatic patients at risk for CD, are anti-tissue-transglutaminase IgA (anti tTGA), anti-endomysium IgA (anti-EMA), and more recently the deamidated gliadin peptide (DGP) [4].

Although the humoral analysis is an uncomplicated and non-aggressive analytic method, it has the disadvantage of antibodies possibly being common to other gut pathologies. For example, anti-endomysium IgA is develop when the intestinal lining is damaged, so is also common in dermatitis herpetiformis. [5]. For this reason many physicians are of the opinion that only video capsule endoscopy or endoscopy with biopsy provide high-quality visual evidence of the scalloping, fissuring and villous atrophy associated with celiac disease.

Despite the unquestionable medical evidence, this approach requires considerable investment of time and resources, overloading the health systems. For this reason the need to perform a biopsy has been questioned and approaches emerge claiming that certain values obtained in humoral analyzes may be conclusive for the final diagnosis of CD.

Recent alarming global statistic indicate that 1 in 100 people is affected by CD [6], which is data of utmost importance for a rapid and effective diagnosis, especially for countries with low economic resources. Recognizing this need for a rapid and effective diagnosis, the guidelines established by the main reference entities for CD diagnosis were systematized in order to facilitate their use. The entities considered were the World Gastroenterology Organisation (WGO), the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), the European Society for Pediatric

Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN). Similarities and differences were highlighted in order to obtain a review global review chart of their guidelines to assist the choice of the diagnostic method decision.

2. Methods

A thorough literature search was conducted using MEDLINE/PubMed (March 2018). From the 326 published citations found, 250 were excluded for different reasons being 76 studies eligible for inclusion while appearing to be relevant to the study question (Figure 1). Studies were identified combined together using the "OR" set operator using the following terms: "celiac disease, diagnosis, guidelines". The first cut-off used was current studies selecting references only from the last 5 years. Other pathologies associated; antibody specificity or indicators for the disease; gluten free diet and the role of health professionals in follow-up treatment; clinical procedures; epidemiological studies; general studies and case studies were also excluded for presenting specific knowledge and not focusing the study question. There were no general language restrictions except for two papers that were only found in the original languages (Russian and Norwegian). All potentially relevant papers (76) were obtained and evaluated in detail by the two authors.

3. Results

Being World Gastroenterology Organisation (WGO) an association of gastroenterology representing over 50,000 individual members (www.worldgastroenterology.org), the information produced by this entity spread easily worldwide. For CD diagnosis WGO guidelines are grouped according to financial resources available: Gold, Medium and Low resources (Table 1). In all groups the CD diagnosis follow the same orientations, with medical history, physical examination and antibodies assessment being common, except for the intestinal biopsy that is not present in case of low resources. For Gold standard the biopsy is mandatory, whereas for Medium resources it depends of antibodies results [7].

For NASPGHAN (The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition; www.naspghan.org) CD is diagnosed definitively by biopsy [8] despite all the other results from medical history, physical examination and antibodies assessment (Table 2).

Addressing European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN; www.espghan.org) childhood or adulthood have different protocols for CD diagnosis. Childhood guidelines have an option to diagnose CD without duodenal biopsies by applying a strict protocol with further laboratory tests [9], as well as for adults in low-resources countries [7,10]. Otherwise for adults, guidelines emphasise the combined use of biopsy and serological analyses [7,10,11,12] (Table 3).

Regarding transition from childhood to adulthood, the Prague consensus report recommended that small intestinal biopsy is not required to reconfirm a childhood diagnosis of CD when the diagnosis has been made according to ESPGHAN or NASPGHAN criteria [13].

British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN; www.bspghan.org.uk) follow the new ESPGHAN in overall diagnostic evaluation [14]. However, BSPGHAN maintain biopsy as a mandatory procedure for all positive adult CD diagnosis. For asymptomatic children but with associated conditions, as first degree relative with CD and some others autoimmune diseases, only the absence of HLA-DQ2/DQ8 excluded the biopsy, in all other situations biopsy is performed (Table 4).

Considering the specificity of these protocols from the most recognized worldwide specialist organizations, the literature review at the present study showed that 72% of the 76 papers analysed (Figure 1) refer at least one of the guidelines mentioned. The other 28% use guidelines follow specific health national guidelines (Figure 2).

Despite the most followed guidelines are the ESPGHAN (33%), several studies referred more than one correct pathway (combined guidelines 26%) and adjusting medical procedures to the patient´s condition evaluation.

This most flexible diagnostic option appears in more analysed papers than the sum of the other studies that follow just BSPGHAN (5%), NASPGHAN (5%) or WGO (3%).

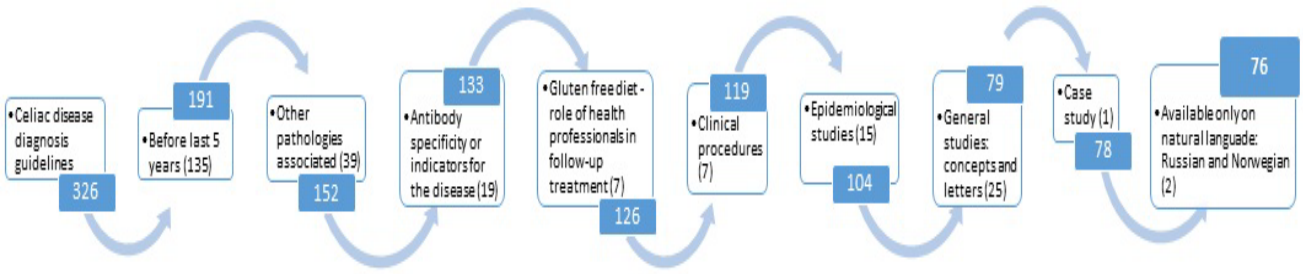

Figure 1. Flow chart of criteria used to select the final 76 studies considered for this study

Table 1. Diagnosing Celiac Disease Options (WGO)

Gold Standard	Medium Resources	Low Resources
• Medical history and physical examination • Celiac disease-specific antibodies: assessment + intestinal biopsy	• Medical history and physical examination • Antibody assessment as a single diagnostic tool • Intestinal biopsies as a single tool	• Medical history and physical examination • Antibody assessment as a single diagnostic tool

Table 2. Diagnosing Celiac Disease Options (NASPGHAN)

Positive Diagnosis
• Confirmation of the diagnosis of CD always require an intestinal biopsy

Table 3. Diagnosing Celiac Disease Options (ESPGHAN)

Children	Adults
• Diagnosis (symptomatic and asymptomatic) will be considered positive if anti-TG2 titres are high (>10 times the upper limit of normal) positive EMA and good response to a GFD; without duodenal biopsies.	• All guidelines emphasise the combined use of biopsy and serological analyses for diagnosis. However, in low-resources countries, a positive TG2 with symptom improvement on a GFD may be considered sufficient for diagnosis.

Table 4. Diagnosing Celiac Disease Options (BSPGHAN)

Children	Adults
• Symptomatic: regardless of the required serological screening never exclude biopsy procedure • Asymptomatic: the absence of HLA-DQ2/DQ8 exclude biopsy needs and positive diagnosis	• Biopsy remains essential for the diagnosis of adult CD and cannot be replaced by serological screening

Figure 2. Results from analyses of guidelines reported on studies identified for the systematic review

4. Discussion/Conclusion

Celiac disease is widespread in modern society and its early diagnosis is essential to improve patient´s quality of life, as well as avoid worsening of symptoms.

Diagnostic methods based on the response of autoimmune system, namely the detection of specific antibodies, have several advantages because they just require few drops of blood, which can also be analysed elsewhere. However, these tests are not considered conclusive for most diagnostic protocols, being always one of the steps from the all process. Only WGO considers these tests, along with medical history and physical examination, to be the final test for a positive CD diagnosis in low economical resources conditions.

For all other protocols, endoscopy and biopsy, invasive and costly method that contribute to the discomfort of the patient and overload of the health systems, appear to be the most reliable method and mandatory. BSPGHAN guidelines are the ones that use it to confirm CD diagnosis. Current ESPGHAN guidelines, which are the most referred guidelines in the papers revised for this research, suggest that a biopsy avoidance strategy may be employed by undertaking further supportive tests (HLA-DQ2 and DQ8 determination may rule out of CD.

To adapted screening strategies, health authorities must pay serious attention to this situation, not only to obtain a less expensive invasive and effective CD diagnosis, but also to adopt an accurate diagnosis as the biopsy. An investment in research, to collect global data for an overview analysis could contribute for better decision-making and widespread knowledge and also trust in a CD diagnosis based on more reliable molecular marker tests.

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References

[1] Sollid, L. M. & Lie B. A. Celiac Disease Genetics: Current Concepts and Practical Applications. *Clinical Gastroenterology and Hepatology*. 2005; 3: 843-851.

[2] Soares, P., P. Sande Lemos, A. M. Pires & A. C. C. Sousa. Celiac Disease and Gluten-free Diet in Portuguese Children – An Anthropometric Marker Contribution Assessment. *International Journal of Celiac Disease*. 2017; 5(2): 62-68.

[3] Tollefsen, S. H. Arentz-Hansen, B. Fleckenstein, Ø. Molberg, M. Ráki, W. W. Kwok, G. Jung, K. E. A. Lundin & L. M. Sollid. HLA-DQ2 and -DQ8 signatures of gluten T cell epitopes in celiac disease. *The Journal of Clinical Investigation*. 2006; 116(8): 2226-2236.

[4] Nandiwada, S. L. & A. E. Tebo. Testing for Antireticulin Antibodies in Patients with Celiac Disease Is Obsolete: a Review of Recommendations for Serologic Screening and the Literature. *Clinical and Vaccine Immunology*. 2013; 20(4): 447-451.

[5] Kaukinen, K., P. Collin & M. Mäki. Latent coeliac disease or coeliac disease beyond villous atrophy? *Gut*. 2016; 56: 1339-1340.

[6] Catassi, C.; G. Simona & A. Fasano. The New Epidemiology of Celiac Disease. *Journal of Pediatric Gastroenterology and Nutrition*. 2014; 59: S7-S9.

[7] Bai, J. C., M. Fried, G. R. Corazza, D. Schuppan, M. Farthing, C. Catassi, L. Greco, H. Cohen, C. Ciacci, R. Eliakim, A. Fasano, A. González, J. H. Krabshuis & A. LeMair. World Gastroenterology Organisation: Global Guidelineson *Celiac Disease. Journal of Clinical Gastroenterology*. 2013; 47(2): 121-126.

[8] Pietzak, M. & R. Colletti. Diagnosis and Treatment of Celiac Disease in Children: Clinical Practice Guideline Summary. 2005; http://www.naspghan.org.

[9] Husby S, S. Koletzko, I. R. Korponay-Szabó, M. L. Mearin, A. Phillips, R. Shamir, R. Troncone, K. Giersiepen, D. Branski, C. Catassi, M. Lelgeman, M. Mäki, C. Ribes-Koninckx, A. Ventura & K. P. Zimmer. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *Journal of Pediatric Gastroenterology Nutrition.* 2012; 54(1): 136-160.

[10] Kelly C. P., J. C. Bai, E. Liu, D. A. Leffler. Advances in diagnosis and management of celiac disease. *Gastroenterology*. 2015; 148(6): 1175-1186.

[11] Ludvigsson J.F., J. C. Bai, F. Biagi, T. R. Card, C. Ciacci, P. J. Ciclitira, P. H. R. Green, M. Hadjivassiliou, A. Holdoway, D. A. van Heel, K. Kaukinen, D. A. Leffler, J. N. Leonard, K. E. A. Lundin, N. McGough, M. Davidson, J. A. Murray, G. L. Swift, M. M. Walker, F. Zingone, D. S. Sanders. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. *Gut* 2014; (63): 1210-1228.

[12] Rubio-Tapia, A., I. D. Hill, C. P. Kelly, A. H., Calderwood & J. A. Murray. American College of Gastroenterology Clinical Guidelines: diagnosis and management of celiac disease. *American Journal of Gastroenterology*. 2013; 108(5): 656-677.

[13] Ludvigsson L. F., L. Agreus, C. Ciacci, S. E. Crowe, M. G. Geller, P. H. R. Green, I. Hill, A. P. Hungin, S. Koletzko, T. Koltai, K. E. A. Lundin, M. L. Mearin, J. A. Murray, N. Reilly, M. M. Walker, D. S. Sanders, R. Shamir, R. Troncone & S. Husby. Transition from childhood to adulthood in coeliac disease: the Prague consensus report. *Gut*. 2016; (65): 1242-1251.

[14] Murch, S., H. Jenkins, M. Auth, R. Bremner, A. Butt, S. France, M. Furman, P. Gillett, F. Kiparissi, M. Lawson, B. McLain, M. Morris, S. Sleet, M. Thorpe. Joint BSPGHAN and Coeliac UK guidelines for the diagnosis and management of coeliac disease in children. *Archives of Disease in Childhood*. 2013; 98: 806-811.
www.worldgastroenterology.org
www.naspghan.org
www.espghan.org
www.bspghan.org.uk.