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CELIAC DISEASE FROM THE VIEW OF GENERAL PEDIATRICISTS: A PILOT STUDY

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Abstract: *Objective:* To evaluate knowledge about celiac disease among pediatricians at a University Hospital in a Brazilian city. Methods: Descriptive cross-sectional study, with application of a questionnaire on clinical manifestations and diagnosis of celiac disease to pediatricians and pediatric residents of a university hospital, between March and August 2023. The data obtained were plotted in Excel to characterize the sample and analyze the responses. Results: The questionnaire was answered by 33 pediatricians and pediatric residents. The symptoms most related to celiac disease were chronic abdominal pain (100%), abdominal distension (100%), chronic diarrhea (96.97%) and failure to thrive (87.88%). Regarding risk factors for investigating celiac disease in children and adolescents, 1st and 2nd degree relatives with celiac disease (84.85%) and selective IgA deficiency (75.76%) were most chosen. For initial screening, 75.76% chose the antitransglutaminase IgA serological test and total IgA measurement. When asked to select the correct alternative, 63.63% believe that duodenal biopsy is the gold standard for diagnostic confirmation. 42.42% indicated that symptomatic patients, with antitransglutaminase antibodies above 10 times the upper limit, are diagnosed without biopsy, 54.54% stated that it is necessary to measure IgG antiendomysial antibodies in patients with IgA deficiency and 57.57% believe it is important genetic test to exclude false negatives. Discussion: The results show that, despite demonstrating general knowledge about the disease, pediatricians still place little value on atypical symptoms and are not familiar with current guidelines, which corroborates underdiagnosis.
Keywords: Celiac Disease; Pediatricians; Early diagnosis; Child; Adolescent.

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder characterized by sensitivity to prolamins found in gluten, which induces the production of antibodies and leads to atrophy of intestinal villi. It can be expressed in the classic form, in which there is a prevalence of gastrointestinal symptoms; atypical, with extraintestinal manifestations such as anemia, osteoporosis, delayed puberty in children and adolescents and herpertiform dermatitis; and asymptomatic, in which villous atrophy and antibody production exist despite the lack of clear symptoms.

If left untreated, in all its forms, CD has serious consequences due to nutritional deficiency resulting from malabsorption and a persistent inflammatory state and systemic involvement with repercussions that go beyond the gastrointestinal scope. Therefore, early diagnosis is important to avoid these outcomes, as well as to ensure that, in the case of children and adolescents, there is no impact on their growth and development.[5]

However, due to the diverse symptoms and low knowledge about diagnostic methods, there is around 95% underdiagnosis worldwide, making it a disease that is still little studied and addressed, even though it affects around 1% of the world's population. Therefore, the delay in diagnosis directly impacts the quality of life of celiac patients, especially when it comes to children and adolescents.

With this in mind, this article aims to evaluate the knowledge of pediatricians and pediatric residents at a University Hospital in a Brazilian city about the clinical manifestations and diagnosis of CD.

MATERIALS AND METHODS

Between March and August 2023, a questionnaire was sent to pediatricians and pediatric residents at a University Hospital in a Brazilian city, via email, containing questions related to the clinical manifestations and diagnosis of CD in children and adolescents. Before starting to answer the questionnaire, the participant must read and agree to the Free and Informed Consent Form (TCLE), and only after this acceptance, they will be directed to the questions.

The questionnaire prepared on the Google Forms platform, by the authors of this study, based on current DC guidelines (Berry et al, 2020), was available through a link, being self-administered and quick, lasting up to 10 minutes. It consisted of an initial identification part with information on age, gender, years of graduation and place of work, to characterize the sample. The second part consisted of questions to assess pediatricians' knowledge, with 3 multiple-choice questions, including the following questions:

- Which of the following signs or symptoms would you associate with CD in children and adolescents: Chronic diarrhea, Delayed puberty, Constipation, Weight-height failure, Short stature, Abdominal distension, Iron deficiency anemia, Osteopenia, Chronic abdominal pain, Arthritis/arthralgia, Diarrhea with blood.
- In which situation(s) below would you consider investigation for CD? 1st and 2nd degree relatives of celiac patients, Down Syndrome, Juvenile rheumatoid arthritis, Turner Syndrome, History of consanguinity, Selective IgA deficiency Type I diabetes
- In the initial screening for CD, which test(s) would you initially request? Upper gastrointestinal endoscopy with biopsies, IgA and IgG antigliadin serology, HLA-DQ2/DQ8 genetic test, IgA antitransglutaminase serology and total IgA dosage, IgA antitransglutaminase serology, IgA and IgG antiendomysial serology, IgA and IgG antigliadin serology, IgA and IgG antitransglutaminase and antiendomysium IgA and IgG.

And a question with statements, so that the participant could only mark the one(s) they considered true, which are below:

- The gold standard continues to be the duodenal biopsy
- Patients with suggestive symptoms and ATG levels above 10 times the upper limit, the diagnosis can be made without the need for endoscopy
- The genetic test (HLA-DQ2/DQ8) can help when the clinic is very suggestive and serological tests are negative, to rule out a false negative, since if the genetic test is negative the probability of CD is small.
- In patients with IgA deficiency, it is recommended to carry out IgG anti-endomysium testing.

As a strategy to improve adherence and reach more participants, physical questionnaires were printed and distributed to professionals who had not responded via the link sent by email. The TCLE was collected for everyone who was willing to participate.

After completing data collection, the results obtained were systematized in an Excel spreadsheet. To characterize the sample analyzed, means and standard deviations were used for numerical variables and percentages for categorical variables. For multiple-choice questions, bar graphs were used arranged in response percentages for each available alternative. As this is a descriptive work, no statistical tests were used.

This study is part of a medical student's scientific initiation project and worked as a pilot project to evaluate pediatricians'

knowledge about celiac disease in Brazil. The project was approved by the Institution's Research Ethics Committee Involving Human Beings and registered with the CAAE:64306322.6.0000.5152.

RESULTS

The cross-sectional descriptive study included 33 participants, pediatricians and pediatric residents from the first to the third year, working at a University Hospital in a city. Everyone agreed to participate in the study by giving their consent through the TCLE.

Of the total of 33 who responded, the majority were women, aged between 20 and 45 years (78.8%), with less than 10 years of graduation and 100% worked in the public sector, although some also worked in the private sector (table 1).

Regarding the clinical picture, it was to highlight the symptoms most suggestive of CD, making it possible to choose more than one alternative. Abdominal distension and chronic abdominal pain were chosen by all participants. Still regarding the most prevalent symptoms, chronic diarrhea, failure to thrive and short stature were reported by more than 80% of pediatricians. Delayed puberty, constipation and iron deficiency anemia were elected by just over 50%. Osteopenia, bloody diarrhea and arthritis/arthralgia were the least selected options (table 2).

Regarding the risk factors that must lead to the investigation of CD in children and adolescents, 1st and 2nd degree relatives of celiac patients (84.85%) and selective IgA deficiency (75.76%) were the options most flagged as screening indicators. Meanwhile, type I diabetes was selected by 57.58% of participants; Down syndrome and juvenile rheumatoid arthritis by 45.45% and Turner syndrome by 27.27%. The item "history of consanguinity" represented only 24.24% of the responses.

Regarding the tests that must be requested in the initial screening, the vast majority opted for the IgA anti-transglutaminase antibody measurement and total IgA measurement. In second place, upper digestive endoscopy with biopsies and IgA and IgG antiendomysial serology tied in percentages, followed in third place by IgA and IgG antigliadin serology and IgA antitransglutaminase serology. No participant indicated genetic testing as a test option for initial screening (table 3).

The last question asked them to indicate what they thought was correct regarding the diagnosis of CD. Of the total responses, 63.63% stated that the gold standard for diagnosis continues to be duodenal biopsy, against 42.42% who selected the option that said that symptomatic patients with antitransglutaminase antibody values above 10 times the upper limit, are diagnosed without the need for intestinal biopsy. Finally, 54.54% stated that it was necessary to search for IgG antiendomysial antibodies in patients with IgA deficiency and 57.57% responded favorably to genetic testing as important to exclude false negatives.

DISCUSSION

In general, pediatricians demonstrated knowledge about the clinical manifestations of CD in childhood, as well as recognizing the variety of signs and symptoms. It was also possible to notice that important risk factors for triggering an investigation were remembered, just as the main screening exams are known by pediatricians. On the other hand, respondents do not seem to be familiar with the new guidelines on diagnosis and management of CD.

It is important to note that there were limitations due to the small sample and the fact that the participants were pediatricians and pediatric residents at a University Hospital, which is characterized by being a tertiary

hospital and, therefore, receives patients with varying complexities that require greater knowledge to manage the cases. However, the answers obtained still allow us to evaluate a certain standard both in the recognition of CD and in the diagnostic approach.

Regarding clinical manifestations, most still associate the clinical picture with the classic symptoms of the disease predominantly related to intestinal impairment, which predominates in younger children, such as diarrhea, distension, abdominal pain and failure to thrive. In fact, gastrointestinal manifestations are present in 50% of cases. The classic symptoms of malabsorption are easier to identify and, although they appear to be more specific, they can confuse and delay the diagnosis, as they are symptoms prevalent in this age group and present in other digestive disorders. Rashid et al (2005) found that a third of families consulted more than two pediatricians before confirmation and that, before diagnosis, these children received other diagnoses including anemia (15%), irritable bowel syndrome (11%), gastroesophageal reflux (8%), stress (8%) and peptic ulcer (4%).

DC's presentation has changed a lot in recent decades. Classic symptoms occur in a minority of patients, while older children present with oligosymptomatic or atypical symptoms, with extra-intestinal symptoms predominating to the detriment of gastrointestinal symptoms. In the present study, it was possible to see that pediatricians recognize that there is a broad spectrum of signs and symptoms in celiac disease and are aware of other less specific symptoms that predominate in older children, such as constipation, iron deficiency anemia, short stature and delayed puberty.9 Positively, these atypical symptoms were mentioned by more than half of the pediatricians interviewed. Short stature, for example, was associated with the disease for 78.79% of participants. In fact, short stature has been reported in 47.5% of celiac patients. According to a study carried out at ``*Universidade de* São Paulo`` (USP) with children who were shorter for their age, 4.7% of them were diagnosed with celiac disease after screening, a significant number and which the authors defined as overweight. disease screening.

However, there is still a lack of knowledge regarding extra-intestinal manifestations such as ostopenia and joint manifestations, which have rarely been mentioned. In an Italian study, 80% of untreated celiac patients had low bone mineral density, which demonstrates the impact of calcium malabsorption on bone metabolism. And even if a gluten-free diet is implemented, vitamin D levels, as well as bone mineral density, can take an average of 6 months to return to normal. Highlighting the importance of pediatricians associating this manifestation with CD, allowing diagnosis before bone restoration is irreversible.

The association of the presence of blood in the feces with the diagnosis of celiac disease, even though it was small, raised concerns, on the one hand because it is not a sign described in the various literature and, on the other hand, it may suggest diagnostic confusion with other inflammatory colitis. whose pathophysiological mechanism is different, such as inflammatory bowel disease.

Regarding the risk factors that would lead pediatricians to carry out screening, the majority recognized the need to carry out screening in 1st and 2nd degree relatives with celiac disease, as there are estimates that they have between 10% and 20% more likely to develop the disease at some stage in life, as it is known that, despite being a multifactorial disease, genetic components are also present among its causes. Based on this knowledge, it is also worth highlighting that screening must not be done just once in a lifetime, but rather regularly, because it is also known that the

individual may develop the disease at any time in their life, including under its asymptomatic form. Consanguinity, on the other hand, has a low correlation and is not considered a risk factor, which seems to be known by the majority of pediatricians interviewed, but even so, the fact that some have selected this option perhaps draws attention to the lack of knowledge about the pathophysiology of the disease.

The factor "selective IgA deficiency" was also listed by most pediatricians as an increased risk. It is actually present in around 1.7% to 7.7% of celiac patients. As the most requested antibody tests to screen for the disease involve immunoglobulin A, its deficiency can lead to false negatives, which increases the number of underdiagnosed patients. Therefore, knowing the possibility of coexistence of these two conditions is essential for using other classes of antibodies.

Epidemiological studies indicate that the prevalence of CD among type I diabetics is 4% compared to around 1% in the general population, a representative value that demonstrates the importance of screening in these individuals. The same occurs with other autoimmune diseases, since, although they involve several aspects as causes, most of them involve genetic factors, and some mutations may be common to different diseases, which justifies their coexistence in many cases. An example in addition to type I diabetes mellitus is juvenile rheumatoid arthritis. In the study, however, less than 60% of pediatricians associated these two autoimmune disorders with CD.

It is important to remember that children with Down Syndrome have an estimated 6-fold increased risk of developing celiac disease.17 The prevalence of the disease in these patients can vary from 5 to 12%. If the screening test is not performed, the diagnosis of celiac disease can be delayed in 82% of patients with Down Syndrome, which causes an increase in mortality. In the present study, more than half of pediatricians seem not to recognize the association of these two diseases and, therefore, are unaware of the health care guidelines for people with Down Syndrome that recommend initial screening at two years of age.19 Reinforcing the need also to disseminate these guidelines among health professionals, as well as training projects.

Regarding the initial screening tests, the results were satisfactory regarding the choice of the total IgA dosage to rule out a possible selective IgA deficiency associated with IgA anti-tissue transglutaminase antibodies for more than 70% of the participants, which is in line with current guidelines who state that these have greater specificity and sensitivity among the others. Another result that we saw as positive was the fact that no participant chose the genetic test to carry out the screening. It is known that 95% of celiac patients have the HLA-DQ2 gene and 5% the HLA-DQ8 gene, but, due to the multifactorial nature of the disease, the presence of these genes alone does not indicate that the individual is celiac, although it does not rule out the possibility of one day developing it. From another point of view, however, this test works as a diagnosis of exclusion, since the absence of these genes excludes the possibility of the disease with a confidence percentage of 99%.

Thus, despite allowing the diagnosis to be excluded, it is not used as a screening method for diagnostic confirmation.

On the other hand, 27% of pediatricians selected the dosage of the three types of antibodies (antitransglutaminase, antiendomysium and antigliadin). In light of current knowledge, antigliadin has low sensitivity and antiendomysium, in turn, despite also being a good method, is not the first to be requested in the initial screening, even because the method for measuring

it is immunofluorescence, which, despite being well modernized, involves a certain subjectivity on the part of those who perform it, which reduces its sensitivity. Therefore, we can infer that when requesting antigliadin or even antiendomysium as initial screening we lose the chance of more assertive results such as those found with the antitransglutaminase dosage, in addition to honoring the healthcare system. And despite demonstrating knowledge of the coexistence of CD and IgA deficiency, as already reported above, just over 50% would request the measurement of IgG antibodies in the face of this deficiency, which reinforces the lack of knowledge about the pathophysiology of the disease, as well as its means diagnoses, which can harm adequate diagnosis and reinforce the possibility of false negative tests.

At the same time, around 20% would recommend duodenal biopsy, a questionable conduct as this is an invasive procedure that must be used in diagnosis and not in screening, even because it requires more improved resources and it would not be viable to carry it out on a large scale by the system. public health. And more than 60% of those interviewed stated that endoscopy was the gold standard for diagnosis, when current European guidelines state that symptomatic patients with antibodies 10 times above normal do not need to undergo endoscopy. This non-biopsy approach was highlighted by less than half of the interviewees, once again showing the connection with old concepts that duodenal biopsy would be the main exam in CD workup. It has been shown that high levels of antitransglutaminase antibody accurately predict Marsh 2-3 histological changes in the duodenum. The objective of this "biopsy-free" approach proposed by current ESPGHAN guidelines is to make the diagnostic procedure less challenging, which deserves to be disseminated among healthcare professionals.

Thus, it is concluded that, although pediatricians demonstrate general knowledge about CD, there is still little reference to atypical symptoms, as already demonstrated in another Brazilian study with pediatricians. There is a need to expand and update the knowledge of health professionals in relation to CD, above all, reinforcing attention to atypical or oligosymptomatic forms. As well, it is important to increase awareness of possible diagnostic approaches among physicians in order to increase adherence to guidelines. Therefore, the development of training courses is necessary to reinforce concepts and support conduct, supporting a more assertive diagnosis. This way, we could change the current reality of around 95% underdiagnosis, with thousands of celiac patients unaware of their condition, exposing themselves to gluten and suffering the consequences of lack of treatment, many of them irreversible.

Finally, the need for more studies on CD and assessments of health professionals' knowledge on the topic is reinforced, given that the present study adopted a limited sample, but its greater scope can generate interesting results to evaluate a more general panorama.

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ATTACHMENTS:

Gender – n (%)	
Feminine	30 (90,9%)
Masculine	3 (9,1%)
Age group - n (%)	
20 to 30 years	13 (39,4%)
30 to 45 years old	13 (39,4%)
> 45 years old	7 (21,2%)
Years since graduation – n (%)	
< 10 years	19 (57,6%)
> 10 years	14 (42,4%)
Location of operation - n (%)	
Only in the Public Sector	21 (63,6%)
Public and Private Sector	12 (36,4%)
Only in the Private Sector	0

Table 1 - Characterization of the sample of Participants (n=33)

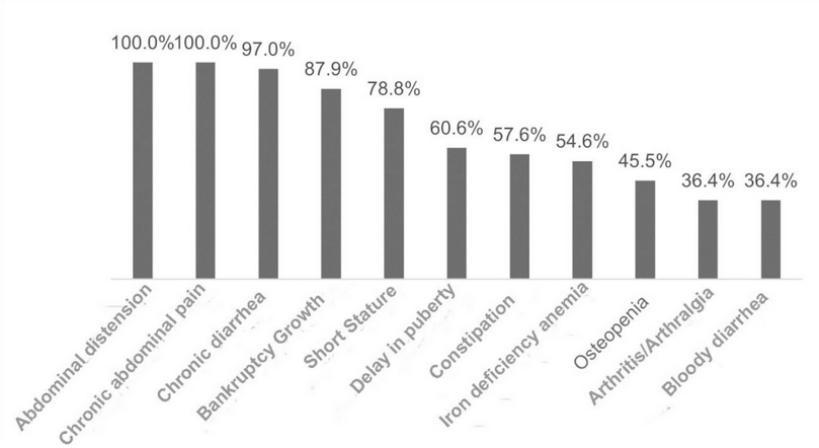

Figure 2: Symptoms suggestive of celiac disease

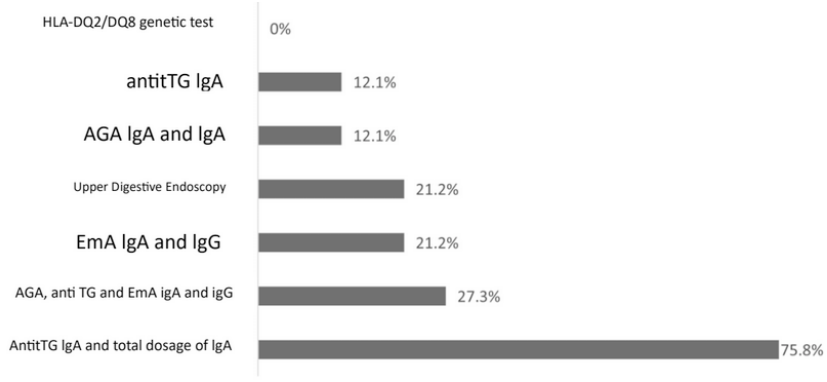

Figure 3: Tests to screen for celiac disease

Anti tTG, anti-transglutaminase antibody; AGA, antigliadin antibody; EmA, antiendomysial; IgA, immunoglobulin A