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Coeliac disease in the ERA of the new ESPGHAN and BSPGHAN guidelines: a prospective cohort study

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ABSTRACT

Objective To evaluate the consequences of the last European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) guidelines for the diagnosis of coeliac disease (CD) by means of a prospective study.

Design Prospective cohort study.

Setting Institute for Maternal and Child Health IRCCS Burlo Garofolo (Trieste, Italy).

Patients Children diagnosed with CD without a duodenal biopsy (group 1), following the last ESPGHAN and BSPGHAN guidelines, and children diagnosed with a duodenal biopsy, matched for sex, age and year of diagnosis (group 2), were prospectively enrolled over a 3-year period. All patients were put on a gluten-free diet (GFD) and were followed up for clinical conditions and laboratory testing at 6 months every year since diagnosis (median follow up: 1.9 years).

Outcome measures Resolution of symptoms, body mass index, laboratory testing (haemoglobin, anti-transglutaminase IgA), adherence to a GFD, quality of life, and supplementary post-diagnosis medical consultations.

Results 51 out of 468 (11%) patients were diagnosed without a duodenal biopsy (group 1; median age 2.1 years) and matched to 92 patients diagnosed with a biopsy (group 2; median age 2.4 years). At the end of follow-up the two groups were statistically comparable in terms of clinical and nutritional status, anti-transglutaminase IgA antibody titres, quality of life, adherence to a GFD, and number of supplementary medical consultations.

Conclusions On the basis of this prospective study, diagnosis of CD can be reliably performed without a duodenal biopsy in approximately 11% of cases. At least during a medium-term follow-up, this approach has no negative consequences relating to clinical remission, adherence to diet, and quality of life of children with CD.

What is already known on this topic

- According to the latest European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) guidelines, coeliac disease may be diagnosed without duodenal biopsy in symptomatic patients with high titres of anti-transglutaminase IgA.
- Prospective data on the consequences of the application of the latest ESPGHAN and BSPGHAN guidelines are still lacking in clinical practice.

What this study adds

- Coeliac disease can be reliably diagnosed without biopsy in at least 11% of all cases and in 37% of children younger than 2 years.
- After 2 years, there are no differences, between patients diagnosed with and without biopsy, in clinical improvement, adherence to diet and quality of life.
- This is the first prospective study that validates the safety and effectiveness of the new ESPGHAN/BPSGHAN guidelines for the diagnosis of coeliac disease in children, at least in a short follow-up.

INTRODUCTION

Coeliac disease (CD) is now defined as a genetically predisposed autoimmune systemic condition characterised by the presence of a variable combination of gluten-dependent enteropathy, other clinical manifestations, and CD-specific antibodies such as serum anti-transglutaminase IgA (anti tTG-IgA) and anti-endomysium IgA (AEA).[1]

Up to 2012, diagnosis of CD invariably required a duodenal biopsy and the demonstration of classical duodenal villous atrophy.[2 3] In 2012, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) proposed a new algorithm for CD diagnosis, introduced for the first time at the ESPGHAN meeting in June 2010 in Istanbul.[1] The new guideline allows CD diagnosis without a duodenal biopsy in selected, highly symptomatic cases with high titres of serum anti tTG-IgA antibodies, positivity for AEA and for human leucocyte antigen (HLA) DQ2 or DQ8. More recently the British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) also reviewed its diagnostic guidelines for CD, reaching similar conclusions.[4] The effectiveness of this new approach has been validated by recent retrospective studies,[5–7] but to our knowledge no prospective study has been conducted yet.

OBJECTIVES

The main aim of this study was to evaluate the clinical consequences of the application of the new ESPGHAN and BSPGHAN guidelines for the diagnosis of CD in a prospective manner. In particular, we want to assess:

1. The rate of cases that may be diagnosed without a duodenal biopsy following the new ESPGHAN/BSPGHAN guidelines;
2. The clinical and laboratory response to a gluten-free diet (GFD), acceptance of diagnosis, adherence to diet, and quality of life of patients who received a diagnosis without a biopsy compared with those who underwent a biopsy.

PATIENTS AND METHODS

We started our study after the introduction of the new ESPGHAN guidelines for the diagnosis of CD at the ESPGHAN meeting in Istanbul, in June 2010. We prospectively enrolled all children (aged 0–18 years) who were diagnosed with CD from January 2011 to May 2014 at the Institute for Maternal and Child Health Burlo Garofolo of Trieste (Italy), the reference centre for CD in a north-eastern region of Italy. According to the new ESPGHAN/BSPGHAN guidelines,[1 4] symptomatic children with anti-tTG IgA antibody serum concentration over 10 times the upper limit of normal and positivity for AEA and CD related HLA were diagnosed without a duodenal biopsy (group 1). Only patients presenting with symptoms highly suggestive of CD (diarrhoea with weight loss, failure to thrive, and/or sideropenic anaemia) were considered symptomatic. Children with suspected CD who did not fulfil all these criteria underwent biopsy.

Baseline data of all new CD diagnoses were collected from the patients' medical reports: sex, age, familiarity for CD, clinical presentation, body mass index (BMI), anti-tTG IgA antibodies and AEA serum values, HLA type, and whether a duodenal biopsy was performed at the time of diagnosis.

Serum anti-TG IgA antibodies were measured using an ELISA assay (Eurospital, Italy) with a cut-off value of 7 U/mL. Serum AEA was measured using sections of human umbilical cord. Briefly, the sections were incubated for 30 min with the subject's serum diluted 1:5. After being washed, sections were incubated with fluorescein-labelled goat antihuman IgA antibodies for 30 min. The slides were washed, mounted in aqueous mounting medium, and examined by fluorescent microscopy. Susceptibility alleles for CD were determined by PCR with allele-specific primers identifying DQ2 and DQ8, using a Dynal Classic SSP-DQ kit. All assays were performed by operators blind to the patients' clinical and laboratory data. For each subject undergoing duodenal biopsy, four specimens were taken: two from the duodenal bulb and two from the distal duodenum. The histological classification was based on Oberhuber's criteria.[8] Intraepithelial lymphocyte (IEL) density was expressed as a percentage of the number of epithelial cells (number of IEL/100 epithelial cells), with a value >25/100 being considered abnormal.

Follow-up and diet

All children diagnosed without a duodenal biopsy (group 1) were matched, according to sex, age and year of diagnosis, with children diagnosed with a biopsy (group 2). Follow-up started at the time of diagnosis for every patient and ended in September 2014.

All children included in the study were put on a GFD and underwent routine clinical examination and laboratory testing; data about BMI (weight (kg)/height $(m)^2$), onset of CD-related disorders, CD-related antibodies, and haemoglobin concentration were collected at 2 months and every year after the diagnosis. At the same time, patients and/or parents were interviewed to assess compliance with a GFD, perceived effects of the diet on health, and its implications for the child's wellbeing. Adherence to diet was evaluated with Biagi's questionnaire,[9] which calculates a score from 0 to 4, where 3 and 4 reflect a strict adherence to diet, and 0, 1 and 2 a bad compliance. A simplified version of the Kindl test (see online supplementary appendix 1), already proposed by Bellini *et al* to investigate quality of life of children with CD,[10] was used to assess the patient's mood and perception of the disease. Both questionnaires were given to every child if older than 6 years old, or to his/her parents, at the last visit or by phone call. The number of supplementary medical consultations, in addition to those previously scheduled at our institute, was ascertained at every follow-up visit. Informed consent was obtained from parents in all cases.

Statistical analysis

Continuous data are presented as median and IQR; categorical data as number and percentage. For continuous data, differences between groups were evaluated with the Mann–Whitney test (we assumed a non-normal distribution of data); and for categorical data, with the Fisher exact test. A p value of less than 0.05 was considered statistically significant. All the analyses were carried out with Stata V.11.2 (StataCorp, Texas, USA).

Ethics committee approval

The study was approved by the independent Ethical Committee of the Institute for Maternal and Child Health IRCCS Burlo Garofolo (CE/27/09).

RESULTS

Population description

Figure 1 describes the study population. Between January 2011 and May 2014, 468 children received a diagnosis of CD at our institute (median age 5.9 years, IQR 3.3–9.9); among them, 51 patients (11%) were diagnosed without a duodenal biopsy (group 1: median age 2.1 years, IQR 1.6–4.0; male to female ratio 0.45), while 417 (89%) were diagnosed after a biopsy.

Most children diagnosed without a biopsy were younger than 5 years (45/51) and almost half of the cases (22/51) were younger than 2 years (figure 2). Overall, the median age at diagnosis of patients diagnosed without a biopsy was significantly lower than that of all cases diagnosed with a biopsy taken

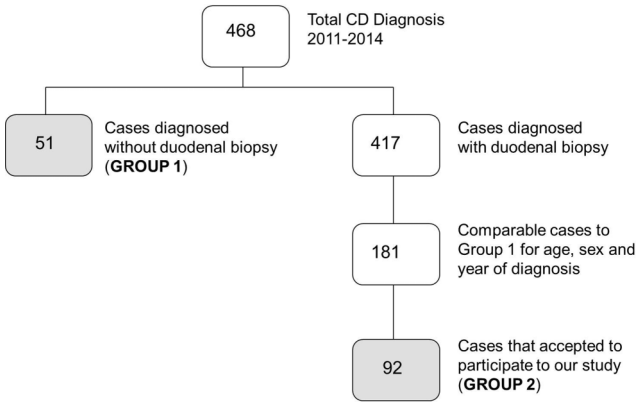

Figure 1 Patient recruitment and definition of the groups that entered the study.

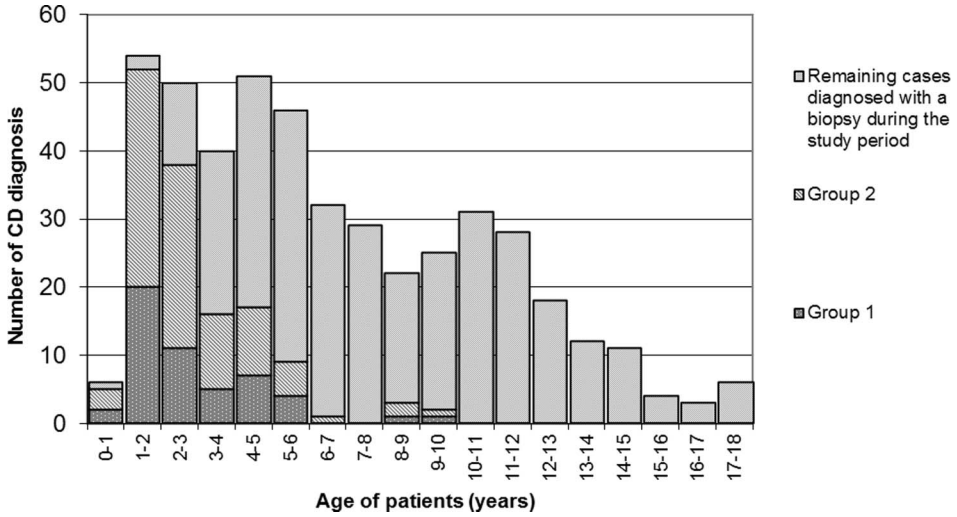

Figure 2 Distribution of age at diagnosis of patients who entered the study diagnosed without (group 1 ▪) and with (group 2 ▨) a duodenal biopsy. The grey part of the bars (▭) indicates the distribution of age at diagnosis of the remaining cases diagnosed with a biopsy during the study period.

together (2.1 years, IQR 1.6–4.0 vs 6.8 years, IQR 4.3–10.6; p<0.001).

Among the 417 children who received a diagnosis of CD based on a duodenal biopsy, 181 were comparable to those of group 1 according to sex, age and year of diagnosis; of these, 92 agreed to participate in the study (group 2: median age 2.4 years, IQR 1.9–3.6; male to female ratio 0.76) (figure 1). Groups 1 and 2 were comparable in terms of sex and median age (table 1). In both groups the median duration of follow-up was 1.9 years.

Clinical and laboratory response to a GFD, adherence to diet and quality of life

Symptoms completely resolved 1 year after commencement of a GFD in 47/51 (92.2%) patients in group 1 and 84/92 (91.3%) patients in group 2 (p=1.00). At the end of follow-up, complete resolution of symptoms was observed in 47/51 (92.2%) patients from group 1 and in 85/92 (92.4%) patients from group 2 (p=1.00). No cases without improving symptoms were recorded. Autoimmune thyroiditis developed in 2/51 (3.9%) patients from group 1 and in 3/92 (3.3%) patients from group 2 (p=1.00); no other autoimmune disorder was detected.

The two groups differed in BMI distribution at the time of diagnosis: the proportion of cases with a BMI below the third centile was 11/51 (22%) in group 1 and 4/92 (4%) in group 2 (p<0.01). Most of these patients improved their nutritional state after the GFD was started: at the end of follow-up, children with a BMI below the third centile were 3/51 (5.9%) in group 1 and 2/92 (2.2%) in group 2 (p=0.35).

Haemoglobin median values at diagnosis were 11.7 g/dL (IQR 10.5–12,3) in group 1 and 11.1 g/dL (IQR 10.5–11.6) in group 2 (p=0.49); 19/51 (37.2%) and 28/92 (30.4%) children respectively had anaemia (p=0.46). At the last control visit, median haemoglobin levels were 12.7 g/dL (IQR 11.7–13.2 and 12.2–13.2) for both groups and the percentage of children with anaemia decreased to 5.9% (3/51) in group 1 and 6.5% (6/92) in group 2 (p=1.00).

The anti-tTG IgA antibody serum level decreased in all patients. The median titres fell within the normal range 1 year after diagnosis and stayed within the normal range even at 2, 3 and 4 years in both groups (figure 3). The percentage of children whose anti-tTG IgA antibodies became negative after diagnosis was similar in group 1 and group 2 at every point of follow-up (at 6 months, 1, 2 and 3 years after diagnosis: 26/51 (51%), 8/38 (21%), 1/22 (5%), 0/14 (0%) in group 1 and 51/92 (55%), 14/73 (19%), 3/47 (6%), 2/29 (7%) in group 2).

No supplementary visit or exam, in addition to those scheduled at diagnosis in our centre, was recommended by family paediatricians or directly requested by the family in both groups. Compliance with a GFD, defined by Biagi's questionnaire, was comparable in both groups (figure 4): 51/51 (100%) patients in group 1 and 90/92 (97.8%) patients in group 2 scored 3 or 4, indicating high adherence to the diet (p=0.55). The modified Kindl test did not show statistical differences concerning the patients' quality of life (how children feel, their difficulties accepting the diet, and their feeling different from others), except for the question about how they feel compared

Table 1 Study population description: patients who received a diagnosis without (group 1) and with (group 2) a duodenal biopsy were comparable in terms of sex and age at the time of diagnosis

	Group 1 (n=51)	Group 2 (n=92)	p Value
Median age (years)	2.1; IQR 1.6–4.0	2.4; IQR 1.9–3.6	0.43
Sex (females, absolute number)	35/51 (68.6%)	52/92 (56.5%)	0.57

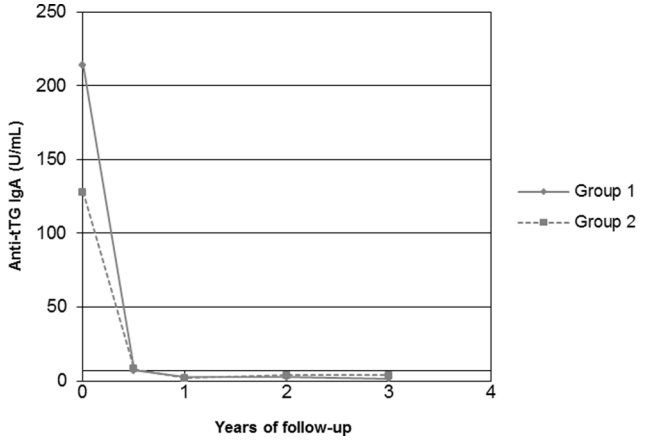

Figure 3 Decrease of serum anti-tTG IgA antibody median titres after commencement of a gluten-free diet.

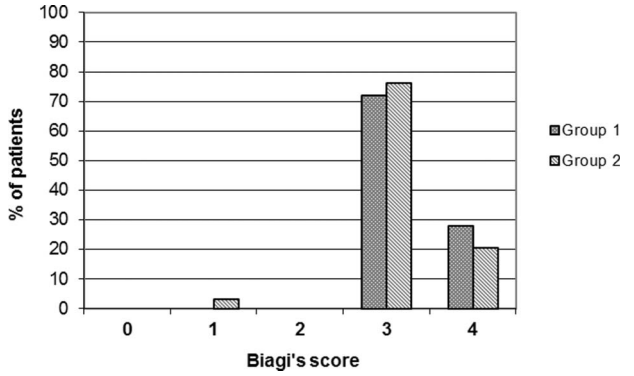

Figure 4 Adherence to a gluten-free diet according to Biagi's score (0, 1, 2=low; 3, 4=high).

with before starting the GFD (100% stated 'better' in group 1, 88% 'better' and 12% 'the same' in group 2; $p<0.01$).

DISCUSSION

This study demonstrates in a prospective manner that, following the new ESPGHAN and BSPGHAN guidelines, diagnosis of CD may be reliably done without a duodenal biopsy in at least 11% of cases. At the end of the follow-up children diagnosed without a biopsy were statistically comparable to those diagnosed with a biopsy in terms of clinical and nutritional status, serum anti-tTg IgA antibody titres, quality of life, adherence to a GFD and number of post-diagnosis medical consultations.

The number of spared biopsies seems to be lower than that predicted by previous studies,[5 11] probably because we applied the new ESPGHAN/BSPGHAN guidelines in a restricted way, considering as symptomatic only those cases with diarrhoea, weight loss, failure to thrive, and/or iron deficient anaemia. This cautiousness in the application of the new ESPGHAN/BSPGHAN guidelines was motivated by a lack of validation of the new diagnostic algorithm by prospective studies. If we had applied the new algorithm to the letter (including other symptoms possibly suggestive of CD), we would have avoided 165 biopsies of the 468 new CD diagnoses (35.2%).

Children diagnosed without a biopsy were largely under the age of 5 years (88%) and presented a BMI below the third centile in a higher percentage of cases (22%) than those diagnosed with a biopsy. This is not surprising because it is known that CD occurs with more severe symptoms, such as malabsorption syndrome, under 2 years of age.[12] Therefore, in this age group, it was possible to spare biopsies more frequently. If we limit the analysis to cases diagnosed under the age of 2 years, the percentage of cases diagnosed without a biopsy following the ESPGHAN/BSPGHAN guidelines would be 37% (22/60).

After the introduction of a GFD, the percentage of cases below the third BMI centile became comparable in groups 1 and 2. Similar to BMI, the median values of haemoglobin in the two groups became comparable after the introduction of a GFD.

Compliance with a GFD was similar in the two groups. Biagi's score, which describes adherence to a GFD, reached high values in both groups; moreover none of the patients in group 1 had low scores (1 or 2), as occurred for one patient in group 2. This observation suggests that good compliance is encouraged at least equally by the symptomatic presentation of the disease and by the execution of a biopsy.

Anti-tTG IgA median titres decreased considerably, showing the same trend and remaining within the normal range over time in both groups. The percentage of children with normal antibody values was comparable in the two groups at every year of follow-up, increasing from about 80% at 1 year to >95% at 3 years after diagnosis, as reported in other series.[13] Despite the serum anti-tTG IgA antibody values not being absolutely sensitive in assessing the compliance with a GFD,[14] they represent another parameter suggesting a similar adherence to diet in the two groups.

It has been reported that in patients with CD quality of life is related to the quality of the GFD[15]; in this sense, given the good compliance, it is not surprising that all patients reported feeling 'good or very good' at the last control visit. As expected, perception of the effectiveness of the diet is even more evident for those diagnosed without a biopsy (100% feeling 'better' after beginning the GFD), probably because they were more symptomatic before starting the GFD. Finally, acceptance of the diagnosis seemed high in both groups; no need for extra testing or specialist visits was noted in either group. In our opinion, this aspect is really important because it shows that the application of the new guidelines is not only safe, but also it does not increase the fear of a wrong diagnosis either in doctors or in families.

The uptake for the study was 100% among those patients diagnosed without a biopsy compared with 50% among those who were diagnosed with a biopsy. The reason for this is probably that the parents of non-biopsied children felt confident about continuing follow-up at our centre, which is a third-level facility and one of the few in Italy to have promptly introduced the ESPGHAN/BPSGHAN guidelines. Many of the parents of patients diagnosed 'traditionally', however, preferred to be followed up by their local paediatrician in their place of residence and therefore declined to enter the study.

Some limitations of our study should be mentioned. First, the median follow-up is short (2 years) and further studies with a longer follow-up are necessary to evaluate changes in adherence to a GFD over the years, especially during adolescence, a period in which the diet is no longer under parental control. Moreover, all the patients who entered the study were assiduously followed and this may have favourably influenced adherence to diet and the low perceived need for further investigations. However, our patients diagnosed without a biopsy were compared with a highly motived control group who accepted to participate in the study: a population particularly prone to have the best possible compliance to a GFD.

CONCLUSIONS

Our study demonstrates for the first time in a prospective way that, with a strict application of the new ESPGHAN and BSPGHAN guidelines, the diagnosis of CD can be reliably made without a duodenal biopsy in at least 11% of cases. At least over a median 2-year follow-up, this approach has no negative consequence on clinical remission, adherence to diet and quality of life. Further studies are necessary to assess the validity of the present ESPGHAN and BSPGHAN guidelines for the diagnosis of CD in children in a long-term follow-up.

Contributors AV conceptualised and designed the study and critically revised the final manuscript. EB and VC acquired the data and drafted the initial manuscript. SM physically followed all the patients and participated in acquiring the data during follow-up. LR participated in designing the study and performed statistical analysis. TN contributed to acquiring and checking the quality of the laboratory data. All authors participated in the revision of the initial and subsequent versions of the manuscript and approved the final manuscript as submitted.

Competing interests None declared.

Ethics approval The Ethical Committee of the Institute for Maternal and Child Health IRCCS Burlo Garofolo.

Provenance and peer review Not commissioned; externally peer reviewed.

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