Digestive and Liver Disease 51 (2019) 1547–1550

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Misuse of serological screening tests for celiac disease in children: A prospective study in Italy

Elisa Franceschini[a], Maria Elena Lionetti[a], Grazia D'Adamo[b], Elisa D'Angelo[b], Simona Gatti[a], Giulia Naspi Catassi[a], Basilio Malamisura[b], Carlo Catassi[a,c,*]

[a] Department of Pediatrics, Università Politecnica delle Marche, Ancona, Italy
[b] Department of Pediatrics, University Hospital of Salerno, Salerno, Italy
[c] Center for Celiac Research and Treatment, Mass General Hospital for Children, Boston, MA 02114, USA

ARTICLE INFO

Article history:
Received 25 April 2019
Accepted 18 June 2019
Available online 3 August 2019

Keywords:
Celiac disease
Screening
Serological testing
Adherence to diagnostic guidelines

ABSTRACT

Background: Despite a well-established diagnostic algorithm for celiac disease, it remains unclear whether prescriptions for celiac serological tests comply with the current pediatric guidelines.
Aim: To analyze the appropriateness of test prescription in children investigated for celiac disease in Italy, compared to the current European pediatric guidelines.
Methods: All children who had performed a first evaluation for celiac disease were prospectively enrolled. Prescribed tests and related indications for testing were recorded, and compared to the European pediatric guidelines.
Results: Overall, 202 children were enrolled (females 59%, mean age 7.1 years ±4.1) in two centers. The reasons for celiac disease testing were typical, atypical symptoms or celiac disease-associated conditions in 46.5%, 49%, and 4.5% of cases, respectively. First-line tests were IgA and IgG anti-transglutaminase antibodies in 88.1% and 29.7% of children, IgA and IgG anti-deamidated gliadin peptide antibodies in 43% and 47%, IgA and IgG anti native gliadin in 15.8%, IgA anti-endomysium antibodies in 44.5%, HLA predisposing genes in 10% of patients. Test redundancy was very common, and the current diagnostic guidelines were correctly followed only in 23/202 patients (11.4%).
Conclusions: Diagnostic European guidelines for celiac disease screening are often disregarded in Italy. Intervention to implement adherence to these guidelines is needed, with the aim of improving resource utilization, and quality of patient care.

1. Introduction

Celiac disease (CD) is a systemic immune-mediated disorder triggered by the ingestion of gluten in genetically susceptible subjects, and characterized by the development of serum specific autoantibodies (e.g. the IgA class anti-tissue transglutaminase antibody), damage of the small intestinal mucosa, and a variable clinical picture [1]. It is one of the most common lifelong disorders, affecting approximately 1% of the European population [2].

The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) revised the CD diagnostic algorithm in 2012. According to this protocol, total serum IgA (tIgA) determination plus serum class A anti-tissue transglutaminase (tTG), or IgG anti-deamidated gliadin peptide (DGP) antibodies in children with selective IgA deficiency (SIgAD), is the first-line screening test for CD. IgA class antiendomysial antibody (EMA) and HLA-DQ2 and -DQ8 determinations are second-line (confirmatory) tests to be performed only in children with IgA anti-tTG positivity. IgG class anti-DGP test can be included in the initial CD screening of children younger than 2 years, since data suggest that this test may occasionally show higher sensitivity than IgA anti-tTG in early-onset CD [3,4]. Finally, determination of HLA genotype may be performed in the initial screening of children belonging to at-risk groups, e.g. CD first-degree family members, due to the high negative predictive value (NPV) of this test [5].

Several studies, including a large European, prospective, multicenter study, recently confirmed the validity and the generalizability of the ESPGHAN CD diagnostic guidelines, not only in symptomatic but also in symptomless cases [6,7]. In Italy, the ESPGHAN protocol has been widely adopted by third-level Centers of Pediatric Gastroenterology and largely promoted by the Italian

* Corresponding author at: Department of Pediatrics, Via F. Corridoni 11, 60123 Ancona, Italy.
E-mail address: c.catassi@univpm.it (C. Catassi).

https://doi.org/10.1016/j.dld.2019.06.016
1590-8658/

Society for Pediatric Gastroenterology (SIGENP). Despite this favorable situation, in our daily practice we got the feeling that blood testing requests for CD screening were largely inaccurate and often redundant. For this reason, we decided to undertake a prospective study aimed to analyze test prescriptions for CD screening/case-finding in children.

2. Materials and methods

We prospectively enrolled children seen at the Celiac Clinic of two referral Centers (Pediatric Department of Ancona and Cava de' Tirreni, Salerno, respectively) between September 2017 and September 2018. We included newly seen subjects younger than 18 years who had already performed their first-line CD serological testing before referral to our celiac clinic. We excluded (a) children with a prescription from a specialized/third-level referral Center, and (b) children that were already on a gluten-free diet at the time of CD serological testing.

For each patient a data sheet including 3 sections was filled in. The first section focused on the clinical suspicion leading to test for CD, divided in 3 main categories: typical symptoms (chronic diarrhea, failure to thrive, malnutrition), atypical symptoms (isolated short stature, delayed puberty, amenorrhea, iron-deficient anemia, recurrent abdominal pain, chronic constipation, chronic fatigue, recurrent stomatitis, dermatitis herpetiformis-like rash, osteopenia/osteoporosis, and abnormal liver biochemistry), or CD-associated conditions (type 1 diabetes mellitus, Down syndrome, autoimmune thyroid disease, Turner syndrome, Williams syndrome, SIgAD, autoimmune liver disease) and/or family history of CD. The second section investigated the serological tests performed for CD testing, that is IgA anti-tTG, IgG anti-tTG, IgA anti-DGP, IgG anti-DGP, IgA EMA, anti native gliadin antibodies (AGA) of IgA and IgG classes, tIgA and HLA-DQ2 and -DQ8 typing. The third section focused on the prescriber (general pediatrician, general practitioner or hospital pediatrician), and patient's features (gender, age, and age at the time of prescriptions).

For the purpose of the study, we evaluated the frequency of each single test prescription and of the combination of prescribed tests. According to the ESPGHAN guidelines [5], we considered appropriate the following prescriptions: (a) IgA anti-tTG and tIgA in children aged between 2 and 18 years; (b) IgA anti-tTG and tIgA, with or without IgG DGP in children younger than 2 years of age; (c) IgA anti-tTG and tIgA with or without HLA typing in children at increased risk for CD, e.g. first-degree relatives of CD patients.

Costs of the prescribed tests for the National Health Service were also calculated, and compared to the estimated cost of ESPGHAN-like prescriptions.

The study protocol was approved by the Ethical Committee of the Marche Polytechnic University. A written informed consent was asked from the legal guardians of participating children.

2.1. Statistical analysis

Data are expressed as mean ± SD and proportions, as required.

3. Results

3.1. Study population

Overall, we obtained data from 202 children. They were 119 girls (59%) and 83 boys (41%), with an age range of 7 months–16 years (mean age 7.1 years ±4.1). CD tests were performed at a mean age of 6.7 years ±4.1 SD. Eighteen children were younger than 2 years of age at the time of CD testing.

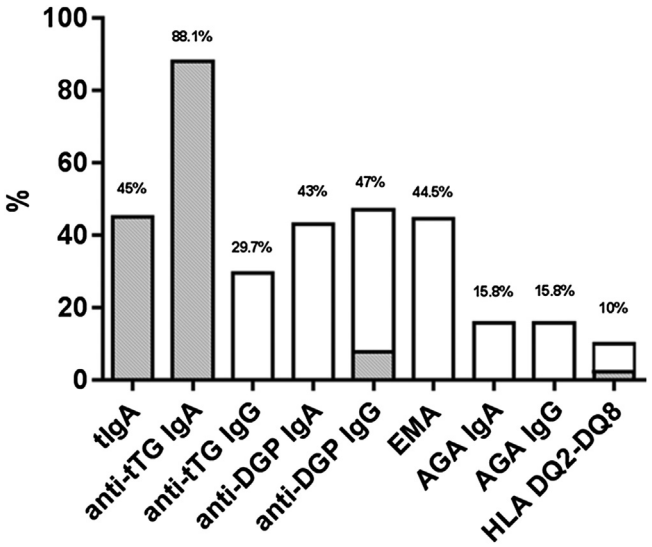

Fig. 1. First-line tests prescribed in children with suspected CD.
Anti-tTG: anti-tissue transglutaminase; anti-DGP: anti-deamidated gliadin peptide; EMA: antiendomysial antibody; tIgA: total serum IgA; AGA: anti native gliadin antibodies.
Grey-shaded bars: appropriate prescriptions; White bars: inappropriate prescriptions.

3.2. Reasons for CD testing

The reason for CD testing were typical symptoms in 94 cases (46.5%), atypical in 99 (49%), or belonging to a CD at-risk group in 9 children (4.5%). Reasons for CD testing (cumulative %) were: failure to thrive (35%), recurrent abdominal pain (32%), chronic diarrhea (24%), iron deficiency anemia (9%), first-degree relatives with CD (7%), constipation (5%), poor feeding (5%), abdominal distension (5%), nausea/vomiting (3%), chronic fatigue (3%), recurrent infection (2%) recurrent aphthous stomatitis (1%), vitiligo (1%), chronic urticaria (1%), alopecia (1%), amenorrhea (1%), type 1 diabetes (1%), and autoimmune thyroiditis (1%).

3.3. Diagnostic tests

Fig. 1 shows the percentage of prescription of each diagnostic test while Table 1 shows the frequency of combinations of prescribed tests and related costs. As for HLA determination, only 2 out of 20 subjects performing this test belonged to at-risk groups.

3.4. Comparison to ESPGHAN guidelines

The ESPGHAN guidelines were followed in 21 out of 175 children (12%) between 2 and 18 years of age; in 2 out of 18 children (11.2%) younger than 2 years; and none out of 9 children belonging to at-risk groups. Overall, we found compliance with the ESPGHAN guidelines in 23 out of 202 children (11.4%).

3.5. Prescribers

The prescriber was the family pediatrician, a general practitioner or a hospital pediatrician in 77.7%, 16.3% and 6.0% of cases, respectively. Among the prescribers, 13.3% of family pediatricians, 6% of general practitioners and none of hospital pediatricians correctly applied the ESPGHAN guidelines.

Table 1
First-line tests performed for suspected celiac disease: the more frequent combinations and related costs.

Anti-tTG IgA	Anti-tTG IgG	Anti-DGP IgA	Anti-DGP IgG	EMA	tIgA	AGA IgA	AGA IgG	HLA DQ2/DQ8	Prescriptions (%)	Cost (euro)
x					x				10.4	20.5
x	x	x	x	x					6.4	74.8
						x	x		5.0	20.6
x				x	x				5.0	43.7
x			x		x				5.0	30.8
x		x	x	x					4.5	59.3
x									4.0	15.5
x	x	x	x						4.0	51.6
x	x	x	x	x	x				3.5	79.8
x	x								3.5	31.0
Others									48.7	

Anti-tTG: anti-tissue transglutaminase; anti-DGP: anti-deamidated gliadin peptide; EMA: antiendomysial antibody; tIgA: total serum IgA; AGA: anti native gliadin antibodies.

3.6. Costs for the National Health System

Overall, the cost of CD prescriptions for the health care system was 12,382 euros, 108% higher than the ESPGHAN-like prescription (5954 euros). The cost per patient was 61.3 ± 57.1 euros (mean $\pm$ SD; range: 15.5–260.6), as compared to 29.5 euros of an ESPGHAN-recommended individual prescription.

4. Discussion

Despite a high level of CD awareness in Italy, this survey confirms that the ESPGHAN diagnostic guidelines, at an early stage of the diagnostic algorithm, are largely disregarded and that the misuse of CD screening tests is very common in this country. We indeed found that the recommended prescription of anti-tTG IgA plus tIgA occurred only in a minority of children undergoing a first CD screening (11.4%), while redundancy of test prescription was very common in clinical practice.

IgA anti-tissue transglutaminase is an excellent screening procedure characterized by high sensitivity (SE) (78%–100%), specificity (SP) (90%–100%) and positive predictive value (PPV) (72%), and is considered the best serological screening marker for CD in IgA-sufficient individuals [8,9]. Although IgA anti-tTG turned out to be the most frequently prescribed test in our survey (88% of children), this investigation was sometimes missing at the initial screening (12%), while more often was inappropriately prescribed in combination with other serological markers. Since the SE of IgG anti-tTG is lower (45%–95%) than IgA tTG, IgG anti-tTG testing should be restricted to the few cases affected by SIgAD [5,8]. IgG anti-tTG should not replace tIgA determination to rule out SIgAD-associated CD, but this happened quite commonly in our survey (20.8%). Anti-DGP antibodies were prescribed in 47% of our patients (IgG) and 43% (IgA), respectively. Anti-DGP antibodies were developed in 2006 as an alternative to IgA anti-tTG for CD screening [10], however the performance of this test has been shown to be lower than anti-tTG, according to most literature data [8–10]. For this reason, the usefulness of IgG anti-DGP test is limited to children younger than two years old or in IgA-deficient individuals. Olen et al. found that anti-tTG is superior to anti-DGP and that combining the 2 assays would increase both cost and the number of unnecessary duodenal biopsies with only a minimal increase in the CD detection rate [11]. Furthermore, Gould and others found that isolated positivity of anti-DGP, of either IgG or IgA class, does not predict CD in IgA sufficient individuals [12]. Conversely, the EMA test is highly specific for CD (SE 86%–100%, SP 97%–100%, PPV 83%) [8]. However, it should be used only as a confirmatory test due to high cost, use of animal substrate (monkey esophagus) and operator-dependency [9]. According to our data, EMA testing was overprescribed (44%) at the first CD screening. First-generation, anti native gliadin AGA determination is no longer recommended for identifying individuals with CD, due to their low SE (42%–100%), SP (47%–94%) and PPV (18–31%) [8,13]. However, AGA test was still prescribed in a considerable percentage of our cases (16%). Finally, the HLA genotyping has a strong NPV (close to 100%), but a very low PPV; therefore, this test is suitable for ruling out CD in children at increased risk for CD, to avoid further investigation [5,14]. The HLA test was prescribed in 20 (10%) of our patients; of them, only two belonged to CD at-risk groups.

The misuse of CD diagnostic test has at least two negative consequences: (a) the specificity of CD screening decreases in cases undergoing multiple testing, due to simple probability rules, with the consequence that an unjustified alarm may arise. For instance, the EMA test may occasionally be positive in a child with a very low level of IgA anti-tTG antibodies. This is an unlikely situation, mostly related to a false positivity of EMA, since tTG is the major antigen responsible for EMA positivity. Likewise, an isolated IgA anti-DGP has no clinical relevance in IgA anti-tTG negative subjects, and no further testing is required in such cases [12]. Worth noting, these false alarms cause anxiety in the family, are a common reason for asking a second-opinion by specialized doctors/centers, and generate increased costs for both patients and the national health system; (b) increased healthcare costs. According to our data, public healthcare costs secondary to the prescriptions of CD testing turned out to be more than doubled than correct, ESPGHAN-like prescriptions. These estimated costs do not include direct and indirect costs such as referral to pediatric gastroenterologist, parental anxiety, school or work non-attendance, that were difficult to quantify.

We are unaware of similar study performed in other European country, but it is well possible that a similar situation exists elsewhere. Salinas and coworkers assessed changes in the requests of serological markers of CD from 2010 to 2014 in primary care in Spain, by collection of data from laboratories: the prescription of IgA anti-tTG per 1000 inhabitants increased significantly over time, though the demand of IgA DGP did not decrease significantly [15]. Pham et al. ascertained, through a questionnaire, whether French physicians followed guidelines recommendations in the suspicion of celiac disease: 90.6%, 30.6% and 64.7% of pediatricians prescribed IgA anti-tTG, EMA and tIgA respectively [16].

The present study has limitations. The number of enrolled patients was relatively small and our results do not necessarily reflect the situation on a countrywide basis. Moreover, we cannot exclude with 100% confidence that tIgA had previously been tested in some children, leading to a certain degree of underestimation of correct prescriptions. Finally we could not evaluate the possible influence of reflex testing (e.g. automatic determination of total IgA level in subjects with a normal value of IgA anti-tTG) and of the so called “celiac panels” that some laboratories tend to adopt.

In conclusion, our study shows that there is a wide gap between test ordering practices and correct, ESPGHAN-like prescriptions in cases undergoing a first-level CD screening. These data reflect the

Italian scenario, a finding that looks particularly unexpected in a country showing a good knowledge and awareness of CD. Further interventions aimed to implement knowledge and adherence to diagnostic guidelines are needed, to improve resource utilization, test appropriateness and quality of patient care.

Conflict of interest

Prof. Carlo Catassi has served as scientific consultant for Dr. Schaer, NOOS, and Takeda. The other authors have no conflict of interest to declare.

References

[1] Fasano A, Catassi C. Celiac disease. N Engl J Med 2012;367:2419–26.
[2] Leonard MM, Sapone A, Catassi C, et al. Celiac disease and nonceliac gluten sensitivity: a review. JAMA 2017;318:647–56.
[3] Lammi A, Arikoski P, Simell S, et al. Antibodies to deamidated gliadin peptide in diagnosis of celiac disease in children. J Pediatr Gastroenterol Nutr 2015;60:626–31.
[4] Liu E, Li M, Emery L, et al. Natural history of antibodies to deamidated gliadin peptides and transglutaminase in early childhood celiac disease. J Pediatr Gastroenterol Nutr 2007;45:293–300.
[5] Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. European society for pediatric gastroenterology, hepatology, and nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54:136–60.
[6] Werkstetter KJ, Korponay-Szabó IR, Popp A, Villanacci V, Salemme M, Heilig G, et al. Accuracy in diagnosis of celiac disease without biopsies in clinical practice. Gastroenterology 2017;153:924–35.
[7] Trovato CM, Montuori M, Anania C, Barbato M, Vestri AR, Guida S, et al. Are ESPGHAN "biopsy-sparing" guidelines for celiac disease also suitable for asymptomatic patients? Am J Gastroenterol 2015;110:1485–9.
[8] Leffler DA, Schuppan D. Update on serologic testing in celiac disease. Am J Gastroenterol 2010;105:2520–4.
[9] Giersiepen K, Lelgemann M, Stuhldreher N, Ronfani L, Husby S, Koletzko S, et al. Accuracy of diagnostic antibody tests for coeliac disease in children: summary of an evidence report. J Pediatr Gastroenterol Nutr 2012;54:229–41.
[10] Sugai E, Vázquez H, Nachman F, Moreno ML, Mazure R, Smecuol E, et al. Accuracy of testing for antibodies to synthetic gliadin-related peptides in celiac disease. Clin Gastroenterol Hepatol 2006;4:1112–7.
[11] Olen O, Gudjónsdóttir AH, Browaldh L, Hessami M, Elvin K, Liedberg AS, et al. Antibodies against deamidated gliadin peptides and tissue transglutaminase for diagnosis of pediatric celiac disease. J Pediatr Gastroenterol Nutr 2012;55:695–700.
[12] Gould MJ, Brill H, Marcon MA, Munn NJ, Walsh CM. In screening for celiac disease, deamidated gliadin rarely predicts disease when tissue transglutaminase is normal. J Pediatr Gastroenterol Nutr 2019;68:20–5.
[13] AGA Institute. AGA Institute Medical position statement on the diagnosis and management of celiac disease. Gastroenterology 2006;131:1977–80.
[14] Björck S, Lynch K, Brundin C, Agardh D. Repeated screening is necessary for detection of celiac disease but can be restricted to at genetic risk birth cohorts. J Pediatr Gastroenterol Nutr 2016;62:271–5.
[15] Salinas M, López-Garrigós M, Flores E, Leiva-Salinas C. Big differences in primary care celiac disease serological markers request in Spain. Biochem Med 2017;27:231–6.
[16] Pham BN, Musset L, Chyderiotis G, Olsson NO, Fabien N. Celiac disease diagnosis: impact of guidelines on medical prescription in France. J Dig Dis 2014;15:435–43.