HLA-DQ Genotyping Combined With Serological Markers for the Diagnosis of Celiac Disease: Is Intestinal Biopsy Still Mandatory?

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ABSTRACT

Objectives: The aim of this study was to evaluate the value of HLA-DQ2/DQ8 allelic genotyping combined with serologic testing for the diagnosis of celiac disease (CD).

Patients and Methods: One hundred seventy children, who underwent jejunal biopsy for digestive symptoms or malnutrition, were tested for HLA-DQ2/DQ8 and serologic markers (tTG and/or anti-endomysial antibodies). Children were classified in 2 groups, according to jejunal histology: group 1, when partial or total villous atrophy was associated with an increased intraepithelial lymphocytosis suggesting CD, and group 2, when these histological criteria were absent.

Results: Eight children were excluded from the study because their intestinal histology was not informative; 82 children were classified in group 1 and 80 in group 2. Eighty-one of 82 children in group 1 were positive for HLA and serologic testing. The other child had negative HLA and serologic testing but marked villous atrophy, and further investigation showed an allergic disease. Among the 80 children in group 2, 53 were negative for both HLA and serologic testing, 22 were positive for HLA but negative for serologic testing, 2 were negative for HLA and positive for serologic testing, and 3 patients were positive for both HLA and serologic testing. The last 3 children were shown to have an autoimmune background and had probably a latent form of CD. The association of HLA-DQ2/DQ8 and serologic markers had a sensitivity of 98.8%, a specificity of 96.2%, a positive likelihood ratio of 26.3, and a negative likelihood ratio of 0.013.

Conclusions: The association of positive HLA-DQ2/DQ8 and serologic testing has a high predictive value for CD. We suggest that symptomatic children with high titers of immunoglobulin (Ig)A tTG could be diagnosed as patients with CD without performing jejunal biopsy. In other children, HLA-DQ2/DQ8 could be useful to exclude the diagnosis of CD if negative. In cases of low IgA tTG titers or in patients with IgA deficiency, intestinal biopsy remains mandatory.

Key Words: celiac disease, genotyping, HLA, transglutaminase

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Celiac disease (CD) is a genetically determined chronic inflammatory intestinal disease induced by an environmental precipitant, gluten (1). The classic form of CD in children is characterized by a malabsorption syndrome and failure to thrive, but in recent years the clinical picture of the disease has changed to include milder forms with extradigestive symptoms (2). According to the revised criteria by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (3), characteristic small intestinal mucosal abnormality, as classified by Marsh and Oberhuber (4), remains mandatory for the diagnosis of CD (5). However, it has been recognized recently that some patients may have gluten-sensitive enteropathy with preserved villous architecture (6–8). The widespread availability of serologic tests has made them useful for the diagnosis of CD. The immunoglobulin A (IgA) anti-endomysial (EMA) and anti-tissue transglutaminase (tTG) antibodies represent the most efficient tests available at the moment, with high sensitivity (89% and 94%, respectively) and specificity (98% and 99%, respectively) (9,10). A total IgA dosage should be incorporated into the routine testing of CD, as selective IgA deficiency, which is more common in patients with CD than in the general population (11), may lead to false-negative results of IgA EMA and tTG. As a result of the lower sensitivity and specificity of the IgA and IgG anti-gliadin antibodies, these tests are no longer recommended for identifying individuals with CD (2).

The evidence for a genetic component to CD susceptibility came from twin studies showing a concordance rate between monozygotic twins of 75% compared to 10% to 30% in dizygotic twins (12). Familial studies also showed an increased prevalence among siblings and relatives of affected individuals (13). Susceptibility to CD is strongly associated with the HLA class II DQ2 or DQ8 haplotypes because more than 95% of celiac patients possess the HLA-DQ2 and/or the DQ8 molecule (14). Indeed, around 90% to 95% of celiac patients possess the HLA-DQ2 phenotype defined by the combination of the DQA1∗0501 and DQB1∗0201 alleles on the same chromosome in *cis*, and more rarely by the combination of the DQA1∗0505 and DQB1∗0202 alleles encoded on separate chromosomes. Most of the 5% to 10% HLA DQ2–negative celiac patients carry the HLA-DQ8 molecule, defined by the DQB1∗0302 allele, usually associated with the DQA1∗0301 allele. Less than 1% of celiac patients do not possess either DQ2, in part, or DQ8 (15).

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This high negative predictive value makes these markers potentially helpful in the diagnosis strategy of CD.

The aim of this study was to assess the value of the determination of HLA-DQ2/DQ8 genotypes combined with serologic markers (IgA EMA and tTG) for the diagnosis of CD.

PATIENTS AND METHODS

Patients

Between March 2003 and March 2006, HLA-DQ2/DQ8 alleles were determined in 170 pediatric patients undergoing serologic testing for CD and small-bowel biopsy to investigate various chronic symptoms.

Serologic Tests

IgA EMA and tTG antibodies were determined in the serum, respectively, by indirect immunofluorescence and enzyme-linked immunosorbent assay technique according to manufacturer (Eurospital, Trieste, Italy).

Serologic testing was considered positive when IgA EMA and/or tTG antibodies were positive according to the manufacturer. The total IgA level was also determined in the serum to rule out selective IgA deficiency.

HLA-DQ Typing

After DNA extraction from blood leukocytes, a polymerase chain reaction was performed with specific DQA1∗0501/0505 and DQB1∗02 primers for the DQ2 heterodimer and DQB1∗0302 primers for the DQ8 molecule (Eu-DQ test, Eurospital). During the study, this technique was replaced with an allelic typing of the *DQB1* gene (PCR-SSO Labtype, OneLambda, Canoga Park, CA), and when the susceptibility DQB1 alleles were identified, the *DQA1* gene was studied (PCR-SSP Uniray, Dynal, Oslo, Norway). Both strategies were first shown to provide identical results. Results were given as positive or negative for the distinct predisposition alleles and led to the conclusion of the presence or the absence of the DQ2 and/or DQ8 susceptibility genotypes.

Intestinal Histology

Two or 3 biopsies were obtained in the third part of the duodenum during an endoscopic procedure, and samples were immediately formalin fixed. Histologic features supporting the diagnosis of CD were architectural changes of the villi and the crypts related to various grades of villous atrophy and an increase of intraepithelial lymphocytes. Histology was considered suggestive of CD when an increase of intraepithelial lymphocytes more than 30/100 enterocytes and a partial, subtotal, or total villous atrophy (3a, 3b, or 3c lesion of the Marsh classification modified by Oberhuber) were identified (4). Histology showing partial villous atrophy but normal intraepithelial lymphocytes was considered as not suggestive of CD.

Patients were then classified into 2 groups according to these histological criteria:

1. Group 1: children with histology suggestive of CD
2. Group 2: children with histology not suggestive of CD

Sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of the test combining HLA-DQ2/DQ8 genotyping and serologic testing were evaluated.

Ethical Considerations

This study received approval from the ethical committee of the University of Bordeaux. Patients were included in the study after written informed consent was obtained from the parents.

RESULTS

Patients

Excluded Patients

Eight of the 170 children were excluded from the study. In 2 children, small-bowel biopsies were performed while they were already consuming a gluten-free diet, which had been started because of positive serologic tests. Both possessed the HLA-DQ2 susceptibility genotype. Histology was considered normal for the first child and showed partial villous atrophy with increased intraepithelial lymphocytosis in the second one.

In 1 child, gluten was previously excluded because of positive serologic tests, and then reintroduced in the diet since only 2 months. He possessed the DQ2 susceptibility genotype, and histology showed partial villous atrophy with normal intraepithelial lymphocytes.

Two children were excluded because of selective IgA deficiency. In 3 children, intestinal biopsy showed intestinal atrophy, which could not be classified because of bad orientation of the sample. One of them had negative serologic markers and did not possess any HLA susceptibility alleles, 1 had negative serologic markers but carried the HLA-DQ8 susceptibility genotype, and the third had weakly positive serologic markers and carried the HLA-DQ2 susceptibility genotype.

Group 1

Histological findings were considered suggestive of CD in 82 of 162 children (50.6%). The male-to-female ratio was 1.05 and the median age was 18 months (range 6–169). Time of introduction of gluten was 3.5 to 8 months (median 5 months). Clinical symptoms leading to intestinal biopsy were weight loss or failure to thrive (n = 66, 80.4% of group 1), chronic diarrhea (n = 45, 54.8%), abdominal distension (n = 32, 39%), iron-deficient anemia (n = 20, 24.3%), poor appetite (n = 15, 18.3%), vomiting (n = 15, 18.3%), muscle wasting (n = 11, 13.4%), recurrent abdominal pain (n = 9, 10.9%), alternating diarrhea and constipation (n = 8, 9.7%), general weakness (n = 7, 8.5%), unhappy behavior (n = 4, 4.9%), exudative enteropathy (n = 1, 1.2%), abnormal behavior (n = 1, 1.2%), iterative ileo-ileal intussusception (n = 1, 1.2%), dermatitis herpetiformis (n = 1, 1.2%), and miscellaneous (n = 3, 3.6%). Two children had Down syndrome, and 1 had type 1 diabetes mellitus.

Group 2

Histological findings were not considered suggestive of CD in 80 of 162 patients (49.4%). The male-to-female ratio was 1.02 and the median age was 54 months (5–197 months). Time of introduction of gluten was 4 to 7.5 months (median 5.5 months).

Small-bowel biopsy was performed to investigate impaired growth (n = 38, 47.5% of group 2 children), chronic diarrhea (n = 21, 26.2%), recurrent abdominal pain (n = 22, 27.5%), vomiting (n = 9, 11.2%), iron-deficient anemia (n = 13, 16.2%), epigastric abdominal pain (n = 7, 8.7%), abdominal distension (n = 4, 5%), poor appetite (n = 6, 7.5%), general weakness (n = 4, 5%), alternating diarrhea and constipation (n = 3, 3.7%), constipation (n = 3, 3.7%), psychomotor disorders (n = 5, 6.2%), gastrointestinal hemorrhage (n = 3, 3.7%), recurrent fever (n = 3, 3.7%), portal

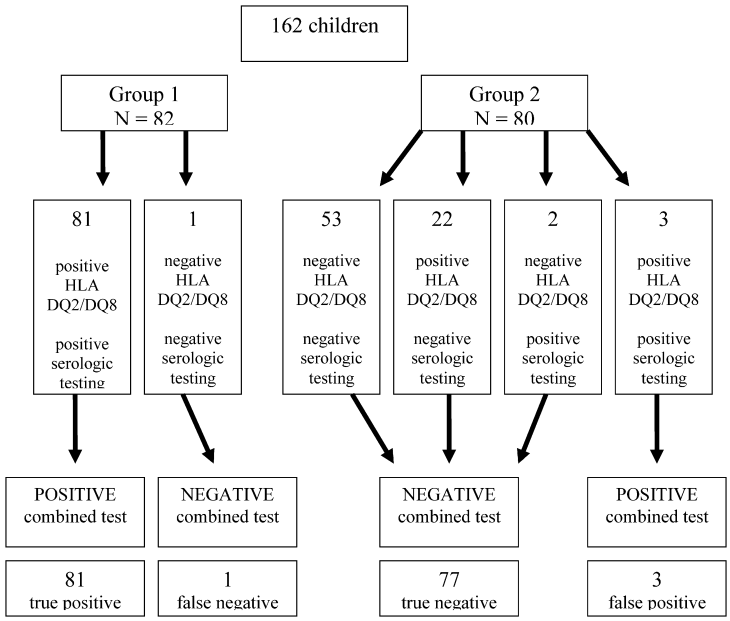

FIGURE 1. Results of HLA-DQ2/DQ8 and serologic testing in 162 children undergoing intestinal biopsy. Group 1: histology suggestive of celiac disease; group 2: histology not suggestive of celiac disease.

hypertension (n = 2, 2.5%), positive serologic markers in patients with diabetes mellitus (n = 2, 2.5 %), and miscellaneous (n = 5, 6.2%).

At the end of the investigations, the following diagnoses were established: gastroesophageal reflux (n = 10, 12.5%), psychological eating disorders (n = 8, 10%), cow's-milk protein allergy (n = 2, 2.5%), iron-deficient anemia (n = 3, 3.7%), *Helicobacter pylori* gastritis (n = 8, 10%), inflammatory bowel disease (n = 3, 3.7%), neglected child (n = 3, 3.7%), fetal alcohol syndrome (n = 2, 2,5%), nutritional deficiency (n = 4, 5 %), food allergy (n = 2, 2.5%), erythematous gastritis (n = 1, 1.2 %), irritable bowel syndrome (n = 1, 1.2 %), brain tumor (n = 1, 1.2%), encephalopathy (n = 3, 3.7%), hepatitis (n = 3, 3.7%), chronic infectious bronchopneumonia (n = 2, 2.4%), systemic lupus (n = 1, 1.2 %), and α-1 antitrypsin deficiency (n = 1, 1.2%). No etiology could be found in 22 cases (27%) at the end of the investigations.

Serologic Tests and HLA-DQ2/DQ8 Genotypes (Fig. 1)

Group 1

Among the 82 children in group 1, 81 had both positive serologic markers (IgA tTG and/or EMA) and positive HLA-DQ2 or DQ8 susceptibility alleles. Seventy children (85.3%) carried the DQ2 heterodimer (2 of them being homozygous for DQB1∗02), 6 (7.3%) possessed the DQ8 genotype, and 5 (6.1%) patients carried both the DQ2 and DQ8 alleles. The diagnosis test, combining both serologic markers and susceptibility alleles, was therefore positive for 98.8% of group 1 children. One (1.2 %) of the 82 children did not possess the HLA-DQ2/DQ8 susceptibility genotype or serologic markers, with normal IgA level, but had grade 3b villous atrophy with increased intraepithelial lymphocytosis. Further intestinal biopsies, performed 1 year later while consuming a gluten-free diet, showed persistent partial villous atrophy with numerous eosinophils, suggesting an allergic process. Gluten-containing diet was reintroduced, and follow-up showed normal weight growth.

Group 2

Among the 80 children in group 2, 53 (66.2%) did not possess the HLA-DQ2/DQ8 susceptibility genotype nor serologic markers. Two of them had partial villous atrophy but normal intraepithelial lymphocyte count. Twenty-two children (27.5%) possessed the HLA-DQ2 and/or DQ8 alleles (10 DQ2, 11 DQ8, and 1 DQ2 and DQ8), but their serologic markers were negative. Two children (2.5%) were DQ2 and DQ8 negative but had slightly positive EMA and tTG antibodies. The remaining 3 children (3.7%) possessed the HLA-DQ2 and/or DQ8 alleles, positive serologic markers, and had partial villous atrophy but a normal level of intraepithelial lymphocytes.

TABLE 1. Efficiency of the combined test (HLA-DQ2/DQ8 and serologic testing) in 162 children undergoing intestinal biopsy

	Group 1, n = 82	Group 2, n = 80	
Positive combined test	True positive 81	False positive 3	Positive predictive value 96.4%
Negative combined test	False negative 1	True negative 77	Negative predictive value 98.7%
	Sensitivity 98.8%	Specificity 96.2%	

Efficiency of the Combined Test

The combination of serologic testing and HLA-DQ2/DQ8 genotyping gave a sensitivity of 98.8% (95% confidence interval 0.98 ± 0.02), a specificity of 96.2% (95% confidence interval 0.96 ± 0.04), a positive likelihood ratio of 26.3, and a negative likelihood ratio of 0.013.

Sensitivity of serologic testing (tTG and/or EMA) alone was 98.8%, specificity 93.7%, positive likelihood ratio 15.8, and negative likelihood ratio 0.013. Sensitivity of HLA DQ2/DQ8 genotyping alone was 98.8%, specificity 68.7%, positive likelihood ratio 3.16, and negative likelihood ratio 0.017 (Table 1).

DISCUSSION

The pathogenesis of CD is well known, and the respective roles played by the tissue transglutaminase and the HLA-DQ2 molecule in gliadin peptide recognition has been precisely documented (1,16) and modeled (17). The immunologic functions of the HLA-DQ8 molecule are still not clearly established, but the identification of a gliadin-derived epitope, which is recognized by the intestinal gluten-specific HLA-DQ8–restricted T cell, has already been reported (18,19). In this work, we studied the diagnostic value of the combined tests to take advantage of the sensitivity and specificity of each of them.

HLA-DQ2/DQ8 genotyping is a test of high sensitivity but low specificity, because the alleles are positive in about 40% of the general population (14), although the prevalence of CD is only 1% on mass screening studies (20). Thus, for most of the authors, the interest of the determination of the DQ2/DQ8 alleles lies in their high negative predictive value (2,9,21–23). In a study of 354 patients (23), Pena-Quintana et al concluded that the value of this test derived from its ability to exclude the diagnosis when a negative result occurred. In a large HLA-risk genotype population, Björk et al (24) found that 4.5% of children younger than 3 years old have an undiagnosed CD compared to none in children with HLA nonrisk alleles. A Finnish study of 76 doubtful cases of CD (22) showed that HLA-DQ2/DQ8 typing was helpful in ruling out CD when small-bowel histological findings were equivocal. Moreover, HLA-DQ2/DQ8 typing often made it possible to rectify the diagnosis when a gluten-free diet was started before performing small-bowel biopsies. Kapitany et al (25) even concluded that diagnosis of CD based solely on histology was not always reliable and that HLA-DQ typing was important to revise diagnosis of DQ2- and DQ8-negative subjects. Karinen et al (26) showed that HLA genotyping was useful in the evaluation of the risk for CD on the first-degree relatives of celiac patients, making it possible to exclude CD if all risk alleles were missing (in about 20% of first-degree relatives), whereas the others should be screened further. Csizmadia et al (27) proposed in children with Down syndrome a 2-step strategy based first on selection of individuals with potential CD by HLA-DQ typing followed in these at-risk children by a longitudinal CD screening by serology.

The value of specific antibodies for CD has already been extensively studied, and IgA EMA and tTG antibodies are presently recognized as the most efficient tests, with high sensitivity and specificity, respectively, above 90% and close to 100%. The National Institutes of Health Consensus Conference on Celiac Disease of June 2004 (5) reported that serologic testing in children younger than 5 years old may be less reliable and required further investigation. However, in the present study on children with a median age of 18 months, IgA tTG and/or EMA were positive in 98.8% of biopsy-proven CD. These results are consistent with other studies concerning young patients, and a literature review by Hill et al (9) concluded that there was no firm evidence that the sensitivity and specificity of the IgA tTG vary with age. For a few years, several authors have suggested that, under precise conditions, positivity of serological testing could be sufficient to diagnose CD and start a gluten-free diet without performing small-bowel biopsy. In a study of 144 adult celiac patients, Valdimarsson et al (28) found a 100% positive predictive value of IgA EMA when patients were symptomatic and concluded that small-bowel biopsy was not necessary for these patients, but that it should be performed in symptomatic patients with negative EMA to correct diagnosis. In a study of 103 pediatric patients, Barker et al (29) proposed that small-bowel biopsy not be performed when tTG titers were high (>100 IU/mL) or low (<20 IU/mL) in the absence of IgA deficiency.

Using a test combining a sensitive parameter (HLA genotyping) with a specific test (EMA and/or tTG) appears as an attractive alternative. In the present study, we found that 98.8% of patients with villous atrophy and increased intraepithelial T lymphocytes were also positive for serologic markers and DQ2 and/or DQ8 susceptibility alleles. This test is of high efficiency because positive likelihood ratio is high (>10), much higher than the positive likelihood ratio of serologic testing alone or HLA genotyping alone and the negative likelihood ratio is low (<0.1). Only 1 of these 82 patients had negative susceptibility HLA alleles and negative serological testing. Follow-up and repeated intestinal biopsies showed that this patient had an allergic enteropathy. In the case of this patient who was considered as a false-negative case in this study, determination of HLA-DQ2/DQ8 alleles could have led to correct diagnosis.

In this work, 3 of the 80 children in group 2 had positive serologic testing and HLA susceptibility alleles, leading to a 96.2% specificity (77/80 children of group 2 actually had a negative combined test) and a 96.4% positive predictive value (among the 84 children with a positive combined test, 81 showed characteristic histological features of CD). These 3 children, who had partial villous atrophy but normal intraepithelial lymphocyte count, therefore represent false-positive cases for serologic and HLA testing. However, a latent form of CD can be suggested in these children because they have autoimmune background, 1 of them with an autoimmune hepatitis and the other 2 from type 1 diabetes mellitus, 2 disorders that are strongly associated with CD (30–32). The high prevalence of CD in children with type 1 diabetes mellitus is definitely established (33–36), but most of these individuals are affected by an asymptomatic form of the disease, and systematic screening is recommended in this population. A recent study involving 400 children with type 1 diabetes mellitus showed that 2.5% of them had positive EMA and/or tTG antibodies, and were affected by a biopsy-proven CD, although most of them were symptom free (33).

Several previous studies concluded that HLA-DQ typing was important in identifying DQ2- and DQ8-negative children, to exclude CD, but did not have additive diagnostic value when IgA tTG or EMA were positive (25). In this work, 2 children had slightly positive EMA and tTG antibodies but negative HLA-DQ2/DQ8 genotyping and normal jejunal biopsies.

Notably, 22 of the 75 (29%) children of group 2 with negative serologic testing possessed the positive HLA-DQ2 or DQ8 susceptibility genotype, which is in accordance with the value usually noticed in the general population (13,37).

Cost analysis is in favor of a noninvasive procedure in France. Upper endoscopy with duodenal biopsies is often performed under general anesthesia and requires a preanesthesic visit and a 1-day hospitalization, but may be performed under sedation in some centers. The cost of this procedure amounts to €460 (under sedation) to €750 (under general anesthesia), whereas the cost of HLA DQ2/DQ8 determination amounts to €240.

CONCLUSIONS

This preliminary study confirms the high sensitivity of DQ2 and DQ8 HLA alleles and the high specificity of tTG antibodies for the diagnosis of CD in children. Along with others, we suggest that high titers of tTG IgA could be sufficient to establish the diagnosis of CD in symptomatic children and start a gluten-free diet without performing intestinal biopsy. In other cases, we propose to perform DQ2/DQ8 genotyping to exclude the diagnosis of CD if negative. In cases of low IgA tTG titers or in children with IgA deficiency, IgG tTG may be helpful, but intestinal biopsy remains mandatory.

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