HLA genotyping as first-line screening tool for coeliac disease in children with juvenile idiopathic arthritis

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ABSTRACT

Objectives Coeliac disease (CD) and juvenile idiopathic arthritis (JIA) often coexist. This association warrants assessment for CD in patients with JIA. We evaluated the clinical relevance and cost-effectiveness of human leucocyte antigen (HLA) genotyping in first-line screening for development of CD in children with JIA.

Patients and interventions 95 patients with JIA were screened for CD using CD-specific antibodies. In case of positivity, a small intestinal biopsy was performed to confirm diagnosis. In addition, HLA genotyping was performed. 110 age-matched and sex-matched Caucasian children from the same geographical area served as controls.

Results CD was diagnosed in 4 of 95 patients with JIA (4.2%), a rate significantly higher compared with controls ($p<0.02$) and 14 times higher than in the general population. Twenty-six patients (27.4%) had one of the variants of the risk genotypes. All four patients diagnosed with CD had a HLA-DQ2.5 genotype: one was homozygote, the remainder heterozygote. Twenty-two patients are, judging by their HLA genotypes, at risk of developing CD and require repeated serological screening. None of the 69 patients without HLA-DQ2/DQ8 genotypes had CD-specific antibodies. Screening with HLA genotyping becomes cheaper than screening without after the second determination.

Conclusions In our cohort of patients with JIA, lack of HLA-DQ2/DQ8 genotypes identified a majority not at risk of CD in whom repeated serological testing is unnecessary. Genotyping is nowadays the most efficient and cost-effective way to screen for CD risk in JIA.

What is already known on this topic?

- Associations between coeliac disease (CD) and juvenile idiopathic arthritis (JIA) have been described with inconsistent results.
- Serological markers are usually used for CD screening; however, new European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines recommend first assessing for the at-risk genotypes human leucocyte antigen (HLA)-DQ2 and DQ8.
- Until now no studies exist investigating the distribution of the genetic risk types in JIA and the cost-effectiveness of the new screening strategy.

What this study adds?

- In our cohort, JIA was frequently associated with CD and warrants general screening.
- We show for the first time that determination of HLA-DQ2/DQ8 eliminates the need for repeated serological testing in the majority of patients with JIA.
- We show that this strategy is the most efficient and cost-effective way for screening for CD in patients with JIA.

INTRODUCTION

Autoimmune diseases are the result of loss of immunological tolerance to self-antigens caused by genetic and environmental factors. Genetic loci associated with susceptibility to clinically distinct autoimmune diseases overlap, suggesting shared pathogenic pathways.[1 2] Associations between different autoimmune diseases similarly are known. The strongest association exists between coeliac disease (CD) and type 1 diabetes (T1D) and protocols for screening patients with T1D for CD are well defined.[3–5] As studies are rare that investigate the association of CD with juvenile idiopathic arthritis (JIA), the most common systemic rheumatic disease in childhood, and as their results are ambiguous[6–10] no clear recommendations for routine CD screening in asymptomatic patients with JIA exist.

Screening for CD has hitherto been performed using CD-specific antibodies, but new guidelines published by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) recommend first assessing for the at-risk genotypes human leucocyte antigen (HLA)-DQ2 and DQ8.[11 12] Approximately 90% of patients with CD present HLA-DQ2.5, encoded by DQA1*05 and DQB1*02 alleles. Almost all DQ2.5-negative patients present HLA-DQ8, encoded by DQB1*03:02 and DQA1*03 alleles or HLA-DQ2.2 encoded by DQB1*02 (without DQA1*05) typically in linkage disequilibrium with DQA1*02.

As the absence of these genotypes has a strong predictive value, patients with JIA who do not have them and who lack symptoms of CD might perhaps not require serological follow-up screening. No study investigating the distribution of HLA-DQ2/DQ8 in patients with JIA existed; hence, we sought to determine the prevalence of CD in a cohort of patients with JIA, to assess the likely value of HLA

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genotyping in first-line screening for CD in similar patients, and to assess the cost-effectiveness of this screening procedure.

PATIENTS AND METHODS

Study design and patient characteristics

This single-centre, prospective study was performed at the Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Austria. The study included 95 patients diagnosed with JIA between January 2007 and December 2014, screened for CD between January 2010 and March 2015.

All patients fulfilled the revised criteria for the diagnosis of JIA.[13] Demographic data, type of JIA onset, age of onset, family history (up to second-degree relatives) for autoimmune diseases, associated autoimmune diseases apart from CD and medication were entered.

Controls

One hundred and ten age-matched and sex-matched Caucasian children from the same geographical area, admitted to our hospital for minor surgical interventions served as controls. Informed consent was obtained from all children and/or their parents.

Laboratory analysis

All subjects were evaluated for CD yearly, using the presence of CD-specific antibodies. We determined IgA antitissue transglutaminase type 2 (TG2) antibodies and in case of positivity additionally anti-endomysial antibodies (EMA). To exclude false absence of anti-TG2 antibodies due to IgA deficiency, serum IgA was measured in every patient. In subjects with low serum IgA levels (total serum IgA <0.2 g/L), IgG-class antibodies against deamidated forms of gliadin peptides (DGP) were determined. Serum IgA anti-TG2 and anti-DGP antibodies were measured by ELISA (respective expected values, <9 U/mL (Eurospital SpA, Trieste, Italy) and <25 U/mL (Euroimmune, Lübeck, Germany)). Anti-EMA IgA-class antibodies were assayed by a standard immunofluorescence method using frozen sections of monkey oesophagus. Serum IgA was measured by immunoturbidity assay on a Cobas C 501 analyser using a commercial reagent kit (Roche, Vienna, Austria). If CD-specific antibodies were demonstrated on two consecutive tests at least 3 months apart,[14] small intestine mucosal biopsy was performed. CD was diagnosed histopathologically when microscopy of an intestinal biopsy sample yielded a Marsh score of 2 or higher on a scale of 0–3, with 0 indicating normal intestinal mucosa and 3 indicating atrophied villi and elongated crypts.[15 16]

HLA genotyping

HLA-DQ typing was performed at the Department of Blood Group Serology and Transfusion Medicine, Medical University of Graz, by allele-specific multiplex PCR (Olerup SSP AB, Stockholm, Sweden). The genetic markers were classified into six groups: (1) homozygote DQ2.5, (2) heterozygote DQ2.5, (3) DQ2.5/DQ8, (4) DQ8, (5) DQ2.2 and (6) neither DQ2 nor DQ8 present.

Cost estimates

Costs of tests, based on tariffs from the Austrian Healthcare Authority (LGBI 83/2014), were compared for each screening strategy.

Statistical analysis

Statistical analyses were performed using IBM SPSS, V.21.0.0 (Armonk, New York, USA). Fisher's exact test was used to compare differences between cases and controls. Statistical tests were two-tailed, and considered significant when $p<0.05$. All values are presented as mean with SD.

The Ethics Committee of our university approved the study (26–360 ex 13/14).

RESULTS

Demographic and clinical data

Ninety-five patients with JIA, from 94 families, were included in the study. Demographic and clinical data of the patients at time of inclusion are summarised in table 1. The mean age of the patients was 10.4±4.0 years. All subtypes of JIA were represented, with the oligoarticular subtype identified in 67.5%, the polyarticular subtype in 11.5%, systemic-onset JIA in 2.1%, enthesitis-related arthritis in 12.7% and psoriatic arthritis in 6.2%. ANA were present in 64% and rheumatoid factor in 3.2% of the patients. Seventy-five patients were on medication. Of these, 71 received immunosuppressive treatment, mostly methotrexate (n=68). Among the 26 patients with risk genotypes were 19 of these 71 patients. Forty-seven patients had an additional treatment with antitumour necrosis factor (TNF)-α therapy, among these were nine patients with risk genotypes. Of the 110 controls (78 females, 32 males), mean age was 10.6 ±3.8 years.

Family history of autoimmune diseases

Thirty-seven patients had first-degree or second-degree relatives with autoimmune diseases, showing a significant difference compared with controls (38.9% vs 3.6%; $p<0.001$). Patients with risk genotypes had a significantly higher prevalence of family history of autoimmune diseases compared with patients without risk genotypes ($p=0.034$). According to JIA subtypes, the psoriatic arthritis group had the highest prevalence of family history of autoimmune disease (66.7%) and the enthesitis-associated

Table 1 Demographic and clinical characteristics of 95 patients with JIA at inclusion

Sex, n (%)	
Male	29 (31)
Female	66 (69)
Age, years; mean+SD (limits)	
At onset of JIA	6.78±3.8 (1.4–15.2)
At inclusion	12.25±3.9 (2.3–17.9)
JIA subtype, n	
Oligoarthritis	64
Polyarthritis	11
Systemic onset	2
Enthesitis-associated arthritis	12
Psoriatic arthritis	6
Laboratory, n	
Antinuclear antibodies present	61
Rheumatoid factor present	3
Medication, n	
Non-steroidal anti-inflammatory drugs	7
Steroids	9
Methotrexate	68
Azathioprine	2
Mycophenolate mofetil	1
Biological treatment	47
Without medication	20

JIA, juvenile idiopathic arthritis.

arthritis group had the next highest (58.5%), followed by the oligoarticular arthritis group (36%) and the polyarticular group (18.2%). No patients with systemic-onset JIA had family members with autoimmune disease. Disorders from which family members suffered included rheumatoid arthritis (n=13), autoimmune thyroiditis (AIT) (n=9), psoriasis (n=8), T1D (n=3), inflammatory bowel disease (n=2) and multiple sclerosis (n=1). No patient had a family member with CD (table 2).

Associated autoimmune diseases apart from CD

We observed a significant increased prevalence of associated autoimmune diseases in patients with JIA compared with controls (11.6% vs 0.9%; p=0002). Among these, we found AIT in eight patients, T1D in two patients and inflammatory bowel disease (IBD) in one patient. Among the four patients diagnosed with CD, one had associated autoimmune thyroiditis and one had T1D. Patients with risk genotypes significantly more often had associated autoimmune diseases than did patients without risk genotypes (p=0.048) (table 2).

CD screening with specific antibodies

Table 3 presents clinical and laboratory data of the patients diagnosed with CD. CD-specific antibody profile was positive in four patients (4.2%), significantly higher compared with controls (p=0.02). Diagnosis was confirmed in all of them by small intestine biopsy. Onset of CD preceded onset of JIA in one symptomatic patient. Three asymptomatic patients were identified by yearly screening, one at the first, one at the second and one at the third. No patient of the control group was tested positive for CD-specific antibodies.

HLA genotyping

Twenty-six of the 95 patients with JIA (27.4%) carried a risk genotype: 1 patient was homozygote DQ2.5, 20 patients were heterozygote DQ2.5, 3 patients were DQ8 positive and 2 patients were DQ2.2 positive. No patient was heterozygote DQ2.5/DQ8. All patients with CD-specific antibodies had the HLA-DQ2.5 genotype; one was homozygote. In the DQ2.5-homozygote patient (table 2), diagnosis of CD preceded diagnosis of JIA by 3.5 years. No patient without the risk genotypes (n=69, 72.6%) had CD-specific antibodies or was diagnosed with CD. IgA deficiency was diagnosed in two patients without symptoms of CD. Both patients had the HLA-DQ2.5 genotype as heterozygotes, neither had IgG anti-DGP antibodies.

Thirty-one of the 110 controls (28.2%) were positive for the risk genotype, 2 were homozygote DQ2.5, 14 were heterozygote DQ2.5, 6 were DQ8 positive and 9 were DQ2.2 positive. None of the controls was heterozygote DQ2.5/DQ8. Patients with JIA significantly more often carried the high-risk genotype DQ2.5 compared with controls (80.8% vs 51.5%, p=0.022), whereas the low-risk genotype DQ2.2 was found significantly

Table 2 CD, risk haplotyping and autoimmunity in patients with JIA and controls

	Patients with JIA		Controls		JIA vs controls
Number of subjects, n	95		110		
HLA risk genotypes, n (%)	26 (27.4%)		31 (28.2%)		NS
HLA-DQ2.5 homozygote	1	21 (80.8%)	2	16 (51.5%)	p=0.022
HLA-DQ2.5 heterozygote	20		14		
HLA-DQ2.5/DQ8	0		0		
HLA-DQ8	3 (11.5%)		6 (19.4%)		
HLA-DQ2.2	2 (7.7%)		9 (29%)		p=0.042
CD, n (%)	4 (7.7%)		0		p=0.020
Associated autoimmune-diseases apart from CD, n (%)	11 (11.6%)		1 (0.9%)		p=0.002
Familial autoimmunity, n (%)	37 (38.9%)		4 (3.6%)		p<0.001

CD, coeliac disease; HLA, human leucocyte antigen; JIA, juvenile idiopathic arthritis.

Table 3 Clinical and laboratory data of patients with JIA diagnosed with CD

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	F	M	M	F
Age (years)	10.2	9.9	13.4	14.5
JIA subtype	Polyarthritis	Psoriatic arthritis	Oligoarthritis	Oligoarthritis
Laboratory	Both antinuclear antibodies and rheumatoid factor present	–	Antinuclear antibodies present	–
Age at onset of JIA (years)	9.1	7.2	9.8	3.3
Age at diagnosis of CD (years)	5.8	8.3	12.5	3.8
Anti-TG2 (IU/mL)	41	150	31	277
Anti-EMA	++	+++	++	+++
Histology (Marsh criteria)	III c	III c	II b	III b
HLA	DQ2.5-homozygote	DQ2.5-heterozygote	DQ2.5-heterozygote	DQ2.5-heterozygote
Family history of autoimmune disease	Inflammatory bowel disease	–	T1D	Autoimmune thyroiditis
Therapy at time of CD diagnosis	None	Non-steroidal anti-inflammatory drugs; intra-articular steroids	Methotrexate	Non-steroidal anti-inflammatory drugs; intra-articular steroids

CD, coeliac disease; HLA, human leucocyte antigen; JIA, juvenile idiopathic arthritis; TG2, transglutaminase type 2.

more often in controls compared with patients (29% vs 7.7%, p=0.042) (table 2).

Cost-effectiveness

HLA genotyping cost was €44.03. Costs for CD-specific antibodies (anti-TG2 and anti-EMA) were €21.88 each. IgA determination cost was €7.29. Serological screening cost without HLA genotyping for 95 patients was €2771.15/year. HLA genotype screening cost in 95 patients was €4182.85, a single expenditure, with €758.42/year for serological screening in the 26 patients at risk for CD, or €4941.27 in the first year and €758.42 thereafter. In the first 2 years, our cohort would thus, with serological studies alone, cost €8313.45 to assess and monitor. Including an initial HLA screening, our cohort would thus in the first 2 years cost €6.458,11 to assess and monitor. The difference of €1855.34 in the first 2 years makes initial HLA genotyping cheaper, with as much as €2012.73 saved every year thereafter in monitoring costs.

DISCUSSION

Prevalence of CD in our study cohort was 4.2%, which is significantly higher compared with controls and 14 times higher than the prevalence of 0.3% found in the general population in our geographic area.[17] This result is in agreement with results of other studies: it lies between the prevalence of 6.7% reported in Italian patients[6] and that of 0.7% in Finnish patients,[7] and supports the need of a systematic screening for CD in this group of patients.

In their recent guidelines, ESPGHAN, BSPGHAN and the National Institute for Health and Care Excellence (NICE) recommend that asymptomatic children and adolescents at an increased risk for CD, such as T1D, Down syndrome, autoimmune thyroid disease, Turner syndrome, Williams syndrome, selective IgA deficiency, autoimmune liver disease and first-degree relatives with CD, should be correspondingly screened.[11 12 18] Neither of these guidelines expressly list JIA among these conditions, and NICE even found that patients with JIA were at no increased risk of CD. The main reason for that is obviously the small number of studies, meeting the eligibility criteria by the three working groups, whose evidence statement is based on a maximum of three studies.[11 12 19] Our data show that JIA should be considered to be added to the list of risk conditions for CD.

Furthermore, ESPGHAN and BSPGHAN recommended typing for HLA-DQ2 and HLA-DQ8 as a first-line screening tool to exclude CD or to select asymptomatic individuals with CD-associated conditions for further CD-specific antibody testing. Screening for CD in the Italian and Finnish studies was done using CD-specific antibodies rather than HLA typing, and no studies investigating HLA genotypes as a genetic marker for CD risk in patients with JIA are available.

In 2014, Elias *et al*[20] evaluated the clinical relevance of HLA genotyping as a first-line screening tool in children with T1D. CD was diagnosed in 6.3% of that cohort, with 86% of the 110 screened children having one of the two risk-associated haplotypes. As only 14% of patients could be spared further screening with CD-specific antibodies, the authors concluded that HLA genotyping was neither distinctive nor cost-effective in patients with T1D. Recently, Weeks *et al*[21] agreed with this conclusion in T1D. In contrast, in our study only 27.4% with JIA (26 of 95 patients) had the haplotypes HLA-DQ2/DQ8, which is comparable with the distribution in controls and the general population in our geographic area.[17] Four of our 23 patients (4.2%) had CD-specific antibodies, with histopathological confirmation of CD in all of them by small bowel biopsy. No patient without the HLA-DQ2/DQ8 genotypes had CD-specific antibodies or was diagnosed histopathologically with CD. Therefore, first-line testing to identify absence of the HLA-DQ2/DQ8 genotypes could eliminate repeated serological testing for CD-specific antibodies in 76% of patients.

Additionally, recent literature outlined differences in risk for CD conferred by each genotype, following a gradient: HLA-DQ2.5 homozygous (highest risk), HLA-DQ2.5 heterozygous or HLA-DQ2.5/DQ8 (high risk), HLA-DQ8 (moderate risk) and HLA-DQ2.2 (low risk).[22] In our study, whereas prevalence of the risk types DQ2/DQ8 did not differ between patients and controls, differentiation of genotypes in DQ2.5, DQ2.2 and DQ8 revealed a significant difference. Since longitudinal data on development of CD in patients with JIA are lacking, these findings possibly might allow better risk stratification for these patients. However, in dealing with patients, it is important to communicate that even found to be at high genetic risk, does not confer the diagnosis CD, in order to avoid misinterpretation, possibly leading to disproportional anxiety, or implementation of unnecessary restrictive diet.

No consensus exists concerning optimum frequency for serological screening in asymptomatic individuals at risk. Whereas ESPGHAN and BSPGHAN recommend screening every 2–3 years,[11 12] International Society for Pediatric and Adolescent Diabetes (ISPAD) recommend CD antibody screening at the time of diagnosis of T1D, annually for 5 years and the biannually, without HLA screening.[11 12 23] Based on our findings, with identification of CD in the three asymptomatic patients at their first, second and third screening, respectively, our chosen practice of a yearly screening, in accordance with the ISPAD recommendations in patients with T1D, seems to be appropriate in patients with JIA. However, further larger studies should be done to confirm our suggested approach.

Increased familial risk for autoimmunity among patients with JIA is well recognised. In our cohort, overall prevalence of autoimmune disorders in relatives was significantly increased, consistent with data from previous studies.[6 24 25] But in contrast to those studies, which found the highest prevalence in the oligoarticular group, we found the highest prevalence in the psoriatic arthritis group, followed by the enthesitis-associated group and then by the oligoarticular group, as a result of a different composition of the study populations. Interestingly, no member of our cohort had a family member with CD, whereas Stagi *et al*[6] reported on 9% in their study.

Associated autoimmune diseases, including CD, were found in 13.7% of our patients with JIA. In two patients clustering of three autoimmune diseases was observed. Both patients were diagnosed with CD. In one of them, T1D was recognised 3 months later and in the other one AIT was diagnosed 4 years after diagnosis of CD. This observation is in agreement with other studies[6–8] and supports the hypothesis of sharing similar pathogenic autoimmune mechanism or a genetic defect in the same responsible genes.[2 26 27]

Unlike patients with T1D, patients with JIA mostly receive immunosuppressive medication, which may influence the generation of diagnostic antibodies. In our study, 71 of 95 patients (74.6%) were being treated with immunosuppressive agents. Among these, 71 were 19 of the 26 patients with a risk genotype. Ecevit *et al*[28] described a woman of HLA-DQ2 genotype aged 25 years, who underwent liver transplantation for CD-associated cryptogenic cirrhosis. Under subsequent immunosuppressive therapy, CD-specific antibodies disappeared without dietary exclusion of gluten; the patient was without

symptoms of CD. Other reports also indicate that CD may respond to immunosuppression in patients whose status does not improve with gluten-free diet.[29 30] Gillett *et al* reported on an old woman aged 47 years, failing sufficient response of her severely diet refractory CD, despite immunosuppressive treatment with ciclosporin and steroids, achieving dramatic response following therapy with infliximab, a chimeric monoclonal antibody against TNF-α. The authors describe the role of TNF-α in the pathogenesis of CD and suggest to consider anti-TNF-α treatment in selected patients.[31] Whereas the four patients, diagnosed with CD were not treated with anti-TNF-α agents at time of diagnosis, one-third of the HLA-DQ2/DQ8-positive patients in our cohort received these at time of CD screening. Therefore, one could speculate that development of CD could be suppressed in these. These reports support the recommendations of ESPGHAN/BSPGHAN to screen genetically in patients with increased risk, especially in those treated with immunosuppressive or biological agents.

Costs are also a point to consider in selection of screening procedures. In our cohort, HLA testing could eliminate costs of repeated antibody testing in most patients. Comparing the costs for the two screening strategies showed cost savings from the second year of follow-up onwards, if yearly screening is desired.

In summary, in our cohort JIA was associated with CD; CD occurred in patients with JIA at a rate 14 times greater than that in the general population. This association warrants general screening of patients with JIA for CD. Determination that the HLA-DQ2/DQ8 genotypes are absent eliminates the need for repeated serological testing in most patients, with resultant cost savings. Prospective HLA genotyping appears appropriate as a first step when screening for CD in patients with JIA.

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Contributors AS-B: conceptualised and designed the study and recruited patients and sampled data. AS-B drafted the initial manuscript and revised the final manuscript. AH: analysed data. WE: performed measurements and analysed data. JJ: helped in designing the study and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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