Enhanced monitoring and screening in pediatric coeliac disease

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CHAPTER 5

Towards an individual screening strategy for first degree relatives of coeliac patients

EUR J PEDIATR. 2018 NOV;177(11):1585-1592

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Abstract

Coeliac disease (CD) is known to be more prevalent in first-degree relatives of patients. In this retrospective cohort study of 609 relatives between 1994 and 2016, we investigated the effect of sex, HLA-type and age at time of index coeliac diagnosis. Pearson's Chi-square test and Kaplan-Meier survival analysis were used as statistical analyses. CD screening was carried out for 427 relatives (70%), resulting in a prevalence of 15%. HLA-typing in 335 relatives showed HLA-DQ2/DQ8 positivity in 87.5%. In 63% of children and all parents, coeliac disease was diagnosed at first screening. It was diagnosed significantly more often in females, HLA-DQ2 homozygosity, and children (all $p<0.05$). In children aged 0-1 year at time of index diagnosis, coeliac disease was diagnosed after consecutive screening in 58%, after 3.9 + 2.5 (max 10) years ($p<0.001$).

CONCLUSION Future screening policies for relatives of coeliac patients should include retesting, especially in HLA-positive relatives younger than 10 years of age. In addition, one-time coeliac specific antibody testing alone could be sufficient to rule out the disease in adolescent siblings and parents of newly diagnosed coeliac patients.

Introduction

Coeliac disease (CD), which can develop at any age, is a chronic, immune-mediated disease in which alterations occur in the mucosa of the small intestine induced by ingestion of gluten in genetically predisposed individuals[1]. Gluten are storage proteins in wheat (gliadin), rye (secalin) and barley (hordein)[2]. The diagnosis of CD is made through detection of the presence of a variable combination of gluten-dependent clinical manifestations, CD specific antibodies, HLA-DQ2 and/or HLA-DQ8 haplotypes and enteropathy[1]. Serological testing for CD is possible through detection of IgA class transglutaminase type 2 antibodies (TG2A), endomysium antibodies (EMA) or antibodies against deamidated gliadin peptides[1,3]. CD can be successfully treated with a life-long gluten-free diet, which restores small bowel histology and clinical complaints in most cases[4]. CD is found to occur in 1% of the general population[5]. It is often unrecognized, which can be partially explained by the variable clinical presentation, from diarrhea, weight loss and abdominal pain, to nonspecific signs and symptoms such as fatigue, osteoporosis, iron deficiency anaemia and no symptoms at all, referred to as silent CD[1]. Later in life, untreated CD can lead to an increased risk of osteoporosis and even cancer[2,6].The disease is multifactorial, and one in which genetics plays an important role. In 90-95% of coeliac patients the HLA-DQ2 haplotype is identified, with HLA-DQ8 being present in most of the remaining patients. Both haplotypes occur in 30-40% of the general population, which indicates that these haplotypes are necessary, but not sufficient, for developing CD[1]. As already demonstrated in many studies, first-degree relatives (FDRs) of coeliac patients are at a higher risk of developing CD than the general population, with a prevalence of CD in FDRs varying from 2.6-11.9%[7-16]. Therefore, the Dutch and European CD guidelines recommend CD screening in individuals at risk of developing CD, such as FDRs[1,3]. In FDRs without the HLA-DQ2 and/or DQ8 haplotypes, the chance of developing CD is nil, so follow-up through further CD investigations can be omitted[3]. On the other hand, FDRs who carry the HLA-DQ2 and/or DQ8 haplotypes, have an increased risk of approximately 10% of developing CD[16-18]. Thus, since CD is a condition that can evolve at different stages in life, repeated serologic tests for CD can be necessary in HLA-DQ2 and/or DQ8 positive FDR's[15,19]. Several studies have shown that the risk of developing CD among FDRs is influenced by multiple factors, such as age, sex, relationship with the index patient and HLA-genotype[11,16,20,21]. However, CD guidelines do not give guidance about the frequency of CD screening and duration of follow-up needed in HLA-DQ2 and/or DQ8 positive FDRs.

The aim of this study in FDRs is to investigate the effect of sex, HLA-type and age at time of CD diagnosis in the index coeliac patient, in order to establish a better screening protocol for these high risk individuals.

Methods

Study design and participants

A historic cohort in the Rijnstate Hospital in Arnhem, the Netherlands, included mothers, fathers and siblings of all 174 consecutive pediatric CD patients (up to 18-years) from 1994 until January 2016. After 2012, two CD-specialised gastroenterologists in our hospital started to refer offspring to the pediatric gastroenterologist, therefor 24 children (10 female) of 16 adult biopsy proven CD patients were also included between 2012 and January 2016. All pediatric coeliac diagnoses were based on ESPGHAN diagnostic criteria and all patients were seen at least once by succeeding pediatric gastroenterologists with a special interest in CD[1,22]. In parents, CD diagnosis was based on a combination of positive CD specific serology and Marsh > 2 duodenal lesions. FDRs were identified using the electronic patient record system, where detailed descriptions of the family setting are registered. Cross-check was done by identifying individuals living at the same address as the coeliac patient in order not to overlook FDRs. The FDRs were categorized in groups according to their age at time of coeliac diagnosis in the index patient: group 1: 0-1 year, group 2: 2-5 years, group 3: 6-10 years, group 4: 11-24 years, group 5: >25 years. Groups 1-4 represent the siblings and children of coeliac patients and group 5 represents the parents of the index coeliac children.

According to (inter)national guidelines, screening was offered to all FDRs. Follow-up of FDRs was also discussed. If parents wanted follow-up screening in their (other) HLA-DQ2 and/or DQ8 positive children annual or biannual visits were planned with screening of at least EMA combined with TG2A in most cases. Standard follow-up was not advised to parents themselves.

Since we focussed on FDRs and their specific risk of developing CD, relationship to the CD index patient was recorded. Also dated CD-specific serology, HLA-typing results (when performed) and diagnostic duodenal biopsies were recorded. In FDRs the follow-up duration until eventual CD diagnosis was defined as the time between diagnosis of the index patient and CD diagnosis in the FDR. Total follow-up duration was defined as the time between diagnosis of the index relative of a FDR and the time of analysis in February 2016. HLA-typing results were considered as unknown if no HLA results were found in the electronic patient record, as negative if negative for DQ2 and DQ8, and as positive if positive for DQ2 and/or DQ8. HLA-DQ2 and/or DQ8 positive results were categorized according to the risk of development of the disease[11,16,18] into a high, intermediate and low risk group as defined in **Table 1**.

Table 1 *HLA risk group classification*

HLA risk group	Haplotypes
High-risk	DQ2DR3/DQ2DR3, DQ2DR3/DQ2DR7
Intermediate-risk	DQ2DR3/DQ7DR5, DQ2DR7/DQ7DR5, DQ2DR3/DQ8DR4, DQ2DR3/other*, DQ2DR7/DQ2DR7, DQ2DR7/other
Low-risk	DQ2DR7/DQ8DR4, DQ8DR4/DQ8DR4, DQ8DR4/DQ7DR5, DQ8DR4/other, DQ7DR5/DQ7DR5, DQ7DR5/other

* Other: refers to any HLA-DQ haplotype except DQ2DR3, DQ2DR7, DQ8DR4 or DQ7DR5.

Statistical analysis

Pearson's Chi-square test, unpaired t-test, Mann-Whitney U test and Kaplan-Meier survival analysis were used where appropriate. For comparison, a log-rank test was used stratified according to sex, HLA risk group or age group. For each item, a difference was found significant if $p < 0.05$. The data was analyzed in version 21.0 of the IBM Statistical Package for the Social Sciences (SPSS).

Medical ethical consideration

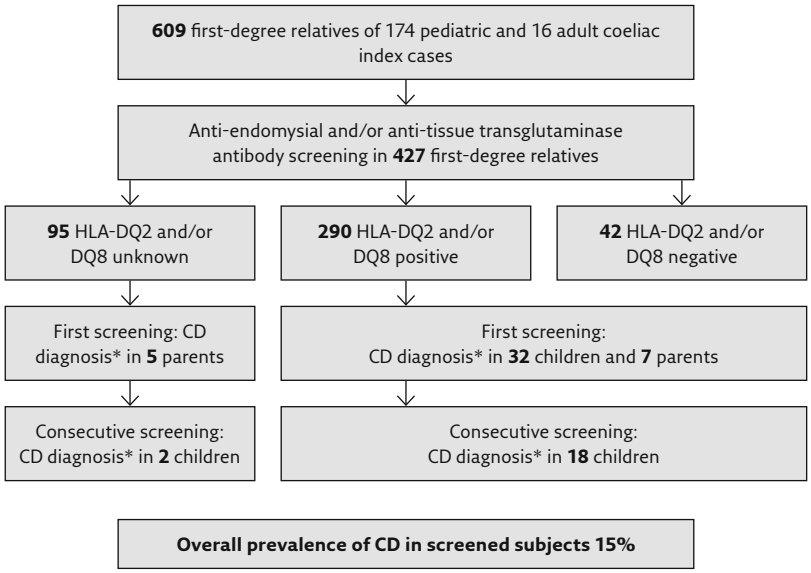
The procedures followed were in accordance with the ethical standards of the Medical Research Involving Human Subjects Act and the principles of the declaration of Helsinki (59th General assembly, Seoul, October 2008) of the World Medical Association. Formal approval from the local feasibility committee of Rijnstate Hospital Arnhem was obtained.

Results

A total of 609 FDRs were identified, for which it was found 70% (n=427) had been screened for CD (205 parents, 181 siblings and 41 offspring). The reasons for not performing screening in the other 182 FDRs were not known. The overall prevalence of CD in the screened subjects was 15% (64/427). In 30% of all cases, CD was diagnosed after the initial screening. The participant flow is shown in **Figure 1**.

Table 2 shows the characteristics of the 427 screened FDRs with regard to sex, relationship to the index patient, age at time of diagnosis of CD in the index patient, HLA risk group and follow-up duration. Significantly more females were diagnosed with CD (61%,

Figure 1 *Flow chart of participants (first-degree relatives of coeliac patients)*



* Coeliac disease (CD) diagnosis in children based on ESPGHAN diagnostic criteria, CD diagnosis in parents based on combination of positive CD specific serology and Marsh 2-3 duodenal lesions.

p=0.031), however this gender effect was observed only in sisters and not in mothers and daughters of CD index patients (**Table 2**). HLA-typing was performed in 332 FDRs and 12.7% of them were found to be HLA-Q2 and/or DQ8 negative and therefore not at risk for CD.

Among the 290 FDRs who were HLA-DQ2 and/or DQ8 positive, CD was diagnosed in 29% of the children (34 siblings and 16 offspring) and 6% of parents (3 mothers and 4 fathers), with a mean follow-up duration after CD diagnosis in the index patient of 2.7 years (SD ± 3 years). In 18% of the siblings and offspring, diagnosis was established without duodenal biopsies according to the latest ESPGHAN criteria because there were symptoms suggestive of CD[1]. In all parents, CD was diagnosed based on duodenal biopsies except in one mother, who was both TG2A and HLA-DQ2 positive and had resolution of symptoms after starting a gluten-free diet.

Table 2 *Characteristics of the 427 first-degree relatives of celiac patients with screening of coeliac disease (CD).*

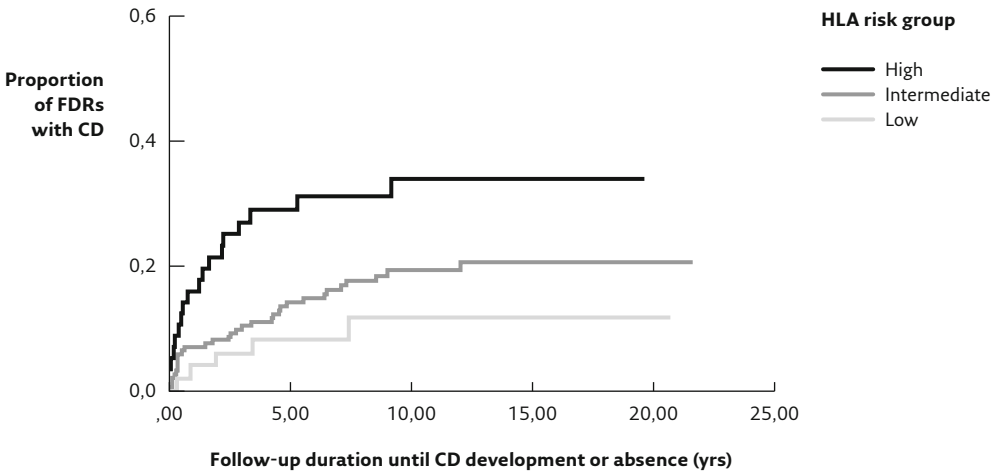
Characteristic	CD +	CD -	HLA-DQ2 and/or DQ8 -
Number of subjects	n = 64	n = 321	n = 42
Age at diagnosis of CD in index patient – years			
Children, p=0.67	4.0 ±4.2	4.3 ±4.7	3.4 ±4.1
Parents, p=0.30	34.8 ±4.2	36.3 ±5.1	34.5 ±4.4
Sex – Female, %, p=0.031			
Relation of FDR to index patient – %, p<0.001	61	47	62
Mother	11	26	38
Father	9	27	14
Sister	39	18	22
Brother	16	22	22
Daughter	11	3	2
Son	14	4	2
HLA risk group – %, p<0.001			
High	28	12	NA
Intermediate	52	47	NA
Low	8	14	NA
Unknown	12	27	NA
Mean follow-up duration in years until CD development or end of follow-up†			
Children, p<0.001	3.1 ±3.4	8.8 ±5.1	NA
Parents, p<0.001	1.5 ±1.7	9.9 ±5.3	NA

† Mean follow-up duration until CD development or not = time between CD diagnosis in the index patient and CD diagnosis in the FDR and/or the time of the study (January 2016).
NA: Not applicable

As shown in **Table 2**, the intermediate-risk HLA genes (DQ2DR3 heterozygosity and DQ2DR7 homozygosity) were the most prevalent, both in FDRs who were diagnosed with CD and those who were not (52% and 47% respectively). In contrast, high-risk HLA genes (DQ2 homozygosity) were significantly more common in FDRs who were diagnosed with CD (28% versus 12% in the FDRs without CD, p=0.001). The Kaplan-Meier survival analysis according to HLA risk group in **Figure 2** shows that FDRs with high risk HLA genes were diagnosed significantly earlier than those in the intermediate or low risk groups (p=0.011). In 90% of the high risk FDRs, CD was diagnosed within 4 years of the diagnosis of the coeliac index case (13 at first screening and 3 during follow-up) compared to 80% and 75% in the intermediate and low risk group respectively.

In the 95 FDRs in whom HLA-typing had not been performed (noticeably more parents than children: 59% vs 33% respectively), CD was diagnosed in 3 mothers and 2 fathers

Figure 2 *Coeliac disease (CD) diagnosis according to HLA risk group by means of Kaplan-Meier survival analysis*



and in 2 siblings, all based on positive CD specific serology and Marsh 3 duodenal lesions. There were no differences with regard to sex and mean follow-up time to CD diagnosis between FDRs with and without performed HLA-typing (data not shown).

Table 3 *Correlation between the age of the first-degree relative (FDR) at time of index coeliac diagnosis and the age of the FDR at own coeliac diagnosis.*

	Children				**Parents**
Age groups	**0-1 yr n = 90**	**2-5 yrs n = 52**	**6-10 yrs n = 45**	**11-24 yrs n = 17**	**25-48 yrs n = 181**
CD diagnosis (n)	24 (27%)	12 (23%)	11 (24%)	4 (24%)	13 (7%)
CD diagnosis at first screening (represented as % of CD diagnoses)	42	90	72	100	100
Mean follow-up duration until CD diagnosis (Q1-Q3 Tukey Hinges)	3.9 (1.9-5.4)	2.8 (0.2-5.2)	2.6 (0.2-6.4)	0.6 (0-1.1)	1.5 (0.5-1.9)
Follow-up duration without CD diagnosis (Q1-Q3 Tukey Hinges)	9.4 (6.1-12.2)	10.1 (5.2-15.1)	6.5 (2.4-10.8)	7.4 (0.5-10.7)	9.9 (5.8-13.9)
Mann-Whitney U test with regard to follow-up duration, p-value	<0.001	<0.001	0.003	<0.001	<0.001

* SD= standard deviation

** Mean follow-up duration in years without CD diagnosis until analysis in February 2016

Table 3 shows the significant association between the age of the FDR at time of coeliac diagnosis in the index patient and the identification of CD after the first screening ($p<0.001$), with young children being diagnosed after a longer follow-up period than older children and adults. Siblings and offspring were significantly more often diagnosed with CD when compared to parents of coeliac patients (25% and 7% respectively, $p<0.001$).

In total, CD was diagnosed at first screening in 63% of the children and in all the parents (**Table 3**). The youngest group (0-1 years) had the lowest CD identification rate at first screening (42%), while all CD cases were identified within 10 years of follow-up. All children aged 2-5 years were diagnosed at first screening, except for one sister, aged 2.2 years at the time of CD index diagnosis, who was diagnosed at the age of 7.1 years (**Table 3**). In children aged 6-10 years, only 2 siblings were not diagnosed during the first screening (sister of 6.7 years and brother of 6.8 years of age at the time of index diagnosis, diagnosed during follow-up at 12 and 14.8 years respectively). Both siblings had complaints suggestive of CD, being the reason for the renewed follow-up screening. All other coeliac children in this age group were identified during first screening. In the adolescent group (11-24 years) all coeliac cases were identified during first screening. In the majority of parents (61%), first CD screening was done within 1 year after diagnosis in the index patient, in 3 parents (23%) after 1-2 years and in 2 parents (15%) after 4.0-5.6 years.

Discussion

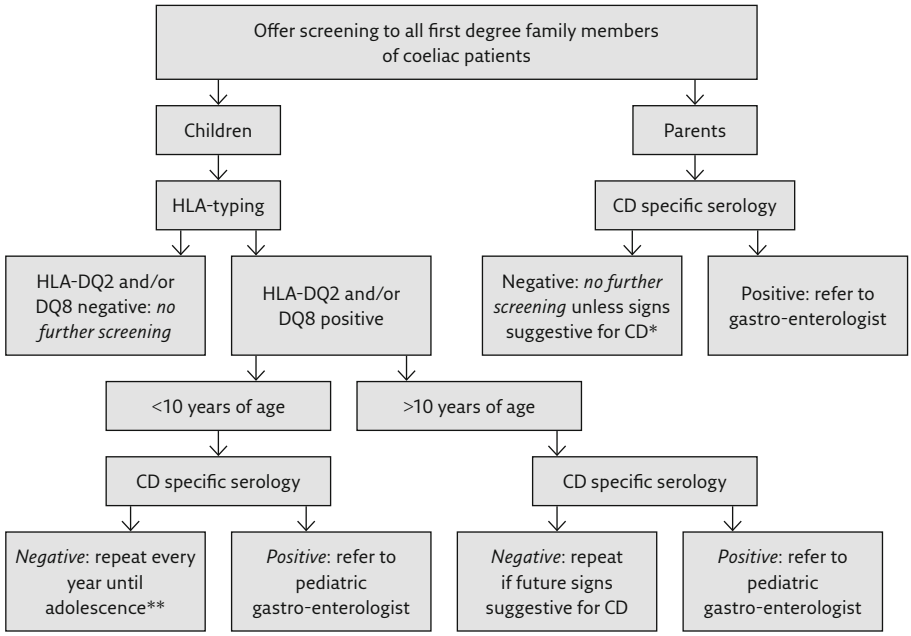
This retrospective cohort study in families of coeliac patients substantiates the higher prevalence of CD found in FDRs, which in our study was 15% after screening. Our data show a higher rate of CD in siblings and offspring when compared to parents of CD patients, as demonstrated by previous studies and a recent meta-analysis[8,21,23]. Again, as previously demonstrated, we found a higher prevalence of CD in sisters of CD patients[21]. In agreement with the results of prospective studies in birth cohorts of FDRs, we have found a significantly higher prevalence, at a younger age, in children who are HLA-DQ2 homozygous[11,24].

Our results suggest that the timing of CD specific antibody testing could be individualized depending on the relationship of the FDR with the index patient and her/his age at time of the index diagnosis. Since all CD cases in adolescents and parents were detected during first screening, further follow-up screening might not be necessary in this age category. Although there were 2 parents with a longer interval between the coeliac diagnosis in the index patient and their own diagnosis, diagnoses in these cases were still the result of the first screening. The reason for this delay could not be retrieved from the patient records, but might be due to the fact that screening was left to the discretion of the parents.

Our findings with regard to CD diagnosis in parents of coeliac patients are in accordance with a Swedish cohort of FDRs who were retested 20-25 years after first CD screening because of newly diagnosed CD in the family[25]. Only 2 new cases of CD were found, with one of these FRDs already having mild enteropathy 20-25 years earlier. On the other hand, our findings support the fact that repeated screening is necessary in offspring of CD patients and siblings younger than 10 years of age in order to be able to diagnose CD. Due to the retrospective nature of our study we can only indicate that repeated screening for CD beyond the age of 10-12 may not be necessary. All children in our cohort who were diagnosed during adolescence, were either adolescents at the time of first screening or had a long period between the first and follow-up screening.

The strength of our study lies in the fact that we have studied a large group of FDRs. The percentage of CD found in our cohort (15%) was similar to the percentages found in other studies[11,21,26] so the results appear representative of coeliac FDRs in general. This

Figure 3 *Screening algorithm for family members of (newly) diagnosed coeliac patients*



* Consider HLA-typing and referral to gastroenterologist in case of negative CD specific antibodies but signs suggestive for coeliac disease: consider gluten challenge and reinvestigation.

** During adolescence: repeat CD specific serology in case of future signs suggestive for coeliac disease

is supported by the distribution of HLA-types found in our cohort which is similar to other cohorts described in the literature[11,16,24], even though the percentage of HLA-DQ2/DQ8 negative FDRs in our study (12.5%) was somewhat lower than described before (14-21%)[11,27,28].

One possible limitation is the retrospective cohort study design. After initial screening of CD, which was done in 70% of FDRs, CD specific antibodies were not tested on a regular basis, since it was left to the FDRs/parents whether follow-up took place[23]. A stringent repetitive screening policy in FDRs might have led to an even higher prevalence of CD than found in our study, therefore stressing further the importance of follow-up. Prospective studies with regular screening of FDRs are needed to be able to develop a tailored and effective screening strategy for CD in FDRs. In the meantime, we propose an algorithm that can be used, preferably within the first months after coeliac diagnosis (**Figure 3**).

Since family members tend to have a lower gluten containing diet when compared to the general population, one has to bear in mind that negative serology in HLA-DQ2 and/or DQ8 positive FDRs can lead to unjust reassurance. In those cases, gluten challenge with repeated serology and duodenal biopsies are justified.

Conclusion

Screening of FDRs of coeliac patients in a clinical setting revealed a prevalence of CD of 15%. Repeated testing of CD specific serology in HLA-DQ2 and/or DQ8 positive siblings and offspring, younger than 10 years of age at the moment of CD diagnosis in the index patient, is necessary to diagnose CD as early as possible. This should be continued until at least early adolescence (10-12 years of age) and is especially true in HLA-DQ2 homozygous siblings of coeliac patients. In addition, one-time CD specific antibody testing could be sufficient to diagnose CD in siblings who are adolescents at the time of diagnosis in the index patient, and parents of newly diagnosed coeliac children. Our results may contribute to developing future recommendations for CD screening frequency and follow-up duration of relatives of coeliac patients.

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