

Respiratory Infections and the Risk of Celiac Disease

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abstract

BACKGROUND AND OBJECTIVES: The increasing incidence of celiac disease (CD) suggests that common infections before the onset of autoimmune diseases could be an important factor in switching the immune response. We aimed to explore the relationship between early clinical events and the development of CD in genetically predisposed infants.

METHODS: In this study, 373 newborns from families with at least 1 relative with CD were recruited, and human leukocyte antigen DQ2- or DQ8-positive infants were followed up with clinical and serological evaluations. Cross tabulation and odds ratios were used to explore the risk associated with single variables, and logistic regression analysis was performed to determine the variables that contributed to the risk of developing CD. Stepwise discriminant analysis was used to determine which variables could distinguish case patients from controls before diagnosis.

RESULTS: The cumulative incidence of CD in this cohort was 6% at 3 years and 13.5% at 5 years of age, and 134 children (14%) developed CD before the sixth year of life. An analysis of adverse events showed a higher frequency of respiratory tract infections among CD patients during the first 24 months of life. In a stepwise discriminant analysis, which included sex and human leukocyte antigen risk class, only respiratory infections in the second and first years of life significantly contributed to discrimination of case patients versus controls.

CONCLUSIONS: A multivariate model of discriminant analysis showed that the frequency of respiratory infections in the first 2 years of life could distinguish children who developed CD from those who did not.



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WHAT'S KNOWN ON THIS SUBJECT: The incidence of celiac disease (CD) is increasing globally, and its transmission is only partially explained by genetic and nutritional factors. Early infections might contribute to the risk of developing CD.

WHAT THIS STUDY ADDS: This longitudinal study of CD screening found that respiratory infections during the first 2 years of life are associated with a higher risk of CD in high-risk infants.

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The incidence of celiac disease (CD) is epidemic in communities that consume gluten. The incidence of CD is increasing globally, especially in emerging countries, where it has become a major public health burden.¹ At least 5 million new cases of CD are expected to be diagnosed in Mediterranean countries in the next 10 years.² Familial cases represent a large proportion of this increase because a significant increase has occurred in the prevalence of CD in infants from at-risk families. We estimated that the familial recurrence is ~13% to 15% during the first 6 years of life and more than 20% later in life.³⁻⁵ When we consider human leukocyte antigen (HLA) DQ2- or DQ8-positive infants from families with a proband, the risk of developing CD is not homogenous across the progeny.⁶ Only up to 40% of the heredity of CD is explained by the HLA haplotype and the 54 other CD-associated genes.⁷ Nutritional factors do not appear to confer additional risk for the development of CD.^{3,8} Before any clinical signs of CD appear and at least 1 year before anti-tissue transglutaminase antibodies (anti-tTG) are produced, infants who develop CD within the first 6 years of life show distinct expression patterns of immune-related and non-immune-related CD-associated genes.⁹

We are interested in understanding whether the process of autoimmunity leading to CD is stimulated or switched on by the occurrence of common infections during the period preceding its onset. The authors of several studies have suggested that early infections might contribute to the risk of developing CD. This connection was proposed in 2013 when a study revealed an association between rotavirus infections and the recognition of gluten peptides.¹⁰ Anti-rotavirus VP7 antibodies are present in the majority (81%) of serum samples from patients with diabetes mellitus type 1 and CD but are also

detectable in a fraction (27%) of children with diabetes mellitus type 1 without CD. Moreover, it was found that anti-rotavirus VP7 antibodies are present in the sera before the onset of CD and the detection of anti-tTG and anti-endomysium antibodies.¹⁰ In the Norwegian Mother and Child Cohort Study,¹¹ 581 children (0.8%) were diagnosed with CD. Children with ≥ 10 infections before 18 months of age had a significantly higher risk of developing CD later in life than children with ≤ 4 infections. The added risk of CD was associated with upper respiratory tract infections, lower respiratory tract infections, and gastroenteritis. In an Italian prospective cohort study, 1227 children developed CD among 203 000 infants; in this study, gastrointestinal infections were significantly associated with a subsequent diagnosis of CD (incidence rate ratio, 2.04).¹² Furthermore, a Swedish retrospective case-control study investigated 3835 children diagnosed with CD before the age of 2 years and found that 36 (0.9%) had a previous diagnosis of respiratory syncytial virus compared with 117 (0.6%) out of 19 102 matched controls (odds ratio [OR], 1.46).¹³ The highest risk was observed in children who developed CD before 1 year of age (OR, 1.82). The authors also described a previous incidence of viral bronchiolitis in 3.4% (132 out of 3835) of the case patients with CD and in 2.0% (390 out of 19 102) of the matched controls (OR, 1.60).¹³

However, epidemiologic studies are difficult to interpret because it is difficult to control for confounding variables and recall bias. Therefore, a prospective study of a cohort of at-risk infants, stratified for HLA genetic risk, is ideal to study risk factors for the development of CD.

The aim of this study was to explore the relationship between early clinical events (including infections) and the development of CD in a

prospective cohort of genetically predisposed infants.

METHODS

Patients

A cohort of 373 Italian newborns with 1 first-degree relative with a confirmed case of CD was enrolled in this study from 2007 to 2015 (191 female participants). Until 2011, the newborns were enrolled and followed up with the PreventCD European project,¹⁴ and after 2011, newborns were enrolled and followed up with the PreventCD protocol. Among the newborns, 248 (124 boys and 124 girls) were genetically predisposed to CD by the presence of the HLA DQ2 or DQ8 haplotype. The predisposed individuals were strictly monitored from birth through the end of their sixth year of life.

The follow-up protocol included monthly clinical and serological assessments during the first 6 months of life, followed by assessments every 3 months until 1 year of age, every 6 months between the first year and the third year of life, and then annually until the sixth year of life.

The mothers were encouraged to breastfeed for at least 6 months, and all children were gradually weaned and introduced to gluten between 6 and 9 months of age.¹⁴

Sample Size Estimation

This prospective cohort study included 248 infants. To estimate the incidence of CD (the percentage of the enrolled participants who developed CD within the first 6 years of life), we compared an expected incidence of 10% in the infants not exposed to infections with a predicted incidence of 25% in the infants exposed to infections, and by using a 95% confidence interval, we estimated a minimum sample of 37 cases of CD.

Recording Growth and Health

The growth and health of each infant was regularly reported at each visit (4, 6, 9, 12, 18, 24, 36, 48, 60, and 72 months) in a personal logbook that was kept at home, shared with the family pediatrician, and systematically copied at the study center. All visits to the family pediatrician and drug prescriptions were reported. Infections were recorded by the family pediatrician or at the center only if they had a duration of >24 hours and required medical attention, according to the usual well-infant clinic protocol adopted regionally by the family pediatrician.

The reported clinical events (gastroenteritis, diarrhea, vomiting, fever, constipation, and upper and lower respiratory tract infections) were grouped into bins of 6 months (eg, 0–6, 7–12, 13–18 months, etc). Incidences of diarrhea and gastroenteritis that occurred in the 3 months preceding the diagnosis of CD were considered related to the diagnosis and, therefore, were excluded from the analysis.

During the 6 years of observation, 35 subjects (14.1%) were diagnosed with CD (14 boys, 21 girls) to be further referred to as the case patients. The children who did not develop CD by the age of 6 years will be referred to as controls. The diagnosis of CD was based on the repeated production of elevated anti-tTG and the development of severe mucosal damage (Marsh type 3c). Of the 35 CD case patients, 14 out of 35 children showed relevant clinical symptoms, whereas 21 out of 35 produced repeated positive anti-tTG antibodies without any clinical signs. To avoid selection bias, we did not exclude any case patient with missing data, and we obtained full log books of all clinically relevant events from 238 children (31 who developed CD and 207 who did not).

TABLE 1 Comparison of CD-Affected Relatives (Family Proband) in the Case Patients (With CD) and Controls (Without CD)

Affected Proband	Controls (%)	Case Patients (%)	Total (%)
Father ± siblings	22 (11)	9 (26.5) ^a	31 (13.2)
Mother ± siblings	106 (53)	14 (41.2)	120 (51.3)
Siblings	72 (36)	11 (32.4)	83 (35.5)

^a Statistical difference observed in case patients with father affected compared with controls ($P = .04$).

Statistics

The OR and the χ^2 test were used to explore the risk associated with single variables, whereas a logistic regression analysis was performed to determine the variables that contribute to the risk of developing CD. To obtain logistic regression scores, we grouped the number of events for each child and each time bin into a binomial classification (present or absent).

A survival analysis was used to observe the occurrence of events over time, with a Wilcoxon rank test used to compare groups.

Stepwise discriminant analysis was adopted to determine which variables were capable of distinguishing case patients from controls before the case patients were diagnosed. Wilks' λ (ranging from 1 to 0) was used to estimate the distance between the 2 groups (case patients and controls) produced by each variable entered into the discriminant function.

Ethical Approval

The study was approved by the medical ethics committee of University of Naples Federico II. The authors vouch for the veracity and completeness of the data and analyses reported and for the adherence of the study to the protocol.

RESULTS

Risk at Birth

The cumulative incidence of new cases of CD was 6% at 3 years and 13.5% at 5 years of age. CD was more frequent in girls (female to male ratio = 21:14 for case patients and 101:106 for controls), but the differences in the sex distribution were not statistically significant ($P = .47$).

No differences were observed in the age of the mother, weeks' gestation, or birth weight between the case patients and controls (Supplemental Table 4). Conversely, significant differences were observed for the type of delivery, with 23 out of 32 of the case patients (72%) and 96 out of 175 of the controls (55%) born by a cesarean delivery ($P = .05$). The proband within the family was also different; 9 out of 34 of the case patients (26.5%) and 22 out of 200 (11%) of the controls had a father that was affected by CD ($P = .04$). The frequency of siblings affected by CD was similar among the case patient and control groups (Table 1).

No significant difference was observed in the mean duration of breastfeeding (case patients, 6.93 months; controls, 5.93 months). Gluten introduction (see "per protocol" described ref 15) was also similar in both groups.

Risk Related to Events

Table 2 shows the incidence (new events, child, year) of symptoms and infections for the case patients and the controls during the first, second, and third years of life. The log books of reported events were complete for 31 case patients who developed CD and 207 controls who did not.

During the first year, when no child produced anti-tTG antibodies, respiratory infections (upper and lower tract) were more common among the case patients than among the controls (58.1% vs 40.1%).

In the second year of life, respiratory infections were again more frequent among the case patients than controls (51.6% vs 32.4%).

TABLE 2 Incidence of Clinical Events (Symptoms and Infections) in Case Patients and Controls in the First 3 Years of Life

	No. of Incident Events		OR (CI)
	31 Case Patients (%)	207 Controls (%)	
First year			
Gastroenteritis	6 (19.4)	46 (22.2)	0.84 (0.32–2.17)
Vomiting	5 (16.1)	35 (16.9)	0.94 (0.34–2.63)
Fever	7 (22.6)	40 (19.3)	1.22 (0.49–3.02)
Constipation	5 (16.1)	13 (6.3)	2.87 (0.94–8.70)
Respiratory infections	18 (58.1)	83 (40.1)	2.07 (0.96–4.44)
Second year			
Gastroenteritis	10 (32.3)	43 (20.8)	1.81 (0.79–4.14)
Vomiting	1 (3.2)	8 (3.9)	0.89 (0.10–6.88)
Fever	4 (12.9)	25 (12.1)	1.07 (0.35–3.33)
Constipation	3 (9.7)	12 (5.8)	1.74 (0.46–6.55)
Respiratory infections	16 (51.6)	67 (32.4)	2.23 (1.04–4.77)
Third year			
Gastroenteritis	6 (19.4)	21 (10.1)	2.12 (0.78–5.77)
Vomiting	1 (3.2)	6 (2.9)	1.11 (0.13–9.60)
Fever	3 (9.7)	18 (8.7)	1.12 (0.31–4.06)
Constipation	1 (3.2)	13 (6.3)	0.49 (0.63–3.94)
Respiratory infections	11 (35.5)	54 (26.1)	1.55 (0.70–3.46)

CI, confidence interval.

In the third year of life, which is when most of the case patients were diagnosed with CD, no clinical event was more frequent in the case patients than in the control group. Only gastroenteritis was marginally increased among the case patients.

Multivariate Analysis

Because clinical events are related each other (eg, fever is likely to be associated with infection, vomiting is associated with gastroenteritis, etc), we conducted a multivariate analysis to explore the differences in the occurrence of risk-related events between the case patients and the control group.

Once all the clinical events were grouped into a present or absent binomial classification, a logistic regression was adopted to estimate the crude OR for developing CD

according to the clinical events during the first 3 years of life (Table 3). Only respiratory infections in the second year of life were associated with a twofold increase in the risk of developing CD (OR, 2.25; confidence interval: 1.03–4.88; $P = .04$). The second variable, which was not included in the model, was respiratory infections in the first year of life, which had a score of 1.58.

We performed a stepwise discriminant analysis to determine which of the clinical events discriminated between the case patients and the controls (Supplemental Tables 5 and 6). For this analysis, we used the full information for the number of clinical events in each time bin (0–6 months, 7–12 months, etc, on a scale from 0 to 5 events) for each child. We included sex and HLA risk class in the model. As shown in Supplemental Table 4, only respiratory infections in the second

and first years of life significantly contributed to the lower Wilks' λ , the index of discrimination. Sex and HLA risk class did not significantly contribute to the discrimination of this model once clinical events were included (data not shown in the tables).

DISCUSSION

Children from families with at least 1 first-degree relative with CD have an estimated probability of 13% of developing CD within the first 6 years of life.

Confirming previous studies, we showed that newborns who were homozygous for the HLA DQ2 haplotype were at a higher risk of developing CD.^{3,5,15} A single copy of HLA DQ2 conferred the second highest risk, whereas the HLA DQ8 haplotype was found more often in the controls. Despite the relatively small numbers in the cohort, we observed significant differences in the survival curve of each HLA haplotype risk group ($P = .02$, data not shown).

A higher rate of cesarean delivery, which was indeed high in our population, was observed in the children who developed CD within the first 6 years of life, contrary to what was suggested by Lionetti et al.¹⁶ We observed that more newborns that had a father affected by CD were subsequently diagnosed with CD (compared with those with a mother or sibling affected). This suggests that the genetic risk transmitted by the father is higher than the risk transmitted by the mother. The authors of several studies have shown that a father with CD may confer a higher risk to the progeny than

TABLE 3 Logistic Regression of the Clinical Events

	B	ES	Wald	Degrees of Freedom	Significance	OR	95% CI	
							Lower	Upper
Respiratory infection	0.812	0.396	4.211	1	0.04	2.252	1.037	4.888
second year constant	−2.244	0.281	63.723	1	0.000	0.106	NA	NA

The Wald statistic is the square of the ratio of the logistic regression coefficient to its SE and has a χ^2 distribution. B, unstandardized regression weight; ES, error standard; NA, not applicable.

affected mothers because of genetic risk factors and not to environmental prenatal factors.^{17,18}

Breastfeeding and gluten introduction could not be analyzed in this longitudinal study because of the study protocol, which strongly encouraged breastfeeding and set the timeline for the introduction of gluten at 6 months.

Compared with gastroenteritis, respiratory infections during the first 2 years of life conferred a twofold increase in the risk of developing CD. According to a multivariate model, the variance explained by respiratory infections was higher than that explained by sex or HLA haplotype. It should be noted that this cohort was selected by the presence of an at-risk HLA haplotype; therefore, no infants in this study were without an at-risk HLA haplotype.

Other longitudinal studies failed to reveal an association between early infections and the development of CD in genetically predisposed infants.³ However, this finding may be because of the complexity of the study design¹⁹ and not because of the absence of a risk effect. When each event is reported with its time point, without grouping into 6-month bins, the flat spread of the events over time causes an aliasing effect that may undermine the observation of significant results. The aliasing effect is produced by listing the mean time of events at different time points without setting a defined time interval. To explore the relationship between an event that may have occurred at any time and the subsequent appearance of CD, we stratified the reported events into 6-month bins, which reduced the time-related bias. Therefore, we could estimate the risk of developing CD in relation to the number of events that occurred during a set time interval.

CD has a strong genetic component, and ~40% of the transmitted genetic risk is explained by specific HLA haplotypes. In addition, 54

CD-associated gene polymorphisms confer up to an additional 10% of the genetic variance.²⁰ Therefore, nearly half of the heredity cannot be explained by known genetic risk factors. Additionally, most of the polymorphisms associated with CD do not produce changes in the amino acid sequence of the gene and are likely to have regulatory and epigenetic functions. To date, the search for environmental factors that explain the epidemic of CD has produced conflicting results.²¹ Neither breastfeeding nor gluten introduction, which have consistently been shown to be associated with a delay in the onset of CD, have been confirmed as factors that contribute to the development of CD.^{3,8,22} In addition, familial and perinatal factors that have been observed in large population cohorts have not been confirmed to be associated with CD.²³

In this study, we report that early infections significantly contribute to the risk of developing CD. It is possible that the exposure to early infection stimulates a genetically predisposed immune profile, which contributes to the switch from tolerance to intolerance to gluten, which is a common food antigen.

In recent studies, researchers have suggested that viruses that infect the intestines can disrupt intestinal immunity at inductive and effector sites of oral tolerance by the suppression of regulatory T cells and the promotion of a type 1 T helper cell response. Indeed, the activation of the type 1 T helper cells immune cascade after exposure to dietary antigens is likely related to the interferon regulatory factor 1, which is not related to the stop to regulatory T cell conversion.²⁴

The numerous reports on the protective effect of early infections against the development of autoimmune and allergic diseases,²⁵ described as the hygiene hypothesis, contradict the previously proposed hypothesis. Indeed, the immune

response to infections may modulate natural immunity via mechanisms that can drive tolerance as well as intolerance, according to the pathways involved.

Environmental factors that occur from the prenatal period to early infancy may actively modulate the immune response to gluten in individuals with peculiar genetic profiles and contribute to the gene–environment interactions by modulating gene expression through epigenetic mechanisms.^{9,20,26}

CONCLUSIONS

The strength of this study is the carefully planned design for a controlled longitudinal cohort study. Each child was monitored at home by the family pediatrician using a personal logbook of clinical events. The production of anti-tTG was strictly monitored at fixed time points. However, there are some limitations to this study. The time span of this study was limited to 6 years of life. Although 13.3% of at-risk infants develop CD by 6 years of age, further diagnoses may appear later in life. Furthermore, no laboratory tests could be used to support the reported incidence of clinical events.

The sample size of the cases is marginally smaller than the optimal predicted, and this may have limited our ability to show the significance of risk factors (type II error); a more precise estimation could be achieved by increasing the sample size.

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ABBREVIATIONS

anti-tTG: anti-tissue transglutaminase antibodies
CD: celiac disease
HLA: human leukocyte antigen
OR: odds ratio

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