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Do early infectious episodes contribute to the risk of celiac disease?

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DO EARLY INFECTIOUS EPISODES CONTRIBUTE TO THE RISK OF CELIAC DISEASE?

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ABSTRACT

Background: Celiac disease, a permanent gluten sensitive enteropathy, is the most common genetic disorder, although largely underestimated public health problem worldwide. The wide spectrum of its multifaceted manifestations is a continuum representing the outcome of a complex interplay of genetic and environmental factors with immunological processes suggesting its multifactorial etiopathogenesis and also involves the risk of malignancy. Despite of the new insights gained by recent advances in knowledge, etiopathogenesis still remains to be elucidated completely. Investigating the Swedish epidemic of CD by epidemiological approach has revealed the possible associations of CD with some environmental factors. Emphasizing the significance of events in early infancy in view of current CD aetiopathogenesis concepts and with relevance to the unique pattern of CD incidence trends in Swedish children, early infectious episodes emerge as seemingly important clue in etiology of CD. This study investigates the possible contribution to the risk from early infectious episodes to development of Celiac disease.

Objectives: This study aims to investigate possible contribution by early infectious episodes to the risk of development of celiac disease and discusses the findings in view of current concepts of CD aetiopathogenesis.

Methods:

Literature-review: A review of available knowledge from studies in the aetiopathogenesis of celiac disease was done to understand the possible association with environmental factors, in particular role of infectious episodes.

Study-design and data-analysis: Data from a Swedish population-based *incident case-referent study* with 627 confirmed cases of celiac disease and 1254 referents was analyzed to investigate a possible predisposition caused by early infections to celiac disease.

Results: Current literature suggests that infections may induce, trigger the development of CD (GI infectious episodes to the major extent) or may activate already latent CD by different mechanisms. However, our study concludes statistically significant risk associated with early infectious episodes of all types to the development of celiac disease. Besides, findings suggest higher risk associated with the combined effect of consumption of larger amounts of gluten and frequent infectious episodes.

Conclusion: This study presents the first epidemiological findings concluding increased risk to development of celiac disease associated with occurrence of infectious episodes during early infancy (before the age of 6 months), and suggests possible involvement of molecular mimicry or other mechanism. The findings also suggest focusing on early infancy and to the events that precede immunopathogenetic processes. Thus, it provides implication for the further exploration of complete immunolopathogenetic mechanisms involved in pathogenesis of celiac disease and it may prove rewarding in designing innovative preventive, immunomodulatory and antigen-centered therapeutic strategies.

BACKGROUND

Celiac disease (CD) or permanent gluten sensitive enteropathy is an immune-mediated enteropathy in genetically susceptible individuals caused by the permanent intolerance to ingested gluten. Although, being recognised as a most common genetic disorder, it remains a considerably underestimated public health problem worldwide attributed to its high prevalence associated with non-specific morbidity and long-term complications and sequelae [1-5].During the last few years significant advances have been made in the realms of genetics, gastroenterology, and immunology. Several recent reviews comprehensively describe the milestones in research of aetiopathogenesis of CD, the risk factors, immunological and environmental associations and suggest that complete elucidation of celiac disease aetiopathogenesis still remains unfinished [20-21] .The concepts of aetiology, pathogenesis and complications are in a process of reshaping by the ongoing research. The wide spectrum of its multifaceted manifestations placing significant burden of disease, is a *continuum* representing the result of a complex interplay of genetic and environmental factors with immunological processes and it ranges from potential susceptibility, latency, 'silence' and manifest symptomatic disease. Critical immunological processes occur, resulting in these phases, and may continue further to end up in serious complications. The complete revelation of so far mysterious multifactorial etiopathogenesis of CD may have significant implications on diagnosis, treatment and prevention strategies. Comparatively little research on environmental factors triggering or perpetuating the disease pathogenesis makes it crucial to emphasize its significance by the study of possible environmental predispositions by epidemiological approach.

The Iceberg of Celiac Disease across the globe

The clinical manifestations of CD are protean in nature in addition to its classical gastrointestinal form. Marked variations of disease manifestations with the age of the patient, the duration and extent of disease, and the presence of extra-intestinal pathologic conditions, a variety of other clinical manifestations of the disease have been described, including atypical and asymptomatic forms [6] giving rise to fractions of under-diagnosis, misdiagnosis, delayed diagnosis and the state where diagnosed symptomatic cases representing only the tip of the iceberg. Moreover, CD poses considerable health burden due to high prevalence, substantially morbid manifestations and long-term and/or potentially fatal complications including high risk[8] of small bowel malignancies, small bowel lymphoma or adenocarcinoma. Celiac disease has been traditionally considered a disorder of Caucasians of northern European ancestry. Earlier large studies reported the prevalence of CD around 1:1000 in Europe. However, due to growingly atypical presentation and silent cases, the true prevalence is believed to be much higher. Studies report the prevalence ranging from 1:130 to 1:300 in Europe [7]. Some populations in Europe have been reported to have the prevalence of CD as high as 1 in 100 individuals [12]. Until recently, the prevalence of CD in USA was considered quite low in comparison to that in Europe. However, findings of a recent 32 state-wide large multicenter study [16] suggest the prevalence of the CD is almost similar to that in Europe, ranging from 4.54% among first-degree relatives of patients with CD to 0.75% in the not-at-risk subjects. The CD also prevails as underdiagnosed disease at varying degree in South America, North Africa, and Asia [6].

Celiac disease in Children

One very interesting recent finding from population-based screening study in school children in Finland revealed the biopsy-proved prevalence of 1:99 [57].Another population-based birth cohort study from UK reveals seroprevalence of undiagnosed CD around 1% in general population at age seven, using IgA-EMA positivity as criterion, whereas prevalence of childhood CD is usually reported less than 1:2500 in that population. Although it has been clearly demonstrated that CD enteropathy can develop at any age, also in adulthood [58, 59], it seems to start in childhood, even in those diagnosed as adults [23].

Earlier, significant differences in the CD incidence and its trends between and within countries with similar geographic and social conditions[10] were observed in the Multicenter Study by the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN). Further, some countries in 1970s, observed rapid decline of Childhood CD, which created the impression of disappearance of childhood celiac disease [13]. In Finland, the decline in incidence of CD in below 2 years age-group was counteracted by rise in incidence among older children [14]. After a relatively steady trend in the 1970s, Sweden witnessed unique trends, in comparison to those found in the neighboring countries. Remarkably, the annual incidence of childhood celiac disease in below two years age-group returned to previous level after showing the epidemic pattern upto the maximum four-fold rise during a 10 years period- mid-1980s to 1997 and below two years age group emerged as the one with most rapid increase in cumulative incidence[11]. Some Italian areas, especially in Sicily and in Algeria, also showed clear increase in celiac disease in infants [10]. In addition to the differences in childhood CD trends across geographic areas and among pediatric age groups, an *unexplained* difference was also observed in the prevalence of CD between adults and children [9]. This in combination with the predominance of disease prevalence among pediatric age groups demonstrated by biopsy or seropositivity, clearly points to role of extrinsic or environmental factors in etiology of CD, and emphasizes importance of early childhood period in pathogenesis of CD.

Celiac Disease Epidemic in Swedish children

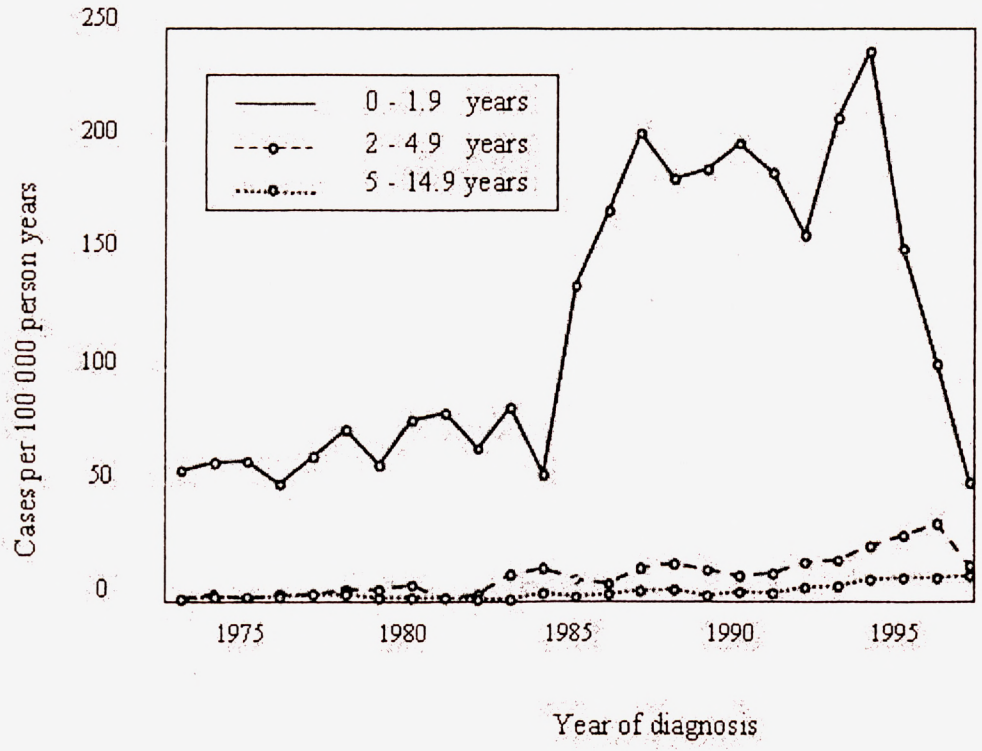
The unique 'Swedish experience' appears astonishing in view of current knowledge of the etiopathogenesis of the CD. The annual incidence rate in children below 2 years of age increased fourfold to 200-240 cases per 100 000 person years from 1985 to 1987, followed from 1995 by a sharp decline to the previous level of 50-60 cases per 100 000 person years [11]. The epidemic pattern of childhood CD trends among below two years of age demonstrate steep rise and later sharp decline, which resembles the trend of some infectious diseases, as such trends have never been reported in past in any diet-related disease or diseases with immunological pathogenesis (**Figure 1).** It points to a possibility, where one or a few causal factors, more particularly environmental factors-influencers influencing large proportion of Swedish infants[11] may have changed over time, causing the resultant effect of such trends. It is also possible that such influencers may have caused disruption of normal response by innate immunity in children. In addition, a higher risk to celiac disease has been observed among girls compared to boys, a difference that was constant, although the epidemic incidence pattern [15], perhaps may be related to sex-associated differences of responses by innate immunity.

Unique pattern of celiac disease trends of annual incidence rate among below two years age-group as a part of Swedish epidemic of celiac disease, points to the inter-country diversities in CD trends over time, implicating possible role of environmental factors- dietary and non-dietary, both, acting singly as well as in combination with other environmental factors, as potential contributors to further the process of pathogenesis. The predominance of below two years age-group, represents the trends of one or more environmental influences acting either independently or in combination- in association with other intrinsic factors. The striking finding from a recent birth cohort study [23], supports the emphasis on early childhood- particularly a vulnerable phase of infancy and intrauterine life, for the exploration of the factors, including triggers- all leading to the breakdown of the development of immune tolerance to gluten.

Figure 1

Annual incidence rates of celiac disease in children below two years age at diagnosis in comparison to children with other age-group at diagnosis of since year 1973.

Reproduced with permission from *Ivarsson A et al (2000)* [11]



OBJECTIVES

The main objective of this study is to explore the potential contribution of risk by early infectious episodes in the development of CD.

The specific objectives of this study were as mentioned below:

1. To perform a literature review in order to understand the role of environmental factors, specifically early infections in etiopathogenesis of celiac disease and creating background knowledge-base.

2. To analyze the data from the Swedish population-based *incident case-referent study* to investigate a possible contribution to the risk by early infections in development of celiac disease.

Thus this study aims to examine the possible contribution to risk by early infections in development of celiac disease and to interpret the findings in relation to current knowledge in etiopathogenesis of celiac disease.

METHODS

Literature review

As mentioned earlier, literature on current concepts of role of environmental factors was reviewed with specific focus on infections in development of celiac disease and early infancy period. The review was made to form the basis of interpreting the findings of the data-analysis.

Incident case referent study

Our data-analysis is based on the population-based incident case-referent study. Earlier the data from the same study was investigated for the role of breast-feeding [50] using epidemiological approach. This study uses the data from the same study for the investigation of role of early infectious episodes in development of celiac disease. Preliminary analysis was done previously [81] and this study strives to make extensive analysis and to interpret the results in view of current concepts. For the incident case-referent study all probable celiac disease cases reported during the 2½ year period from November 1, 1992 to April 30, 1995 at selected 14 pediatric clinics in Sweden, with a voluntarily provided personal identification number, were invited for the participation. This constituted 665 (93%) out of total 714 children with suspected celiac disease. The diagnosis of celiac disease was verified in accordance to ESPGAN criteria, in 627 children, who had 1254 referents. A questionnaire was mailed and from 601 cases (96%) and 1124 referents (90%) responded with answered questionnaire [11, 50].

Earlier there have been studies on seasonality [51] and sex-associated risk [70] to development of celiac disease, which were based on population-based of incidence registration covering the period from 1973 to 1997.

Subjects

Each case of CD was matched with two referents for date of birth, sex, and area of residence (n = 1254). The referents were selected through the national population register. Out of 601 cases (96%) and 1124 referents (90%), who answered the questionnaire, complete information on key variables concerning exposure to infectious episodes and potential confounders was available for 509 cases (81%) and 892 referents (71%); 468 cases and 727 referents were also part of matched sets, corresponding to 75% of the eligible case-referent triplets (Table 1).

Table 1

Overview of participation of cases and referents in different age group

Criteria	Age groups[1]			
	0-1.9 years		2-14.9 years	
	Cases n (%)	Referents n (%)	Cases n (%)	Referents n (%)
Cases with verified diagnosis[2] and their referents	475(100)	950(100)	152(100)	304(100)
Questionnaires				
Answered	455(96)	856(90)	146(96)	268(88)
Completed[3]	399(84)	695(73)	110(72)	197(65)
Part of matched set of a case and 1 or 2 referents	373(79)	581(61)	95(63)	146(48)

[1] Age of the cases when the biopsy was performed

[2] Criteria of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition [17, 18]

[3] information required on variables on infectious episodes, infant feeding and socioeconomic status

Questionnaire

A comprehensive questionnaire, which included the questions seeking information about the child and his or her family with respect to the exposure to infectious diseases during early years of life, socioeconomic situation of the family, and dietary pattern during infancy- was used. Special interest in celiac disease was not revealed. The questionnaire asked whether the child ever got any episode of illnesses during the first 6 months of life. The questionnaire lists specifically commonly occurring illnesses- including the acute infectious episodes- in infant population of Sweden. Further, the degree of exposure to infectious episodes is ascertained by the component question on frequency of their occurrence. In addition, there was also a question on any hospitalisation during this period. The duration of breast feeding was ascertained by question on whether the child had ever been breast-fed, and if so, the age (in months) at the last breast-feeding. The food-frequency component of the questionnaire, which contained semi-quantitative information on portion sizes (3 levels), was used [50] on the basis of experience from an earlier study [19]. The pattern of introduction for each food item was assessed on the basis of the age (in months) of the infant at the time when the first portion was given, on the size of the first portion, and on the average portion size and frequency 2 week later [50].

Definitions

Early infections: All infectious episodes occurring in early infancy –from birth to 6 months of age are taken into account. As infections after six months of age may be the part of manifestations of celiac disease. Types of common infections were specified in the questionnaire and also information about the infections other than those specified was collected.

The early infectious episodes were classified as all types of infectious episodes, all types of infectious episodes excluding gastrointestinal (GI) infectious episodes and GI episodes. They were also further subcategorised as viral and non-viral episodes in order to study significant differences, if any.

Potential confounder variables: Exclusive or partial breast-feeding was included as duration of breast feeding. The first post-partum month, during which gluten-containing flour introduced, was defined as age at gluten introduction. BF status at introduction of gluten is a variable constructed by combining breast-feeding status in relation to age at introduction of gluten-containing flour. Age at introduction of gluten was categorized in accordance to recommended age at introduction- 5-6 months, earlier and later.

Amount of gluten containing flour in home prepared food was calculated on basis of standard Swedish recipes, and the amount in marketed food products, was computed from the information provided by the manufacturers. Amount of flour consumed each feeding episode, was divided in thirds on the basis of distribution of flour intake by the referents. Later on, considering comparable risk estimates, small and medium amounts were merged resulting in two categories: small-medium and large- and were accepted for analysis.

Statistical Analyses

Each case was matched with one or two referents and those with complete information on infectious episodes, age at introduction of gluten, breast-feeding duration and quantity of gluten consumed daily at two weeks after the first portion- were included in final analyses.

As it was important to understand the epidemic in the younger age group, which showed a notably unique epidemic pattern, Analyses were performed separately for children diagnosed within age-intervals of 0-1.9 and 2-14.9 years of age, respectively. After ensuring the subjects with available data on basic characteristics, the data was checked for the availability of information on variables of interest: early infectious episode variables and potential confounders-socioeconomic status, age at introduction of gluten-containing flour, breast-feeding status at introduction of gluten and amount of gluten-containing flour. The frequency variables of early infections variables were checked for any missing and inconsistent values. Subjects with missing data in infections and confounder variables were excluded from final analyses. Included subjects were described with regard to exposure to infectious episodes, exposure pattern to potential confounders in relation with basic characteristics after cleaning the dataset. Associations between covariates were examined in order to identify possible confounding or effect modification. Models were developed to assess the adjusted and unadjusted effect of potential confounding variables and infectious episodes variables. Bivariate and multivariate matched logistic regression was used to evaluate the possible risk. The population attributable fraction was estimated by a formula [$AF_p = p_c$ (OR-1)/OR], where p_c = prevalence of exposure under study among the cases. Adjusted odds ratio was taken into account here.

Statistical analyses were done with SPSS 13.0.

Confidence intervals (95%) of odds ratios, excluding 1.0 are defined as statistically significant. Chi-square p-values were defined significant at the level of 5%. Microsoft Excel was used for the chart functions.

Ethical considerations

The incidence register and the case-referent study have been approved by the Swedish Data Inspection Board and the Research Ethics Committees of all Swedish Medical Faculties. After providing written and verbal information to the participants, informed consent was obtained. [50]

RESULTS

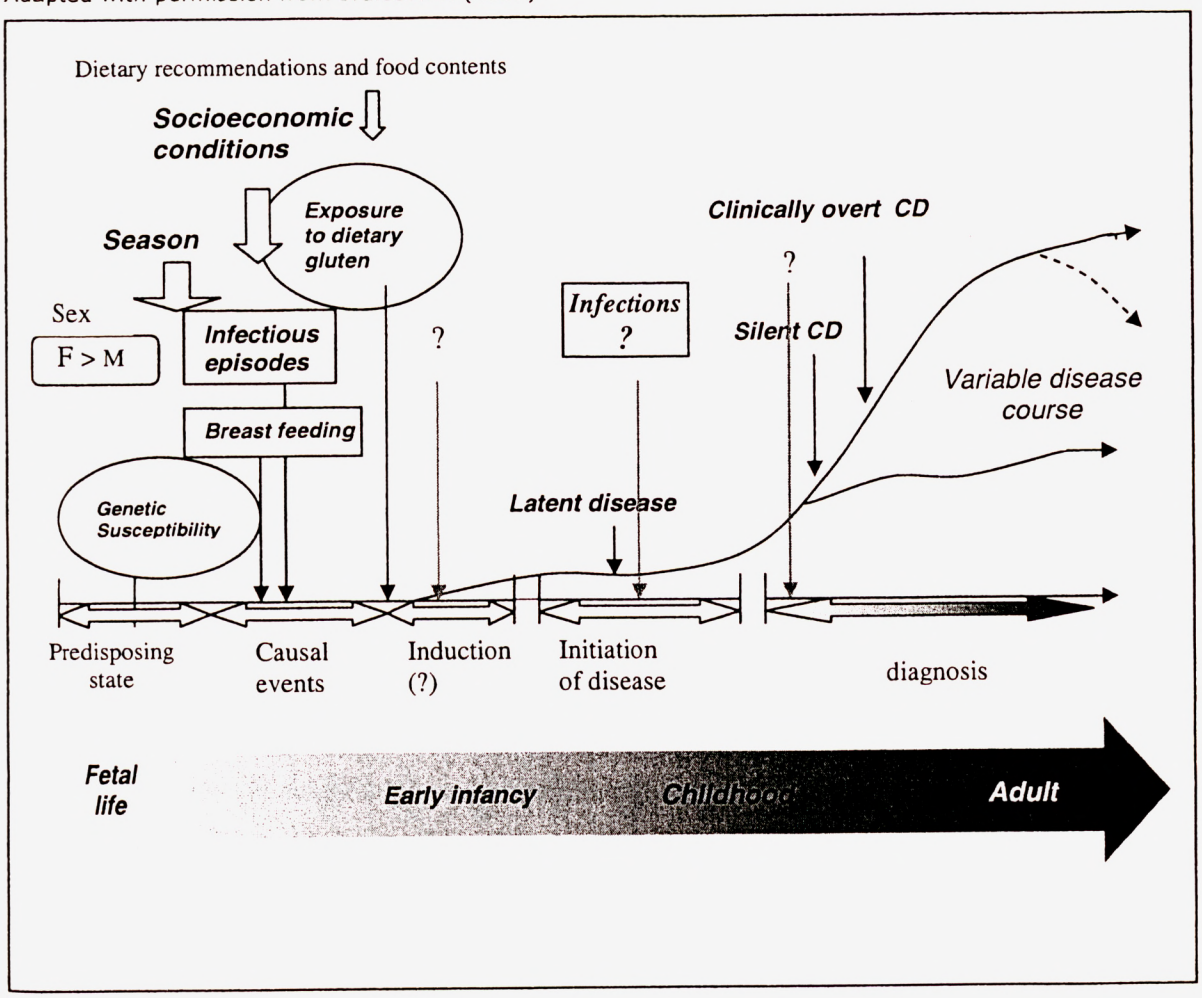
Literature-review was made to understand the role of environmental factors in the pathogenesis of celiac disease with focus on infections in particular, from PUBMED and MEDLINE with the MeSH terms celiac disease, coeliac disease, pathogenesis, infections – separately and in combinations. Literature from EMBASE, WEB OF SCIENCE and COCHRANE was also searched.

The multifactorial etiology of celiac disease

Celiac disease is a permanent intolerance to ingested gluten in susceptible individuals, manifests as an immunologically mediated inflammation of the small-intestinal mucosa [8]. With the view of recent research, CD is now recognised as polygenic disorder with multifactorial etiology [22] with certain similarities of etiology of inflammatory bowel disorders [60, 61] with respect to involvement of genetic, environmental, immunological and infectious factors, despite of considerable differences in pathogenetic mechanisms of the both. The complex aetiopathogenesis of celiac disease remain to be elucidated [20-21]. The genetic susceptibility conferred by HLA and non-HLA genes together with gluten and possibly additional environmental factors or triggers are involved in disease development. Celiac disease today has achieved significant clinical and scientific importance, because it represents "a model disease" with complex interplay of environmental, genetic and immunologic factors.

Infections represent non-dietary environmental factor for the development of CD. In the following discussion, the role of infections and their possible mechanisms of influence on disease development are described in relation to role of other etiological factors.

Figure 2:
Multifactorial aetiology of celiac disease.
Adapted with permission from Ivarsson A (2005) [15]



Importance of genetic susceptibility: There are certain reasons to assert that genetic susceptibility forms a necessary cause, but can not be the sufficient cause for the development of CD. The differing disease incidences and its trends with time between and within populations and even within families of cases can not be explained by genetic susceptibility as a sufficient cause. Genetic predisposition is supported by ~10% prevalence in first-degree relatives and 80%–100% concordance in monozygotic twins, compared with 20% in dizygotic twins [24]. CD has been recognized as a polygenic disease[22,28]. It is suggested that each genetic risk factor, taken separately, can be frequent in the general population and it is the combination and interactions between some of them and also their interactions with the environmental factors that induce the intestinal pathology[28]. Therefore, perfectly defining a state of genetic predisposition appears to be complicated.

The vast majority of CD cases represent HLA-DR3-DQ2 haplotype, or alternatively HLA-DR5-DQ7/HLA-DR-DQ2 heterozygous. In about 80-95% of cases, strong predisposing genotypes are found in the HLA class II region, carrying either DQ2 or DQ8 heterodimer [25]. The DR heterodimer (DR53), encoded by the DRA1 and DRB4 genes in the DR4, DR7, and DR9 individuals is also suggested [26]. Here it is important to note that a part of familial aggregation remains to be explained by DQ and DR heterodimers in HLA component [27], suggesting additional HLA and non-HLA risk factors. Research focusing these areas is in

progress. However, it is evident from successive genome scans showed that apart from HLA, there is no genetic risk factor with a large effect involved in CD [89].

Environmental factors are implicated to play an important role, as discussed earlier. The epidemic of CD in Swedish children provided the unique opportunity to study the role of environmental factors-both dietary and non-dietary- involved in the pathogenesis of CD.

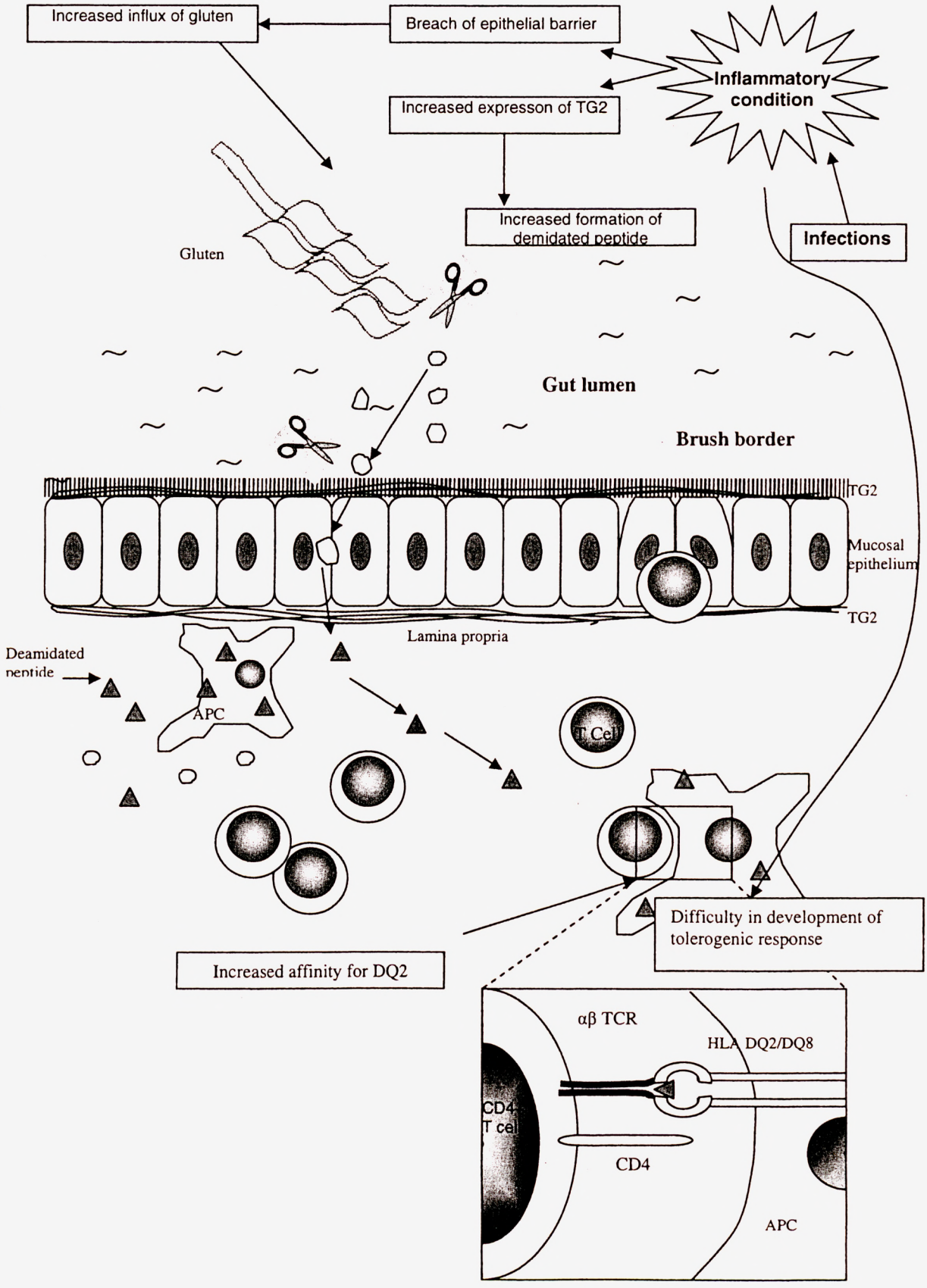
It is generally accepted that the dietary exposure to gluten proteins is necessary factor for the development of CD. Studies based on incidence registration during this epidemic, have provided better insights. Role of infant feeding practices as a risk to CD before two years age is discussed [11, 51]. The protective effect of introducing the gluten-containing foods into infant diet in small amounts, while breast-feeding is still ongoing is also discussed [50].More pronounced effect was found in infants who were continued to be breast-fed beyond the time of gluten introduction. Risk was found to increase with introduction of larger quantity of gluten.

Apart from the dietary factors, role of non-dietary environmental factors has also been indicated. Among children with age at diagnosis below two years, children born in summer are at increased risk for CD in comparison to those born in winter [51] -pointing to the seasonal pattern of causal environmental exposure(s). Further, it is suggested that the temporal relationship indicates that it might be due to environmental causal exposure(s) in particular infections during the fetal or early infancy and/or their interaction with introduction of gluten.

Cell-mediated immune response in development of celiac disease

CD is T-cell mediated inflammatory disorder with autoimmune characteristics [21]. Mucosal exposure to gluten in presence of genetic predisposition may induce the CD4+ T-cell mediated immune response. It is accepted that CD is represents Th_1 mediated disorder [87] which occurs with increased IFN- γ expression [88] but at low levels of IL-12 (interleukin), the major Th_1-inducing cytokine [21, 44]. Some of recent studies assert that pathogenesis of CD is initiated either by the simultaneous presence of bystander infections, stimulating adaptive immune response which favour T-cell recognition of gliadin only in CD patients. Infections may also trigger the latent CD [71]. The role of infections is considered in leading to disruption of normal homeostasis (characterized by hypo-responsive state), and thus leading to skew towards Th_1 type of response due to failure of active inhibition of intestinal immune responses [90]. Further, evidence also demonstrates strikingly increased density of intraepithelial lymphocytes (IEL) in lamina propria [40], which may lead to immune activation, resulting in non-proliferative activation of T-cell receptor (TCR) α/β+ CD4+ T-cells in lamina propria and at the same time, it is associated with simultaneous proliferative activation of TCR α/β+ or γ/δ + CD8+ intraepithelial lymphocytes (IEL), and is believed to be due to direct and primary antigen-driven response [56].

Figure 3
Hypothetical model of pathogenesis of gluten intolerance suggested by *Sollid LM*
Adapted with permission of author : Sollid LM (2002) [30]



Involvement of cell-mediated immunity is also reflected in much of the literature focusing the pathogenesis of CD. There are different mechanisms suggested for the activation of cell-mediated pathogenesis.

Latest evidence comes from the physiopathogenic scheme of pathogenesis of gluten intolerance by Sollid [30] **(Figure 3).** CD is described as disease characterized by either lack of or improperly established gluten tolerance. Deamidation has been considered central to the disruption of gluten tolerance, on the basis of absence of T-cell responses among healthy individuals and the preferential T-cell responses to deamidated gluten fragments in celiac disease. Further, change in conformation of gliadin-DQ2 complex is also suggested, on the basis of increased affinity for DQ2, caused by deamidation of gliadin. This study relates inflammation (which may be induced by infection) with the increased expression of tissue glutaminase (TG2) and is supported by experimental evidence [31] and also cites the evidence [32-33] that TG2 promoter contains response-elements for the pro-inflammatory cytokines IL-6 and TNF. Not only that, it is further stated that in inflammatory conditions the tolerogenic responses to oral antigens are difficult to evolve due to adjuvanticity of inflammatory agent[34-35]. Thus ultimately it may result in failure of establishment of gluten tolerance.

Humoral immune response in development of celiac disease

Although, as described earlier, CD is a disorder with mounting of predominant Th1 type of response, importance of humoral immunity should not be ignored. As widespread in situ endomysial, reticulin, and jejunal binding of transglutaminase (TG2)-specific IgA antibodies in the tissues of cases of CD has been demonstrated [92]. Further, CD related anti-tTG autoantibodies can inhibit enzyme activity and thus can influence the modulation of cell mediated response [93]. Thus, there is enough reason to believe the importance of humoral response in development of disease.

Moreover, beginning from the time of birth, gastrointestinal tract is constantly challenged by various antigens from food as well as infectious agents. During neonatal period, the immunological protection in intestine is primarily provided by locally secreted immunoglobulin A (IgA), which remains quantitatively and functionally defective for a variable period after birth and it is postulated that higher vulnerability to infection and the more prevalent sensitization to dietary antigens seen in early infancy [48, 77]. Therefore, it can be asserted that the early infancy is the highly susceptible period for the immune dys-regulated state and therefore, the occurrence of critical events of pathogenesis may involve this period in significant proportion of cases.

As mentioned earlier, some studies support this assertion [23]. Experimental studies suggest that maternal breast milk IgA can forestall the production of natural IgA in gut associated lymphoid tissue of the offspring and thus promote the development of local humoral immunity at least [49]. This in part explains the protective effect of breast feeding [50] on CD.

Role and mechanisms of induction or activation of CD by infectious episodes

Immune hypothesis of CD pathogenesis is the most accepted one and is supported by some of the studies [72, 73, 74], but has been considered incomplete for not accounting for the triggering events initiating the pathogenetic process [67]. Later on there are many studies on pathogenesis of celiac disease, suggesting involvement of infections, as a trigger, in pathogenesis of CD [30, 21, 36, 39, 46]. However, so far there is not enough evidence to draw a firm conclusion about any causal role by infections.

Here basic mechanisms by which an infection can induce, trigger or activate the disease development process- are discussed.

1. Effect on intestinal mucosal permeability: Early studies suggested gastroenteritis to be a risk to CD, due to the increased intestinal mucosal permeability, thereby increases the influx of macromolecules, which in turn results in immune response [29, 43]. Later on, there have been many studies suggesting possible role of infections, by mechanisms other than the effect on intestinal permeability.

2. Molecular Mimicry: The molecular mimicry hypothesis proposes that microbial peptides with sufficient sequence similarity to self-peptide (gliadin peptide in case of CD) can lead to activation of T-cells. Kagnoff *et al* [36] presented the molecular mimicry hypothesis integrating the genetic, environmental and immunological factors for the pathogenesis of CD. To investigate the possible role of environmental

factors, they identified the 54kD E1b protein of Human adenovirus type 12 (Ad12) sharing the sequence homologies with α-gliadin component. They suggested that the frequent occurrence of specific HLA haplotypes that govern the host immune response to specific viral infection. Due to molecular mimicry between the viral protein and α–gliadin, encounter of the immune system with a protein produced during intestinal viral infection may result in sensitization. This hypothesis was further supported by a study showing greater degree of stimulation of peripheral blood T-cells from patients with CD than those from healthy individuals or from patients of ulcerative colitis or Crohn's disease by using synthetic peptide identical to virus peptide [41]. However, one study specifically on patients with childhood celiac disease diagnosed at less than one year of age, did not support this hypothesis [37] Some other studies did not favour this hypothesis [38, 42].

Later on the hypothesis of molecular mimicry was supported to certain extent by Barbeau *et al* [67], proposing role of **superantigen** of viral or bacterial origin due to its molecular mimicry with HLA class II dimer-bound forms of gliadin peptide. It was distinct from Kagnoff's hypothesis in predication of immune response on inheritance of genes coding HLA-DQ and DR molecules. However, despite of some contrasts and lack of convincing evidence in favour of molecular mimicry at present moment, the possibility of molecular mimicry has not been completely ruled out.

3. Bystander activation: Bystander activation has been thought to occur during infections due to local production of cytokines. Scott et al [39] presented hypothetical scheme presuming the bystander activation of subepithelial antigen-presenting cells (APC) by subclinical viral or bacterial infections as an early event, can follow IFN-γ production by intraepithelial CD8+ or lamina propria CD4+ or CD8+ T cells. Subsequent activation of macrophages provide sufficient co-stimulatory signals to trigger gluten-reactive T-cells in situ by immunogenic gluten peptides associated with HLA-DQ molecules in genetically predisposed individual.

Role of triggers in causing enhanced expression of IFN-α in mucosa in cases of CD [45] further explains the involvement of infectious episodes. Asserting the CD may remain latent for the many years, Cerf-Bensussan *et al* [46] suggests that triggering of clinically overt CD upon treatment by IFN-α and detection of this pro-inflammatory cytokine in the intestine of patients with active CD underlines the possible role of viral infections in the dys-regulation of the local immune response. Viruses are strong inducers of IFN-α and IL-15 [47] which could favor the loss of oral tolerance by inducing the IFN-γ pathway and the activation of antigen-presenting cells. IFN-γ is considered central to initiate the cascade of events leading to epithelial damage. Further they argue a possibility that small amounts of gliadin peptides may be sufficient to trigger the disease in predisposed patients or the initial triggering of the abnormal immune intestinal response may require a specific alteration of the epithelial barrier, which could be the case early in life, upon first introduction of gluten in young children, because of the immature intestinal barrier or later after infectious intestinal episodes.

Besides the mechanisms discussed here, there exists a possibility of unknown mechanisms.

Despite of increased availability of advanced techniques, so far the evidence by isolation of the infectious agents as etiological factors, is lacking. However, recent finding of presence of rod-shaped bacteria in jejunal biopsies demonstrated from more than one third active CD patients-both treated and untreated, and not in controls probably due to altered glycosylation [52] concludes a possible defect in innate immunity and recommends further exploration. Another important suggestion is about the possibility of involvement of infectious component, probably by either activation of CD4+ T cells by adjuvant like effects, producing local stress inducing expression of MIC antigens, or expression of transglutaminase contributing the deamidation [53], and is in accord to the hypothetical scheme of pathogenesis of gluten intolerance [30] mediated by deamidation.

So far, there is also a lack of epidemiological evidence suggesting role of infections. However, recently a population-based study in Swedish population [55] has suggested the influence of intrauterine environment, showing the increased risk for CD that is associated with low birth weight for gestational age (OR=1.5, 95% CI 1.2-1.9) and independently neonatal infections diagnosis (OR=1.4, 95% CI 1.2-1.7), which are the markers of intrauterine environment. Further, the authors conclude the possible involvement of molecular mimicry or other mechanism than effect on barrier function, for the risk associated with the unspecific neonatal infections.

During the Swedish celiac diseases epidemic, the pattern of seasonality of CD risk has been attributed to a possibility of the exposure pattern to infections independently or in interaction with any of other environmental factors. Moreover, the likelihood of certain exposure(s) with a seasonal pattern contributing the Swedish epidemic of coeliac disease has been discussed with the view of their apparent exhibition of effect by causal exposures only during first years of life [51]. Such effect, in interaction with dietary factors, acting during infancy and affecting the susceptibility towards immune dys-regulated condition or non-tolerogenic response to gliadin- should influence risk of development of CD, and therefore the CD incidence in interaction with such seasonal exposures.

Briefly, current evidence indicates that infections may lead to immune dysregulation and stimulation of Th_1 type of response, and consequent induction of further pathogenetic events. Foetal life and early infancy should represent the phases of high vulnerability. Thus, infections may exert their influence on the immunological processes in interaction with dietary exposures among genetically susceptible individuals. However, the assertion of role of infections may not be applicable in all cases of CD [46].

Results of data-analysis

This study shows greater risk associated with infectious episodes in early infancy, while comparing three or more episodes with fewer episodes in below two years of age group. Moreover, the results on dietary variables confirmed previous study from the same dataset [50].

Characteristics of the children

Among the subjects included in final analysis, 80 % were diagnosed before two years of age. In addition, there was also predominance of females (2:1). Median delay between first symptoms compatible with celiac disease and diagnosis was found 3 months in 0-1.9 years age group and in above two years age-group no reliable estimates could be made (*Table 2*).

Table 2

Characteristics of celiac disease cases and referents

Characteristics	Age groups[1]			
	0-1.9 years		2-14.9 years	
	Cases [n=373]	Referents [n=581]	Cases [n=95]	Referents [n=146]
Sex: Male: n (%)	123 (33)	190 (33)	41 (43)	61 (42)
Female: n (%)	250 (67)	391 (67)	54 (57)	85 (58)
Age at first symptoms(months)[2]	11.0(9.0,13.0)[3]	---	27.0(18.6, 73.7)	---
Age at diagnosis(months)	14(12, 18)	---	58(32, 98)	---
Delay between diagnosis and returning of questionnaire (months)	2.2(1.3,3.7)	2.4(1.3, 4.2)	3.0(1.8, 4.6)	3.2(1.9,6.0)

[1] Age of the cases when the biopsy was performed

[2] Information missing for 20 cases (5.35%) in the group aged 0-1.9 y and for 36 cases (38%) in the group aged 2.0-14.9y.

[3] Median (25^{th} and 75^{th} percentile)

Early infections and risk for celiac disease

More cases than referents were exposed to some of the common infectious episodes of childhood - ear infections, fever, gastroenteritis, pneumonia, pertussis and scarlet fever. However, the differences were statistically significant only for gastroenteritis (p=0.049) (**Table 3 A**).

Significant differences about the exposure to infectious episodes were found in cases diagnosed below two years age group, which were not found at an older age-group. The older age-group also had insufficient statistical power. Thus, as mentioned earlier, only group with age at diagnosis below two years were included in analysis. 37% cases and 28% referents experienced three or more infectious episodes before six months of age (p=0.005). While excluding the GI episodes, the difference between cases and referents reduced (34% versus 27%), but continued to be statistically significant (p=0.02). Gastrointestinal infections had statistically non-significant difference, however with insufficient statistical power. There were more children exposed to antibiotics in comparison to referents. However, with respect to the frequency of antibiotic exposure, no significant differences were found between the children with exposure to antibiotics less than thrice and those three or more than three times (p=0.4). (**Table 3 B**)

Table 3 A:
Early infectious episodes among cases and referents

Type of Infectious episode*	Age at diagnosis (groups)					
	0-1.9 years			2-14.9 years		
	cases	Referents		cases	Referents	
	n (%) [n=373]	n (%) [n=581]	p-value	n (%) [n=95]	n (%) [n=146]	p-value
Cold	251 (67.3%)	402 (69.2%)	0.57	56 (58.9%)	87 (59.6%)	1.00
Ear Infection	57 (15.3%)	64 (11.0%)	0.06	6 (6.3%)	13 (8.9%)	0.63
Pneumonia	3 (0.8%)	9 (1.5%)	0.39	2 (2.1%)	2 (1.4%)	0.65
Gastroenteritis	29 (7.8%)	27 (4.6%)	0.05	7 (7.4%)	7 (4.8%)	0.41
Fever	75 (20.1%)	108 (18.6%)	0.56	15 (15.8%)	30 (20.5%)	0.40
Urinary tract infections	6 (1.6%)	5 (0.9%)	0.36	3 (3.2%)	3 (2.1%)	0.68
Pertussis	6 (1.6%)	6 (1.0%)	0.55	-- 0%	1 (0.7%)	--
Scarlet fever	1 (0.3%)	1 (.2%)	1.00	0 0%	0 0%	--
Three-Day Fever	28 (7.5%)	56 (9.6%)	0.29	15 (15.8%)	15 (10.3%)	0.23
Chicken Pox	6 (1.6%)	17 (2.9%)	0.28	0 0%	4 (2.7%)	--

* Commonly occurring infectious episodes are specified in questionnaire. Information about infectious episodes other then specified any was collected in subsequent column of the questionnaire (data not shown here)

Table 3 B

Exposure to infectious episodes in early infancy and celiac disease risk in age at diagnosis below two years age among cases and referents

Exposure		Cases [n= 373] n (%)	Referents [n=581] n (%)	*p-value* [1]
Infectious episode(s) of any type before six months of age				
	≥3 episodes	136(37)	161(28)	0.005
	0-2 episodes	237(63)	420(72)	
Infectious episode(s) of any type before six months of age; excluding gastroenteritis				
	≥3 episodes	127(34)	156(27)	0.020
	0-2 episodes	246(66)	425(73)	
GI infectious episode(s) of any type before six months of age				
	≥3 episodes	4(1.1)	2 (0.3)	0.22
	0-2 episodes	369(98.9)	579(99.7)	
Antibiotics treatment before 6 months age				
	Yes	26	23	0.3
	No	74	77	
Frequency of Antibiotics treatment before 6 months age				
	0-2 episodes	82(85)	118(88)	0.4
	≥3 episodes	15(16)	16(12)	

[1] chi-square test

Table 4

Exposure to pattern to dietary confounders and socioeconomic status of celiac disease cases and referents

Exposure		Age at diagnosis (groups) [1]					
		0-1.9 years			2-14.9 years		
		Cases	Referents		Cases	Referents	
		[n= 373]	[n=581]		[n= 95]	[n=146]	
		n (%)	n (%)	*p-value* [2]	n (%)	n (%)	*p-value*
Breast feeding at introduction of flour :							
	Discontinued	202(54)	192 (33)		36 (38)	54 (37)	
	Continued	88 (24)	147 (25)	<0.001	26 (27)	37 (25)	0.887
	Continued beyond	83 (22)	242(42)		33 (35)	55(38)	
Age at introduction of flour :							
	1-4 months	29 (8)	60 (10)		9 (10)	22 (15)	
	5-6 months	311 (83)	430 (74)	0.002	70 (74)	107 (73)	0.281
	7-12 months	33 (9)	91 (16)		16 (17)	17 (12)	
Amount of flour per day two weeks after the first portion :							
	Large	184 (49)	208 (36)	<0.001	40 (42)	50 (34)	
	Small-medium	189 (51)	373 (64)		55 (58)	96 (66)	0.224
Socio-economic group :							
	High-Medium	193(52)	358(62)		59 (62)	92 (63)	
	Low	180(48)	223(38)	0.003	36 (38)	54 (37)	0.892

[1] Age of the cases when the biopsy was performed

[2] chi-square test

Bivariate analyses were done, followed by multivariate matched analysis with 373 matched cases and referents using matched conditional logistic regression **(Table 5).** It revealed statistical significant risk on bivariate analysis with odds ratio of 1.56; 95% CI: 1.17-2.08 on comparing three or more episodes with fewer number of episodes before six months of age. On multivariate analysis, the risk estimate was slightly reduced with odds ratio of 1.51 and 95% confidence interval (CI) being 1.11-2.05 [Model I]. The risk was found to reduce slightly on exclusion of gastrointestinal episodes in model II with (OR: 1.43 with 95% CI: 1.04-1.96). On exclusion of age at gluten introduction and socio-economic status from the model, the risk associated with early infectious episodes remains unchanged (model III and IV). Risk could not be estimated with GI infections, due to insufficient statistical power.

Infections were further categorized into viral, viral excluding gastrointestinal, non-viral infectious episodes. The justification for such categorization was to assess any possible associations with differences in immunological processes responding viral and non-viral infections. Statistically non-significant risk was found with viral infections (adjusted odds ratio 1.25, 0.91-1.718) with matched analysis (data not shown). Other categories did not reveal significance.

Table 5 : Early infectious episodes and risk of celiac disease

Exposures[2]	Bivariate Matched analyses OR (95 % CI) [1]	Multivariate Analyses OR (95 % CI)			
		Model I	Model II	Model III	Model IV
Early infectious episodes					
0-2 episodes	1.0	1.0		1.0	1.0
>=3 episodes	1.56(1.17, 2.08)	1.51(1.11,2.05)		1.51(1.12, 2.06)	1.49(1.10, 2.01)
Early infectious episodes excluding GI infections					
0-2 episodes	1.0		1.0		
>=3 episodes	1.48 (1.10,1.98)		1.43(1.04,1.96)		
Early GI infectious episodes					
0-2 episodes	NS				
>=3 episodes					
Breast feeding at introduction of flour					
Discontinued	1.0	1.0	1.0	1.0	1.0
Continued	0.55(0.39,0.78)	0.62(0.43,0.87)	0.62(0.43,0.88)	0.62(0.43,0.88)	0.60(0.42, 0.85)
Continued beyond	0.32(0.23,0.45)	0.41(0.29,0.58)	0.41(0.29,0.58)	0.39(0.28,0.56)	0.37(0.26, 0.52)
Age at introduction of flour					
1-4 months	1.0	1.0	1.0		
5-6 months	1.78(1.08,2.93)	1.55(0.92,2.63)	1.53(0.91,2.58)		
7-12 months	0.80(0.42,1.49)	0.79(0.41,1.53)	0.78(0.41,1.50)		
Daily amount of flour 2 weeks after first portion					
Small-medium	1.0	1.0	1.0	1.0	1.0
Large	1.94(1.45,2.60)	1.45(1.05,2.00)	1.46(1.06,2.01)	1.48(1.08,2.03)	1.46(1.07,2.01)
Socio-economic status					
High-medium	1.0	1.0	1.0	1.0	
Low	1.50(1.16,1.95)	1.35(1.02,1.78)	1.34(1.01,1.77)	1.35(1.02,1.78)	

[1] Odds ratio (95% confidence interval)

[2] Exposures are defined in Subjects and methods;

[3] Likelihood ratio statistics: Model I, II: degrees of freedom (df)=7, $p<0.001$; for Model III, IV: df=5 &4 respectively, $p<0.001$

Dietary Exposure patterns and socioeconomic status among cases and referents

Significant differences were found in below two years age group with respect to dietary exposure and socioeconomic group. The differences were not found in above two year age group. **(Table 4)**

Significant differences on **breast feeding status** at the time of introduction of gluten were found ($p<0.001$) **(Table 4)** and strong protective effect was observed among children breastfed at the time of introduction of flour with odds ratio on bivariate analysis for continued BF- OR: 0.55(0.39, 0.78), and became even stronger among those with continued breast-feeding beyond the early gluten challenge **(Table 5)**. (OR: 0.32; CI: 0.23, 0.45), which was confirmed in first multivariate model with OR: 0.62(0.43, 0.87) and OR: 0.41 (0.29, 0.58) respectively. Thus the protective effect showed a trend with continuation of breast-feeding at the time of introduction of flour. The same effect persisted with similar magnitude even on exclusion of GI infections (model II).

Age at introduction of flour was also associated with significant difference ($p=0.002$) **(Table 4)** in below two years age group. Introduction of gluten at the 5-6 months was associated with greater risk in comparison to introduction at 1-4 months, with bivariate odds ratio: 1.78(1.08,2.93), **(Table 5)** and on further delaying the introduction (7-12 months) did not show significance. However, on multivariate analysis the none of risk category was able to show any statistically significant risk, in part due to lack of adequate statistical power.

Daily amount of gluten consumption two weeks later showed strong significance. $p<0.001$ **(Table 4)** in below 2 years of age group. Exposure to large amounts was associated with statistically significant risk on bivariate analysis and was found to be limited to borderline significance on multivariate analysis (OR: 1.94; CI : 1.45-2.60 and 1.45; CI 1.05-2.00, respectively). **(Table 5)**

More cases than referents (48% versus 38%) belonged to lower **socioeconomic group** and differences were significant while comparing lower socioeconomic group with high-medium socioeconomic group ($p=0.003$) **(Table 4).** On bivariate analysis, it showed significance, (OR: 1.50 with 95% CI: 1.16, 1.95), which reduced to borderline significance in multivariate analysis (OR: 1.35; 95% CI: 1.02-1.78). **(Table 5)**

Combined effect of amounts of gluten and frequency of infectious episodes:

The risk was found to increase substantially on considering the combined effect of early infectious episodes in association with gluten quantity. From the reference stratum of children with exposure to small-medium gluten quantity and fewer then three infections, the risk was found to three times in higher risk stratum- larger gluten amounts and three or more infectious episodes (Odds ratio 3.12 with 95% CI: 2.02-4.81). On adjusting for other two variables- socioeconomic status and breast-feeding status at introduction of gluten by multivariate conditional logistic regression, the magnitude of risk was found to decrease. Odds ratio: 2.36 with 95% CI 1.49 to 3.75. **(Table 6)**

Table 6
Infectious episodes during early infancy and risk of celiac disease

Exposures[2]		Bivariate analyses	Multivariate Analyses
		OR (95 % CI) [1]	OR (95 % CI)[3]
Amount of flour per day two weeks after the first portion	Frequency of infectious episodes <6 mo		
Small-medium	0-2	1.00	1.0
Small-medium	≥3	1.34(0.91,1.98)	1.30(0.86,1.95)
Large	0-2	1.73(1.21,2.45)	1.29(0.88,1.89)
Large	≥3	3.12(2.02,4.81)	2.36(1.49,3.75)

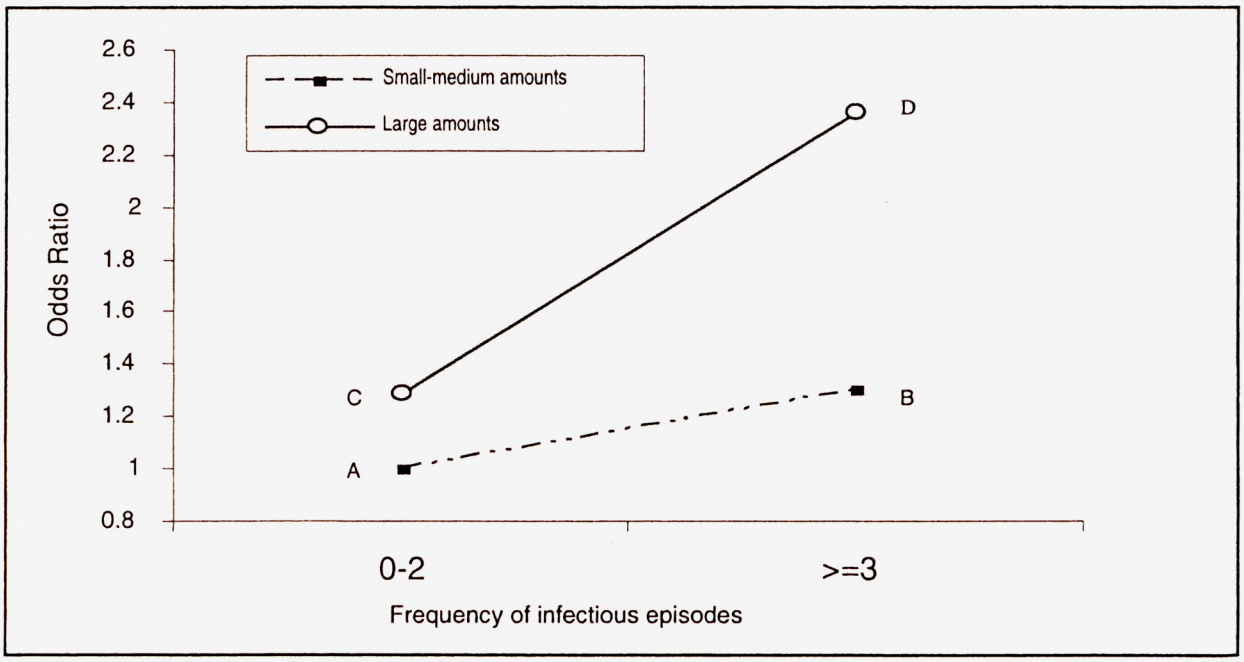
[1] Odds ratio (95% confidence interval)
[2] Exposures are defined in Subjects and methods
[3] Adjusted for socioeconomic status and breast feeding status at introduction of gluten

Clear rise in risk is plotted. (**Figure 4**) The adjusted odds ratios are (with 95%CI): A: 1.0; B: 1.30(0.86, 1.95); C: 1.29(0.88, 1.89); D: 2.36(1.49, 3.75). (**Table 6**)

Figure 4

Interaction of frequency of infectious episodes before 6 months of age with amount of gluten-containing flour consumed.

Risk estimates are based on matched multivariate logistic regression with 373 matched sets of cases and referents, and are adjusted for socio-economic group and whether breast-feeding was ongoing or not at the time of gluten introduction.



Public health impact

With the statistically significant risk of early infectious episodes (OR: 1.51; CI: 1.11-2.05), the population attributable fraction is estimated at 12.5 % in context to this study population of children below two years age group, as an independent effect of early infections. It is important here to consider infections in interaction with other exposures. The risk increase in children exposed to larger amount of gluten containing flour is estimated at 15.7 % of AF. The effect in combination with early infectious episodes results in AF of 24 %, suggesting that sufficiently favourable gluten challenge (small-medium amounts of flour), along with prevention of early infections may spare about one fourth of cases of celiac disease.

DISCUSSION

This study reveals increased risk associated with infectious episodes occurring during early infancy. Higher risk is associated with consumption of larger quantity of gluten. The findings were not conclusive for age at gluten introduction. Socioeconomic group and daily amount of flour two weeks after the first portion shows statistically significant risk of development of celiac disease. Thus these findings on dietary variables confirm the results of earlier research paper [50] including the suggestion of protective effect of breast feeding at the time of introduction of gluten.

As discussed earlier, current concepts of CD focuses to the major extent on gastrointestinal infections. While, the increased risk found in this study, is unspecific to the type of infectious episodes occurring during early infancy. The risk does not change significantly even on exclusion of GI infections. Thus, our study presents the first epidemiological findings suggesting the potential contribution of risk by non-specific infectious episodes occurring in early infancy (before 6 months of age). We suggest that infectious episodes, in general, strong enough to develop immune dys-regulated state or to cause a skew towards Th1 response- should contribute the risk to the development of celiac disease on the basis of a suggestion of bacterial or viral infection induced selective enhancement of differentiation of T helper cells to Th1 subtype with resultant suppression of th2 subtype [94] and the observation of protective effect of early childhood infections on Th2 mediated disease [95]. Repeated episodes may have more likelihood of developing such state, conducive enough to support the development of CD particularly during the vulnerable period of early infancy, in part due to lack of complete immune maturation. With regard to the GI infections, our study cannot provide any conclusive findings, due to lack of sufficient statistical power.

Our findings in relation to indication of possible defect in innate immunity [52] on the basis of demonstration of bacteria in jejunal biopsy in celiac disease cases and suggestion of independent risk associated with neonatal infections [55], forms a clear basis for the further exploration to determine the possible role of exposure to infections in particular during early infancy and foetal life.

Further, the risk of infectious episodes in combination with quantity of gluten (in the form of large-amounts of flour) may result in a significant impact in contributing the causation, as discussed in results section. Therefore, the risk posed by infectious episodes should not be underestimated.

Methodological considerations:

This study was population-based with high participation rate. Therefore, it is possible to generalize the findings for the population of the country at large. However, these findings should be relevant to populations in other countries also, particularly when some of the recent studies discussed here in literature review section, suggest role of infections in the etiopathogenesis of celiac disease. The finding also appears coherent to the earlier research paper based from the same incident case-referent study, demonstrating protective effect of continued breast-feeding at time of introduction of gluten[50] and its possible explanation has been discussed in this section. In addition, as mentioned earlier, findings of this study with respect to findings about the dietary exposures are in agreement with this previous study [50].

This study uses well-established criteria of diagnosis, and thus accuracy of diagnosis is ascertained. The study was introduced without any reference of celiac disease, and thus the possibility of information bias and differential misclassification bias was reduced. Further to reduce the information bias, only incident cases were included, so as the recall period can be reduced. However, this was longer in older age group as well as associated with insufficient statistical power.

With respect to the missing information among cases and referents, we have the further plan to analyse it.

Role of infections in autoimmune disorders:

There has been evidence relating infectious agents with autoimmune process [54] and infections are believed to be culprits for the activation of autoreactive T cells. CD is recognised as a model disease with autoimmune characteristics associated with a high prevalence of various other autoimmune disorders such as type 1 diabetes, dermatitis herpetiformis, autoimmune thyroiditis,

collagen diseases, autoimmune alopecia, and autoimmune hepatitis [21]. It differs from most autoimmune disorders with respect to undisputed triggering by dietary gluten. Its association with type I diabetes or insulin dependent diabetes mellitus (IDDM) is well known [78-80] since a long and possible explanation of common genetic HLA specificities- alleles DR3 and DQ2 [82, 83] and pathogenetic linkage [84] is proposed. As genetic make-up is believed to have role in configuring the adaptive immune response, exposure to antigens such as infections, may potentially influence the existing state of immunoregulation, and in presence of genetic susceptibility, may lead to abnormal immune response. More relevantly, role of several viral infections in childhood IDDM is suggested and supported by epidemiological studies [65, 66]. Therefore, considering pathogenetic linkage and commonality of genetic make-up, role of infectious episodes is also expected in development of CD. In addition to IDDM, role of infections in pathogenesis of other autoimmune diseases- such as triggering of rheumatic fever and Guillain-Barré syndrome, Lyme arthritis is also discussed [54]. Similarly, role of infectious agents in inflammatory bowel disease is suggested [62] and it becomes relevant to CD considering involvement of infections in pathogenesis Crohn's disease [85,86] – which is similar with respect to Th_1 mediation. It has been suggested that adjuvant properties of infectious agents may underlie such trigger effect leading to initiation and development of autoimmune diseases, by activation of autoreactive T-cells under pathogenic conditions [63].

While considering association of infections with autoimmunity, it is also important to consider the effect of innate immunity on cell mediated response. In case of autoimmune disorders such as IDDM and Crohn's disease, the innate immune system is described to be protective either by clearing the pathogens that trigger or exacerbate disease or by regulating the presentation of antigens to T-cells [91]. With the recognition of infections as well as gliadin as potential activators of innate immune response [47], and recent suggestion of possible defect of innate immunity [52] - significance of innate immunity in development of CD has become increasingly obvious.

Therefore, infectious etiology appears relevant to celiac disease. Adjuvant properties of infections and resultant possibility of gluten intolerance, role of genetic susceptibility and of innate immunity- appear to be the underlying factors. Thus, although not fulfilling criteria for establishing the role[54], infectious episodes emerge as an important clue to so far unelucidated aetiopathogenesis of CD.

Counteractive exposures

Latest knowledge suggests the role of infections in causing inflammatory state, leading to increased risk of failure of establishment of normal tolerogenic response to ingested gluten. Further, it is suggested that infections lead to inflammatory state, to increased expression of transglutaminase and consequently increased formation of deamidated gluten peptide with altered DQ2 affinity [30]. Therefore, factors suppressing the immune response with ingested gluten should reduce the risk of CD. Earlier, the protective effect of breast-feeding at the time of introduction of gluten has been shown [50]. The actual mechanism of protective effect is not yet clear. Juto *et al* suggested that IgA antibodies from human milk may lead to diminution of immune response to ingested gluten by mechanisms such as reduced uptake by agglutination of antigen to immune complexes on mucosal surface [75]. Moreover they suggest the possibility of T cell specific suppressive effect on the basis of animal experimental studies [76]. Findings demonstrating reduced CD4+ T cells among breastfed infants also favour greater maturity of immune system [64] among breast-fed infants and thereby reduced the possibility of failure of tolerogenic response. Breast-feeding may confer protective effect indirectly by limiting amounts of gluten at the time of first introduction and perhaps also by delaying introduction. Interestingly, inverse association is also suggested to exist between breast-feeding and autoimmune disorders, such as IDDM and inflammatory bowel disease [68, 69], indicating possibly a varying extent of similarities in mechanisms influencing the immune system as a basis to this inverse relationship and it is interesting to explore the possible role of infections in such mechanisms.

Thus our finding presenting infections as an important clue is in accord with the conclusions from past studies [52,55] as discussed and is relevant looking to the association of CD with autoimmune disorders. To conclude, although suggestion of possible infectious etiology of celiac disease here is based on the findings from the children diagnosed below the age of two years, considering the extent of undiagnosed subclinical or latent celiac disease, it appears to pose certain extent of risk to the cases occurring later in life also and it becomes interesting to study the extent of influence on life-time risk. It is equally interesting to study the risk from early infancy infectious exposures in relation to sex of a child, considering sex-associated differences in innate immune response.

CONCLUSION

The findings of this study conclude the risk associated with early infectious episodes. This study forms the first epidemiological evidence concluding infectious episodes during early infancy. Thus, it provides implication for the further exploration of role of infectious episodes in interaction with immunological mechanisms involved in pathogenesis of celiac disease.

Present situation concludes celiac disease seems to be the outcome of dysregulated immune response to gluten as consequence of complex interactions of gene-gene (epistasis) and gene-environmental factors in relation with the immunological processes. Despite of improved understanding, the pathogenesis of CD remains mystery until the complete aetiopathogenesis remains unrevealed. Although, the identity of genes predisposing to CD may add the new dimension to diagnosis of CD, better elucidation of early immunopathogenic events, which may be responsible for either initiation or perpetuation of CD- is vital to develop the innovative preventive, immunomodulatory and antigen-centered therapeutic strategies for normal establishment and restoration of immune tolerance to gluten. It is also required that considering the nature of the disease, the studies focusing fetal and early infancy processes may undoubtedly prove pivotal role in this process.

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