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When and how should gluten be introduced into the infant's diet?

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Coeliac disease (CD), or permanent gluten-sensitive enteropathy, develops because tolerance to ingested wheat gluten (gliadins and glutenins) and related proteins from wheat rye and barley never develops, or is broken after it has developed. CD is characterized by inflammation of the small intestine, resulting in crypt hyperplasia, villous atrophy and flattening of the mucosa. Other characteristics are an increased number of intraepithelial lymphocytes (IELs) and lamina propria lymphocytes, increased serum concentrations of immunoglobulin A (IgA) antibodies towards gliadin and the autoantigen tissue transglutaminase. When gluten is withdrawn from the diet the mucosal morphology is restored, the specific antibody levels become normal and symptoms of the disease disappear (1). CD is an acquired disorder, which can be diagnosed from early infancy with classical symptoms such as diarrhoea, malabsorption and failure to thrive, to adulthood with a wider and more diffuse spectrum of symptoms (2). Poor dietary compliance and undiagnosed disease, which is frequent in adult populations, are associated with increased morbidity and mortality (3).

CD is a chronic inflammatory disease with a strong polygenic component, although most of the genes involved are still unknown (4). Over 90% of patients express the major histocompatibility complex (MHC) class II molecule HLA-DQ2 and the remainder usually HLA-DQ8, both of which predispose for the disease (5). Exposure to gluten or certain peptides thereof, in genetically predisposed individuals, is a prerequisite for CD development, and once established the disease can be turned on and shut off by introducing gluten into or withdrawing gluten from the diet. CD is associated with an abnormal T-cell-initiated immune response to gluten, but the detailed pathogenesis still remains to be elucidated. The Swedish epidemic of CD with classical symptoms in children below 2 years of age, which surfaced for a little longer than a decade from the mid-1980s, strongly supports an aetiological role of environmental factors, such as early infant feeding practices (6, 7), and thus a multifactorial aetiology.

Large amounts of gluten: independent risk factor

The recent Swedish incident case-referent study contributed to the identification of some of these causal environmental risk factors. For the first time the design of the study allowed assessment of the consumption of gluten-containing cereals on an individual level (8). Introduction of gluten-containing foods in large amounts, compared with small or medium amounts, was an independent risk factor for CD development [adjusted odds ratio (OR) 1.5, 95% confidence interval (CI) 1.1–2.1]. By the use of multivariate analyses, differences in breast-feeding practices and the age of the infant when first introduced to gluten-containing foods could be adjusted for. Moreover, the type of food used as the source of gluten, i.e. solid foods or milk cereal drinks (MCDs), was not a significant independent risk factor.

These results strongly suggest that introduction of gluten in larger amounts increases the risk of CD (8). The rise in incidence was preceded by a two-fold increase in the average daily consumption of gluten estimated by the use of MCDs, and later the decline in incidence coincided with a decrease in consumption by one-third (6).

Is it a dose-dependent or a threshold effect?

Gluten-sensitized individuals respond in a time-related and dose-dependent fashion to gliadin (9). Recently, an explanation for the HLA-DQ2 gene dose effect for the development of CD was proposed. Individuals homozygous for the HLA-DQ2.5 molecule on their antigen-presenting cells present a broader range of gliadin pep-

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tides to T-cells than HLA-DQ2.5/2.2 heterozygous individuals, whereas HLA-DQ2.5/non-DQ2 heterozygous individuals are poor presenters and have only a slightly increased risk of developing CD (10). These results and others are indicative of a quantitative model for disease development. However, it is still not settled whether gluten as a risk factor for CD acts in a dose-dependent manner or whether there is a threshold effect. If the latter is true it is likely that the amount of gluten required to pass the threshold is lower in HLA-DQ2.5 homozygous than in heterozygous individuals.

Thus, there is evidence to suggest that during infancy consumption of a large amount of gluten-containing flour, which increases the antigen dose, increases the risk of CD. However, the amount of gluten tolerated may be modulated not only by the genetic predisposition of the individual but also by environmental exposures besides gluten.

Is the age of gluten introduction important?

It is possible that there is an age interval during which humans have a decreased ability to develop oral tolerance to a newly introduced dietary antigen (11). Hypothetically, the age of the infant at the introduction of gluten into the diet may influence the risk for CD. A bivariate association, indicating an increased risk for CD, was found when dietary gluten was introduced within the age interval of 5–6 months. However, this association no longer remained when adjusting for differences in dose of gluten given during introduction and breast-feeding variables (8).

CD and type 1 diabetes mellitus are interlinked. Recently, two cohort studies on children with increased risk for type 1 diabetes mellitus investigated the association between the age at introduction of dietary gluten and indicators of autoimmunity. One of them concluded that it is beneficial to introduce gluten within an interval of 4–6 months of age, compared with both earlier and later introduction (12), while the other study concluded that age at introduction did not influence the risk of autoimmunity (13). Both studies considered differences in breast-feeding duration in the analyses, but not the amount of dietary gluten given during the introduction.

Thus, whether or not the infant's age at the time of gluten introduction is a risk factor for CD has not been settled. Most studies refute it as an independent risk factor, but it should remain on the agenda for further exploration.

Infections may be a risk factor

In the 1980s Kagnoff et al. (14) suggested that gastrointestinal infection with adenovirus type 12 could initiate CD, a hypothesis later questioned. Gastrointestinal infections cause a disruption in the barrier function of the small intestinal mucosa, which theoretically could result in an increased antigen penetration and unfavourable immune response. Compared with referents, CD cases were more often born in the summer (15), and therefore more often introduced to gluten during the winter when infections are more frequent. Thus, it is conceivable that the Swedish epidemic was partly caused by a change in the infectious panorama, or an interaction between infant feeding and infections.

Recently, it was discovered that rod-shaped bacteria are frequently associated with the intestinal mucosa of CD patients, both with active and with inactive disease, but not with that of controls, as revealed by scanning electron microscopy (16). Moreover, the presence of bacteria is associated with a particular lectin-staining pattern of the intestinal mucosa. It seems therefore that unique carbohydrate structures of the glycocalyx/mucous layer are likely to be discriminating features of CD patients. These glycosylation differences could facilitate bacterial adhesion. Adhesion/infection by these yet undefined bacteria could precipitate disease in genetically susceptible individuals. There is also a strong IEL response in CD with a highly significant increased expression of the cytokines interferon-γ (IFN-γ) and interleukin-10 (IL-10), without a concomitant increase in the expression of tumour necrosis factor-α or transforming growth factor-β, and with marked shift of the IFN-γ and IL-10 production from the lamina propria to the epithelium. This may cause both recruitment of IELs and a leaky epithelium. Hence, the epithelial reaction may be critical for disease development (17).

An incident case-referent study (8) found that children who experienced three or more infectious episodes before 6 months of age had increased risk of CD before 2 years of age (adjusted OR 1.4, 95% CI 1.0–1.9). This was true even when episodes of gastroenteritis were excluded, and after adjustments for differences in infant feeding patterns. The

risk of CD increased considerably if, in addition to having many infections, the child was introduced to gluten in large amounts, compared with small and medium amounts. Thus, it is possible that common infections, both gastroenteritis and other types of infections, play a causal role in the development of CD.

The explanation may be that infectious episodes increase gut permeability, followed by increased antigen penetration and activation of the immune system. If so, a dose effect of gluten would be reasonable. Furthermore, infections drive the immune system towards a Th1-type response, which is also typical for CD.

Breast-feeding reduces the risk

The immune defence is not fully developed at birth. In the breast-fed infant this is compensated for by immunity transferred from the mother to the infant via the milk (18, 19). Hence, introduction of a dietary antigen while the child is still being breast-fed may increase the likelihood of developing oral tolerance to that antigen. However, the role of breast-feeding in the prevention of immunoglobulin E (IgE)-mediated allergies is controversial. In the 1950s, based on case series, it was suggested that breast-feeding delays the onset of CD. An increase in the breast-feeding rate was also suggested as a possible factor contributing to the declining incidence of CD in the early 1970s in the UK (20, 21). In an incident case-referent study (8), the main finding was that the risk of CD was reduced if the child was being breast-fed during the period when gluten-containing foods were introduced (OR 0.59, 95% CI 0.42–0.83). This protective effect was more pronounced if the child continued to be breast-fed beyond the period of gluten introduction (OR 0.36, 95% CI 0.26–0.51), with an increasing effect for every month of breast-feeding. These risk estimates are adjusted for the age of the infant when gluten was introduced into the diet and the amount of gluten given. A protective effect of breast-feeding was further supported by an ecological study using aggregated data to explore any temporal relationship between the changes over time in incidence rate and changes in infant dietary patterns (6). Both the rise and later fall in the incidence of CD were temporally related to a change in the proportion of infants introduced to gluten while still being breast-fed. It is important to note that at the time of these studies the majority of Swedish infants were being breast-fed for 6 months or longer, i.e. most of the infants were introduced to cow's milk products and other foods while still being breast-fed. Also, for most infants the termination of breast-feeding did not coincide with the introduction of infant formula, but rather with increased ingestion of complementary foods.

Thus, these findings strongly support breast-feeding as directly reducing the risk of CD, and not merely influencing the risk indirectly through changes in other exposures.

Conclusions

Breast-feeding during the dietary introduction of gluten is protective against CD. This protective effect is biologically plausible taking into account our present knowledge of breast milk composition and the impact of breast-feeding on immune responses, along with current knowledge concerning the pathogenesis of CD. A gradual introduction of gluten also seems to be beneficial. The exact mechanism behind the protective effect of breast-feeding is not yet known. However, it is tempting to speculate that this could be mediated either by reducing the number of infections or by the immune-modulating effect of breast milk, for instance by providing down-regulatory transforming growth factor-β_1. The observation that CD patients often have rod-shaped bacteria adhering to the mucosa suggests that the effect could be mediated via an effect on the bacterial colonization of the gut.

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