

Infant feeding history shows distinct differences between Swedish celiac and reference children

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Infant feeding history was investigated in 72 celiac and 288 age-matched reference children in a retrospective questionnaire study. The reply rate was 100% in celiac and 91.6% in reference children. The celiac children were breast-fed for a significantly shorter time than reference children, and they were less often breast-fed at the introduction of gluten. The age of the children at gluten introduction was similar, but the celiac children were significantly more often introduced by a gluten-containing follow-up formula, while the reference children more often started on a gluten-containing porridge. The results can be interpreted in two ways. First, it could be argued that breast milk *per se* protects against symptoms of celiac disease in childhood. It could, however, also be claimed that breast-feeding merely modulates the gluten introduction, causing a less abrupt introduction of gluten in the baby diet and thereby fewer overt symptoms of the disease.

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Since the introduction of well-defined criteria for childhood celiac disease (CD) (1, 2) by ESPGAN (European Society for Pediatric Gastroenterology and Nutrition), it has been possible to compare the prevalence of this disease in different countries. Several countries have reported decreasing incidences in recent years (3, 4). In Sweden, however, the recent trend has been toward a sharp increase of this disease. After a period of a fairly stable incidence of approximately 1 per 1000 live births during the 1970s and the early 1980s (5), the latest figures show 3.5 cases per 1000 births in children born after 1982 (6). Now the Swedish figures seem to have stabilized, but at this high level, which is both higher than before, and higher than reported from most other countries (7). At about the same time as the increase in prevalence, the advice in Sweden on how to feed babies was changed in 1982–3 to delayed introduction of gluten at 4–6 months of age. It may very well be that the rise in prevalence was caused by this heavy gluten diet starting abruptly at 6 months. Therefore, some Swedish pediatricians argued that bottle formulas should not contain gluten (8). Other colleagues hypothesize that the current infant-feeding practice leads to the early diagnosis and treatment of most celiac children, including those whose vague symptoms might otherwise have been overlooked (9, 10).

To clarify the feeding practice in infancy, we administered a questionnaire study to parents of celiac children diagnosed during a 3-year period in our catchment area. The same questionnaire was also used for four age-matched, reference children selected to match each celiac child.

Material and methods

The study was performed at the three pediatric departments in Östergötland County, southeast Sweden, serving a population of approximately 91000 children under 18 years of age. The age of the children was 3.0 (3.1; 1.4–5.1) years (mean median and range) when the questionnaire was completed. In the celiac children, the first biopsy had been performed at 1.1 (1.1; 0.8–2.0) years. The interval between the first biopsy and the questionnaire was 1.9 (2.1; 0.3–3.3) years. The three participating units were chosen because they have long cooperated in investigation and follow-up of children with suspected/verified CD, making the study group sufficiently homogeneous.

Study and reference groups

For this study, we selected children who had undergone a first small intestinal biopsy showing mor-

phologic changes suggestive of CD according to the Alexander classification (11) during 1989–91, and who had been under 2 years old at biopsy ($n = 72$). For each celiac child, we selected four age-matched reference children living in the county, i.e., being of the same age as the index child when the questionnaire was returned ($n = 288$). Nine older children with CD and a first biopsy performed during 1989–91 were not included in the study, since they had been more than 2 years old at the first biopsy, a fact which was thought to make a correct recall of feeding routine impossible.

The questionnaire

A questionnaire was mailed to the families, asking basic questions on the feeding of their babies. The aim of the study was explained as a general survey of feeding practice in our region, and the terms “celiac disease” and “gluten intolerance” were not mentioned. The questions covered breast-feeding duration, time and mode of gluten introduction, and ingestion of a whole-grain formula. Parents could return the questionnaire in a prestamped envelope without answering the questions, and 18/288 reference families did so. A letter of reminder was mailed to all families who had not returned the questionnaire after 14 days. If this too was not answered, the families were telephoned by the authors. Altogether, answers were received from 264/288 families, i.e., 91.6% of reference children. All families, 72/72, of celiac children completed the questionnaire. The questionnaires were very carefully answered by most parents. In five cases, answers were given to 10/11 questions, and in one case to 8/11 questions, while all the other questionnaires were fully completed.

Validation of questionnaire replies and morphologic assessment

To validate the questionnaire information, we also wrote to the well-baby clinics about their records of feeding for each child. The families were informed of this, and could withhold their permission, as 19 families did. Information from the well-baby clinics was thus obtained for 317 of the 336 families that had answered the questionnaire. The original morphologic classification of the first intestinal biopsy in the 72 celiac children was made by two different departments of pathology. To eliminate the possible bias of differences in judgment, all samples were re-evaluated by one of the authors (L. F.). The evaluation was blinded. The original classification of Alexander grades III–IV, i.e., compatible with CD, was validated in all 72 samples. Follow-up of the children has been performed, and 69 of them have a definite diagnosis of CD according to the original

ESPGAN criteria (2). Another two of them have shown a normalized mucosa after gluten-free diet, but the gluten challenge is not yet completed. One child fulfills the criteria for transient gluten intolerance; i.e., she has a normal mucosa in spite of 2 years of gluten-containing food.

Feeding advice

The well-baby clinics are held in remarkably high esteem by Swedish parents, and 99% of Swedish children are attended by the specially trained nurses there, giving advice on, e.g., suitable feeding of the baby. The basic recommendation of early feeding is to breast-feed the baby, and approximately 70% of Swedish mothers do so, at least partially, until 4 months of age. After weaning, most Swedish babies are given a follow-up formula by bottle, manufactured by one of the two leading manufacturers of baby food in Sweden. From 1973 to 1983, the follow-up formulas used before 4 months did not contain gluten cereals. In 1983, the National Board of Health and Welfare recommended a delayed introduction of gluten until 6 months, and the commercially available products were changed accordingly. One reason for the change was a wish to separate the introduction of cow's milk, which forms the basis of all these formulas, from the introduction of gluten. Moreover, at approximately the same time, a new whole-grain flour formula with a high gluten content was introduced from 8 months, to increase the fiber content of the diet, in accordance with suggestions to the whole population. Many parents reported that babies were unable to digest this bran-rich formula and stopped it due to infant diarrhea.

Ethics and statistics

The study was approved by the Human Research Ethics Committee at the Faculty of Health Sciences, Linköping University. For analysis of differences

Table 1. Duration of exclusive and partial breast-feeding as stated by parents and well-baby clinics, respectively, for babies with celiac disease (CD) and reference children (R). Values are given in months with mean, median, and range. Statistical significance tested with Mann-Whitney test

	Parent reply		<i>P</i>	Well-baby clinics		<i>P</i>
	CD (<i>n</i> = 72)	R (<i>n</i> = 264)		CD (<i>n</i> = 69)	R (<i>n</i> = 232)	
Breast exclusively	2.7 2.5 0–8	3.7 4 0–10	0.0002	2.4 2 0–6	3.4 4 0–10	0.0004
Breast partial	4.0 3.9 0–12	6.1 6 0–33	0.0001	3.9 3.5 0–9	5.3 5 0–20	0.002

between the groups, we used the chi-square test and the Mann-Whitney U test.

Results

Breast-feeding

The CD children were breast-fed for a significantly shorter time than the reference children (Table 1), and this was the case for both exclusive and partial breast-feeding. The difference was highly significant for both the parental replies, and those obtained from the well-baby clinics (Table 1). The cessation of breast-feeding was not caused by the symptoms of CD, since the interval between weaning and symptoms was 6 months (median). Three babies with CD were still breast-fed at biopsy.

Breast-feeding and gluten introduction

The families were asked whether the baby was still breast-fed at the time of gluten introduction. This was the case for 20.8% of CD babies, and 43.2% of reference babies ($P = 0.002$).

Age at gluten introduction

For CD babies, the age at gluten introduction was 6.0 months (6; 4–7) months (mean, median and range); for reference babies, 6.1 (6; 4–10) months (NS). The corresponding figures obtained from the well-baby clinics were, for CD babies: 6 (6; 5–7) months and for reference babies 6.1 (6; 2–12) months (NS).

Mode of gluten introduction

The families were asked whether the gluten introduction was performed with a formula, with porridge, or with both. The CD babies started with a formula more often than the reference babies ($P = 0.03$) (Table 2).

Ingestion of whole-grain formula

The question asked was whether the infant had been taking a commercially available whole-grain formula, from what age, for how long, and why this parti-

cular formula had been stopped. This formula had been taken by 72.2% of CD babies, and 68.1% of reference children (NS). The age at introduction was 8.3 (8; 6–12) months for CD, and 9.2 (8; 6–32) months for reference children ($P = 0.02$). The age when the child stopped taking this formula was 11.7 (11; 7–23) months for the CD babies, and the reason for stopping was diarrhea (52.4%) and diagnosis of the disease (47.6%). The reference children took this formula for 13.9 (12; 0.3–52) months, and 15 of 181 children still took it at the completion of the questionnaire. For reference babies, the reason the formula was stopped was either that the baby did not want to take the bottle any longer (53.7%), or the appearance of symptoms (46.3%) such as diarrhea (91.8%), constipation (4.1%), or vomiting (4.1%).

Discussion

In this retrospective, questionnaire study, we have shown some basic differences in the early feeding pattern of CD children as compared to reference children. The CD children were breast-fed for a significantly shorter time, and they were significantly less often breast-fed at the introduction of gluten. However, their age at gluten introduction did not differ significantly, nor did the proportion of children exposed to a special bran-rich formula thought to cause diarrhea among a large proportion of the babies. However, the CD babies tended to be a little younger when they started the whole-grain formula. Previous studies of the early feeding of CD children have shown divergent results. According to Auricchio et al. (12) and Greco et al. (13), prolonged breast-feeding protects against CD, and early gluten introduction does not increase the risk of the disease. It should also be noted that early gluten introduction in that study meant before the end of the second month, i.e., considerably earlier than in this study. However, Anderson et al. (14) report opposite findings: prolonged breast-feeding has no protective effect, but early introduction of gluten is a risk factor.

The protection afforded by breast-feeding against CD has been explained in several ways. The reason should be the unique composition of human milk, which is especially suited to the baby, and includes such protective factors as IgA against gluten in the breast-milk (15); T-cell-suppressive factors (16, 17); and colostrum, which has a stimulating effect on the maturation of the small intestinal mucosa (18). Our finding that CD babies were significantly less often breast-fed at gluten introduction agrees with this hypothesis.

However, breast-feeding influences the exposure to other food antigens, such as the proteins of cow's

Table 2. Parental reply to question: how was gluten introduced in food of baby: by cereal-containing follow-up formula with gluten, by porridge, or by both at same time? CD = children with celiac disease; R = reference children. Values in percentage; significance tested with chi-square test

	CD	R	P
Follow-up formula	73.6	60.8	0.03
Porridge	9.7	23.6	–
Both formula and porridge	16.7	15.6	–

milk and also the amount of gluten ingested. The load of gluten given to the CD babies was presumably higher, since they were more often introduced to gluten by bottle, usually involving at least two bottles of gluten-containing formula and possibly also gluten-containing porridge for a third meal. The shift to gluten-containing formulas for the baby already accustomed to the bottle is usually quite rapid. The reference babies, on the other hand, were more often breast-fed at gluten introduction, and were significantly more often introduced by porridge, which usually comprised one meal a day, often oatmeal porridge with a relatively low content of gluten. In this respect, the main difference caused by breast-feeding was to diminish and delay gluten introduction to the baby.

A recent study comparing the feeding recommendations for babies in Lund and Copenhagen found that the Swedish babies consume considerably more gluten during their first year of life than the Danish: at 8 months, 40 times more; at 12 months, four times more (19). The celiac children in Lund undergo their first biopsy at 1.5 years, and in Copenhagen at 5.5 years. The prevalence of the disease in Lund is 0.126/1000, and in Copenhagen 0.01/1000 ($P < 0.001$). According to the authors, the higher rate of disease in Lund is not caused by an increased awareness of the disease, since a similar proportion of all children have undergone biopsy in the two areas (19).

The cause of CD is not yet clear, but several reports stress genetic factors (20–22). Still, environmental factors may influence whether or not this genetic propensity will cause development of overt disease (23). The genetic differences between inhabitants of Lund and Copenhagen are minor, and the authors conclude that the striking difference of gluten intake causes the difference of prevalence. However, comparisons of prevalences should be based on small-intestinal biopsy judgments and efficient screening programs, since detection of subjects with CD has been described as “the tip of the iceberg” (24), and it is generally accepted that we detect only a minority of the cases. Careful epidemiologic studies of subjects without symptoms, such as blood donors (25), have shown a prevalence of 1/256 of the disease in adults in our catchment area. Furthermore, an Italian study of schoolchildren, performed in the same way as the blood donor study with serologic screening of a large number of subjects without symptoms, (24) revealed a similar prevalence of the disease. Serologic studies of adults in the UK also indicate a considerable underdiagnosis of CD (26). In this light, the current Swedish figures may indicate only that most of the subjects with the genetic propensity are “unmasked” by the current feeding practice, and had the good

fortune to be raised on a gluten-free diet during the growth period. Whether this is true or not remains to be determined. A current Swedish multicenter study, involving 1/4 of the Swedish child population, focuses on feeding habits in a more detailed way than this study with the natural limitations of its retrospective character. However, with the high rate of replies obtained, and the validation from the well-baby clinics reinforcing the parental replies, it seems likely that the results of this study are valid. But the true interpretation of the results is beyond the scope of this study. Presumably, the interpretation of the high rate of CD in Swedish children requires a large-scale, intervention study with careful serologic surveillance to find also atypical cases of CD.

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