How important is the timing of gluten introduction for children with celiac disease?

GLOSSARY

MARSH SCORING SYSTEM
Histologic grading system for celiac disease; a score ≥2 is indicative of celiac disease

HLA CLASS II MOLECULES
Molecules on the surface of antigen-presenting cells that modulate immune response by presenting extracellular peptides to helper T cells

Original article Norris J *et al.* (2005) Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of the disease. *JAMA* **19:** 2343–2351

SYNOPSIS

KEYWORDS autoimmunity, celiac disease, gluten-free diet, infants, timing

BACKGROUND

The factors associated with the development of celiac disease in childhood are unknown.

OBJECTIVES

To examine the timing of gluten introduction into the diet of infants and its effect on the development of celiac disease autoimmunity (CDA).

DESIGN AND INTERVENTION

This prospective, observational study enrolled newborn babies or children aged 2–3 years at increased risk for celiac disease, expressing human leukocyte antigen (HLA)-DR3 or HLA-DR4 alleles, or with a first-degree relative with type 1 diabetes. Children with a severe congenital malformation or disease were excluded. For children studied from birth, diet was recorded by interview at 3, 6, 9, 12 and 15 months; parents reported all food the infant had consumed over the previous 3 months. The early diet of the older children was recorded retrospectively by questionnaire. Gluten exposure was defined as the intake of foods containing wheat, barley or rye. The times of initiation and termination of breast-feeding were also recorded. In children enrolled from birth, blood samples were taken for measurement of tissue transglutaminase (tTG) autoantibodies at 9, 15 and 24 months and yearly thereafter. For children aged 2–3 years, tTG autoantibody measurements were taken at study commencement and yearly thereafter. Samples were collected and analyzed more frequently in children who were positive for tTG autoantibodies. Clinical evaluation and small-bowel biopsy were offered to children with positive tTG antibodies. Biopsy specimens were assessed according to the MARSH SCORING SYSTEM. CDA was defined by the presence of tTG on ≥2 consecutive follow-up visits or on 1 visit but with a positive small-bowel biopsy.

OUTCOME MEASURES

The primary outcome measure was time to CDA development. The secondary outcome measure was time to CDA development in patients with a positive biopsy for celiac disease as defined by a MARSH score ≥2.

RESULTS

A total of 1,560 children were included in the study; 1,307 were followed up from birth and 253 from the age of2–3 years. Overall, 1,356 (87%) children were breast-fed. CDA was identified in 51 children, of whom 32 completed study evaluation and biopsy. Exposure to gluten within 3 months of birth correlated with a 5-fold increased risk of CDA compared with exposure between 4 months and 6 months of age. Exposure to gluten at ≥7 months of age was also correlated with a marginally higher risk of CDA development compared with exposure at age 4–6 months (HR 1.87; 95% CI 0.97–3.60). CDA-positive children with biopsy-diagnosed celiac disease showed that exposure to gluten in the first 3 months or in the 7th month or later was associated with a greater risk of CDA compared with exposure between 4 and 6 months of age. (HR 22.97; 95% CI 4.55–115.93; $P = 0.001$ versus HR 3.98; 95% CI 1.18–13.46; $P = 0.04$, respectively).

CONCLUSION

The development of celiac disease autoimmunity in children at increased risk of celiac disease is associated with the timing of gluten introduction to the child's diet.

COMMENTARY

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The publication by Norris *et al.* highlights two major aspects of celiac disease. First, the complex nature of its etiology and pathogenesis, and second, the practical issue of what parents can do to minimize the risk of their children developing the disease. Contradictory advice concerning breast-feeding and the timing of gluten introduction into the infant diet has been offered to mothers for many years despite the lack of solid evidence.

Celiac disease occurs as a result of the interplay between genetic and environmental factors. For its development an individual must carry the alleles that encode for the HLA CLASS II MOLECULES DQ2 or DQ8 (related to HLA-DR3 and HLA-DR4) and ingest gluten.[1]

The HLA genes, however, only account for 40% of the genetic influence for this disorder and furthermore these genes occur in up to 40% of the population. In addition, a vast number of people ingest wheat products. Why then does celiac disease only occur in 1% of the population when so many are at risk? The answer lies in the other genetic and environmental factors that contribute to the disease.

Evidence shows that environmental factors contribute to the development of celiac disease in childhood. Some studies have shown that breast-feeding might modulate the presentation of the disease. One study revealed that children with celiac disease who were breast-fed had delayed onset and less severe, more atypical presentations of celiac disease compared with children who were not breast-fed.[2] In addition, information has been provided by an analysis of the Swedish epidemic of celiac disease in infants in the early 1980s.[3] Factors associated with this epidemic were lack of breast-feeding, large amounts of gluten in infant formula and the occurrence of infections in early life. The greatest protection was afforded to those infants who received small amounts of gluten while still being breast-fed.[4] National guidelines were introduced following the publication of these studies, which resulted in a reduction in the number of children diagnosed with celiac disease.

The study by Norris *et al.* demonstrated that protection was afforded to infants when gluten was administered 4–6 months after birth. The risk of developing celiac disease was increased most by the early introduction of gluten (≤3 months after birth); however, it was also associated with delayed introduction (>7 months after birth).

The best advice seems to be that infants born into families with celiac disease should be breast-fed for at least 6 months and receive gluten in their diet at age 4–6 months following birth. Both early, and delayed, introduction of gluten should be avoided. The American Academy of Pediatricians' policy statement on breast-feeding recommends exclusive breast-feeding until 6 months. They do, however, add a statement about 'unique needs' that "may indicate a need for the introduction of complementary foods as early as 4 months of age".[5] Perhaps these recommendations need to specifically address celiac-disease-related autoimmunity.

Many questions remain, including: what is the significance of breast-feeding as opposed to the timing of gluten administration? In addition, do these practices merely delay the onset of celiac disease? Celiac disease is common and physicians will face more questions about this disease in the future as more patients are identified.

References

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Competing interests
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PRACTICE POINT
Infants should be breast-fed for at least 6 months and receive gluten in their diet between 4 months and 6 months of age