



EDITORIAL

Gluten introduction and coeliac disease risk[☆]



Introducción del gluten y riesgo de enfermedad celíaca

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Based on previous epidemiological studies on celiac disease (CD), especially those by Anneli Ivarsson and collaborators on the so called Swedish CD epidemic in the mid 1980s, in the last decade it has been hypothesized that early introduction of small quantities of gluten, preferably during a period of breastfeeding, may reduce the risk of CD.¹ Moreover a study by Norris et al reported that in infants at genetic risk, introduction of gluten at ≤ 3 months of age or at ≥ 7 months was associated with a higher risk of CD autoimmunity and of CD development.² Thus a "window of opportunity" for gluten introduction between 4 and 6 months of age was almost generally accepted by the scientific community. Accordingly the ESPGHAN Committee on Nutrition recommended avoiding gluten introduction before 4 months or later than 6 months of age.³

To specifically investigate the potential of CD prevention through dietary intervention, a prospective European multicenter project "Prevent Coeliac Disease" (PreventCD, www.preventcd.com, FP6-2005-FOOD-4B-36383 - PREVENTCD) was carried out in which the collaboration between hospitals, universities, laboratories and industries from 7 European countries and Israel, was achieved, under the coordination of the Leiden University Medical Center, the Netherlands. The results of this investigation have been published in the 2 October issue of the NEJM.⁴

In summary, 994 infants at high risk for CD, because of having one first degree relative already diagnosed with CD

(father, mother or sibling) and carrying at least one HLA risk gene (DQ2 and/or DQ8) were recruited shortly after birth. After informed consent from the parents was obtained they were blindly randomized to receive, at 16 weeks of age, either 100 mg of gluten daily or placebo (lactose) and breast feeding was strongly encouraged. At 24 weeks of age a fixed progressively increasing gluten intake was advised for both groups and after 11 months of age free gluten consumption was allowed.

Up to the age of 3 years, the participants were screened for the development of celiac disease by determination of celiac antibodies (anti-tissue transglutaminase antibodies) in serum. In addition, health status, growth and feeding habits (breastfeeding, formula feeding and gluten consumption) were monitored. Celiac disease was diagnosed according to the accepted European guidelines and involves small bowel biopsies in the vast majority of the cases. The study endpoint was the frequency of celiac disease at the age of 3 years, which was found to be 5.2% in the whole cohort. No differences in incidence were observed between children that had been introduced to gluten at 16 weeks and those that received placebo and no gluten until the age of 24 weeks. Moreover CD development was neither influenced by the duration of breastfeeding nor by continuing breastfeeding during gluten introduction.

The authors conclude "the introduction of small quantities of gluten at 16 to 24 weeks of age did not reduce CD risk".⁴ Other environmental factors such as rotavirus vaccination, gastrointestinal or respiratory tract infection, were also not related to the development of CD.

In the same issue of NEJM an Italian multicenter study addresses the hypothesis that delaying gluten introduction till 12 months of age in at-risk infants may reduce the risk of

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CD development.⁵ Although at 2 years of age a statistically significant higher percentage of infants which had gluten introduced at 6 months had developed CD, as compared to those with gluten introduced after 12 months (12% vs 5%), at 5 and 10 years of age the differences between the 2 groups were no longer statistically significant. At 10 years of age 25.8% of children with high-risk phenotype (DQ2/DQ2) had overt CD as compared to 15.8% in those bearing other at-risk phenotypes. Although the authors suggest that delaying CD development to later ages may have some potential benefit on developing organs such as the brain, there is no evidence to support this premise.

The authors conclude *“neither the delayed introduction of gluten nor breastfeeding modified the risk of CD among at-risk infants, although the later introduction of gluten was associated with a delayed onset of the disease”*⁵

Thus both studies come to the same main conclusions, i.e. in at-high-risk infants neither the timing of gluten introduction nor the duration of breastfeeding and the continuation of breast feeding during gluten introduction have proven to exert a protective effect on CD development. Carrying the DQ2/DQ2 genotype was found by the two investigation groups to be an important predictive factor for CD.

The relevant consequences of these studies are that no clear recommendations on gluten introduction in at-risk infants can be established. In addition other environmental factors have been found not to be related to disease development, thus leaving research in this field open to intriguing and exciting new investigation hypothesis. In the short term, special attention will be paid to the potential impact of gut microbiota particularly in early life.

An additional issue is if data obtained for at-risk infants, such as the populations included in both studies, can be extrapolated to the general infant population, thus not

supporting current European guidelines on complementary feeding which recommend gluten introduction not earlier than 4 and not later than 7 months.³

Faced to the anguish of parents looking for advice to prevent CD development, pediatricians have to deal with a difficult situation as at the moment no evidence supports any specific recommendation neither on the timing nor on the pattern of gluten introduction. However, in agreement with the general recommendations of the ESPGHAN committee on Nutrition not to delay complementary feeding introduction beyond 26 weeks of age, introduction of gluten at around 6 months seems, for the time being, a reasonable and sensible option.³

References

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