Fred Brouns August 20, 2019

Should young children be screened for presence of Celiac Disease related genetic pre-disposition?

In our recent paper " Adverse Reactions to Wheat or Wheat Components" , Brouns et al; 2019 (https://onlinelibrary.wiley.com/doi/full/10.1111/1541-4337.12475) we commented that the initiation of CD in children may be related to the food that a child receives early in life and that the effects of breastfeeding and the timing of introduction of additional feeds, (weaning) including bread, on the initiation of CD are not clear.
However, is commonly recommended that the intake of small quantities of gluten (usually bread and pasta) should start gradually before the age of 6 months, often simultaneously with breastfeeding. The reason for this recommendation is that the immune modulatory properties of breastfeeding and the development of the intestinal microbiota may contribute to the prevention of auto-immune diseases.
In earlier work it was shown that increased intake of gluten in Swedish children, due to changes in infant feeding, did lead to increased prevalence of CD in children younger than 2 years. Other work also lead to conclude that the amount of gluten consumed in early childhood does play a role in CD etiology, with the prerequisite that the genetic factor, carrying HLA-DQ-2 , HLA-DQ=8, is present.
In two new studies published in August 2019 in the American Journal of Gastroenterology it has now been shown that increased levels of gluten consumption in the first 2 years of life does increase the risk of developing CD in children that are genetically pre-disposed to develop the disease.

In a Norwegian study "**Gluten Intake in Early Childhood and Risk of Celiac Disease in Childhood,** A Nationwide Norwegian Cohort Study" by Lund Blix et al. (American Journal of Gastroenterology: August 2019 - Volume 114 - Issue 8 - p 1299–1306
doi: 10.14309/ajg.0000000000000331) it was shown that Children in the upper quartile of gluten intake compared with the lower quartile had an modestly increased risk of CD (adjusted relative risk 1.29, 95% confidence interval 1.06–1.58). The association with gluten amount was independent of the age at introduction of gluten. Gluten introduction ≥6 months was also an independent risk factor for CD.

In a US cohort study "**Gluten Intake and Risk of Celiac Disease,** Long-Term Follow-up of an At-Risk Birth Cohort" by Mårild et al (American Journal of Gastroenterology: August 2019 - Volume 114 - Issue 8 - p 1307–1314. doi: 10.14309/ajg.0000000000000255)
It was observed that children in the highest third of gluten intake between the ages of 1 and 2 years had a 2-fold greater risk than those in the lowest third. The risk of developing CD autoimmunity increased by 5% per daily gram increase in gluten intake in 1-year-olds.

For the final interpretation of this data and drawing conclusions regarding the meaning for public health it is critical to look at the specific study groups as well as the robustness of the data. The authors commented that the study group was composed of high-risk children based on the presence of the CD related genetics. Further that there is no established method for exact assessment of gluten intake and that self-reported data may be subject to bias depending on possible erroneous recall of consumption, the collection of data only once per year (instead of regularly to calculate means over time) as well as the gluten

content products data base used as well as product/food recipes (which may have changed over time). Thus, it is difficult to conclude that extrapolations to acute intake in the past as well as chronic intake during early childhood are 100% correct. Nevertheless, both studies showed increased risks of developing CD in individuals with a genetic predisposition when being on a higher level of gluten intake ate the age of 1-2 years, which is in line with other earlier indicative observations. It was also noted that “at least one other time-varying factor must be present for CDA to develop, which would explain why high gluten intake between the ages of 1 and 2 years was more strongly associated than the longer-term cumulative intake. For example, early childhood is associated with a higher frequency of infections and immature immune functions, which in concert with gluten intake, might modify CD risk”.

Many questions remain.
Based on the current observations Mårild et al stated: “ Still, ours and other currently available data should be interpreted with caution, given diverse results from the prospective studies in this field and a lack of randomized intervention studies”. “we do not know the extent to which these results can be generalized to other populations. Furthermore, although the association between gluten intake in 1-year-olds and later CDA was adjusted for multiple covariates, the observational nature of our data prevents from excluding the possibility of unmeasured confounding. This study also lacks analyses of dietary patterns that may be associated with gluten intake level and the risk of CD). Therefore, pending corroborative evidence, we do not recommend a change in pediatric feeding practices”.

Research should be intensified to find out how to reduce CD risks optimally. A possible need for early screening of the presence of the CD related genetic predisposition in children, carrying HLA-DQ2 and HLA-DQ8 and the option of personalized nutritional guidance, should be evaluated.
An important target for research is the question why some individuals (2-3%) of those that have a genetic predisposition to develop celiac disease do develop the disease while the remainder does not. Which factors drive the initiation of the disease?

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