Publication of the Month

April 04/10: Testing of EmA positive samples

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Childhood coeliac disease: towards an improved serological mass screening strategy
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Introduction:

The advantages of diagnosing coeliac disease (CD) as early in life as possible are beyond debate: early diagnosis avoids complications of the disease in later life (e.g. delay in growth), and the recovery of the intestinal lesion after a gluten-free diet is much better in young children than in adults.

Coeliac disease may be detected efficiently by screening for specific antibodies in serum, especially for antibodies against endomysium (EmA) and tissue transglutaminase (tTGA), but ESPGHAN criteria prescribe that the diagnosis should be confirmed by a small-bowel biopsy, revealing the characteristic alterations in gluten-sensitive enteropathy.

In a serological mass screening programme, as it is used in the study of Hogen Esch et al., it is important to avoid false-positive test results as these will give unnecessary stress to the patients or their parents and may result in unnecessary small-bowel biopsies.

Content:

In 1997-1998 6127 asymptomatic children aged 2-4 years were screened for coeliac disease (CD) by anti-endomysium (EmA) testing. Of the 75 EmA-positve children, 57 were forwarded for biopsy. 26 (46%) turned out to have normal small-bowel biopsies.

For a more detailed serological analysis, the 57 EmA positive children were retested lately by several serological ELISA-tests, which resulted in the following sensitivities and specificities:

Serological test	manufacturer cut-off (U/mL)	Sensitivity (%)	Specificity (%)
$tTGA_{gp}$ (in house)	7	93,5	26,9
$tTGA_{hr\ I}$ * (Phadia)	8	93,5	52,0
$tTGA_{hr\ II}$ * (Eurospital)	7	96,8	12,0
$tTGA_{hr\ II}$ ** (in house)	6	100,0	30,4
Anti-DGP (IgA+G)* (Inova)	20	100,0	40,0
Anti-DGP/tTGA (IgA+G)* (Inova)	20	100,0	4,0
IgA AGA (in house)	4	32,3	88,5
IgG AGA (in house)	12	54,8	84,6

* n = 56 (one child with normal small-bowel biopsy could not be evaluated because of lack of serum).
** n = 54 (three children with normal small-bowel biopsy could not be evaluated because of lack of serum).

Comment:

The specificity of EmA testing in the first screening of more than 6000 children was rather low. Only 54% of biopsied EmA-positive children had coeliac disease. The mean time between blood withdrawal and biopsy was 6 months. The authors presume that some of the EmA were only transient and a second measurement shortly before biopsy would have increased the specificity for celiac disease in these children. Possibly, by a second measurement after 6 months, unnecessary biopsies would have been avoidable.

The 57 EmA positive sera (26 of those being biopsy negative) were retested with different other methods. The results were calculated as sensitivity and specifcity, although here only low specificities have to be expected as all were EmA positive. Therefore these results show more of a concordance with EmA than a “real” test efficiency. EmA negative sera were not evaluated.

The authors adjusted the cut-off points according to ROC optimization and, thus, could increase specificity of the different tests (accompanied by a clear reduction of sensitivity). However, as there is a strong bias with these samples, this approach is questionable.

Measurement with other methods than EmA may increase the specificity and so unnecessary biopsies could be avoided. However, it is still open whether the EmA positive but biopsy-negative children of this study developed coeliac disease in the follow-up and how the different serological tests would have performed with the initial screening population.