Antigliadin and antiendomysium antibody determination for coeliac disease

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Abstract

The value of IgG and IgA gliadin antibodies (AGA) was compared with that of IgA endomysium antibodies (EMA) for the diagnosis of coeliac disease. Three hundred and six of 340 (90%) children with untreated coeliac disease (flat mucosa) had EMA and 338/340 (99.4%) had IgG AGA and/or IgA AGA. Only 1/340 (a 7 year old boy with selective IgA deficiency) had neither AGA nor EMA. Absence of EMA is more frequent in coeliac patients younger than 2 years than in older patients (32/277 compared with 1/62). EMA were present in 4/211 (2%) of comparison subjects (normal mucosa), IgA AGA in 12/211 (6%), and IgGA AGA in 74/211 (35%). The specificity of AGA cannot be calculated from these figures as they are biased. The combined determination of AGA and EMA, taking advantage of the high sensitivity of AGA and the high specificity of EMA, gives an excellent prediction of the condition of the mucosa: 247/248 patients (99.6%) with positive EMA and positive IgG AGA and IgA AGA had a flat mucosa, whereas 136/137 patients (99.3%) with neither AGA nor EMA had a normal mucosa.

During a gluten free diet EMA and AGA disappear. Their presence or absence is therefore an indicator of dietary compliance. After reintroduction of gluten into the diet 110/134 (82%) of the patients who had a flat mucosa at diagnosis relapsed, but 24/134 still had a normal mucosa after 2–15 years of challenge. All these patients without a morphological relapse were less than 2 years old at diagnosis so we conclude that patients who are young at diagnosis should be challenged. AGA often reappear earlier than EMA. After one month of challenge 93% of patients are AGA and 69% EMA positive. After more than three years of gluten intake the percentage of AGA positive patients decreased to about 50% whereas the percentage of EMA positive sera was then highest (93%). Therefore EMA are more sensitive for the detection of ‘silent’ relapse after prolonged periods of gluten intake.

It is well known that the formation of small amounts of antibodies to ingested proteins is a normal physiological occurrence. Low concentrations of antibodies to proteins in nutrients can therefore be demonstrated in nearly all subjects if the test method used is sensitive enough. This is also true for antibodies against gliadin (AGA).

In 1958 it was first shown by Berger in the Basel Children's Hospital that raised concentrations of antibodies to gliadin were associated with gluten enteropathy.1 We subsequently tried to establish a simple and reliable test for measuring AGA in different immunoglobulin classes.2 This test was expected to be useful for diagnostic purposes.3–6 The aim was therefore to discriminate between patients with coeliac disease and patients with other malabsorptive disorders and not to detect the very low concentrations of antibody physiologically present in nearly all healthy individuals.

In the last few years several papers have appeared on the determination of antibodies against gliadin as a screening test for coeliac disease. Most authors agree that IgG antibody determinations are sensitive but not pathognomonic but IgA antibodies are more specific but less sensitive.7–19

In 1983 Chorzelski et al described IgG antibodies against endomysium (EMA) and found a close correlation between these antibodies and patients with dermatitis herpetiformis. Later they also found EMA in patients with coeliac disease.20 21 EMA are directed against extracellular reticular fibres in the endomysium that surrounds the smooth muscle cells of many species.

Our aim was to compare the diagnostic significance of IgG AGA and IgA AGA with that of IgA EMA for coeliac disease in children.

Patients and methods

PATIENTS

We studied 551 patients who had undergone a first jejunal biopsy because of suspected coeliac disease from children’s hospitals throughout Switzerland and Germany. Their ages ranged from 4 months to 18 years. All were under investigation for either gastrointestinal disease, failure to thrive, iron deficiency anaemia, short stature, or various malabsorptive disorders. Their sera were sent to the Laboratory for Microbiology and Immunology of the Children’s Hospital in Basel for determination of AGA. At the beginning of the study the patients underwent biopsy without the results of the AGA determination being known. During the course of the study this procedure gradually changed as we came to clinical conclusions from the AGA results. For example, as a precaution patients who were positive for AGA were later biopsied even when the suspicion of coeliac disease was only slight. Therefore the percentage of false positive results increased during the study period. For an unknown number of patients who were negative for AGA we have no docu-
mention regarding a jejunal biopsy. The influence of this selection on the statistical evaluation of AGA results is discussed later. The jejunal biopsies were performed and analysed in different hospitals in Switzerland and in Germany. At the time of blood sampling and jejunal biopsy all children were on a gluten containing diet. A total of 340 children showed a flat mucosa (total or subtotal hyperplastic villous atrophy with hyperplasia of the crypts). In 211 with a normal mucosa or only partial villous atrophy coeliac disease could be excluded. These children were studied as a comparison group. Children with a flat mucosa in the small intestine after exclusion of cows’ milk intolerance and viral diseases, and with regression of all symptoms in a few weeks after the introduction of a gluten free diet, were considered to have coeliac disease irrespective of whether their diagnosis had been confirmed by a biopsy after challenge.

For the following reasons we did not wait for all patients with coeliac disease to be biopsied three times. (1) Some centres of paediatric gastroenterology now refrain from challenging children with gluten. They accept that approximately 5% of originally well documented patients will not relapse after challenge. (2) The question of the incidence of transient coeliac disease is still unsettled and it remains uncertain whether the few patients who do not relapse after challenge are patients with transient coeliac disease or are incorrectly diagnosed.

The other patients who were entered in the study included 86 children who had multiple blood samples taken after varying periods on a gluten free diet. There were 135 children with morphological relapse after reintroduction of gliadin into their diet (110 with initial biopsy, 25 without initial biopsy). Twenty four children were included who did not have mucosal relapse after reintroduction of gliadin into their food, although their mucosa was flat on the initial biopsy specimen. Finally there were 10 patients without mucosal relapse after reintroduction of gliadin, without an initial biopsy.

At the time of the determinations for AGA the biopsy results were not known. Determinations for EMA were often performed retrospectively on the serum samples still available.

METHODS
The fluorescent immunosorbent test was used for the determination of AGA as described elsewhere.3 5 3 3 3 EMA were determined as follows: unfixed cryostat sections of monkey oesophagus (Virimum Diagnostika GmbH) were incubated with the patient’s serum that had been diluted 1:10 in phosphate buffered saline. The antibodies bound to the endomysium of the smooth muscle cells were made visible by overlaying the sections with a fluorescent anti-IgA serum in an appropriate dilution. Under the fluorescence microscope a brilliant green network was seen particularly in the lamina muscularis.

STATISTICAL ANALYSIS
As is clear from the description of the patients the data reported here are not the result of a planned investigation for which the hypotheses to be tested were stated in advance. Statistical analysis was therefore restricted to exploratory data analysis and confirmatory significance tests were applied only with great caution.

Sensitivity and specificity
Sensitivity is defined as the percentage of positive results in patients with the disease in question. Specificity is defined as the percentage of negative results in patients not suffering from the disease in question. In the case of AGA, estimates of sensitivity and specificity are biased by the fact that only a small proportion of the patients with negative AGA tests underwent biopsy.

Most sera sent to our laboratory have negative results for AGA. On the other hand a positive test for AGA was regarded as an indication for biopsy. The prevalence of false positive cases shown in table 1 was therefore higher than in the original population. In order to compensate for this bias a method proposed by Beggs and Greenes was used.22

No such direct connection between the test result and the decision to perform a biopsy exists for EMA. Neither in children with a flat mucosa nor in those with a normal mucosa could a significant association between the tests for AGA and EMA be demonstrated (c2 test in 2×2 tables). Estimates of sensitivity and specificity can therefore be calculated from the present data without gross systematic errors. From a theoretical standpoint a planned experiment for the determination of sensitivity and specificity would be desirable. In order to obtain substantially more accurate estimates than in the present study, several hundred subjects with a flat mucosa as well as with a normal mucosa would be necessary. On ethical grounds such a procedure cannot be advocated.

Predictive values
The positive predictive value of a test is defined as the proportion of true positives in the total number of positives, and the negative predictive value of a test is defined as the proportion of true negatives in the total number of negatives. Both predictive values are related to the prevalence of the disease in the population studied and therefore are not characteristic constants of the test procedure. In the present data the positive predictive value of the case where all three antibody tests were positive was estimated as

<table>
<thead>
<tr>
<th>IgA</th>
<th>IgG</th>
<th>Age (years)</th>
<th>Total</th>
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<tr>
<td></td>
<td></td>
<td>0–2</td>
<td>2–18</td>
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<tr>
<td>+</td>
<td>+</td>
<td>208</td>
<td>39/90 (39)</td>
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<tr>
<td>+</td>
<td>-</td>
<td>37</td>
<td>19/19 (100)</td>
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<tr>
<td>-</td>
<td>+</td>
<td>0</td>
<td>2/3 (67)</td>
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<tr>
<td>-</td>
<td>-</td>
<td>0</td>
<td>1/2</td>
</tr>
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Total: 245/277 (88) 61/63 (97) 306/340 (90)

*One patient with selective IgA deficiency.
+/-, positive/negative for antibody.
Antigliadin and antiendomysium antibody determination for coeliac disease

247/248 = 0.996 (see later in table 3). It may be argued that this estimate grossly exaggerates the true predictive value because of the above mentioned bias in the present data. This argument is not valid for the data were collected in such a way that false positive cases would probably have been detected. On the other hand the negative predictive value of the case where all three tests gave a negative result was estimated as 136/137 = 0.993. This value is probably too low as in a large number of negative cases the state of the mucosa was not examined.

Results

ANTIBODIES IN CHILDREN WITH UNTREATED COELIAC DISEASE AND CONTROLS

The different combinations of results for IgG AGA and IgA AGA were correlated with the results for EMA in 551 children who had a jejunal biopsy. Of 340 patients with untreated coeliac disease (flat mucosa), 306/340 (90%) had EMA. 355/340 (99%) were positive for IgG AGA, and 274/340 (81%) were positive for IgA AGA (table 1). The prevalence of EMA was roughly the same in patients with and without IgA AGA. Only one of the two coeliac children ever found to have no AGA produced EMA. The other was a patient with a selective total IgA deficiency who therefore could not produce either IgA EMA or IgA AGA. Two of the three children with only IgA AGA, a very rare situation which has so far been found only in adolescents, also had EMA.

Absence of IgA EMA is more frequent in patients younger than 2 years than in older subjects (32/277 compared with 1/62, the patient with IgA deficiency is omitted from the statistical analysis). This difference is significant: \( p = 0.0082\), Fisher's one tailed exact test in 2 x 2 tables.

We found EMA in only 4/211 disease controls (table 2). Altogether 207/211 (98%) of the

patients with a normal mucosa or only partial villous atrophy were negative for EMA. Twelve of 211 (6%) had IgA AGA and 74/211 (35%) IgG AGA. The estimated sensitivity of the EMA test is 90% and its estimated specificity is 98%. The sensitivity and specificity of AGA cannot be evaluated from the present figures as they have a statistical bias (compare selection of patients and statistical discussion). In former papers the sensitivity was calculated to be at least 96% and the specificity 97%.

If we summarise the results of determinations of AGA and EMA and distinguish between patients with three, two, or only one positive antibody test (table 3), it is obvious that the combined determination of these antibodies gives an excellent prediction of the condition of the mucosa, particularly in patients with three concordant antibody results. It takes advantage of the very high sensitivity of AGA determination and the very high specificity of EMA determinations. Of the 248 patients with three positive tests, namely positive EMA and positive IgA AGA as well as IgG AGA, 247 (99.6%) had a flat mucosa and were therefore serologically correctly diagnosed as having coeliac disease. Only one showed a normal mucosa. The percentages of patients with a flat mucosa decreased if only two or one tests were positive. Altogether 136 out of 137 (99.3%) patients with neither AGA or EMA had a normal mucosa and were also serologically correctly diagnosed as not having coeliac disease. Conversely the percentage of patients with a normal mucosa decreases if one, two, or even three tests are positive. Of a total of 551 biopsied patients with AGA and EMA determinations, 385 (70%) had three concordant antibody results. One hundred and sixty three (30%) of the 551 patients did not have concordant antibody results, which means that the condition of the mucosa cannot be predicted with the same certainty. Nevertheless, the frequency of a flat mucosa is very high if the test for EMA is positive, even with a negative test for IgA AGA.

ANTIBODIES IN CHILDREN ON A GLUTEN FREE DIET

AGA like EMA disappear on a gluten free diet. IgA AGA disappear very quickly in two to six months so that they are useful as a diet control. By contrast IgG AGA need a long time, sometimes more than a year, to become negative. EMA persist longer than IgA AGA but not as long as IgG AGA. Figure 1 shows the percentages of sera that are still positive in 86 patients

<table>
<thead>
<tr>
<th>Table 2</th>
<th>EMA correlated with AGA in disease controls (normal mucosa or partial villous atrophy). Results are number of EMA positive sera/total number (%)</th>
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<tbody>
<tr>
<td>IgA AGA</td>
<td>IgG AGA</td>
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<tr>
<td>+</td>
<td>+</td>
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<tr>
<td>-</td>
<td>+</td>
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<td>+</td>
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</tr>
<tr>
<td>Total</td>
<td></td>
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</table>

+/-, positive/negative for antibody.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Predictive values of different test results from 551 patients</th>
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<tbody>
<tr>
<td>Antibody test</td>
<td>No of cases with:</td>
</tr>
<tr>
<td>EMA</td>
<td>IgG AGA</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
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+/-, positive/negative for antibody.
who had multiple blood samples taken after increasing periods on a gluten free diet.

REINTRODUCTION OF GLUTEN INTO THE DIET

(a) Clinical results

To demonstrate the persistence of gluten intolerance gluten is often reintroduced into the diet of patients with coeliac disease. In our study a total of 169 patients were challenged and rebiopsied after varying periods on gluten containing food. The highest percentage of patients who relapsed after gluten challenge was seen in the first 15 to 35 days. The percentage of sera showing a pathological mucosa after challenge was 9/134 (7%). In 9/134 (7%) of patients the challenge period was seven or more months.

Ten children had no mucosal relapse after at least two years of challenge. They were probably never affected by gluten intolerance. On the other hand 134/169 patients were diagnosed with a jejunal biopsy showing a flat mucosa. Altogether 110 (82%) of 134 children relapsed after varying periods of challenge, but 24 (18%) showed a normal mucosa after at least two years of challenge. It must be assumed, however, that some of these patients could relapse later on because their challenge period before biopsy was too short to definitely exclude persistent gluten intolerance. Thus 9/134 (7%) had undergone a challenge period of two to four years, but 15/134 (11%) still showed a normal mucosa even after four to 15 years of regular gluten intake, although their mucosa was flat at the initial biopsy (table 4).

The children with relapse were initially diagnosed at an age between 5 months and 10-9 years (median 1-3 years). All children without relapse were younger than two years at diagnosis (6 months–1-7 years, median: 10 months).

The age at challenge varied widely from just under 3 to 18 years in patients both with and without relapse. The final morphological outcome therefore does not seem to be influenced by the age at challenge.

Persistent gluten intolerance was definitively demonstrated in 110 patients who had been biopsied at diagnosis. Some of them had to be biopsied two or even three times during challenge before the relapse became morphologically manifest, which results in 125 biopsies being carried out in 110 patients. Twelve (28%) of 43 patients who were biopsied after one month of challenge still had a normal mucosa. If the biopsy was postponed until between two months and one year of gliadin loading, only 2/33 (6%) did not yet show a morphological relapse (their challenge period was seven or 10 months), and only 1/19 (5%) if it was postponed from one to two years (challenge period 20 months). All biopsies done after at least two years of challenge were pathological.

(b) Antibodies during challenge

AGA titres after challenge in patients with relapse were often not as high as the original titres in untreated coeliac disease. In about 50% of sera only IgG AGA were found and in a few cases only IgA AGA. We therefore can discuss only AGA irrespective of the isotypes found. Before challenge the percentage of antibody positive patients (fig 2) was low (AGA 23%, EMA 13%) but not zero; this is a reflection of dietary non-compliance. AGA are generally produced shortly after the beginning of the challenge, as shown in fig 2. Fifty (93%) of 54 patients with antibody tests produced AGA after 14 to 35 days. The percentage of sera with AGA is highest (97%) after a challenge period of about four weeks to three months and decreases thereafter to only 49% after three or more years of gliadin intake. As regards individual patients, some of them showed the following antibody time course. The AGA increased in an initial phase but later declined again and in some patients even became negative, although the biopsy specimen showed a severely damaged mucosa at the end of the challenge. The increase and decrease of AGA in individual patients explains the diminishing percentages of patients positive for AGA during long challenge periods (fig 2). EMA are produced later in the challenge than AGA but they do not disappear after a prolonged challenge (fig 2). In the first month of challenge only 69% of patients had EMA. The highest percentage (93%) of patients positive for EMA was reached after three and more years of gliadin intake.

AGA were found in 9/54 patients (16%) without morphological relapse and EMA were present in 6/54 (11%). These antibody positive patients were challenged for between three months and four years. Some of them, espe-

Table 4  Clinical results of 169 rebiopsied patients after challenge with gliadin containing food. Results are number (%)

<table>
<thead>
<tr>
<th>Patients with relapse: mucosa pathological after challenge</th>
<th>Patients without relapse: mucosa still normal after challenge period from</th>
<th>2-4 Years</th>
<th>4-15 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without initial biopsy (n=35)</td>
<td></td>
<td>25 (71)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Patients with a flat mucosa at initial biopsy (n=134)</td>
<td></td>
<td>110 (82)</td>
<td>4 (11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 (7)</td>
<td>15 (11)</td>
</tr>
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Figure 1  Frequency of IgA AGA, IgG AGA, and EMA after introduction of a gluten free diet (157 sera from 86 children; number of sera in each group is shown).
Antigliadin and antiendomysium antibody determination for coeliac disease

It is now generally accepted that IgG antibody determinations are sensitive but not pathognomonic for coeliac disease whereas IgA antibody determinations are much more specific but less sensitive.\(^5\)\(^8\)\(^9\)\(^\text{18}\)\(^\text{19}\) As coeliac disease is 10-15 times more frequent in people with selective IgA deficiency than in those with normal IgA it is not advisable to omit IgG antibody determinations, although IgA antibodies are more specific.\(^24\)

In the last few years an additional test for EMA has been introduced and shown to be highly specific for coeliac disease.\(^2\)\(^3\)\(^20\)\(^21\)\(^25\)-\(^28\) Our aim was to compare AGA with EMA for diagnostic purposes. In an earlier study we examined AGA in untreated coeliac disease and in disease controls and obtained a sensitivity of at least 96% and a specificity of 97% for combined IgG AGA and IgA AGA determinations.\(^5\)

In the present study 35% of children with a normal mucosa had IgG AGA, mostly in very low titres, and 6% had IgA AGA. It is not possible to calculate the specificity of AGA from these figures as they have a statistical bias (see earlier). EMA, however, has an estimated sensitivity of 99%. Thirty four of 340 children (10%) with untreated coeliac disease had no EMA. All except two of them were younger than 2 years at diagnosis. This shows that the sensitivity of EMA is age dependent (80% in children <2 years, 97% in children >2 years). It may be speculated that some of the patients without EMA might have produced EMA at a later age. Substance is lent to this conjecture by the development of EMA during challenge, where the relative frequency of cases positive for EMA increases with the duration of challenge with gluten.

The specificity of EMA was very high at 98% (207/211). The combined determination of AGA and EMA, taking advantage of the high sensitivity of AGA and the high specificity of EMA, obviously gives an excellent prediction of the condition of the mucosa (table 3). Particularly in those patients with three concordant antibody tests (IgG AGA, IgA AGA, EMA either all tests positive or all tests negative) the chance of an incorrect prediction is extremely small. For example, only one out of 248 patients (0-4%) with three positive antibody tests had a normal mucosa, whereas only one out of 137 patients (0-7%) with three negative tests had a pathological mucosa.

As a consequence of many studies\(^5\)-\(^9\)\(^\text{18}\)\(^\text{19}\) it has recently become the custom of many paediatric gastroenterologists not to take biopsy specimens from patients when no antibody can be found\(^29\) unless a strong clinical suspicion of coeliac disease is contradictory to the serological result. A positive antibody result, however, is taken as an indication for biopsy. The question arises of whether it would not also be possible to refrain from carrying out a biopsy in children younger than 2 years if the three antibody tests (IgG AGA, IgA AGA, EMA) are positive. In this age group the number of children without relapse on challenge is very high, 11-18% in our study, even if these patients presented a flat mucosa at initial biopsy. A challenge after remission is therefore required in all cases if the children are less than 2 years old at diagnosis.

(c) The value of antibodies in indicating the appropriate time for jejunal biopsy during challenge

One hundred and fifty biopsy findings from the 135 patients with final relapse (110 with and 25 without biopsy at diagnosis) were correlated with the respective antibody results at the time of biopsy (table 5). All patients except four had antibodies (either AGA or EMA or both) at the time of biopsy if the mucosa was pathological. One patient was negative after one month, two after two to 12 months, and one after more than two years of challenge, although the mucosa was pathological at the time. Six of 15 patients whose mucosa was still normal at the first biopsy during challenge were already antibody positive. It may be concluded that nearly all patients with a relapse produced antibody but that it sometimes appears before the mucosa becomes pathological.

Discussion

AGA were first described in 1958.\(^1\) Since then much has been done to improve antibody determination techniques. Two methods in particular have been widely used and thoroughly proved: the fluorescent immunosorbent test and the enzyme linked immunosorbent assay (ELISA). The results of both assays are comparable and have been extensively reviewed.\(^18\)\(^23\)

<table>
<thead>
<tr>
<th>Length of challenge</th>
<th>1 Month</th>
<th>1-2 Months</th>
<th>2-3 Years</th>
<th>&gt;3 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat mucosa</td>
<td>37/38</td>
<td>36/38</td>
<td>22/22</td>
<td>36/37</td>
</tr>
<tr>
<td>Normal mucosa</td>
<td>3/12</td>
<td>1/2</td>
<td>0/1</td>
<td>0/0</td>
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There were 150 biopsies and blood samples from 135 patients with final relapse.
Only a challenge followed by biopsy will save many children (5–18%) with transient coeliac disease from having unnecessarily to follow a lifelong gluten free diet. Therefore the biopsy for diagnosing coeliac disease would not be eliminated but only postponed. This proposal for one biopsy at the end of the diagnostic procedure instead of one at the beginning in children younger than 2 years with three positive antibody tests is contrary to the revised criteria for diagnosis of coeliac disease, which demand an initial biopsy for correct diagnosis in any case.

Nevertheless with a view to the future this possibility should be included in the general discussions of European paediatric gastroenterologists.

AGA and EMA decline on a gluten free diet, as has already been shown by other authors, and may therefore be used as an indication of dietary compliance.

After reintroduction of gluten into the food many patients with coeliac disease relapse. But the question of the incidence of transient coeliac disease is still unsettled. It is evident from their figures that a flat mucosa in young children does not constitute proof of lifelong coeliac disease. Persistent gluten intolerance was demonstrated in 82% of patients with a flat mucosa at diagnosis. Some of them had to be biopsied several times before the relapse was morphologically evident. Thus 12 out of 43 patients (28%) who had been biopsied after one month of challenge did not yet show any signs of relapse. In most patients the morphological relapse becomes EMA evident after three to 10 months of challenge. All biopsies done after at least two years of gluten intake were pathological.

After reintroduction of gluten containing food, not only AGA but also EMA are produced again. In many patients AGA appears earlier than EMA so that after a short period of challenge the percentage of patients positive for AGA (93%) is higher than the percentage of those positive for EMA (69%). The percentage of sera positive for AGA is highest after a challenge period of about one to three months (97%), but after prolonged periods of gluten intake it decreases to only about 50%. This decline in the number of patients positive for AGA after long periods of challenge reflects the titre for AGA in individual patients, where an initial increase and later on a decrease or sometimes even a negative titre may be observed although the mucosa is damaged at the end of challenge. By contrast the percentage of sera positive for EMA is highest (93%) after one or more years on normal food and stays at the level even after very long periods of gluten intake. Therefore EMA are more sensitive for the detection of a ‘silent’ relapse after prolonged periods of gluten intake.

In conclusion, nearly all patients with persistent gluten intolerance produce antibodies at some time, but they show a wide individual variation as regards time and the type (AGA, EMA) and quantitates of the antibodies they produce. The pathophysiological role of AGA and EMA is still unknown. As we showed recently, EMA is probably identical with an antijejunal antibody directed against collagen fibres in human jejunum. We consider this antibody to be an autoantibody of coeliac disease.

Uniparental disomy and genomic imprinting

Sex is dead. Oh, really? Yes, well it must be because, according to a distinguished group of geneticists,¹ it has left a legacy—the fact that chromosomes and genes come in pairs. Be that as it may, the phenomenon of genomic imprinting (see Archivist 1991:80) is a fascinating one which seems as yet to have no very satisfactory explanation. The most commonly quoted clinical example of this phenomenon is, of course, the fact that Angelman’s syndrome and the Prader-Willi syndrome appear to result from a deletion in the same region of the long arm of chromosome 15 (15q 11–13) and the deletion is always of maternally derived material in Angelman’s syndrome and of paternally derived in the Prader-Willi syndrome.

It was reported in 1989 that the Prader-Willi syndrome could result from uniparental maternal disomy—that is, both chromosomes coming from the mother.² Now two of a total of 76 patients with Angelman’s syndrome have been shown to be disomic for the paternal chromosome 15.³ As the patients are in all respects similar to others with this syndrome it seems unlikely that the absence of other maternally derived genes on this chromosome has any appreciable deleterious effect. Thus imprinting is clinically relevant in probably only a small proportion of the genome. It is not yet established that the responsible gene is the same in the two syndromes but if not identical they are very close or overlapping.

From the point of view of genetic counselling the finding is of some significance. When parental chromosomes are normal the risk of recurrence is low for Prader-Willi syndrome but higher (more than 8%) for Angelman’s syndrome. If parental disomy can be demonstrated, however, that indicates a very low risk in either syndrome.

ARCHIVIST