

Controversy

Diagnosis of coeliac disease: time for a change?

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Diagnosing coeliac disease is not easy. Current recommendations stem from a 1970 statement of the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN)¹ and call for: histological evidence of the lesion; evidence of its disappearance after an adequate period on a gluten free diet; and evidence of its recurrence after the reintroduction of gluten into the diet. Such a procedure, which seems to be widely accepted in Europe,² is probably optimal for a firm diagnosis, but has several drawbacks, particularly in the light of new developments that have since taken place. Firstly, the time required for the final diagnosis is unduly long (three years on average); secondly, it does not take into account the variability in clinical expression of the disease; thirdly, it does not take into account the fact that after the age of 2 years it is highly unusual for subtotal villous atrophy to be caused by diseases other than coeliac disease²; and, fourthly, it means re-exposing a child to the offending agent in order to reproduce the mucosal damage. Furthermore, even this challenge (which is now known to be potentially harmful to the child's growing potential^{3 4}) might be inconclusive, as evidence is now mounting that relapse may take longer than two years.^{2 5 6}

It is therefore not surprising that several workers have started to adopt a somewhat more flexible attitude to the diagnosis that takes into account some

new laboratory investigations (particularly the presence of anti gliadin antibodies) and improved knowledge of the clinical range of the disease that has been acquired since the diagnostic protocol was introduced almost 20 years ago.

For these reasons, the Italian Working Group for Paediatric Gastroenterology (which was formed in 1976 and has 250 members) undertook an evaluation of the current approach to the diagnosis of coeliac disease in Italy to verify whether a simplified, more

flexible approach was possible. The following points were retrospectively assessed, in a total of 3138 patients with coeliac disease from 33 different centres: (i) the importance of human leucocyte antigen (HLA) typing and the presence of anti gliadin antibodies; (ii) the need for repeated intestinal biopsy in so called 'atypical' cases or in cases presenting in older children; (iii) the predictive value of the presence of 'flat mucosa' in a child with clinical or laboratory evidence, or both, suggesting coeliac disease; and (iv) the feasibility and evaluation of gluten challenge.

The collected data were analysed and presented by invited experts in a two day meeting in Trieste in May 1987. During the meeting each point was discussed and a final consensus was reached, in a session chaired by A Rubino. The most important points are summarised below.

Importance of HLA typing

A total of 324 patients, all of whom were diagnosed according to the strict criteria of the ESPGAN protocol, have had HLA typing carried out (table 1). HLA class II types are found more often in patients with coeliac disease which confirms work from the rest of Europe.^{7–10} The predictive value of these is limited, however, as such antigens may also be found in healthy controls, and they are not always present in patients. In our series, 7.7% of patients with coeliac disease did not have either HLA-DR3 or HLA-DR7. If HLA-DQ2 is also considered, this figure decreases to 5%. It should be noted, however, that even the patients with coeliac disease who did not have HLA-DQ2 or HLA-DR3 and HLA-DR7, or both, have so far all had HLA-DR4 isolated from their plasma.

From the point of view of the diagnosis, therefore we can conclude that the finding of one of these

Table 1 Association between HLA type and coeliac disease

Country (No of cases)	HLA-DR3 (%)	Relative risk	HLA-DR7 (%)	Relative risk	HLA-DR3 and DR3-DR7 (%)	Relative risk
Ireland ⁷ (92)	86	9.2	25	0.7	21	4.3
Germany ⁸ (42)	64	7	48	2.7	26	7.5
France ⁹ (22)	63.7	6.6	54.5	4.5	—	—
Spain ¹⁰ (163)	71.2	11.5	61.4	2.6	38	11.5
Italy (324)	61	6.3	53.7	3.4	22.5	10.5

antigens, although consistent with the diagnosis of coeliac disease, can not be assumed to prove it. On the contrary if no such antigens are found, this is of great diagnostic importance, because it implies that coeliac disease can confidently be ruled out.

Importance of antigliadin antibodies

One of the most important discoveries in the last few years has been the method for detection of serum antigliadin antibodies in patients with coeliac disease. Although the method is not yet standardised, and its discriminating capabilities are not yet confirmed, it looks as if it will be a useful diagnostic tool. To calculate their importance and define their diagnostic role, data on serum antigliadin antibodies detected in the various phases of the diagnostic procedure laid down in the ESPGAN protocol were analysed. The collected data (table 2) refer to children who were in phase I (359 cases of florid disease, while on a gluten-containing diet), in phase II (452 cases in clinical remission while on a gluten free diet), in phase III (286 patients being challenged with a diet containing gluten), 880 controls who were age matched patients with various gastrointestinal disorders not accompanied by flat mucosa, and 496 healthy children.

The sensitivity of IgG antigliadin antibodies

comes close to 100% in patients in phase I; on the other hand, IgG antigliadin antibodies are detected in a comparatively high percentage (21.7%) of patients with other gastrointestinal disorders. For IgA antigliadin antibodies they show a somewhat lower sensitivity (90.5%), but a better specificity, being present in only 3% of patients who do not have coeliac disease. It should not be forgotten that the incidence of IgA deficient subjects (which obviously reduce the number of subjects with IgA antigliadin antibodies) is about 2-3% in patients with coeliac disease—that is, much higher than in the general population.

Finally, the specificity of antigliadin antibodies when tested against healthy controls is high. We believe that these conclusions are true, despite the fact that the methods used differed among the centres (enzyme linked immunosorbent assay (ELISA) in most, immunofluorescence in a few). Our conclusion is based on the large sample size, and the consistency of the results compared with most other reported series.¹¹⁻¹³

Another test widely used for the diagnosis of coeliac disease is the one hour blood D-xylose absorption test. When considered alone in our patients, this test agreed with the jejunal histology in 70%. When the xylose test was used in combination with estimation of antigliadin antibodies, however,

Table 2 Antigliadin antibodies in patients with coeliac disease and in controls

	Diagnostic phase No of patients	Total No (%) with antigliadin antibodies	No (%) with IgA antigliadin antibodies	No (%) with IgG antigliadin antibodies
Patients with coeliac disease:				
I	359	353 (98.3)	325 (90.5)	351 (98.0)
II	452	185 (40.9)	53 (11.7)	181 (40.0)
III	286	269 (94.0)	236 (82.5)	262 (91.6)
Patients with other gastrointestinal disease	880	197 (22.3)	27 (3.0)	191 (21.7)
Healthy controls	496	17 (3.4)	3 (0.6)	14 (2.8)

the agreement of both tests with the histological picture was 98% in a series of 48 recently diagnosed patients.

In summary, the diagnostic accuracy of estimating antigliadin antibodies is quite high: almost no patients with florid coeliac disease lack IgG antigliadin antibodies, and few patients who have IgA antigliadin antibodies do not have coeliac disease. Furthermore, when they are used together and are both positive, serum antigliadin antibodies and blood xylose testing seem to be consistent with the jejunal morphology of the patient with coeliac disease.

Cases that are 'atypical' or present in older children, or both

Data regarding age and mode of onset were obtained from 1126 patients with coeliac disease. Ninety four (8.4%) were labelled 'atypical', as they did not present with diarrhoea. Their mean age at onset of symptoms was 2.9 years (significantly higher than in typical cases). Characteristically they commonly presented with iron deficiency anaemia, failure to grow and put on weight, anorexia, vomiting (often specifically related to gluten-containing meals), and constipation. In a further group of 44 patients (3.9%), the symptoms began after the age of 2 years (late onset coeliac disease), at a mean age of 6.2 years. Again, among other symptoms, half these older children presented with short stature.

Considering the time elapsing between onset of symptoms and first biopsy (on average 3.8 years in the series of 94 'atypical' patients, 3.6 in the 44 late onset patients), it is evident that the mean age is much higher—6.7 years for the former group of patients with coeliac disease, 9.8 for the latter. At these ages, and in our geographical area, there is practically no differential diagnosis for subtotal villous atrophy responding to gluten withdrawal. A particular subgroup of 'atypical' patients with coeliac disease comprises those affected by dermatitis herpetiformis (Dühring's disease). They can be diagnosed with full confidence from a skin biopsy specimen by an experienced dermatologist,¹⁴ thus obviating the need for intestinal biopsy.

Diagnostic importance of the initial finding of subtotal villous atrophy in a child suspected of having coeliac disease

From the clinical records from 30 centres, we found that 3293 children underwent intestinal biopsy for suspected coeliac disease, and were found to have crypt hyperplastic subtotal villous atrophy. Among them, 3138 (95%) were eventually diagnosed as

having coeliac disease after completing the full diagnostic procedure. It should be emphasised that 2400 of them strictly followed the diagnostic phases of the ESPGAN protocol; the remaining 738 patients were diagnosed as having coeliac disease by 'simplified' diagnostic schemes, most of them omitting the second biopsy (table 3). Interestingly, the percentage of patients eventually diagnosed as having coeliac disease was no different among those who followed the ESPGAN protocol (95%) and those who did not (95.8%), suggesting an overlapping diagnostic accuracy between the rigid protocol and the more flexible attitude.

Focusing on the 155 patients (4.7%) in whom the diagnosis of coeliac disease was unconfirmed at the end of the diagnostic procedure, the following observations can be made: (i) the most common single diagnosis was cows' milk sensitive enteropathy (n=32, 20.6%), followed by transient gluten intolerance (n=24, 15.5%); (ii) the mean age of the patients at the time of first biopsy was 8 months, further highlighting the fact that the differential diagnosis of coeliac disease is essentially a problem of infancy; (iii) the data refer to patients that were, in most cases, seen at a time when estimation of antigliadin antibodies was not possible. It is therefore likely that that estimation could have improved the diagnostic value of the first biopsy.

These observations indicate that when facing a child whose history is consistent with coeliac disease and whose first biopsy specimen shows an unequivocal crypt hyperplastic subtotal villous atrophy, in our geographical area one has at least a 95% chance that one is dealing with coeliac disease: a diagnostic accuracy not too frequently found in paediatric practice. Furthermore, it is clear that adding the diagnostic weight of estimation of HLA and anti-

Table 3 *Association between 'flat mucosa' at first biopsy and eventual diagnosis of coeliac disease*

	No	%
All patients:		
Patients suspected of having coeliac disease with a 'flat mucosa'	3293	100
Eventual diagnosis of coeliac disease	3138	95.3
Other diagnoses	155	4.7
Diagnosis by strict adherence to ESPGAN protocol:		
Patients suspected of having coeliac disease with a 'flat mucosa'	2523	100
Eventual diagnosis of coeliac disease	2400	95.1
Other diagnoses	123	4.9
Diagnosis by other 'simplified' procedures:		
Patients suspected of having coeliac disease with a 'flat mucosa'	770	100
Eventual diagnosis of coeliac disease	738	95.8
Other diagnoses	32	4.2

gliadin antibodies will further increase that percentage, particularly by omitting false positive diagnoses.

Methods of gluten withdrawal and reintroduction: clinical and diagnostic implications

Table 4 shows the data concerning age at diagnosis and duration of the diagnostic phases in 361 patients with coeliac disease; these are the 15 most recently diagnosed patients from each centre. The mean age of diagnosis (3.2 years) seems somewhat higher than in the past, in accordance with the present trend of the disease as reported by others.¹⁵ Mean duration of the gluten free diet seems quite long, even longer than that recommended by the ESPGAN protocol, thus increasing the likelihood of poor compliance to the diet and delaying the time to conclusive diagnosis. Most important, however, is the duration of challenge (seven months), which seems too long. In most patients the mucosal relapse occurs within three months,^{16 17} although individual variations in the speed of mucosal relapses are well recognised, and in the occasional patient a particularly long time may elapse.⁵

In any case, prolonging the duration of the challenge in the patients with coeliac disease does not seem to be of any benefit: the histological, clinical, and biochemical data from 195 patients with coeliac disease show that the bulk of laboratory results (excluding estimation of anti gliadin antibodies) and the clinical response do not correlate with histological signs of relapse. Only in 48.8% of our cases did such a correlation exist, similar to what has previously been reported by others.^{6 16 17} Thus prolonging gluten challenge does not help in providing clear cut evidence on which to decide the time for biopsy and in addition has harmful effects on the child's weight and growth. Recent evidence, on the other hand, indicates that anti gliadin antibodies rise within a few weeks of the reintroduction of gluten.¹⁸ Thus by monitoring the rise in anti gliadin antibodies, most challenges may be stopped after 60 days.¹⁸

If we consider that 95% of the patients are already correctly diagnosed after the first biopsy, and that

this figure may only increase by the use of estimations of anti gliadin antibodies, to link the final diagnosis to the outcome of the challenge might actually result in underdiagnosis of the disease. On one hand, the support offered by clinical and laboratory data is poor, and on the other hand, it is well known that a number of patients do develop the mucosal lesion late.^{5 6} Finally, it must not be forgotten that a prolonged challenge, particularly during periods of increased growth (infancy and adolescence), may interfere with linear growth.^{3 4} The bulk of this evidence would then suggest that a gluten challenge is not necessary for diagnosis and may actually prove to be harmful.

Conclusions

After having carefully evaluated and thoroughly discussed all the evidence that has been outlined briefly above, the Working Group for Gastroenterology came to the following conclusions: (1) in many instances of suspected coeliac disease (and in our geographical area) the diagnostic approach may differ from that recommended in the ESPGAN protocol. It must be firmly stated, however, that at present no diagnosis of coeliac disease can be made without the characteristic histological picture of the duodenal-jejunal mucosa. (2) In cases presenting with a history and clinical picture suggestive of coeliac disease, laboratory data (including anti gliadin antibodies) consistent with coeliac disease, a clear histological picture of a crypt hyperplastic subtotal villous atrophy, an obvious clinical and laboratory response to the gluten free diet, and as long as the diagnosis of cows' milk sensitive enteropathy can be ruled out, the definitive diagnosis of coeliac disease can be made. On this basis, gluten must be permanently excluded from the diet, and regular follow up should be instituted.

Whenever the diagnosis is uncertain on the basis of history or clinical or laboratory evidence, or both, or the appearance of the mucosa at initial biopsy is considered doubtful, strict adherence to the ESPGAN protocol is recommended (including gluten challenge to be carried out at an early age), with the possible exception that the second biopsy may be omitted, provided that all pertinent data (including estimation of anti gliadin antibodies) are in agreement.

Spontaneous gluten reintroduction is to be avoided by all costs. Whenever, in order to prevent it, or in accordance with family pressure, it is decided to perform a medically supervised gluten challenge, it is recommended that such a challenge should not be done during the pubertal spurt of infantile growth and that the diet containing gluten is maintained for

Table 4 Age and diagnostic phases of coeliac disease in 361 selected patients

	No of patients	Mean (range)
Age at diagnosis (years)	361	3.2 (0.4-26)
Duration of gluten free diet (months)	322	17.7 (3-78)
Age at challenge (years)	320	5.1 (1.5-25.2)
Duration of challenge (months)	319	7.0 (0.2-71)

no longer than three months in the first instance. Evaluation of relapse may, but does not necessarily have to, be confirmed histologically; such confirmation may not be needed when clinical and laboratory evidence (including a rise in anti gliadin antibodies titre) is clear.

These considerations and recommendations are reported as a matter for further discussion and in the hope that they will stimulate comments and criticism from all paediatricians who take part in investigation or clinical management, or both, of young patients with coeliac disease.

The data summarised here were collected at the following centres: Clinica Pediatrica dell'Università, Ancona; Istituto di Pediatria Clinica e Sociale, Università di Bari; Divisione di Pediatria, Ospedale Maggiore 'GA Pizzardi' Bologna; Istituto Clinica e Biologia Eta' Evolutiva dell'Università Cagliari; Clinica Pediatrica dell'Università di Catania; Clinica Pediatrica Ia dell'Università; Istituto G. Gaslini, Genova; Divisione Pediatrica, Ospedale Generale, Mantova; Clinica Pediatrica IIa dell'Università di Messina; Clinica Pediatrica Ia, Università di Milano; Clinica Pediatrica IIa, Università di Milano; Clinica Pediatrica IIIa, Università di Milano; Clinica Pediatrica IVa—Ospedale 'L Sacco', Milano; Clinica Pediatrica Ia dell'Università di Modena; Divisione Pediatrica, Ospedale G Salesi, Ancona; Divisione Pediatrica, Ospedale degli Esposti, Bologna; Divisione Pediatrica, Ospedale Bufalini, Cesena; Divisione Pediatrica, Ospedale S Michele, Cagliari; Divisione Pediatrica, Ospedale S Carlo, Milano; Dipartimento di Pediatria dell'Università di Napoli; Divisione Pediatrica, Ospedale SS Annunziata, Napoli; Clinica Pediatrica, Università di Padova; Divisione Pediatrica, Ospedale dei Bambini, 'G Di Cristina', Palermo; Clinica Pediatrica dell'Università di Parma; Clinica Pediatrica dell'Università di Pavia; Clinica Pediatrica I, Università La Sapienza, Roma; Clinica Pediatrica III, Università la Sapienza, Roma; Clinica Pediatrica dell'Università, Torino; Clinica Pediatrica dell'Università, Trieste; Servizio Pediatrico Speciale, Ospedale Borgo Trento, Verona; Divisione Pediatrica, Ospedale infantile Alessandri, Verona; Clinica Pediatrica dell'Università, Palermo; Clinica Pediatrica Illa Università di Bologna; Ospedale Bambino Gesù, Roma; and Clinica Pediatrica dell'Università, Verona.

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Commentary

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The 'cause' of coeliac disease is not yet known in molecular terms. The diagnosis of coeliac disease remains empirical and is currently based on two well established facts. The first is that gluten causes a malabsorption syndrome with small bowel enteropathy in susceptible subjects.¹ Secondly, withdrawal of gluten from the diet leads to complete restoration to normal of the patient and his intestinal mucosa.²

A third important contribution to our thinking about coeliac disease was provided by the (then) European Society for Paediatric Gastroenterology (ESPGA) in its publication of the 'Interlaken criteria'.³ In these criteria, coeliac disease was affirmed to be a permanent condition of gluten intolerance, and it was implied that, in order to substantiate an initial diagnosis of coeliac disease, the permanence (or at least persistence) of gluten intolerance should be confirmed in each individual