SPECIAL REPORT

Revised criteria for diagnosis of coeliac disease

Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition

It is now 20 years since the diagnostic criteria for coeliac disease (subsequently known as the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) criteria) were proposed at the Interlaken meeting of the society in 1969.[1] These criteria were further enunciated at the second symposium on coeliac disease in 1974, namely:

- Structurally abnormal jejunal mucosa when taking a diet containing gluten.
- Clear improvement of villous structure when taking a gluten free diet.
- Deterioration of the mucosa during challenge.[2]

This sequence of three biopsies was instituted at a time when coeliac disease was regarded by the authors of the Interlaken statement as a life long condition that always started in childhood (at least as far as the small intestinal lesion was concerned). Sensitivity to gluten was regarded as a permanent condition that lead to a change in the mucosa as soon as gluten was ingested by the child, although with remarkably variable clinical expression. This sequence of small bowel biopsies was a means of differentiating coeliac disease from other, transient, causes of abnormal small intestinal mucosa by proving, at the time of challenge, the long lasting sensitivity to gluten. In practice it served also to establish positively the diagnosis of coeliac disease. The subsequent widespread use of these serial biopsies has taught physicians a great deal about the long term evolution of gluten induced enteropathy.

The 'Interlaken critiera' were reviewed by ESPGAN in 1978.[3] It was already apparent by then that gluten challenge, central to the definition of coeliac disease according to these criteria, was in fact carried out by only two thirds of members of ESPGAN. Futhermore, it was suggested that the ESPGAN criteria might not invariably be required for diagnosis of all patients, as they confirmed the initial diagnosis made at the time of the first biopsy in the large number of 619 of 652 cases (95%). The ESPGAN criteria were, however, not modified.[3]

Ten years later experience of the management of coeliac disease is even greater. New diagnostic tools—antigliadin, antireticulin, and anti-endomysium antibodies—have proved to be reliable indicators of sensitisation to gluten, at least at the time of diagnosis. Further reports have been published in which the ESPGAN criteria (three serial small intestinal biopsies related to gluten elimination and provocation) have been used in a remarkably large series of 3293 children from Italy.[4] These authors, however, suggest that in most cases gluten challenge is not essential for diagnosis. In addition, the variability of mucosal sensitivity to gluten in a noticeable proportion of cases over a period has been observed.[5–7]

In view of evidence that coeliac disease is more variable in its long term evolution than previously thought on the one hand, and of the increasingly expressed view that gluten challenge may not be mandatory for the diagnosis of coeliac disease, on the other, a workshop on 'Diagnostic criteria of coeliac disease' was organised by ESPGAN in Budapest in May 1989. The present report, which summarises the outcome of that meeting, is therefore aimed at clarifying the ESPGAN position concerning the practical clinical diagnosis of coeliac disease.

Practical approaches to diagnosis of coeliac disease

SIMPLIFIED PROCEDURE

The first requirement for the diagnosis of coeliac disease is the finding of a characteristic small intestinal mucosal abnormality on histological examination of a biopsy specimen. This must remain the initial step in diagnosis. The second requirement is a clear cut clinical remission on a strict gluten free diet with relief of all symptoms of the disease. This response should be reasonably rapid occurring within a matter of weeks rather than many months. These two requirements remain mandatory for the diagnosis of coeliac disease. Gluten challenge is not mandatory.

In asymptomatic patients, however (as is often the case in first degree relatives of patients with coeliac disease), a control biopsy is needed to prove mucosal recovery when the patient is taking a gluten free diet.[8] Control biopsy is thus always a suitable way of verifying the effect of the diet when the clinical response is equivocal.

Initial diagnostic biopsy

It is recommended that the small intestinal mucosal biopsy should always be taken with a biopsy capsule rather than through the endoscope to ensure diagnostically adequate specimens that may be orientated correctly for histological section. It is ideal to examine the biopsy specimen first with the dissecting microscope in order to recognise at once the typical flat mucosa and also to assist with correct orientation for section.[9] It is vitally important that histological sections are well orientated and of adquate size for diagnosis. It is as important to recognise the characteristic mucosal structure

Queen Elizabeth Hospital for Children, Hackney Road, London E2 8PS
J A Walker-Smith (Secretary)

Department of Paediatrics, University of Naples, Italy
S Guandalini

Hôpital des Enfants Malades, Paris, France
J Schmitz

Kinderspital, Zurich, Switzerland
D H Shmerling

University of Tampere, Finland
J K Visakorpi

Correspondence to: Professor Walker-Smith.

Arch Dis Child: first published as 10.1136/adc.65.8.909 on 1 August 1990. Downloaded from http://adc.bmj.com/ on September 19, 2020 by guest. Protected by copyright.

that is found in coeliac disease. It is best described as hyperplastic villous atrophy with hyperplasia of the crypts and an abnormal surface epithelium. Morphometry and histochemistry are important aids to diagnosis. The intraepithelial lymphocyte count is raised, and then falls when a gluten free diet is introduced.[10] The application of monoclonal antibodies to these lymphoid cells may in the future be a further aid to diagnosis.[11]

Antibody studies

In recent years it has become clear that circulating IgA gliadin, IgA antireticulin, and IgA antiendomysium antibodies have a high degree of sensitivity and specificity for the diagnosis of coeliac disease.[12–16] When such antibodies are present at the time of diagnosis in a child with a typical small intestinal mucosa, and when they disappear in parallel to a clinical response to a gluten free diet, weight is added to the diagnosis of coeliac disease that may now be said to have been finally established.

These tests should be carried out in an experienced laboratory with well established normal values. It is important to appreciate, however, that the diagnosis of coeliac disease cannot be made on the presence of these antibodies alone—firstly, because occasional false positives and false negatives may occur; and secondly, because coeliac disease has rarely been described in hypogammaglobulinaemia and somewhat more often in association with IgA deficiency.[17] Furthermore, these antibodies are more specific in communities where there are few other causes of enteropathy rather than in those communities where other causes of enteropathy are common (especially the developing world). In such communities, however, when biopsy is unavailable, the presence of abnormal concentrations of two antibodies strongly suggests that coeliac disease is a diagnostic possibility.[18] Not only is their disappearance when a gluten free diet is taken a further marker of response to the diet, but their presence or absence may constitute a guide to dietary compliance.

GLUTEN PROVOCATION (INTERLAKEN PROCEDURE)

Under certain circumstances there is a need to carry out a gluten challenge and to fulfill all the original ESPGAN criteria. This is when there is any doubt about the initial diagnosis—for example, when no initial diagnostic biopsy was done, or when the biopsy specimen was inadequate or in some way uncharacteristic of coeliac disease. In communities where other causes of enteropathy occur (such as cows' milk sensitive enteropathy, postenteritis syndrome, and giardiasis) care must be taken to exclude these. This may be difficult, however, and in the case of transient gluten intolerance there may be no possible way to do this, at least on present evidence.[19 20] As these disorders chiefly occur in children aged 2 years or less at presentation, it may be practical to recommend gluten provocation in children in this age group. Challenge should not be undertaken for at least two years, and preferably not before the age of 6 years, because it can damage the dentition if done earlier.[21]

In addition, in older children and teenagers who intend to abandon the gluten free diet in an uncontrolled way themselves, it is clearly preferable to do this under controlled conditions as a gluten provocation test with serial biopsies as recommended in the ESPGAN criteria. It should ideally be done well before puberty or after the end of the pubertal growth period.

It remains essential when gluten provocation is carried out to obtain a control biopsy specimen while the patient is taking a gluten free diet. A further biopsy is then taken when there is a noticeable clinical relapse after challenge, or in any event after three to six months. If the mucosa remains normal, however, follow up is as important as ever and another biopsy should be done if symptoms reappear or after two years. Though the two year rule is practical in most circumstances,[3] there are now several reports of children taking as long as five to seven years to relapse after gluten provocation.[22–24] Indeed, the diagnosis of transient gluten intolerance is one that is difficult to establish even if the possibility of late relapse after many years is recognised. Thus if examination of a biopsy specimen after two years on a gluten containing diet shows normal mucosa, long term follow up is essential, with further biopsies taken if symptoms recur or if an antibody test becomes abnormal. The antibody tests are now recognised as valuable adjuncts to evaluation of gluten provocation and they provide a guide to the timing of biopsy.[25] In view of the now recognised variability in the response of the small intestinal mucosa to gluten, as well as in the clinical expression of the disease, long term follow up into adult life of those who do not relapse is vital.

When carrying out a gluten provocation test it is important to ensure an adequate gluten intake either as measured amounts of gluten powder or by dietetic monitoring of gluten intake—for example, a minimum of two slices of bread for older children.

Conclusions

The diagnosis of coeliac disease does not require further confirmation if the initial diagnosis is based firstly on the appearance of flat small intestinal mucosa with the histological features of hyperplastic villous atrophy while the patient is eating adequate amounts of gluten, and secondly on unequivocal and full clinical remission after withdrawal of gluten from the diet. The finding of circulating antibodies (IgA gliadin, antireticulin, and antiendomysiun) at time of diagnosis and their disappearance when the patient is taking a gluten free diet add weight to the diagnosis.

The exceptions to this approach are when there are doubts about the initial diagnosis and the adequacy of the clinical response to a gluten free diet. A gluten challenge must then be carried out.

Finally it is of paramount importance that these practical recommendations do not

Arch Dis Child: first published as 10.1136/adc.65.8.909 on 1 August 1990. Downloaded from http://adc.bmj.com/ on September 19, 2020 by guest. Protected by copyright.

decrease the accuracy of the initial diagnosis of coeliac disease, for two reasons. Firstly, this diagnosis will lead to a child being followed up for years with strict adherence to a gluten free diet, as it still seems probable that intestinal sensitivity to gluten is a permanent condition. It is clearly most important that a diagnosis with such long term implications is accurate.

Secondly, not much more is known now about coeliac disease than 10 years ago: the relative importance of genetic and environmental factors (gluten and others) in the development of the disease; the pathophysiology of the enteropathy (the respective roles of gliadin toxicity and abnormal immune responses); and the role of a gluten free diet in the prevention of malignancy—although one recent report supports its protective effect for the first time.[26]

Only careful prospective follow up of patients in whom the disease has been accurately diagnosed, and continuing research into the basic defect in coeliac disease, will allow definitive diagnostic criteria to be established and provide long term guidelines for the management of patients with coeliac disease.

1 Meuwisse GW. Diagnostic criteria in coeliac disease. *Acta Paediatr Scand* 1970;**59**:461.
2 Visakorpi JK. Definition of coeliac disease in children. In: Hekkens WThJM, Pena AS, eds. *Coeliac disease*. Proceedings of the Second International Coeliac Symposium, Noordwijkerhout, The Netherlands, 1974. Leiden: Stenfert Kroese, 1974:10–6.
3 McNeish AS, Harms K, Rey J, Shmerling DH, Walker-Smith JA. Re-evaluation of diagnostic criteria for coeliac disease. *Arch Dis Child* 1979;**54**:783–6.
4 Guandalini S, Ventura A, Ansaldi N, *et al*. Diagnosis of coeliac disease: time for a change? *Arch Dis Child* 1989;**64**: 1320–25.
5 Schmitz J, Jos J, Rey J. Transient mucosal atrophy in confirmed coeliac disease. In: McNicholl B, McCarthy CF, Fottrell PF, eds. *Perspectives in coeliac disease*. Lancaster: MTP, 1978:259–62.
6 Kamath KR, Dorney SFA. Is discordance for coeliac disease in monozygotic twins permanent? *Pediatr Res* 1983;**17**:422.
7 Maki M, Visakorpi JK. Normal small bowel histology does not exclude coeliac disease. *Pediatr Res* 1988;**24**:411.
8 Auricchio S, Mazzacca G, Tosi R, Visakorpi J, Maki M, Polanco I. Coeliac disease as a familial condition: identification of asymptomatic coeliac patients within family groups. *Gastroenterology International* 1988;**1**:25–31.
9 Shmerling DH. Peroral intestinal mucosal biopsies in infants and children. *Helv Paediatr Acta* 1970:Suppl XXII.
10 Ferguson A, Murray D. Quantitation of intraepithelial lymphocytes in human jejunum. *Gut* 1971;**1299**:88–92.
11 Spencer J, Issacson PG, Diss TC, MacDonald TT. Expression of disulfide-linked and non-disulfide linked forms of the T cell receptor γ/δ heterodimer in human intestinal intraepithelial lymphocyte. *Eur J Immunol* 1989;**19**:1335–8.
12 Savilahti E, Viander M, Perkkio M, Vainio E, Kalimo K, Reunala T. IgA gliadin antibodies: a marker of mucosal damage in childhood coeliac disease. *Lancet* 1983;**i**:320–2.
13 Unsworth DJ, Walker-Smith JA. Antigliadin and antireticulin antibodies in childhood coeliac disease. *Lancet* 1983;**i**:874–5.
14 Maki M, Hallstrom O, Vesikari T, Visakorpi JK. Evaluation of a serum IgA-class reticulin antibody test for the detection of childhood coeliac disease. *J Pediatr* 1984;**105**:901–5.
15 Burgin-Wolff A, Gaze H, Lentze M, Nussle D. Gliadin and endomysium antibody determinations in childhood coeliac disease. In: Kumar P, Walker-Smith JA, eds. *Proceedings of international coeliac symposium*. Leeds: Leeds University Press, 1990.
16 Chorzelski TP, Beutner EH, Sule J, *et al*. IgA antiendomysium antibody. A new immunologic marker of dermatitis herpetiformis and coeliac disease. *Br J Dermatol* 1984;**111**:395–402.
17 Webster ADB, Slavin G, Shiner M, Platts-Mills TAF, Asherson GL. Coeliac disease with severe hypogammaglobulinaemia. *Gut* 1981;**22**:153–7.
18 Khoshoo V, Bhan MK, Unsworth DJ, Kumar R, Walker-Smith JA. Anti-reticulin antibodies: useful adjunct to histopathology in diagnosing coeliac disease, especially in a developing country. *J Pediatr Gastroenterol Nutr* 1988;**7**: 864–6.
19 Walker-Smith JA. Transient gluten intolerance. *Arch Dis Child* 1970;**45**:523–6.
20 Walker-Smith JA. Transient gluten intolerance: does it exist? *Neth J Med* 1987;**31**:269–78.
21 Aine L. Dental enamel defects and dental maturity in children and adolescents with coeliac disease. *Proc Finn Dent Soc* 1986;**82**(suppl 3):1–71.
22 McNicholl B, Egan-Mitchell B, Fottrell PF. Variability of gluten intolerance in treated childhood coeliac disease. *Gut* 1979;**20**:126–32.
23 Shmerling DH, Francx J. Childhood coeliac disease: a long term analysis of relapses in 91 patients. *J Pediatr Gastroenterol Nutr* 1986;**5**:565–9.
24 Polanco I, Larrauri J. Does transient gluten intolerance exist indeed? In: Kumar P, Walker-Smith JA, eds. *Proceedings of international coeliac symposium*. Leeds: Leeds University Press, 1990.
25 Maki M, Lahdeaho ML, Hallstrom O, Viander M, Visakorpi JK. Postpubertal gluten challenge in coeliac disease. *Arch Dis Child* 1989;**64**:1604–8.
26 Holmes GKT, Prior P, Lane MR, Pope D, Allan RN. Malignancy in coeliac disease – effect of a gluten free diet. *Gut* 1989;**30**:33–9.

Arch Dis Child: first published as 10.1136/adc.65.8.909 on 1 August 1990. Downloaded from http://adc.bmj.com/ on September 19, 2020 by guest. Protected by copyright.