ORIGINAL ARTICLE

What happens to patients with positive tissue transglutaminase and endomysium antibody results in general practice?

D Sinclair, H Duncan

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See end of article for authors' affiliations

Correspondence to:
Dr D Sinclair, Department
of Clinical Biochemistry,
Queen Alexandra
Hospital, Portsmouth PO6
3LY, UK; david.sinclair@
porthosp.nhs.uk

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Background: A previous study showed that many patients with positive gut related antibodies (anti-tissue transglutaminase (TTG) and/or anti-endomysium (EMA) antibodies), indicative of coeliac disease, were not offered a duodenal biopsy, despite the recommendation of the British Society for Gastroenterology guidelines.

Aims/Methods: To investigate whether the addition of a comment on the advisability of referral to a gastroenterologist and biopsy to each positive gut related antibody result would improve the referral rate to investigate possible coeliac disease.

Results: The referral rate improved from 30.1% of patients who were referred and 18% subsequently biopsied before the addition of the comment, to 79.8% who were referred after the introduction of a specific laboratory comment attached to positive antibodies to TTG and/or EMA. All patients with these positive antibodies who were referred for consultant opinion were subsequently biopsied.

Conclusions: To ensure that British Society for Gastroenterology guidelines are followed, laboratories should incorporate more explicit details on the recommended course of action for general practitioners on their receipt of positive gut antibodies to TTG/EMA.

Coeliac disease (CD) is a life long inflammatory condition of the gastrointestinal tract and a small intestinal biopsy is mandatory to confirm the diagnosis. According to British Society for Gastroenterology (BSG) guidelines,¹ patients with CD should be reviewed by a gastroenterologist. This type of referral is important not only in terms of patient education, but also because of potential longterm complications of CD, which include osteoporosis and lymphoma.

“Coeliac disease is a life long inflammatory condition of the gastrointestinal tract and a small intestinal biopsy is mandatory to confirm the diagnosis”

Recent evidence suggests that CD has a UK prevalence of 1/300,² and that approximately 150 patients at any one time are cared for in an average district general hospital.¹ However, there is probably an under-recognition of the condition and patients presenting to general practitioners with either lethargy, anaemia, or symptoms of irritable bowel syndrome should be screened to exclude CD. CD presents at all ages with very varied symptoms. Patients may present with clinical or haematological features, or may be identified by serological screening of asymptomatic relatives.

We recently published a study which concluded that many patients with positive gut related antibodies were not offered a duodenal biopsy, despite the recommendation of the BSG guidelines.³ During the period studied, we found 67 of 1450 patients with positive IgA endomysium antibodies, but 55 of these had no subsequent biopsy records—that is, 82% of patients with gut related antibodies had no duodenal biopsy results and 47 patients (69.9%) had not been referred. This was clearly too high, and to try to improve on this we added the following comment to each positive gut related antibody result: “Referral for further gastroenterological investigations including duodenal biopsy is suggested as per current BSG

guidelines for the management of suspected coeliac disease”. Before this, our comments accompanying positive antibodies to tissue transglutaminase (TTG) and/or endomysium (EMA) were merely informative (for example, “consistent with coeliac disease”), rather than indicating a particular course of action. This study describes the effect that the addition of this new comment had on referral for gastroenterologist opinion and biopsy.

MATERIALS AND METHODS

In total, 5632 patients screened for the presence of gut related antibodies between the dates 1 April 2001 and 16 May 2003 were identified by computer search. Patients are screened for total serum IgA and IgA TTG antibodies,⁴ and positive TTG results are further investigated by looking for IgA EMA antibodies. Any patient found to be IgA deficient was investigated by looking for IgG EMA antibodies.

All patients under 16 years of age and being cared for by paediatricians were excluded, as were patients who had already been referred to a consultant gastroenterologist or who had already been diagnosed with CD or dermatitis herpetiformis.

The EMA assays were performed by indirect immunofluorescence using monkey oesophagus and anti-human IgA (or IgG if the patient was IgA deficient) (Binding Site, Birmingham, UK). Serum was diluted 1/10 in phosphate buffered saline (pH 7.4) and sections are interpreted using blue light fluorescence on an Olympus BX40 microscope.

IgA TTG assays were performed using the Pharmacia Celikey enzyme linked immunosorbent assay (Pharmacia, Uppsala, Sweden), according to the manufacturer's instructions.

Abbreviations: BSG, British Society for Gastroenterology; CD, coeliac disease; EMA, anti-endomysium antibodies; GFD, gluten free diet; TTG, anti-tissue transglutaminase antibodies

RESULTS

During the period 1 April 2001 to 16 May 2003, from an adult population of almost one million, we tested 5632 sera for antibodies to TTG/EMA (table 1). The sera came from 78 general practitioner surgeries and 400 general practitioners. Of these 5632 sera, 180 had positive antibodies to TTG/EMA.

We did not include the 41 children in our study because they were referred to the paediatricians rather than gastroenterologists, and neither did we include the 48 adults already diagnosed with CD/dermatitis herpetiformis, or referred for investigation. There were two patients in whom we found a disagreement between the TTG and EMA results. These were weakly positive for TTG and negative for EMA and have been followed up separately.

There were 89 adult patients, who were not previously referred for gastroenterology opinion or diagnosed with CD/dermatitis herpetiformis, about whom we made a comment suggesting referral, according to the BSG guidelines. Of these, 71 were referred and all had duodenal biopsy performed; however, the remaining 18 patients have no record of being biopsied. For these 18 patients, one of us (DS) contacted the requesting clinician with a request for information on whether they had referred the patient for a gastroenterologist opinion and their current management. Table 2 shows that these patients fell into six categories. One failed to attend for gastroenterology opinion but was placed on a gluten free diet (GFD) by the general practitioner, and one fell into this category after referral to a physician.

Two patients were started on a GFD but no consultant opinion was sought. One patient was no longer registered with the general practitioner surgery and has been lost to follow up. Four letters went unanswered two months after receipt and no repeat blood samples, biopsy data, or gastroenterology opinion episodes were logged on to our hospital computer systems for these patients.

Nine patients had not been placed on a GFD and neither gastroenterology opinion sought nor biopsy performed, according to the data returned. Of these nine patients, one had moved away and the general practitioner has now contacted the patient's new general practitioner with a request to follow this up. One has no record of requesting or receiving the results. One patient did not attend for follow up with the general practitioner and is asymptomatic one year on. One general practitioner denies having received the result and is now reviewing the patient. One patient has declined further investigation and a GFD. One general practitioner is reviewing a "symptom free" patient after receiving our letter. One set of results appears to have prompted a referral to a consultant audiologist, but no gastroenterology opinion has been sought. One set of

Table 2 Results of the survey of the 18 patients in whom we made comment recommending referral, but for whom there is no record of a biopsy

Reason	N
1 Not on GFD, not referred to gastroenterologist, and not biopsied	9
2 On GFD but not referred for consultant opinion	2
3 On GFD; referred to physician but not biopsied	1
4 Patient no longer registered; unable to track; no referral or biopsy data found on HIS	1
5 No reply to letter; no referral or biopsy data	4
6 On GFD, referred to gastroenterologist but did not attend	1
Total	18

GFD, gluten free diet; HIS, hospital information system.

antibody results was dismissed as irrelevant by the general practitioner. One patient cancelled follow up appointments because all symptoms had resolved.

DISCUSSION

Our study has shown that the addition of a comment advising clinicians to refer patients with positive gut related antibodies to a consultant gastroenterologist has greatly increased the proportion of patients referred and biopsied appropriately.

The 18 of 89 (20.2%) patients whom we suggested should be referred and biopsied but have not yet been biopsied is still a substantial number, although we are encouraged by the improvement on the 81% who had no biopsy result before our addition of a comment suggesting referral.³ With regard to referrals alone, the 69.9% of patients whom we found previously had not been referred or did not attend for specialist gastroenterology opinion,³ fell to 19.1% (17 of 89) after the addition of the comment. Although some clinicians have chosen to manage their patients with positive antibodies to TTG/EMA without recourse to a consultant opinion, we feel that the improvement in referral and biopsy rate as a result of our comments has made it a worthwhile exercise and we would recommend its use more widely.

There is very little information in the literature on this topic and if our results prove to be representative of other areas, then considerable efforts need to be made in education to ensure that patients with positive antibodies to TTG/EMA are seen by the appropriate medical staff.

"We feel that the improvement in referral and biopsy rate as a result of our comments has made it a worthwhile exercise and we would recommend its use more widely"

Of concern are the 15 patients who appear not to have been reviewed by a gastroenterologist, with only two of them known to have been placed on a GFD by their general practitioners. Four general practitioners have not responded to the letter and the remaining nine had nine different reasons for the absence of either a biopsy or consultant gastroenterologist review. Such a review is recommended by the BSG guidelines,¹ so that the full implications of this diagnosis can be discussed with the patient. It is notable that some general practitioners have responded to our audit letter by further reviewing their patients. It will be interesting to see how many of the four general practitioners who have not responded either repeat the blood tests or refer their patients after receipt of our letter; so far, two months after receipt of our letter, we have yet to receive further blood samples from these patients.

In keeping with the BSG guidelines, all the patients referred for gastroenterology opinion had biopsy samples

Table 1 Biopsy data from patients with positive antibodies to TTG/EMA

	Known CD/DH?	Referral comment made?	Biopsy done?	Number
Adult	Unknown	Yes	Yes	71
Adult	Unknown	Yes	No	18
Adult	Known CD or DH	No	Not relevant	29
Adult	Unknown	Already referred to gastroenterology	Not relevant	19
Adult	Unknown	No	No	2*
Child	Unknown	No	Unknown	41

The total number of positive gut antibody results from 1 April 2001 to 16 May 2003 was 180.

*In these two samples there were discrepancies between the TTG and the EMA results.

CD, coeliac disease; DH, dermatitis herpetiformis; EMA, endomysium; TTG, tissue transglutaminase.

Take home messages

- We investigated whether adding a comment on the advisability of referral to a gastroenterologist (and subsequent biopsy) to each positive gut related antibody result improved the referral rate to investigate possible coeliac disease
- The rate improved from 30.1% of patients who were referred and 18% subsequently biopsied before the addition of the comment to 79.8% who were referred and biopsied after addition of the comment
- To ensure that British Society for Gastroenterology guidelines are followed, laboratories should incorporate more explicit details on the recommended course of action for general practitioners on their receipt of positive gut antibodies to endomysium and tissue transglutaminase

taken. Of the original 18 patients for whom we had no biopsy records, all are perhaps at greater risk because they have not been reviewed by a gastroenterologist.

Of greatest concern of all are the nine patients who have not been started on a GFD and have not been seen by a specialist, despite positive results from laboratory tests whose sensitivity and specificity for CD is high,⁴ although clearly some of these patients may have refused further investigations or may have failed to attend appointments. The four general practitioners who have not responded have not referred their patients for gastroenterology opinion, but we have no data on whether they have placed their patients on a GFD.

Authors' affiliations

D Sinclair, Department of Clinical Biochemistry, Queen Alexandra Hospital, Portsmouth PO6 3LY, UK

H Duncan, Department of Gastroenterology, Queen Alexandra Hospital

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