

## Population screening for coeliac disease in primary care by district nurses using a rapid antibody test: diagnostic accuracy and feasibility study

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### ABSTRACT

**Objective** To evaluate the feasibility and diagnostic accuracy of screening for coeliac disease by rapid detection of IgA antibodies to tissue transglutaminase performed in primary care.

**Design** District nurses screened 6 year old children using rapid antibody testing of finger prick blood. They also collected capillary blood samples for laboratory determination of IgA and IgG antibodies to endomysium and IgA antibodies to tissue transglutaminase. Children with positive rapid test results were directly sent for biopsy of the small intestine.

**Setting** Primary care in Jász-Nagykun-Szolnok county, Hungary.

**Participants** 2690 children (77% of 6 year olds living in the county) and 120 nurses.

**Main outcome measures** Positivity for antibodies to endomysium or transglutaminase in the laboratory and coeliac disease confirmed at biopsy.

**Results** 37 children (1.4%, 95% confidence interval 0.9% to 1.8%) had biopsy confirmed coeliac disease. Only five of these children had been diagnosed clinically before screening. Rapid testing had a 78.1% sensitivity (70.0% to 89.3%) and 100% specificity (88.4% to 100%) for a final diagnosis of coeliac disease by biopsy. Sensitivity was 65.1% (50.2% to 77.6%) and specificity was 100% (99.8% to 100%) compared with combined results of IgA and IgG laboratory tests. Trained laboratory workers detected 30 of the 31 newly diagnosed IgA competent patients with the rapid test kit used blindly. Median time to biopsy after a positive rapid test result was significantly shorter (20 days, range 4-148) than after a positive laboratory result (142 days, 70-256;  $P<0.001$ ). Children with coeliac disease detected at screening were smaller and had worse health status than their peers but they improved on a gluten-free diet.

**Conclusions** A simple rapid antibody test enabled primary care nurses to detect patients with coeliac disease in the community who were not picked up in clinical care. Extra training is needed to improve sensitivity.

### INTRODUCTION

Antibody tests have shown the prevalence of coeliac disease to be 0.3-1.2% in unselected European, North

American, South American, and Indian populations. Although the burden of undiagnosed coeliac disease might be high<sup>1</sup> and the disease is treatable, screening of the general population by venous blood sampling and conventional laboratory methods would be expensive, difficult to organise, and might not be acceptable to subjects. Rapid methods of antibody detection have recently become available that can be performed at the point of care using blood from finger pricks.<sup>2</sup> The detection of IgA antibodies in coeliac disease has already been validated for clinical case finding in gastroenterology settings.<sup>3,4</sup> In this study, we explore the feasibility of screening for coeliac disease by means of a rapid antibody test performed by local healthcare workers in primary care.

### METHODS

#### Subjects and screening procedure

We screened 6 year old children in Jász-Nagykun-Szolnok County, Hungary. District nurses were asked to screen all children in their care born between 1 June 1998 and 31 May 1999, who were due to start school in 2005 at their preschool physical examination. Nurses measured antibodies to transglutaminase on site using 10 µl of whole blood from a finger prick and a test that gives results in 5-10 minutes. Children with positive results on this rapid test were referred directly for small bowel biopsy.

At the same time, the nurses collected 80 µl of blood for the laboratory determination of IgA antibodies to endomysium and transglutaminase in plasma (the reference tests). These tests each have 95-98% sensitivity and 98-99% specificity for coeliac disease compared with biopsy of the small intestine.<sup>5</sup> To increase sensitivity and ensure that we detected coeliac disease in IgA deficient children, we combined both tests and also measured IgG antibodies to endomysium in all samples. Children who were negative in all three laboratory tests were not investigated further.

To check for correct sampling and to perform an interobserver comparison between the nurses and the laboratory, the nurses also submitted any diluted blood left over from the rapid test. See [bmj.com](http://bmj.com) for details of

the Biocard coeliac disease test kit, laboratory antibody testing, and biopsy evaluation.

#### Clinical evaluation

We determined the children's weight and height centiles using reference values for Hungarian children<sup>6</sup> and recorded any symptoms. We used standard laboratory methods to determine blood count and to measure serum iron, transferrin, and ferritin. Human leucocyte antigen (HLA) DQ alleles were determined by polymerase chain reaction in children with positive antibody tests. Parents of newly detected patients with coeliac disease and sex matched controls with negative antibody results answered a generic validated child health questionnaire. We also asked the parents of patients with coeliac disease to answer the questionnaire after the children had spent six months on a gluten-free diet.

#### Statistical analysis

We calculated the sensitivity, specificity, positive predictive value, and negative predictive value of the rapid tests and compared them with those obtained for laboratory antibody tests and biopsy. We compared median antibody titres before and after dietary treatment and haemoglobin values and body mass index before and after the gluten-free diet.

## RESULTS

### Screening results

In total, 3518 births were registered in the county between 1 June 1998 and 31 May 1999. Of these children, 2690 (76.5%) joined the study and we screened 2676 children. See [bmj.com](http://bmj.com) for details of exclusions. Each of the 120 participating nurses screened a median of 18 children (range 4-95). Antibodies to transglutaminase were detected by onsite rapid testing in 28 children (1.05%). No invalid tests were reported. The parents of 25 of these children consented to small bowel biopsy, and all children showed severe villous atrophy with crypt hyperplasia indicating coeliac disease. Median time from screening to biopsy was 20 days (4-148).

Capillary blood samples for laboratory testing were available from 2609 (97.5%) of the screened children. IgA and IgG antibodies to endomysium were found in 42 specimens, and IgA antibodies to tissue

transglutaminase were above the 5 U/ml cut-off value in 41 of these 42 specimens. One other sample was positive only for IgG antibodies to endomysium, but negative for all IgA autoantibodies. Jejunal biopsy and measurement of plasma total IgA showed this patient had coeliac disease with selective IgA deficiency (0.01 g/l). All 28 children who screened positive on site were also positive in laboratory tests for antibodies to endomysium (median titre 1:40, range 1:10-1:320) and transglutaminase (median 78.6 U/ml, range 8.3-501). Antibody values in the other 14 children with IgA antibodies to endomysium were low or borderline (endomysium: 1:2.5, 1:2.5-1:40; transglutaminase: 10.5, 3-63.2). These 14 children were also invited to biopsy, and villous atrophy was found in six of the 13 children whose parents consented. One procedure was unsuccessful and the villous architecture of the small bowel was normal in the other six children, even though they reported a normal intake of gluten. These six children had an HLA-DQ2 background, slightly raised numbers of intraepithelial lymphocytes, and patchy deposition of transglutaminase antibodies in their small bowel specimens.

The median time from screening to biopsy was significantly longer (142 days, 70-256,  $P < 0.001$ ) in children with positive antibody results in the laboratory only.

Coeliac disease was newly diagnosed in 32 (1.2%) of the screened children, 24 girls and eight boys. Five other children had been diagnosed before screening, so the prevalence of biopsy confirmed coeliac disease in the investigated cohort was 1.38% (0.94% to 1.82%; one in 73). The frequency of antibody positivity was 1.79% (1.29% to 2.30%).

**Comparison of screening by nurses and in the laboratory** Nurses (untrained evaluators) identified 25 of the 31 IgA competent children with coeliac disease who had villous atrophy. They also correctly evaluated 2566 negative samples and thus achieved 99.4% agreement with laboratory antibody test results (table 1). The positive predictive value of rapid testing was 100% (99.8% to 100%) and the negative predictive value was 99.4% (99.0% to 99.7%). Table 2 compares the rapid test results with the final diagnosis of coeliac disease by biopsy; the positive predictive value was 100% (88.4% to 100%). In children with a positive laboratory test

**Table 1 | Onsite rapid test for IgA antibodies to transglutaminase compared with laboratory tests for IgA and IgG antibodies to endomysium and IgA antibodies to transglutaminase**

Laboratory test result	Rapid test result		
	Positive	Negative	Total
Positive serology result in the laboratory for any of the antibodies tested	28	15*	43
Negative antibody result in the laboratory	0	2566	2566
Sample not available for laboratory evaluation	0	67	67
Total	28	2648	2676

Sensitivity 65.1% (95% confidence interval 50.2% to 77.6%; specificity 100% (99.8% to 100%).

\*One patient had selective IgA deficiency.

**Table 2** | Onsite rapid test for IgA antibodies to transglutaminase compared with final diagnosis of coeliac disease on the basis of laboratory antibody positivity (IgA and IgG) and biopsy of small intestine

Biopsy result (all patients positive for laboratory antibody tests)	Rapid test result		
	Positive	Negative	Total
Villous atrophy indicative of coeliac disease	25	7*	32
Normal villous structure	0	6	6
Biopsy not performed	3 (refused biopsy)	2635	2638
Total	28	2648	2676

Sensitivity 78.1% (95% confidence interval 70.0% to 89.3%); specificity 100% (88.4% to 100%).

\*One patient had selective IgA deficiency.

result, the rapid test had a negative predictive value of 46.2% (23.2% to 70.9%).

The rapid testing on site was less sensitive than the combined laboratory antibody tests. The diagnosis of coeliac disease could not be confirmed in 11 of the 43 antibody positive children, however, so the diagnostic efficiency of the rapid test was almost as high (99.3%) as that of laboratory screening (99.6%).

To establish whether the rapid test was less sensitive than the laboratory tests, we retested samples from the 31 children with coeliac disease who were positive for IgA antibodies to endomysium and 177 randomly selected children who were negative for these antibodies with the Biocard kit in a blinded fashion in two different laboratories. All but one coeliac sample (96.8%) were judged as positive when read by experts, but the positive test lines were often faint. In these cases, the line became clearer if the time to reading was increased to 10-15 minutes. These findings show that the rapid test is as sensitive as the laboratory tests and that the nurses made no major sampling errors. The lower sensitivity on site is probably caused by the nurses interpreting faint test lines as negative results.

#### Clinical findings and response to treatment

None of the 32 children diagnosed with coeliac disease after screening had been judged chronically ill or sent for further investigation. Common clinical problems found in untreated coeliac disease were present in 27 of the 32 patients.

Mean weight, height, and body mass index of children with screen detected coeliac disease were lower than those of their peers who were negative in the laboratory antibody tests. These children also scored lower in the generic health questionnaire.

All 32 children newly diagnosed with coeliac disease had improved blood results and reported better health after six months on a gluten-free diet.

## DISCUSSION

### Main findings

Coeliac disease is still largely underdiagnosed<sup>7-9</sup> or diagnosed after a long delay, even when patients have symptoms.<sup>10</sup> This study shows that a rapid method for near patient detection of coeliac disease antibodies is an efficient way to find new cases; nurses identified around 80% of patients with undiagnosed coeliac disease at the

routinely performed preschool health check. To screen all children in a one year cohort in the county, each nurse performed around 20 rapid tests; this required little time and effort and fitted in with the nurses' normal working day. The rapid test seemed to be as accurate as laboratory testing and had a high positive predictive value and specificity. Some training is needed. A rapid test used in primary care is simple, easy to organise, and the results are available at the screening session; these factors might improve compliance and reduce costs.<sup>11</sup> Undiagnosed coeliac disease had negative effects on the children's health and development, but these effects were improved by a gluten-free diet.

### Is population screening justified?

Antibody tests can reliably identify patients with undiagnosed coeliac disease,<sup>5,12</sup> but screening is controversial because of doubts about its cost effectiveness,<sup>13,14</sup> the reluctance of asymptomatic people picked up by screening to undergo biopsy and to follow dietary restrictions,<sup>11,14</sup> and the lack of proof of long term benefit to the community.<sup>11</sup> However, the overall cost-benefit balance may be favourable even when benefits are only moderate if screening is simple. With the rapid screening test, nurses immediately notified the parents about a positive test result and less than 10% refused to give their permission. The time to biopsy was also significantly shorter. These young children tolerated sampling from a finger prick, so we anticipate that this method would be acceptable for most people.

Chronic gastrointestinal disorders and anaemia probably affect academic performance, and young adults with undetected coeliac disease tend to under-achieve at degree level.<sup>15</sup> Thus, early detection of coeliac disease may be important for both the individual and society. However, we still do not know whether people with seropositivity but with preserved villous structure need treatment.<sup>12</sup>

### Implications for screening policy

The best age for screening is debatable. Disease specific antibodies appear in the serum around the age of 2-3 years,<sup>16</sup> and family members of Hungarian patients rarely developed seropositivity after the age of 6.<sup>17</sup> In our study, prevalence at age 6 (1.4%) was higher than in most European studies of older children and adults.<sup>7</sup>

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Coeliac disease is difficult to recognise in primary care because symptoms can be non-specific or absent

Assays to detect disease specific antibodies in blood are suitable for case finding and screening

Proposals for screening have been criticised for being costly, difficult to organise, and of uncertain benefit

**WHAT THIS STUDY ADDS**

We describe a simple, rapid, and cheap method for detecting IgA antibodies that enabled primary care nurses to recognise most undiagnosed patients with coeliac disease at age 6

Screen detected patients had worse health status than peers, but this improved after treatment

Thus, most patients can already be identified at this age, and dietary compliance is likely to be better in these young children than teenagers.

Our results indicate that one step rapid detection of antibodies to transglutaminase had high positive predictive value for the presence of intestinal lesions. Rapid test results also agreed equally well with the conventional laboratory tests as different laboratory antibody tests agreed in clinical settings.<sup>18</sup> The sensitivity of the rapid test was only around 80%, and the test missed the seropositive cases without villous atrophy. However, the nurses had not received training and were relatively inexperienced—the data came from the first 15-30 tests that they performed. Most patients who were not picked up by the onsite test had low antibody titres (1:2.5), which are difficult to recognise even for many clinical laboratories. The design of the study may have caused further confounding—nurses sent all patients with positive results directly for endoscopy, and they may have been reluctant to do this if the test line was faint. The expert readers' results show that training could greatly improve sensitivity. In theory, this might reduce specificity, although this did not happen here.

**Cost effectiveness and limitations**

The Biocard coeliac disease test cost around €10 (£7; \$14.5) from pharmacies in 2005 in Hungary. Prices for large scale screening might be much lower. Further studies are needed to evaluate the costs in relation to the prevention of late complications.

**Conclusions**

A simple rapid test performed in primary care at the preschool check-up identified most undiagnosed cases of coeliac disease in the community. Such a procedure could easily be adopted in countries with more limited financial resources. Early treatment may help improve the quality of life of affected people in the long term.

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**Contributors:** IRK-S designed the study, evaluated serological results, and wrote the manuscript with the help of the other authors. KS performed the biopsies, the clinical evaluation, and follow-up of patients identified by screening. JP and AI organised the screening and collected the data from the nurses. KU and ÉL performed the histological evaluation of the biopsies. ÉN evaluated the clinical data and helped in the statistical analysis. KK performed the immunohistochemistry. AK, SS, and LK helped with HLA testing. MM helped design the study, evaluate the data, and prepare the manuscript. IRK-S is guarantor.

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**Competing interests:** MM and IRK-S are the inventors of the patent application "Methods and means for detecting gluten-induced disease" (PCT/FI02/00340, international publication number WO02/086509 A19). Finn Medi Research (owned by Tampere University and Tampere University Hospital, Finland) has commercialised the innovation and licensed it to Ani Biotech, which used it to develop the Biocard coeliac test. FinnMedi Research and Ani Biotech were not involved in this study.

**Ethical approval:** Ethical committee of Heim Pál Children's Hospital (permission IKEB 30/2005).

- Metzger MH, Heier M, Mäki M, Bravi E, Schneider A, Löwel H, et al. Mortality excess in individuals with elevated IgA anti-transglutaminase antibodies: The KORA/MONICA Augsburg cohort study 1989-1998. *Eur J Epidemiol* 2006;21:359-65.
- Korponay-Szabó IR, Raivio T, Laurila K, Opre J, Király R, Kovács JB, et al. Coeliac disease case finding and diet monitoring by point-of-care testing. *Aliment Pharmacol Ther* 2005;22:729-37.
- Raivio T, Kaukinen K, Nemes É, Laurita K, Collin P, Kovács JB, et al. Self transglutaminase-based rapid coeliac disease antibody detection by a lateral flow method. *Aliment Pharmacol Ther* 2006;24:147-54.
- Nemec G, Ventura A, Stefano M, Di Leo G, Baldas V, Tommasini A, et al. Looking for celiac disease: diagnostic accuracy of two rapid commercial assays. *Am J Gastroenterol* 2006;101:1597-600.
- Rostom A, Dube C, Cranney A, Saloojee N, Sy R, Garrity C, et al. The diagnostic accuracy of serologic tests for celiac disease: a systematic review. *Gastroenterology* 2005;128(4 suppl 1):S38-46.
- Darvai S, Ágfalvi R, Joubert K. Reference values for investigation of growth and development of Hungarian children aged 0-10 years. [In Hungarian.] *Anonymus Kiadó Budapest* 1997.
- Van Heel DA, West J. Recent advances in coeliac disease. *Gut* 2006;55:1037-46.
- Ravikumara M, Nootigattu VKT, Sandhu BK. Ninety percent of coeliac disease is being missed. *J Pediatr Gastroenterol Nutr* 2007;45:497-9.
- Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003;163:286-92.
- Zipser RD, Patel S, Yahya KZ, Baisch DW, Monarch E. Presentations of adult celiac disease in a nationwide patient support group. *Dig Dis Sci* 2003;48:761-4.
- Mearin ML, Ivarsson A, Dickey W. Coeliac disease: is it time for mass screening? Review. *Best Pract Res Clin Gastroenterol* 2005;19:441-52.
- Mäki, Mustalahti K, Kokkonen J, Kulmala P, Haapalahti M, Karttunen T, et al. Prevalence of celiac disease among children in Finland. *N Engl J Med* 2003;348:2517-24.
- Fasano A. European and North American populations should be screened for coeliac disease. Protagonist. *Gut* 2003;52:168-9.
- Kumar PJ. European and North American populations should be screened for coeliac disease. Antagonist. *Gut* 2003;52:170-1.
- Verkasalo MA, Raitakari OT, Viikari J, Mamiemi J, Savilahti E. Undiagnosed silent coeliac disease: a risk for underachievement? *Scand J Gastroenterol* 2005;40:1407-12.
- Simell S, Kupila A, Hoppu S, Hekkala A, Simell T, Ståhlberg MR, et al. Natural history of transglutaminase autoantibodies and mucosal changes in children carrying HLA-conferred celiac disease susceptibility. *Scand J Gastroenterol* 2005;40:1182-91.
- Korponay-Szabó IB, Kovács J, Lőrincz M, Török E, Gorács G. Families with multiple cases of gluten-sensitive enteropathy. *Z Gastroenterol* 1998;36:553-8.
- Tesei N, Sugai E, Vazquez H, Smecuol E, Niveloni S, Mazure R, et al. Antibodies to human recombinant tissue transglutaminase may detect coeliac disease patients undiagnosed by endomysial antibodies. *Aliment Pharmacol Ther* 2003;17:1415-23.

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