

Serological testing in screening for adult celiac disease

HR Gillett, HJ Freeman. Serological testing in screening for adult celiac disease. *Can J Gastroenterol* 1999;13(3):265-269. Assays for celiac-related antibodies are becoming widely available, and the present review aims to clarify the use of these investigations in the diagnosis of, management of and screening for adult celiac disease. The sensitivities and specificities of various antibody tests are discussed, along with their clinical use as an adjunct to small bowel biopsy, and as a first-line investigation for patients with atypical symptoms of celiac disease or patients at high risk of developing sprue.

Key Words: *Adult, Celiac disease, Endomysium, Gliadin, Reticulin, Serology*

Épreuve sérologique de dépistage de la sprue cœliaque

RÉSUMÉ : Les dosages d'anticorps liés à la maladie cœliaque deviennent largement accessibles, et la présente synthèse a pour objectif de clarifier l'utilisation de ces tests pour le diagnostic, le traitement et la prise en charge de la sprue cœliaque. Les sensibilités et les spécificités de plusieurs tests contenant divers anticorps sont discutées, ainsi que l'utilisation clinique de ces tests comme adjuvants à la biopsie de l'intestin grêle, et comme investigation de première ligne chez les patients accusant des symptômes atypiques de la sprue cœliaque ou chez ceux qui sont à risque élevé de la développer.

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Celiac disease is a histological diagnosis, and, in patients in whom there is a clinical suspicion of the condition, small intestinal biopsy remains the first diagnostic procedure. Several assays for the detection of celiac-related antibodies are widely available, and, although these serological tests do not replace the need for small intestinal biopsy for diagnosis, they can be extremely useful as an adjunct to diagnosis. Positive antibody tests can help guide clinicians towards biopsy in patients at high risk of developing celiac disease or in patients with a low index of suspicion for the disease. The present review aims to clarify beliefs about the role of serological tests in screening for, diagnosis of and follow-up of adult celiac disease.

The most widely used of these serological tests are assays for antigliadin antibodies (AGAs) and tissue antibodies, such as antireticulin (ARAs) and endomysium (EmAs) antibodies. AGAs are usually measured with the use of ELISA, whereas tissue antibodies are detected with the use of indirect immunofluorescence assay. Sensitivi-

ties and specificities for these techniques vary widely from study to study, and comparison is made increasingly difficult by the use of different commercial kits and 'in-house' assays. Table 1 shows the sensitivities, specificities, and positive and negative predictive values of various assays. One group performed two studies using the same diffusion-in-gel ELISA assay for immunoglobulin (Ig) A and IgG AGAs, and found that the combined sensitivity fell from 95% in the first study to 77% in the second (1,2). The specificities of the two studies were comparable (98% versus 95%). Another group compared two 'in-house' techniques and three commercial kits, and found that, for IgG AGAs, sensitivity varied from 69% to 91% and specificity from 2% to 59%, and, for the IgA isotype AGAs, sensitivity ranged from 61% to 87% and specificity from 9% to 94% (3). Titres of AGA may also be raised in patients with atopic eczema (4), pemphigoid (5) or rheumatoid arthritis (6), and in healthy individuals (7-9).

IgA ARAs are generally detected using rodent kidney,

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TABLE 1
Sensitivities, specificities, and positive and negative predictive values of serological assays for celiac disease

Author (reference)	Antibody	Assay	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Bodé and Gudmand-Hoyer (2)	IgA + IgG AGA combined	DIG-ELISA (in-house)	77	95	71 to 90	97
Friis and Gudmand-Hoyer (1)	IgA + IgG AGA combined	DIG-ELISA (in-house)	95	98	90	99
Berger and Schmidt (3)	IgA AGA	FIST (in-house)	66	9	47	17
		ELISA (in-house)	79	57	70	59
		Eurospital	61	94	93	57
	IgG AGA	Labodia	87	35	62	58
		Pharmacia	76	67	74	59
		FIST (in-house)	84	2	51	8
		ELISA (in-house)	82	15	54	36
		Eurospital	82	50	67	59
		Labodia	91	22	59	57
Hällstrom (10)	IgA ARA	In-house	91	100	100	98
		In-house	44	100	100	89
	IgA EmA	SciMedx MO	91	100	100	98
Ferreira et al (11)	IgA ARA	In-house	91	99	91	99
	IgA EmA	In-house MO	100	99	91	100
Volta et al (12)	IgA EmA	Medic MO	95	100	100	99
		In-house HUC	95	100	100	99
Ladinsler et al (13)	IgA EmA	Biosystems MO	90	100	100	97
		In-house HUC	100	100	100	100
Sategna-Guidetti et al (14)	IgA EmA	In-house MO	95	100	100	95
		In-house HUC	95	99	99	95
McMillan et al (15)	IgA EmA	Biodiagnostics MO	89	100	100	96
	IgG EmA	Biodiagnostics MO	39	99	92	80
Valdimarsson et al (16)	IgA EmA	SciMedx MO	74	100	100	96
Cataldo et al (17)	IgA EmA	Eurospital MO	94	98	98	98
Uibo et al (18)	IgA EmA	In-house MO	97	100	100	99

Eurospital, Trieste, Italy; Labodia, Yens, Switzerland; Kabi Pharmacia Diagnostics AB, Uppsala, Sweden; SciMedx, New Jersey; Medic, Turin, Italy; Biosystems, Genova, Italy; and Biodiagnostics, Upton upon Severn, United Kingdom. AGA Antigliadin antibody; ARA Antireticulin antibody; DIG Diffusion-in-gel; EmA Endomysium antibody; FIST Fluorescent immunosorbent test; HUC Human umbilical cord; Ig Immunoglobulin; MO Monkey esophagus.

liver or stomach as the substrate. Generally, the sensitivity for celiac disease is reported to be 91%, with a specificity of 99% to 100% (10,11). IgA EmAs can be detected using either monkey esophagus or human umbilical cord as the substrate. In general, published results obtained with the use of human umbilical cord by laboratories employing in-house assays have quoted sensitivities and specificities of 95% to 100% and 99% to 100%, respectively (12-14). Published results obtained with the use of commercial kits previously used monkey esophagus as the substrate, and the results obtained varied; sensitivity ranged from 74% to 95% and specificity from 98% to 100% (10,12,13,15-

17). Two groups used the same kit and reported very different specificities – 74% (16) and 91% (10). The groups that used their own in-house assays tended to report better results; sensitivity ranged from 95% to 100% and specificity from 99% to 100% (11,14,18). Commercial kits using monkey esophagus are being phased out in favour of kits employing human umbilical cord, thereby reducing cost. In-house assays to detect tissue antibodies may be impractical in laboratories without pathology facilities or experience.

Although the use of AGAs alone is of limited value for identifying celiac disease in adults, it does offer some ad-

vantages over the use of tissue antibodies. ELISAs for measuring AGAs are quantitative rather than semiquantitative, as is the indirect immunofluorescence technique, and titres generally fall quickly with dietary gluten exclusion (19,20), offering noninvasive laboratory monitoring of response to treatment. EmAs disappear with treatment but may take as long as a year to do so (10,21). Both antibodies can reappear with gluten challenge or relaxation of diet and, therefore, have been used to predict mucosal relapse on oral gluten challenge (22-24), but reappearance of the antibodies is often variable. In one study of Italian children, all patients not on a strict gluten-free diet or following gluten challenge were positive for IgA EmA, but not all had raised titres of IgA AGA (17).

Selective IgA deficiency (SIgAD) affects between one in 400 and one in 700 individuals (25). The prevalence of SIgAD among patients with celiac disease was reported to be as high as 2% to 3% (26-28). Because IgG AGA is often measured along with AGAs of the IgA subclass, increased titres can indicate celiac disease in the presence of SIgAD. In SIgAD patients, celiac disease would obviously be missed if IgA EmAs or ARAs were relied on to detect patients requiring biopsy. A few groups have reported the use of IgG EmA or ARA testing in these patients (26,29,30), but this is not common clinical practice. It is, therefore, prudent to use a combination of IgA and IgG AGAs, and IgA EmAs or ARAs for serological testing in celiac disease. If the IgG class of AGAs is not used, then SIgAD should be excluded by measuring total serum IgA. In a large multicentre study of Italian schoolchildren, a two-step strategy was used, namely IgA and IgG AGAs were tested in the first step. Any child with IgA and/or IgG AGA positivity was recalled, and the AGA assays were repeated, along with testing for IgA EmA and total IgA levels. Intestinal biopsy was then performed on the children with positive IgA AGA and/or IgA EmA levels, or those with raised IgG AGA titres and SIgAD (31). No similar large, multicentre studies have been performed in adults.

Small intestinal biopsy remains essential for the diagnosis of celiac disease, but, because it is now accepted that a spectrum of mucosal lesions occurs in gluten-sensitive enteropathy (32), positive celiac serology is useful as an adjunct to the diagnosis. Although patients with classical symptoms of sprue (such as chronic diarrhea or malabsorption) should undergo biopsy regardless of the results of serology, patients in whom the index of suspicion for celiac disease is low can be saved from an invasive procedure by negative serology. When IgA AGA, IgG AGA and IgA EmA tests are all negative, the chance of finding a flat mucosa on small bowel biopsy in an adult is approximately 2% (33). Conversely, the use of serology as a case-finding tool can lead to the diagnosis of celiac disease in patients with minor or atypical symptoms at an early point in the investigation of their symptoms. A study in Finland revealed that 37% of celiac patients diagnosed in the study period presented with minor symptoms, such as belching and tempo-

rary loose stools (34). Few data are available on the cost effectiveness of serological testing in celiac disease, but one study from London, Ontario, examined this retrospectively (35). The group compared IgA EmA followed by biopsy if serology was positive with performing biopsy on all patients. The IgA EmA specificity was very poor, only 64%; despite this, with the use of a cost minimization model, using serology first in patients with a low clinical suspicion of the disease was found to be less expensive than performing biopsies on all patients (35). Celiac antibodies are, however, of little value in establishing the diagnosis of dermatitis herpetiformis, despite the high probability of celiac disease in these patients. AGAs are present in only 50% of dermatitis herpetiformis patients (36), ARAs in 20% (37) and EmAs in 70% (38).

Because the natural history of truly silent celiac disease is not known, the use of serology testing for mass screening for celiac disease in healthy populations is not accepted (31,39). Many studies have examined the prevalence of celiac disease in patients with associated conditions by using serological testing followed by small intestinal biopsy. In type I diabetes, the prevalence of celiac disease was reported to be 3.13% to 6.4% (40-42) using IgA EmA testing. Two studies found that celiac disease was associated with Down's syndrome in over 4% of patients (43,44). Long term studies are yet to be performed on the outcome of treatment of celiac disease found by serology in these patients, but it is becoming increasingly accepted that patients with insulin-dependent diabetes or Down's syndrome should be tested for celiac-related antibodies and that small bowel biopsy should be performed if the antibodies are present. The frequency of testing has not been determined, but it is important to recognize that celiac disease may develop several years after diagnosis of type I diabetes (45). Another important point to note is that patients with positive tissue antibodies but normal small intestinal mucosa may have latent celiac disease; 28% of ARA-positive patients with normal jejunal mucosa developed villus atrophy on subsequent biopsy within seven years (46).

In the future, many different patient groups will be tested for celiac-related antibodies. This is likely to lead to testing for celiac disease crossing into many different medical specialities. The association between celiac disease and epilepsy has been recognized for many years (47). More recently, celiac disease was diagnosed in 24 of 31 patients with epilepsy and unexplained cerebral calcification (48), and in 16% of patients with neurological dysfunction of unknown cause (49), suggesting that patients in neurology clinics should be screened for celiac disease. A group of patients with Turner's syndrome, a condition known to be associated with autoimmune disease, were recently studied. Positive IgA EmA was found in four of 35 patients, and celiac disease was confirmed on biopsy in three of these patients (the fourth patient refused biopsy) (50), suggesting an association between these two conditions. The prevalence of celiac disease among patients with

primary biliary cirrhosis was found to be 6% to 7% (51,52). The prevalence of primary biliary cirrhosis among celiac patients was found to be 0.3% to 3% in the same studies, suggesting that mutual screening for these two conditions should be undertaken.

First-degree relatives of individuals with celiac disease have a higher prevalence of the disease (53,54), and many of these individuals have few or no symptoms of the disease. Celiac serology is, therefore, useful in screening for the condition in first-degree relatives to identify which individuals should be offered a gluten-free diet in an attempt to reduce the long term risks of the disease. We stress, however, that any individual at high risk of celiac disease who has symptoms suggestive of the disease should have a small bowel biopsy performed regardless of the serology results.

In 1997, Dieterich et al (55) identified that EmAs were directed against tissue transglutaminase, enabling the development of an ELISA test for quantifying titres of this antibody. Not only will this be of great significance in the management of patients in that titres of a specific antibody for celiac can be monitored in treated patients, but this also brings researchers another step closer to unravelling the role that tissue antibodies play in the pathogenesis of celiac disease.

CONCLUSIONS

Assays for the measurement of celiac-related antibodies are widely available but are still of variable accuracy. It is, therefore, essential for clinicians to be aware of the results obtained by their local laboratories. Laboratories should be able to quote the sensitivity and specificity of their assays, and not just the manufacturer's figures if a commercial kit is used. Knowledge of external, quality-controlled results is also valuable. Clinicians should be aware of the association between SIgAD and celiac disease, and recognize that testing for IgA tissue antibodies is of no value in these patients. Testing for IgG class antibodies may be useful, but only IgG AGA tests are widely available.

Celiac serology does not replace small bowel biopsy in the diagnosis of celiac disease but is useful as an adjunct to biopsy for identifying patients in whom biopsy is appropriate, and for monitoring response to and compliance with a gluten-free diet. Testing for celiac antibodies in groups with associated conditions is becoming more widespread, and is likely to expand further as more associations are identified and if long term follow-up shows that treatment of celiac disease in these patients has a beneficial effect. Furthermore, the identification of more cases of subclinical or silent celiac disease with the use of serology will expand our knowledge of this form of the disease and the frequency of malignant and nonmalignant complications in this group of patients compared with those with classical or symptomatic disease.

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