

Testing for Celiac Disease

Celiac disease is an autoimmune disorder of the small intestine leading to damage of the mucosa, resulting in malabsorption. Clinical presentation is varied given the possibility of widespread nutritional deficiencies, but those most commonly seen are bloating, anemia, fatigue, weight loss, constipation and diarrhea. Celiac disease is diagnosed more often in Caucasian or western populations. It is estimated that 1:250 people to 1:67 people^[1, 2] may be afflicted with the disease, and more than 2 million people in the United States are currently undiagnosed^[3]. Unfortunately, the clinical presentation of patients with celiac disease ranges from asymptomatic to severe, making it difficult to diagnose and often taking many years^[1]. Many diseases are associated with a diagnosis of celiac disease including iron deficiency anemia, IBD, non-Hodgkin's lymphoma, osteoporosis, type 1 diabetes, dermatitis herpetiformis, IgA deficiency, peripheral neuropathy, and autoimmune disorders^[4-7]. Those with unexplained fatigue, with a first or second degree relative with celiac disease or who have an autoimmune condition, are at higher risk for developing celiac disease and should be tested for it and continually monitored for its possible development. Those with celiac disease also have a 3-10 times greater risk of developing autoimmune diseases, such as arthritis and lupus^[4-7]. Early diagnosis and treatment may decrease the incidence of related diseases associated with celiac disease^[8].

Celiac disease is often referred to as an immune mediated response to gluten^[9, 10]. Technically gluten is a protein fraction of wheat. Gliadin is the offending protein in wheat. Prolamins of related proteins such as rye (secalinalpha) and barley (hordein) also cause reactions. Gluten is found mainly in wheat, rye and barley, but is also found in products we use every day, such as stamp and envelope adhesive, medicines, and vitamins. IgA antibodies generally develop against these gluten and prolamins. The difficulty of diagnosis may be complicated because 2% of celiac patients are also IgA deficient^[11, 12]. Once a diagnosis of celiac disease is made, regular checks of serological markers can aid in the monitoring of dietary compliance. If a patient does not respond well to treatment, several possibilities should be considered. The majority of the time it will be poor dietary compliance because gluten is hidden in many foods and medications, and completely clearing it from the diet can be difficult. Symptoms, such as diarrhea, may also linger for several months after a single gluten intake^[4, 5]. There are also reports of non-responsive celiac disease that should be considered if the patient is correctly diagnosed, strictly adhering to diet, and has no other reasons for continuing symptoms^[5].

What is the purpose of the test?

The purpose of our test is to accurately define those who are likely to have celiac disease. These individuals should discuss the need for an intestinal biopsy with their healthcare provider. Though newer tests are extremely accurate, an intestinal biopsy is still considered the "gold standard" for diagnosis.

What specimens are used?

A serum sample is used for the three different tests included in the Celiac panel: Total Immunoglobulin A (IgA), IgA Transglutaminase antibody, and Anti-gliadin IgA II.

IgA

IgA is the second most abundant immunoglobulin and is the major immunoglobulin found in mucosal surfaces. Assessing IgA status is recommended for two reasons. First, a selective IgA deficiency can lead to false negatives in a celiac test. If the patient has reduced or absent IgA they will not appropriately respond to the IgA Transglutaminase antibody test whether they have celiac disease or not. Therefore, a serum IgA should be done to ensure those with IgA deficiency are not overlooked. Patients found to be IgA deficient will need to be evaluated with an IgG Transglutaminase antibody test. The second reason to assess IgA is because patients found to be IgA deficient are at 10-20 times greater risk of developing celiac disease^[17]. Therefore, even if they have a negative IgG Transglutaminase antibody test they should be followed and evaluated over time, especially if they have a family history of celiac disease. Patients with congenital IgA deficiency are prone to autoimmune diseases.

IgA Transglutaminase antibody

The IgA Transglutaminase antibody ELISA test has a high sensitivity (95-98%) and specificity (94-95%) in identifying those with untreated celiac disease, and has been identified as the best indicator of celiac disease as an initial screen^[2, 14, 15]. A meta-analysis of the accuracy of IgA Transglutaminase antibody ELISA also found it to be sensitive and specific^[16]. The IgA Transglutaminase antibody is an immune response to tissue transglutaminase. Tissue transglutaminase is an

enzyme in the GI mucosa and works during tissue injury. It is rarely found in those without celiac disease, but is found in over 90% of those with untreated celiac disease ^[13]. IgA Transglutaminase antibody has been shown to be accurate in diagnosing those with celiac disease, who are currently eating gluten, and have mounted an immune response.

If a patient is negative for the IgA Transglutaminase antibody tests, it may mean they do not have celiac disease or that they have not yet developed antibodies at a detectable level. In a study of over 1,500 children expected to be at high risk of developing celiac disease, all eventually tested positive and also had at least one negative IgA anti-human tissue transglutaminase test. Confusing the matter, not all children who tested positive for IgA Transglutaminase antibody also had a positive bowel biopsy.

Anti-gliadin IgA II

Anti-gliadin IgA II develops against prolamins making this test useful in assessing adherence to diet and strengthening the diagnosis. In previous years, Anti-gliadin IgA II was used for diagnosis, but its sensitivity and specificity were found to be significantly lower than IgA Transglutaminase antibody. Patients must be on a gluten-containing diet for at least 2 months prior to the test. Anti-gliadin IgA II is used to assess dietary compliance because it decreases significantly after avoiding dietary prolamins and will generally be negative after the diet is adhered to for 6-12 months ^[13]. Children under 2 years of age are generally not able to mount an appropriate IgA Transglutaminase antibody response and thus the Anti-gliadin IgA II is recommended ^[3,9]. Though rare, Anti-gliadin IgA II can be found in patients with other inflammatory bowel conditions ^[3,18,19].

When do you test for IgG?

If a person is IgA deficient they would not have an IgA response, thus none of the IgA tests would be accurate. Both the IgG Transglutaminase antibody test and the Immunoglobulin G antigliadin antibody have been found to be appropriate tests in an IgA deficient patient ^[20]. Immunoglobulin G antigliadin is less sensitive (75-85%) and specific (75-90%), but it can be used to track dietary compliance ^[21].

When would you use the older IgA anti-endomysial antibody (EMA) test?

In a study of 109 children, IgA anti-endomysial antibody was negative in those with normal mucosa ^[22]. IgA Transglutaminase antibody is the antibody directed against the endomysium (connective tissue surrounding smooth muscle fibers of the gut) and it therefore, does not necessarily add more information than the IgA anti-human tissue transglutaminase alone. IgA anti-endomysial antibody has also been found to have a high specificity (97-100%), though it has a lower sensitivity (85-98%) than IgA Transglutaminase antibody ^[14, 22].

Interpretation of your patient's results:

Clinical presentations should be closely monitored.

1. When IgA Transglutaminase antibody, Anti-gliadin IgA II and serum IgA are all positive, it means that the patient has an almost 100% certainty of having celiac disease.
- 2 When IgA Transglutaminase antibody and IgA are positive and Anti-gliadin IgA II is negative, it will generally identify a patient who has celiac disease, but has been following a gluten-free diet for 6-9 months. Upon following a gluten-free diet the IgA antigliadin antibody decreases in 6-9 months ^[23], while the IgA Transglutaminase antibody will take approximately 12-18 months ^[24].
- 3 When Anti-gliadin IgA II antibody and IgA are positive and IgA Transglutaminase antibody is negative we would suspect that the person may not have celiac disease. IgA antibodies are present so their IgA Transglutaminase antibody should give a positive result if they had celiac. It is possible that Anti-gliadin IgA II can be positive for other conditions besides celiac, such as Crohn's disease, irritable bowel syndrome, or food protein intolerances ^[3, 14]. Antigliadin is not as sensitive for celiac diagnosis as IgA Transglutaminase antibody, though it does have a very high specificity, making it a good marker of compliance.

Summary:

Due to the high risk of celiac disease in Caucasian or western populations, and the detrimental health consequences undiagnosed celiac can produce, running a test for celiac disease on a patient with symptoms such as fatigue, long term diarrhea, a family history of celiac disease or has an autoimmune disease is highly recommended. These new celiac tests are more sensitive and specific than previous tests and will guide the clinician in diagnosis, treatment, and follow-up treatment.

References

- 1 Leffler, DA and Kelly CP, Update on the evaluation and diagnosis of Celiac disease. *Curr Opin Allergy Clin Immunol*, 2006. 6(3): p. 191-6.
- 2 Hill, PG and McMillan SA, Anti-tissue transglutaminase antibodies and their role in the investigation of coeliac disease. *Ann Clin Biochem*, 2006. 43(Pt 2): p. 105-17.
- 3 Westerberg, DP, *et al.*, New strategies for diagnosis and management of Celiac disease. *J Am Osteopath Assoc*, 2006. 106(3): p. 145-51.
- 4 Lee, SK and Green PH, Celiac sprue (the great modern-day imposter). *Curr Opin Rheumatol*, 2006. 18(1): p. 101-7.
- 5 Sabel'nikova, EA, *et al.*, [Celiac disease as a cause of iron deficiency anemia]. *Ter Arkh*, 2006. 78(2): p. 45-8.
- 6 Samolitis, NJ, *et al.*, Dermatitis herpetiformis and partial IgA deficiency. *J Am Acad Dermatol*, 2006. 54(5 Suppl): p. S206-9.
- 7 Tanure, MG, *et al.*, Prevalence of Celiac disease in Brazilian children with type 1 diabetes mellitus. *J Pediatr Gastroenterol Nutr*, 2006. 42(2): p. 155-9.
- 8 Ventura, A, Magazzu G, and Greco L, Duration of exposure to gluten and risk for autoimmune disorders in patients with Celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. *Gastroenterology*, 1999. 117(2): p. 297-303.
- 9 NIH, NIOH, NIH Consensus Development Conference on Celiac Disease. 2004 (June 28-30, 2004).
- 10 Thompson, T, Wheat starch, gliadin, and the gluten-free diet. *J Am Diet Assoc*, 2001. 101(12): p. 1456-9.
- 11 Prince, HE, Norman GL, and Binder WL, Immunoglobulin A (IgA) deficiency and alternative Celiac disease-associated antibodies in sera submitted to a reference laboratory for endomysial IgA testing. *Clin Diagn Lab Immunol*, 2000. 7(2): p. 192-6.
- 12 Cataldo, F, *et al.*, Prevalence and clinical features of selective immunoglobulin A deficiency in coeliac disease: an Italian multicentre study. Italian Society of Paediatric Gastroenterology and Hepatology (SIGEP) and "Club del Tenue" Working Groups on Coeliac Disease. *Gut*, 1998. 42(3): p. 362-5.
- 13 Wong, R, *et al.*, Antibody and genetic testing in coeliac disease. *Pathology*, 2003. 35: p. 285-304.
- 14 Farrell, RJ and Kelly CP, Celiac sprue. *N Engl J Med*, 2002. 346(3): p. 180-8.
- 15 Fasano, A and Catassi C, Current approaches to diagnosis and treatment of Celiac disease: an evolving spectrum. *Gastroenterology*, 2001. 120(3): p. 636-51.
- 16 Zintzaras, E and Germeris AE, Performance of antibodies against tissue transglutaminase for the diagnosis of Celiac disease: meta-analysis. *Clin Vaccine Immunol*, 2006. 13(2): p. 187-92.
- 17 Anderson, R, Coeliac Disease. *Australian Family Physician*, 2005. 34(4): p. 239-242.
- 18 Kumar, V, *et al.*, Comparative studies of different gliadin preparations in detecting antigliadin antibodies. *J Pediatr Gastroenterol Nutr*, 1986. 5(5): p. 730-4.
- 19 Hadjivassiliou, M, *et al.*, Does cryptic gluten sensitivity play a part in neurological illness? *Lancet*, 1996. 347(8998): p. 369-71.
- 20 Cataldo, F, *et al.*, IgG(1) antiendomysium and IgG antitissue transglutaminase (anti-tTG) antibodies in coeliac patients with selective IgA deficiency. Working Groups on Celiac Disease of SIGEP and Club del Tenue. *Gut*, 2000. 47(3): p. 366-9.
- 21 Holtmeier, W and Caspary W, Celiac Disease. *Orphanet Journal of Rare Diseases*, 2006. 1(3).
- 22 Matusiewicz, K, *et al.*, [Diagnostic validity of anti-tissue transglutaminase and anti-endomysium antibodies in children with Celiac disease]. *Pol Merkuriusz Lek*, 2006. 20(115): p. 17-21.
- 23 McGough, N and Cummings JH, Coeliac disease: a diverse clinical syndrome caused by intolerance of wheat, barley and rye. *Proc Nutr Soc*, 2005. 64(4): p. 434-50.
- 24 Tommasini, A, *et al.*, Mass screening for coeliac disease using antihuman transglutaminase antibody assay. *Archives of Disease in Childhood*, 2003. 89(6): p. 512-515.

