OPEN

Variability in Celiac Serology Testing by Provider Type: A Single-Center Experience

*Ankur Chugh, MD, and †Stanley F. Lo, PhD

Objective: To evaluate the ordering practices of celiac disease (CD) serologies by providers at a tertiary, academic, Children's Hospital and compare them to guidelines and best practices.

Methods: We analyzed celiac serologies ordered in 2018 by provider type (pediatric gastrointestinal (GI) specialists, primary care providers (PCPs), and nonpediatric GI specialists), and identified causes for variability and nonadherence.

Results: The antitissue transglutaminase antibody (tTG) IgA was ordered (n = 2504) most frequently by gastroenterologists (43%), endocrinologists (22%), and other (35%). Total IgA was ordered with tTG IgA for screening purposes in 81% of overall cases, but endocrinologists ordered it only 49% of the time. The tTG IgG was ordered infrequently (1.9%) compared with tTG IgA. Antideaminated gliadin peptide (DGP) IgA/IgG levels were also infrequently ordered (5.4%) compared with tTG IgA. The antiendomysial antibody was ordered sparingly (0.9%) compared with tTG IgA, but appropriately by providers with expertise in CD, similar to ordering for celiac genetics (0.8%). Of the celiac genetic tests, 15% were ordered in error. The positivity rate of the tTG IgA ordered by PCPs was 4.4%.

Conclusions: The tTG IgA was appropriately ordered by all types of providers. Endocrinologists inconsistently ordered total IgA levels with screening labs. DGP IgA/IgG tests were not commonly ordered but were inappropriately ordered by one provider. The low number of ordered antiendomysial antibody and celiac genetic tests suggests under-utilization of the nonbiopsy approach. The positive yield of tTG IgA ordered by PCPs was higher compared with previous studies.

Key Words: quality improvement, guidelines, adherence, primary care providers

What Is Known

- Antitissue transglutaminase antibody (tTG) IgA is recommended for celiac disease screening test and should be ordered with a total IgA level.
- Antideaminated gliadin peptide (DGP) tests were previously recommended in patients < 2 years old.
- Antiendomysial antibody (EMA) is recommended on a second sample for the nonbiopsy approach; celiac genetic tests were previously a criterion for the nonbiopsy approach.

What Is New

- tTG IgA was appropriately ordered by all provider types.
- Endocrinologists inconsistently ordered total IgA with tTG IgA in yearly screening labs.
- DGP IgA/IgG were ordered infrequently but still consistently by certain providers.
- Further education is needed for gastroenterologists and primary care providers without celiac disease expertise to boost utilization of the EMA and genetic tests for celiac disease.

INTRODUCTION

The initial diagnostic test for celiac disease (CD) is serology testing. Tissue transglutaminase (tTG) IgA and total IgA levels are the recommended *screening* tests for CD (1,2). Antideaminated gliadin peptide (DGP) IgA/IgG levels were previously recommended to screen for CD in children < 2 years old (3), but are no longer recommended in recent guidelines (2). Genetic testing for CD is recommended in specific situations and was previously part of the nonbiopsy approach but no longer (2). Antiendomysial IgA antibody (EMA) is recommended on a second sample as a part of the nonbiopsy approach (2).

Due to evolving guidelines with updated testing recommendations and differences between North American and European guidelines, we aimed to characterize CD serologies ordered by provider type and compare them with established guidelines and best practices. We hypothesized that there was a wide variety of ordering patterns, specific to provider subtype.

METHODS

Patients and Data Collection

As a part of a quality review, we analyzed all celiac serologies ordered at Children's Wisconsin (CW) in 2018, a tertiary academic medical center, along with four regional satellite clinics. Data were collected on the serology tests which included tTG IgA antibody levels, tTG IgG antibody levels, DGP IgA and IgG levels (all done on Fadia 250, Fisher Scientific), EMA (Quest Diagnostics) levels, CD genetics (HLA DQ2/DQ8 Genotype and Risk, Prometheus Labs), and total IgA levels. Collected data also included ordering provider, date of testing, and age of patients. Tests were ordered by any type of provider, and orders were grouped by gastrointestinal (GI) specialists, primary care providers (PCPs), endocrinologists, and other specialists. The GI specialists included 20 physicians at CW (4 of whom had expertise in CD), 5 GI nurse practitioners, and 2 community GI

Received April 15, 2022;accepted February 7, 2023.

From the *Section of Pediatric Gastroenterology, Hepatology, and Nutrition, Medical College of Wisconsin/Children's Hospital of Wisconsin, Milwaukee, WI; and †Department of Pathology, Medical College of Wisconsin/Children's Hospital of Wisconsin, Milwaukee, WI.

The authors report no conflicts of interest.

Correspondence: Ankur Chugh, MD, Section of Pediatric Gastroenterology, Hepatology, and Nutrition, Medical College of Wisconsin/ Children's Hospital of Wisconsin, 9000 W. Wisconsin Av, 6th Floor Clinics, Suite 610, Milwaukee, WI 53226. E-mail: achugh@mcw.edu

JPGN Reports (2023) 4:2(e302)
ISSN: 2691-171X
DOI: 10.1097/PG9.0000000000000302

TABLE 1. Ordering of tTG IgA, tTG IgG, and total IgA by provider type

		GI	Endo	Total
tTG IgA	Normal, %	94.9	94.5	96.2
	Elevated < 10× normal, %	4.0	4.3	2.6
	Elevated > 10x normal, %	1.1	1.2	1.2
	Total No.	1120	561	2603
	% of Total	43	22	
tTG IgG	Total	8		47
	% vs tTG IgA, %	0.7		1.9
IgA	IgA with tTG, %	87	49	81

GI = gastroenterology; tTG = antitissue transglutaminase antibody.

providers. We compared the ordering of the tests to recommendations from the 2005 NASPGHAN Celiac Guidelines (4), 2016 NASPGHAN Clinical Report (expert opinion) (1), and 2012 and 2020 ESPGHAN Guidelines (2,3). Elevated serologies that were used to trend levels in already diagnosed patients with CD were excluded. Analyses behind the rationale of ordering the EMA or celiac genetics test were performed by chart review by one provider with expertise in CD. The CW Institutional Review Board deemed this project exempt.

RESULTS

TTG IgA was the most frequently ordered serology (n = 2504), with gastroenterologists ordering 43%, endocrinologists 22%, and the remainder by PCPs and other specialists. Total IgA was ordered with tTG IgA 81% of the time; however, endocrinologists ordered it in only 49% of their cases. TTG IgG was rarely ordered (1.9% versus the tTG IgA), and less so by GI specialists (0.7%) (Table 1). DGP IgA/IgG levels were ordered 5.4% (versus the tTG IgA), and primarily by GI providers (72%). Of the 134 DGP tests, one provider ordered 24% of the tests, and only 19% were done in children < 2 years old (Table 2). Of the EMA tests, 70% were by GI providers, of which 94% were ordered by one GI provider focusing on CD. The EMA was ordered appropriately to clarify the diagnosis (48%), as a part of the nonbiopsy approach (13%), and inappropriately by PCPs to screen or trend labs (26%). When the EMA was ordered as part of the nonbiopsy approach, all tests were ordered by 1 provider and done appropriately on a second sample. Of the CD genetic tests, 85% were ordered by GI providers or at their recommendation, and 15% were ordered in error. When the genetic test was ordered appropriately, reasons included clarification of diagnosis (35%), already on gluten-free diet (20%), nonbiopsy approach (15%), and rule out CD (15%) (Table 3). These reasons were chosen since genetic testing is not impacted by gluten intake, and without the requisite genes, patients are unlikely to have or develop CD.

TABLE 2. Ordering pattern of DGP

DGP IgA/IgG	
No. tests	134
Ordered by GI	72% (97)
Non-GI	28% (37)
One specific GI provider	21% (28)
DGP IgA+	7% (9)
DGP IgG +	11% (13)
No. tests in patients < 2 years old	19% (26)

DGP = antideaminated gliadin peptide antibody; GI = gastroenterology.

DISCUSSION

tTG IgA and tTG IgG

tTG IgA was the most ordered celiac serology, in-line with the 2012 NASPGHAN and 2020 ESPGHAN recommendations of the tTG IgA as the preferred screening test, with the latter recommending "testing for total IgA and TGA-IgA as initial screening in children with suspected CD. In patients with low total IgA concentrations, an IgG-based test (DGP, EMA or TGA) should be performed as a second step. Testing for EMA, DGP or AGA antibodies (IgG and IgA) as initial screening in clinical practice is not recommended" (2). Our institution decouples tTG IgA and IgG levels and allows separate ordering. Total IgA was typically ordered with tTG IgA (81% of the time for individual patients), but 51% of time endocrinology providers stopped ordering the total IgA if the first IgA result for the patient was normal.

Endocrinologists screen patients with Type 1 Diabetes (T1D) for CD every 1–3 years, based on varied guidelines. Based on discussion with our immunology colleagues, they acknowledge the possibility of IgA deficiency developing at any time. Thus, we recommend that our endocrinology colleagues consistently order both the tTG IgA and total IgA to screen for CD. However, we acknowledge that IgA deficiency is relatively rare (~5% of patients with CD), and that one could question the cost/benefit if screening serologies are ordered yearly instead of every 3 years, as acknowledged in the 2005 NASPGHAN Guidelines (4). Of the 745 total IgA tests ordered by GI, 12/745 (1.6%) had a true IgA deficiency (IgA < 20). Of these, 3/12 (25%) were deemed inappropriate or non-compliant with guidelines (ie, should have ordered a follow up IgG test, or should not have ordered the repeat IgA test due to a known IgA deficiency).

The positivity rate of tTG IgA for GI was 5.1%, consistent with previous prevalence studies showing a 4% rate (5). The rate for tTG IgA > 10× was 1.1%, suggesting limited opportunities for use of the nonbiopsy criteria. Recognizing that different assays have different upper limits of normal, it is important to note that our assay is an immunoassay with fluorescence detection (EliA Celikely IgA, Fisher Scientific).

Endocrinology positivity rates were 5.5%, similar to GI and with previous studies showing 5%–8% (range 3%–16%) prevalence of CD in T1D (6).

The positivity rate for PCPs was 4.4%, higher than previous studies showing a 1% rate for PCPs (7), thus suggesting that PCPs are ordering the tests with greater specificity and awareness of symptoms than in the past.

The tTG IgG was rarely ordered by GI providers, which is appropriate, as the test is to be used in cases of IgA deficiency. Unfortunately, we did not have the underlying data to confirm that these tests were ordered appropriately in cases of IgA deficiency.

TABLE 3. Ordering pattern and rationale of EMA and celiac genetics

	EMA	Celiac genetics
No. tests	23	20
No. times serologies > 10× normal	32	32
Ordered/recommended by GI	70% (16/23)	85% (17/20)
By GI with celiac expertise	94% (15/16)	94% (16/17)
Non-GI	30% (7/23)	15% (3/20)
Rationale, %		
European criteria/nonbiopsy preference	13	15
Serologies/biopsy confusion	44	35
Already on gluten-free diet	4	20
Rule out	0	15
Initial screen/trending	26	0
Mistake	0	15
Unclear	13	0

EMA = antiendomysial antibody; GI = gastroenterology.

DGP IgA and DGP IgG

Our institution has the DGP IgG and DGP IgA coupled in a single ordering panel. Previously, this test had been recommended in patients <2 years of age (2012 ESPGHAN Guidelines) (3). However, emerging literature has challenged this (8,9), and ESPGHAN 2020 Guidelines no longer recommend it (2). This test was not commonly ordered in our institution, but when ordered, the bulk were by non-GI providers, one specific GI provider, and were ordered in patients > 2 years of age. The positive rate of these tests was higher than the tTG IgA, at 6.7% and 11% for the DGP IgA and IgG, respectively. Of four patients found to have CD in whom tTG IgA levels were normal, the DGP IgA and IgG levels diagnosed one of these cases (0.7%), suggesting that small number of cases can be missed by excluding the DGP IgA/IgG from screening.

EMA IgA

The EMA is recommended as a part of the nonbiopsy approach, on a second specimen sample. We noted under-utilization of this test by almost all providers (including GI), except for one provider with celiac expertise who ordered this test both for the nonbiopsy approach and to help clarify the diagnosis in challenging clinical scenarios. When the data were shared with our GI physicians internally, reasons for the lack of use included either lack of awareness with the guidelines or the patient already being on a gluten-free diet. Some PCPs used this test for screening and monitoring purposes, which is not its intended use.

Celiac Genetics

CD genetic testing was previously recommended with the nonbiopsy approach in 2012 ESPGHAN Guidelines (3). The Guidelines also discussed the benefit in screening high-risk family members (with the negative test being helpful) but acknowledged the potential high cost (3). The test was not ordered commonly at our institution, but when it was ordered by providers focused on CD, it was ordered accurately. When PCPs ordered the test, it was always done in error, as chart review demonstrated their intent was to order CD serologies. Note that the 2020 ESPGHAN Guidelines no longer include genetic testing as a part of the nonbiopsy approach (2).

CONCLUSION

Our study shows that at a single tertiary medical center, tTG levels are used by all provider types as the initial screening test for CD. However, we found overuse of the DGP by one provider, inconsistent ordering of total IgA by endocrinologists, under-use of EMA, CD genetics, and the nonbiopsy approach among GI providers, and occasional accidental ordering of celiac genetic testing by PCPs.

Strengths of the project include the size of samples analyzed, the breadth of the institution which includes all subspecialists and 100 PCPs, and the evaluation of the rationale behind the ordering of tests. No prior reports document ordering of CD serologies by provider type across disciplines.

Limitations of the project include utilizing a single center, collecting only 1 year of data, and the generalizability to other institutions that may have different ordering panels, lack of expertise in CD, and a lack of an electronic medical record.

Planned interventions include targeted education for specific providers/groups and electronic medical record-based solutions to improve lab stewardship. The goal of these interventions is to improve compliance with guidelines and best practices, which could lead to more accurate diagnoses, reduced costs for patients, and increased use of the nonbiopsy approach. Clearer guidelines are also needed from societies regarding testing for total IgA levels and its frequency in screening of CD, especially in patients with T1D.

REFERENCES

1. Hill ID, Fasano A, Guandalini S, et al. NASPGHAN clinical report on the diagnosis and treatment of gluten-related disorders. *J Pediatr Gastroenterol Nutr*. 2016;63:156–165.
2. Husby S, Koletzko S, Korponay-Szabó I, et al. European society paediatric gastroenterology, hepatology and nutrition guidelines for diagnosing coeliac disease 2020. *J Pediatr Gastroenterol Nutr*. 2020;70:141–156.
3. Husby S, Koletzko S, Korponay-Szabó IR, et al; ESPGHAN Working Group on Coeliac Disease Diagnosis. European society for pediatric gastroenterology, hepatology, and nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr*. 2012;54:136–160.
4. Hill ID, Dirks MH, Liptak GS, et al; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2005;40:1–19.
5. Chumpitazi BP, Mysore K, Tsai CM, et al. Interprovider variation of celiac disease testing in childhood chronic abdominal pain. *BMC Gastroenterol*. 2013;13:150.
6. Cohn A, Sofia AM, Kupfer SS. Type 1 diabetes and celiac disease: clinical overlap and new insights into disease pathogenesis. *Curr Diab Rep*. 2014;14:517.
7. Fitzpatrick KP, Sherman PM, Ipp M, et al. Screening for celiac disease in children with recurrent abdominal pain. *J Pediatr Gastroenterol Nutr*. 2001;33:250–252.
8. Khan MR, Silvester JA, Sparks B, et al. The utility of IgA-based serologic markers in diagnosing celiac disease in children 24 months of age or younger. *J Pediatr*. 2020;224:158–161.e2.
9. Dickerson JA, Lee D, Pacheco MC. Deamidated gliadin peptide in pediatric patients with moderately increased tissue transglutaminase; does it help? *Clin Chim Acta*. 2019;492:20–22.