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Original Research Article

Role of Blood TTG and Small Intestine Biopsy in Diagnosis of Celiac Disease

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ABSTRACT

Blood tests are the first step in diagnosing celiac disease and can help determine the need for further evaluation for confirmation of celiac disease. It is important that patients continue to consume gluten as normal and do not start a gluten-free diet, as this can result in false negative test results. Although high titers in serological testing are indicative of celiac disease, they alone do not provide a definitive diagnosis of celiac disease and a biopsy of the small intestine is required for a definitive diagnosis[1]. Similar to serological testing, a normal, gluten-containing diet must also be maintained in order for the histological testing to be accurate. In recent years, testing for IgA and IgG antibodies to deamidated gliadin peptide (DGP) has been clinically introduced and available. The DGP antibody has a remarkably higher specificity for celiac disease than native gluten, the anti-gliadin (AGA) antibodies. In particular, IgA/IgG antibodies to DGP are useful among patients who have selective Immunoglobulin A (IgA) deficiency. IgA deficiency is between 10 to 15 times more common among patients with celiac disease than in the general population, occurring in an estimated 2% to 3% of patients with celiac disease. Thus, total IgA should be quantified. Notably, IgA/IgG anti-DGP testing provides a valuable alternative to IgG anti-tTG testing in the case of IgA deficiency. It is important to note that because of accuracy and cost matters, IgA anti-tTG with total IgA levels be the first choice for testing on the population level, followed by IgA/IgG anti-DGP testing in patients who are IgA deficient.

Keywords: celiac disease, anti-tissue transglutaminase IgA, screening, malignant lymphoma.

INTRODUCTION

The objective of this study was to compare celiac disease (CD) - specific antibody tests to determine if they could replace jejunal biopsy in patients with a high pretest probability of CD. This retrospective study included sera from 100 CD patients and 150 controls. All samples were analyzed for IgA and IgG antibodies against native gliadin (ngli) and deamidated gliadin peptides (dpgli), as well as for IgA antibodies against tissue transglutaminase and endomysium. Celiac disease (CD) is an immune-mediated enteropathy that is caused by intolerance to gluten in genetically susceptible individuals. Its prevalence among the European population is approximately 1%, [1,2] and is even higher among the elderly. [3] Thus, CD is one of the most frequently occurring lifelong diseases. Serological tests to diagnose CD have improved substantially in the last 20 years. In 1998, [4] we proposed a low-risk and cost-effective algorithm to diagnose various forms of gluten-sensitive enteropathy that achieved a positive predictive value (ppv) of 99%, using a combination of different antibody determinations: anti-endomysium (EMA),

IgA anti-tissue transglutaminase (IgA anti-tTG), and IgA and IgG anti-native gliadin (IgA and IgG anti-ngli). In a population with a high pretest probability of disease, synchronous determination of three or four CD-specific antibodies has a very high ppv and negative predictive value (npv), and may eliminate the necessity of small-bowel biopsy in many patients suspected of having CD. [4] In recent years, the use of ngli as an antigen in antibody-detection tests has been replaced with deamidated gliadin peptides (dpgli), which perform better diagnostically than ngli. [5-12] Our goal in this study was to investigate whether using dpgli instead of ngli, alone or in combination with other tests (EMA and IgA anti-tTG), reduces the number of jejunal biopsies without missing CD patients during the diagnostic procedure

There are several serological tests that are sensitive in the evaluation of celiac disease. These include antibodies to:

- Endomysium
- Transglutaminase
- Deamidated gliadin

Tissue transglutaminase antibody (tTG)-IgA in adults and most children is reported with a sensitivity and specificity greater than 90% and 95%, respectively. [2-4] Endomysial antibody (EMA)-IgA usually correlates with tTG. It is more costly and is identified manually, thus it is not the first line marker. [4] The IgA-tTG is the best choice for both the adult and most pediatric populations. Some research indicates that IgA-EMA or IgA-tTG is, in fact, as comparable or more accurate than antigliadin (AGA) antibodies among children younger than three years old. [2,5 - 8] Since the levels of anti-tTG and EMA tend to wane in the absence of gluten ingestion, these markers are useful to monitor adherence to a gluten-free diet. This serology may be checked 3 to 6 months after diagnosis and from then forward minimally once approximately every year in patients who are in clinical remission. Testing can also be performed at any time in individuals with persistent or recurrent symptoms. [11] Further, serologic testing can be conducted on patients who were diagnosed in the past but have been followed by a physician for a suboptimal length of time. Additionally, serology tests have a role in monitoring patients who were told they "outgrew celiac disease" at one point in time. Celiac disease is a lifelong autoimmune condition that cannot be outgrown and the only treatment is a strict gluten-free diet. Finally, it is particularly important to note that because the sensitivity and specificity vary significantly among each of the celiac disease serum antibody assays, it has been recently recommended that physician groups indicate the specific antibody test. [1] Tests available include Tissue Transglutaminase Antibody (IgA) (test code 8821) and Endomysial Antibody Screen (IgA) with Reflex to Titer (test code 15064).

Physicians and hospitals can initiate testing for celiac disease by assessing the following antibodies. Celiac disease serology will normalize if the patient is on a gluten-free diet. Therefore, confirm that the patient is maintaining a normal, gluten-containing diet in order to ensure for the most accurate test results.

- Total Immunoglobulin A Antibody
- IgA-tTG (test code 8821)
- If the IgA-tTG is positive, IgA-EMA with Reflex to IgA-EMA Titer (test code 15064) will be performed.
- If total IgA concentration is low IgG-tTG antibody test (test code 11070) will be performed.
- Deamidated Gliadin Peptide Antibody (IgA (test code 11228/IgG (test code 11212) can be ordered for IgA deficient patients as well.

An esophagogastroduodenoscopy (EGD) and biopsy should be performed on the small intestine with 4-6 samples, one including the duodenal bulb. [1] Primary care providers and other non-gastroenterology specialists should refer patients to a gastroenterologist in order to confirm celiac disease. Remember, a

normal, gluten-containing diet must also be maintained in order for the histological testing to be accurate.

Complex genetics contribute to pathology as typical dominant or recessive traits are not followed. The most contributory genetic material is the HLA class II: HLA-DQ2 (DQA1*05/DQB1*02), which is the most common, and/or HLA-DQ8 (DQA1*03/DQB1*0302) genes. One or both of these are present in celiac disease, accounting for up to 40% of the genetic load. Different alpha and beta variants exist and can determine disease risk. Quest identifies these to allow for individual patient interpretation. Examples of high risk variants include HLA-DQA1*03, HLA-DQA1*05, HLA-DQB1*0201 and HLA-DQB1*0302. A high negative predictive value is appreciated so if these genes are absent it is very unlikely that celiac disease can manifest. Though the genes are common, presenting in approximately 30% to 40% of the general population in Asia, only 1% to 3%-4% respectively develop celiac disease. Family members of persons with celiac disease who have positive genetic testing are at an increased risk for developing celiac disease and should have their serology tested for celiac disease. While a consensus on the timeline of serology testing of family members of persons with diagnosed celiac disease does not exist at this time, clinical practices generally recommend follow-up testing every 1 to 3 years. Genetic testing is first and foremost a tool to rule out the risk for developing celiac disease. It is the only celiac disease test that does not have to be performed on a normal, gluten-containing diet. Genetic testing is particularly useful in infants and children with familial history or suspected celiac disease. Genetic testing when negative in these young patients can spare the concern for disease surveillance for life. When accounting for other factors it is considered useful to aid in diagnosis. Some scenarios include young children who don't produce adequate tTG or EMA antibodies, those on immunosuppressant drugs and those with other potential conditions causing the same histological changes in the small intestine as those of celiac disease, such as giardia, milk allergy and other autoimmune diseases like Crohn's.

Most especially, genetic testing can provide guidance with a particular dilemma that seems to be currently widespread - self-diagnosis of a gluten-related disorder. In those patients without a formal diagnosis, having self initiated the gluten-free diet for several months, having negative antibodies and/or biopsy and who will not undergo gluten challenge genetic testing can provide a scientific approach to an obscure scenario.

The National Institutes of Health (NIH) Consensus Statement on Celiac Disease recommends the following five key elements to celiac disease management:

- Consultation with a skilled dietitian
- Education about the disease
- Lifelong adherence to a gluten-free diet
- Identification and treatment of nutritional deficiencies
- Access to an advocacy group
- Continuous long-term follow-up by a multidisciplinary team

MATERIALS & METHODS

Keeping all these developments a study was conducted in GGS Medical College, Faridkot. We recruited 100 patients and 150 healthy individuals for the screening, between 2010 and 2014, at GGS Medical College & Hospital, Faridkot. They were clinically diagnosed according to their problems. Their diagnoses comprised, gastric and/or duodenal ulcer, acute or chronic leukemia, viral hepatitis and/or liver cirrhosis carcinoma in gastrointestinal tracts, or inflammatory bowel disease estimate the role of TTG and biopsy. The serum samples were assayed using ORG 540A

Anti-Tissue-Transglutaminase IgA (American Research Products, Belmont, MA) in accordance with the manufacturer's protocol in a blinded fashion. In short, the diluted serum samples were incubated in the microplate wells coated with human recombinant tissue transglutaminase for 30 minutes at room temperature. Following 15-minute incubation with enzyme conjugate, containing polyclonal rabbit anti-human IgA labeled with horseradish peroxidase, Tetramethylbenzidine substrate solution was dispensed for another 15 minutes. After reaction was stopped with hydrochloric acid, the optical density at 450nm of each well was read with bi-chromatic measurement with a reference at 650nm. Each serum samples, calibrators, and controls were processed in a duplicated manner. The upper limit of a normal range of serum TTG-IgA for healthy control group was presumably adapted from the manufacturer's guideline, at the cut-off value of 10.0 U/ml. The lower detection limit for TTG-IgA was 1.0 U/ml. A previous review about diagnostic accuracy of serologic tests using human recombinant TTG-IgA revealed 98.1% of sensitivity and 98.0% of specificity among Caucasian adult population .Upper gastrointestinal endoscopy and multiple duodenal biopsies were performed for the individuals with a positive result for TTG-IgA. When the endoscopic examination was not performed, we looked for the biopsied samples or surgical specimen of small intestine obtained during surgery in the past, if any. Formalin-fixed biopsy specimens were stained with hematoxylin and eosin and were studied under a light microscopy, searching for the architectural changes in intestinal mucosa, such as increased intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy. In short, the presence of immune response in the epithelium and the degree of architectural changes in the mucosa was assessed and categorized in the grading manner from type 0 to type 3.

Figure 1 shows a scatter diagram of TTG-IgA values of the enrolled subjects. The mean TTG-IgA value of the healthy group was 0.7 U/ml (2SD=1.7 U/ml), whereas that of the patient group was 2.5 U/ml (2SD=24.4 U/ml, maximum value 294 U/ml). Twelve of the patient group (2.8%) tested positive for TTG-IgA, whereas none of the healthy volunteer group were positive ($p<0.01$). Compared with the TTG-IgA negative patients, the positive patients were higher in age ($p<0.05$), though sexual predominance was not observed.

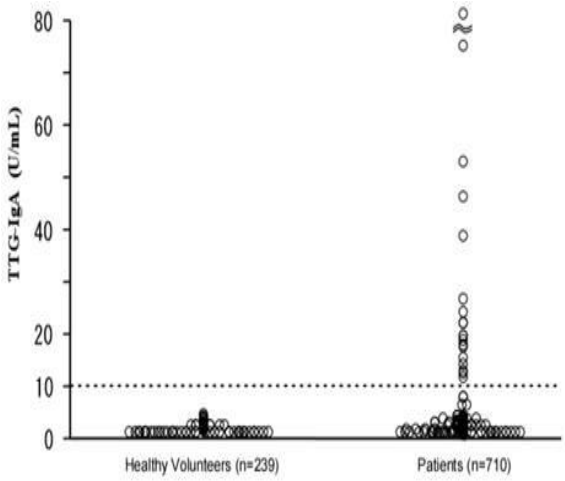

Figure 1: Scatter diagram of serum anti-tissue transglutaminase IgA antibody (TTG-IgA) in the enrolled subjects.

Of the 10 patients with positive TTG-IgA values, duodenal biopsy or small bowel mucosal specimen was available in seven patients. All seven were with the median age of 54 years (range; 27-74 years). Four of the seven were male. There was no documentation of symptomatic family history. Of the seven patients, three died from the unknown cause and another from anasarca. Two others are alive on gluten-free diet.

RESULTS

Sera from 250 patients with CD and 150 control patients were tested for IgG and IgA antibodies against dpgli and ngli proteins. IgG antibody determination for dpgli was superior to that for ngli. Specificity was 68% vs. 92% and

sensitivity was 79% vs. 85% for ngli and dpgli, respectively; ppv was 76% vs. 93% and npv was 72% vs. 83% for ngli and dpgli, respectively. For IgA antibody determination, sensitivity was 61% vs. 78% for ngli and dpgli, respectively, while the specificity and ppv remained at a high level of 97% (McNemar's test for significant changes $P < 0.00001$, Table 1). Because dpgli antigens were clearly superior to ngli, we used only dpgli for further CD-specific antibody determinations.

Table 1: Antibody tests against deamidated gliadin (dpgli) vs. native gliadin (ngli) in 100 CD patients and 150 controls

	IgA anti-ngli	IgA anti-dpgli	IgG anti-ngli	IgG anti-dpgli
Sensitivity	61%	78%	79%	85%
Specificity	97%	97%	68%	92%
Positive predictive value	97%	97%	76%	93%
Negative predictive value	67%	78%	72%	83%

Table-2: Antibody profile in each of 149 CD patients and 119 controls

IgA anti- tTG	IgA anti- dpgli	IgG anti- dpgli	CD n = 100	Controls n = 150	Total n = 250	Classification
+	+	+	69	1	110	110 positives
+	+	-	7	1	8	
+	-	+	15	4	19	
+	-	-	13	10	23	60 not
-	+	+	0	0	0	classified
-	+	-	0	2	2	
-	-	+	3	5	8	
-	-	-	2	96	80	80 negatives

Table-3 Performance of single antibody tests and selected combinations n = 250, 100 CD patients and 119 controls Performance of single antibody tests and selected combinations n = 229, 79 CD patients and 150 controls

	fn	**fp**	**nc**	**sens**	**spec**	**ppv**	**npv**	**effic**	**lr+**	**lr-**
Single tests				%	%	%	%	%		
IgA anti-dpgli	33	4	0	78	97	97	78	86	23	0.23
IgG anti-dpgli	22	10	0	85	92	93	83	88	10	0.16
IgA anti-tTG	5	16	0	97	87	90	95	92	7	0.04
EMA	3	18	0	98	85	89	97	98	6	0.02
Combinations of 2 tests IgG anti-dpgli +										
IgA anti-tTG	2	5	39	83	82	96	98	83	20	0.04
IgG anti-dpgli + EMA	1	6	39	84	82	95	99	83	17	0.01
IgA anti-dpgli + IgG anti-dpgli	15	1	37	73	89	99	88	80	87	0.11
Combinations of 3 tests IgA anti-dpgli +										
IgG anti-dpgli + EMA	1	1	62	72	81	99	99	76	86	0.01
*IgA anti-dpgli + IgG anti-dpgli + IgA anti-tTG **	*2*	*1*	*60*	*73*	*81*	*99*	*98*	*76*	*87*	*0.01*
IgG anti-dpgli + EMA + IgA anti-tTG	0	5	45	83	80	96	100	81	20	0.00
Combination of 4 tests IgG anti-dpgli +										
IgA anti-dpgli + EMA + IgA anti-tTG	0	1	65	72	79	99	100	75	86	0.00

We also determined the levels of IgA anti-tTG and EMA in sera from the 100 CD patients and 150 controls (Table 2). Because the IgA anti-tTG and EMA results were comparable, we have omitted the EMA results; instead, we have shown the IgA anti- tTG, and IgA anti-dpgli, and IgG anti-dpgli antibody levels of each individual and compared them with the histological result. We used a multiple test consisting of three individual tests, which produce a total of eight possible results. We defined the outcome of the multiple tests as positive only when all three individual tests were above the cut-off, and as negative only when all three individual tests were below the cut-off. The majority of the patients (79/100) had either positive (40) or negative (39) results in all three tests. Nearly all patients (79/100) who tested positive for antibodies in all three tests had CD according to histological findings. The ppv was 99% in our population, with a CD frequency of 59% (Table 3). Patients who did not test positive for CD-specific antibodies in any of the three tests were almost all free of CD according to the results of jejunal biopsy (96/98 patients); the npv was 98%. Patients with discordant antibody results (60/268 patients, 22%) could not be defined as positive or negative for CD with

the multiple tests and remained unclassified. The likelihood positive ratio (lr+) was 87 and the likelihood ratio negative (lr-) was 0.01 (Table 3). These findings indicate that a biopsy is avoidable if all antibody values are either above or below the cut-off. In patients with discordant antibody results, an intestinal biopsy is necessary to diagnose or exclude CD.

The definitive diagnosis of celiac disease in the present study, however, could hardly be verified. The lack of HLA screening test would be another shortcoming of the present study. Kaukinen et al emphasize that a negative HLA finding does not rule out CD when the clinical context shows otherwise, though such condition may be rare. Meanwhile, different HLA typings and genetic variation are known to confer same phenotype in the diseases, such as in autoimmune hepatitis, for example. Although our data is too small to indicate alternative HLA typings. Large proportion of our subjects had malignant lymphoma and 40% of TTG-IgA positive patients were lymphoma patients. Again, it must be noted that the identical mucosal changes found in the present study could be observed those with malignant lymphoma or the therapies against lymphomas, which is the inevitable drawback. Despite of our selection bias, it could be speculated that our results may support the possible increased prevalence of CD-associated B-cell lymphoma. Our result, however, showed the non-significant increase in TTG-IgA positivity among the patients with gastrointestinal lymphoma. Conversely, it could be speculated that such lymphomatous infiltration might have influenced antigenicity to produce TTG-IgA. Baldas et al showed an age-related increase in TTG-IgA titers among the non-celiac general population, suggesting the cutoff points for serological screening to be carefully evaluated. Unlike their result, the age-dependent increase in TTG-IgA titer was found to be minimal in our subjects. Although the influence of age on TTG-IgA titers should also be taken into account at the interpretation of this study results, the validity of our cutoff value is beyond the scope of this study. Another diagnostic pitfall of our present study may be the lack of longitudinal observation with strict gluten free diet and gluten challenge. Increasing application of serology for its diagnosis seems to have encouraged a shift from three-biopsy diagnostic algorism to one-biopsy algorism, leading possible cases of over diagnosis. Confusion in the definition of strict gluten free diet may also be the case in longitudinal observation. The retrospective nature of the present study is hardly up to these points. Our extensive literature search has revealed possible cases with under diagnosed celiac disease and dermatitis herpetiformis, the latter of which is known to be pathognomonic for CD among population. They should encourage the discussion of CD among Indian population, and our study result might show the relevance of serologic tests as screening for the disease in the population.

DISCUSSION

Since the advent of serologic screening tools and growing awareness of the disease, a substantial number of undiagnosed cases have been increasingly recognized in different parts of the world, and the epidemiological interests seem to prevail even. This is an attempt to study the possible diagnosis of CD in Punjab India. Our screening program among 100 patients identified seven cases (7.0 %) with both positive TTG-IgA and the pertinent mucosal changes, compatible with celiac disease. The present study would shed light on the discussion of possible diagnosis of celiac disease. The diagnosis of CD has traditionally depended upon intestinal biopsies and has been extended to include an array of serological markers. The guidelines of the European and North American societies for

gastroenterology require a biopsy for diagnosis. Recently, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition published guidelines allowing the diagnosis of CD without a biopsy in some situations. CD is usually diagnosed when the duodenal and jejunal mucosa display villous atrophy, crypt hyperplasia, and an increase in intraepithelial lymphocytes. However, different diseases not related to gluten-sensitive enteropathy can induce a flat mucosa, thus mimicking CD. Moreover, patients with gluten-sensitive enteropathy and normal small bowel mucosal architecture have also been described. Most likely because of a lack of technical proficiency with grasping biopsy forceps or endoscopic procedure, biopsy specimens have been shown to be sufficient for diagnosis of CD in only 90% of cases . Furthermore, CD may be missed during histological examinations owing to variations in different pathologists' assessments. Because of this, and because of the inconvenience and high cost associated with jejunal biopsy and the high prevalence of CD in the general population, less-invasive tests are required. In the last 20 years, serological tests for the diagnosis of CD have improved substantially. For practical and ethical reasons, patients with negative serology sometimes did not undergo a biopsy unless clinical indications of CD were evident. This procedure causes a verification bias because the gold standard (histology of the mucosa) is not always available for negative tests. On the other hand, a positive test result demanded a biopsy even when there was only a slight clinical suspicion of CD. Today, it is nearly impossible to overcome this bias for ethical reasons; therefore, the bias may be present in many studies. The data contained in Table-3 however, indicate that the criteria for choosing the best tests must be defined. For clinicians who want to reduce the number of jejunal interventions in a population with a high frequency of CD, the best test is the one with the lowest sum of false-positive and false-negative diagnoses: the test with the highest ppv, the highest npv, a high likelihood ratio positive, and a low likelihood ratio negative. In our study, a combination of four antibody tests yielded a ppv of 99%, an npv of 100%, an lr+ of 86, and an lr- of 0.00. For practical reasons, we may omit EMA from our combination of antibody tests, and instead chose the test combination of IgG anti-dpgli + IgA anti-dpgli + IgA anti-tTG (Tables 2 and 3), with a ppv of 99%, an npv of 98%, an lr+ of 87, and an lr- of 0.01, as the first step in our diagnostic procedure. Out of 100 patients, 80 (80%) were correctly classified with these serological tests: they had either three tests above or three tests below the cut- off. Intestinal biopsy was necessary as a second diagnostic step in the remaining 60 patients (22%), who had discordant antibody results. This two-step diagnostic procedure reduces the number of intestinal biopsies and increases the sensitivity of the entire diagnostic procedure; only CD patients without any CD-specific antibodies would be missed.

Recently, Vermeersch et al. illustrated the utility of likelihood ratios for the interpretation of CD serology. The likelihood ratio for CD was much higher for double positive test than for single positive test results. Our results showed comparable test results for single and double positive analyses. (Table-3) Similarly, triple positive tests had a high likelihood ratio. However, the best test for CD exclusion was the triple negative test which had a significantly lower likelihood ratio than the double negative test results reported by Vermeersch et al. ($p=0.000037$).

Therefore, we speculate that the combined tests with the very high likelihood ratio positive and the very low likelihood ratio negative achieved in the present study group will also identify

patients in populations with a low CD frequency.

CONCLUSION

Antibody tests for dpgli yielded superior results compared with ngli. A combination of three or four antibody tests including IgA anti-tissue transglutaminase and/or IgA anti- endomysium permitted diagnosis or exclusion of CD without intestinal biopsy in a high proportion of patients (78%). Jejunal biopsy would be necessary in patients with discordant antibody results (22%). With this two-step procedure, only patients with no CD-specific antibodies would be missed. Tests for dpgli were superior to ngli for IgG antibody determination: 68% vs. 92% specificity and 79% vs. 85% sensitivity for ngli and dpgli, respectively. Positive (76% vs. 93%) and negative (72% vs. 83%) predictive values were also higher for dpgli than for ngli. Regarding IgA gliadin antibody determination, sensitivity improved from 61% to 78% with dpgli, while specificity and positive predictive value remained at 97% ($P < 0.00001$). A combination of four tests (IgA anti-dpgli, IgG anti-dpgli, IgA anti- tissue transglutaminase, and IgA anti-endomysium) yielded positive and negative predictive values of 99% and 100%, respectively and a likelihood ratio positive of 86 with a likelihood ratio negative of 0.00. Omitting the endomysium antibody determination still yielded positive and negative predictive values of 99% and 98%, respectively and a likelihood ratio positive of 87 with a likelihood ratio negative of 0.01. There is no single test - not even jejunal biopsy - that can conclusively diagnose or exclude CD in every individual. Therefore, we propose the following two-step diagnostic procedure: The first step is the combined, simultaneous determination of IgA anti-dpgli and IgG anti-dpgli + IgA anti-tTG and/or EMA. The vast majority of patients will have either three positive or three negative results, obviating the need for a biopsy. The second step, jejunal biopsy, should be performed only in patients with discordant antibody results (i.e., in patients whose CD status cannot be classified by antibody tests alone). In any case, effects of a gluten-free diet must be controlled serologic tests using TTG-IgA might be relevant to identify those with undiagnosed CD among Indian population.

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