

IgG Antibodies against Deamidated Gliadin Peptides for Diagnosis of Celiac Disease in Patients with IgA Deficiency

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BACKGROUND: Assays for IgG antibodies against deamidated gliadin (IgG-anti-dGli) are comparable in performance with tests detecting IgA antibodies against tissue transglutaminase (IgA-anti-tTG) in diagnosing celiac disease (CD). IgA-anti-tTG are absent in IgA deficiency, a condition often associated with CD. In IgA deficiency, IgG-anti-tTG, which have a lower overall diagnostic accuracy, are routinely measured. We examined whether IgG-anti-dGli would be useful for diagnosing CD patients with IgA deficiency.

METHODS: We studied 34 IgA-deficient CD patients, 185 IgA-competent newly diagnosed children with CD, 316 children without CD, 400 adult blood donors, and 6 control IgA-deficient individuals without CD. Anti-dGli and anti-tTG were measured by ELISA, and endomysium antibodies (EmA) were measured by immunofluorescence on monkey esophagus (IgA as well as IgG class for all antibodies). We calculated diagnostic sensitivity (percentage of patients above cutoff with 95% CIs) according to age-specific cutoffs for 95% diagnostic specificity and according to cutoffs proposed by the manufacturer of the assays.

RESULTS: No IgA-deficient CD patients were positive for any IgA-based antibody assay. Diagnostic sensitivity of IgG-anti-tTG was 91.2% (95% CI 76.3%–97.7%) according to age-specific cutoffs and 82.4% (66.1%–92.0%) according to manufacturer cutoffs. The diagnostic sensitivity of IgG-EmA was 75.8% (58.8%–87.4%) and the sensitivity of IgG-anti-dGli was 88.2% (72.8%–95.9%) according to both cutoffs.

CONCLUSIONS: IgG-anti-dGli and IgG-anti-tTG have comparable diagnostic sensitivities for IgA-deficient celiac patients. IgG-anti-dGli may be useful for diagnosing CD in IgA-deficient patients.

Patients with celiac disease (CD)¹² do not tolerate gluten in their diet (1). CD patients produce antibodies against gliadin and autoantibodies against histological structures called endomysium and its dominant antigen tissue transglutaminase (tTG). IgA-class antibodies against endomysium (EmA) and IgA-class antibodies against tTG (anti-tTG) have higher diagnostic accuracy than antibodies against native gliadin. Increased concentrations of IgA-class anti-tTG or EmA are an important indication for duodenal biopsy and subsequent histological confirmation of the diagnosis (1). Normalization of anti-tTG and/or EmA concentrations after introduction of a gluten-free diet is a further criterion for diagnosis of CD (1). However, CD is associated with selective IgA deficiency (sIgAD) (2). To avoid false-negative serologic testing, IgA deficiency should be excluded in all patients suspected for CD. Two testing algorithms have been proposed: either all patients are screened for IgA deficiency (3) or total IgA is measured in only those patients with IgA-anti-tTG below an established cutoff (4, 5). IgG antibodies against tTG (IgG-anti-tTG) have high diagnostic sensitivity for CD in IgA deficiency (6–9); however, their diagnostic sensitivity in IgA-competent CD patients is low (10, 11).

In addition to antibodies directed against native gliadin, assays for antibodies against deamidated gliadin (anti-dGli) have recently been described for serological diagnosis of CD (10–16). The immune response to dGli in IgA-competent CD patients was found not to be restricted to IgA, but could be demonstrated also for the IgG class of these antibodies (13, 15, 16). Interestingly, in IgA-competent children, the IgG-anti-dGli appear to have a higher diagnostic

¹² Nonstandard abbreviations: CD, celiac disease; tTG, tissue transglutaminase; EmA, endomysium antibodies; anti-tTG, antibodies against tTG; sIgAD, selective IgA deficiency; anti-dGli, antibodies against deamidated gliadin.

accuracy than the respective IgA-anti-dGli (10, 11). Assays for IgG-anti-dGli were superior to tests measuring antibodies to native gliadin and comparable in performance with IgA-anti-tTG in diagnosis of CD. A combination of the new test for IgG-anti-dGli with the assay of IgA-anti-tTG increases the fraction of patients in whom the diagnosis of CD can be confirmed or excluded with very high probability (10, 11).

The high diagnostic accuracy of the IgG class of anti-dGli makes them a potential tool for diagnosis of CD in IgA-deficient patients. Recently, 8 IgA-deficient CD children were described (11, 17, 18) who all had low concentrations of IgA-anti-tTG and IgA-anti-dGli but high concentrations of IgG-anti-dGli. Two further studies, each including 20 IgA-deficient CD patients, revealed higher accuracy of IgG-anti-dGli detection compared with antibodies against native gliadin (9, 19). However, IgG-anti-dGli did not achieve as high a diagnostic accuracy as IgG-anti-tTG. In this study, we retrospectively compared the IgG-anti-dGli test with IgG-anti-tTG and IgG-EmA assays using sera from 34 IgA-deficient CD patients (Table 1).

All sera were provided by the contributing clinicians without further selection. The patients included 24 children (mean age 10 years, range 2–16 years, 20 girls) and 10 adults (mean age 42 years, range 21–67 years, 7 women). Sera from 30 patients (Table 1) were obtained at time of diagnostic duodenal biopsy while on a normal (gluten-containing) diet. Also included were 4 celiac patients with dietary transgressions (gluten-containing diet despite recommendations). Diagnosis was based on histological analysis of duodenal biopsies performed according to the revised criteria of the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (1). Intestinal pathology of all patients was in accordance with Marsh II/III criteria. The concentration of total IgA, measured nephelometrically, was <0.05 g/L in 29 patients, and defined as sIgAD. In the other 5 patients, IgA concentrations were below age-specific cutoffs, but >0.05 g/L (patients with low IgA concentrations). We also investigated 6 subjects (3 female, 3 male; 3 children, 3 adults) with sIgAD and normal biopsy (no CD) as controls. All patients gave informed consent. The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Leipzig.

In all sera, we measured both IgA- and IgG-class anti-dGli, anti-tTG, and EmA by means of commercially available test systems (Euroimmun). We measured anti-dGli by anti-gliadin (GAF-3X)-ELISA (detects antibodies reactive to deamidated gliadin-analogous fusion peptides composed of 3 repetitive dimers representing synthetic analogs of deamidated gliadin nonapeptides) (10); anti-tTG by antitissue transglutaminase ELISA, coated with recombinant in-

sect cell-expressed tTG; and EmA by indirect immunofluorescence analysis using a combination of primate esophagus, primate small intestine, and primate liver. Diagnostic sensitivity was calculated using (1) age-specific cutoffs for 95% specificity, derived from 316 biopsy-controlled children without CD as reported (11) and 400 adult blood donors, and (2) cutoffs proposed by the manufacturer of each test kit. We computed 95% CIs according to the modified Wald method.

Irrespective of the different cutoffs, none of the 34 IgA-deficient CD patients was positive for IgA-anti-tTG, IgA-EmA, or IgA-anti-dGli. All 3 IgG-based assays (IgG-anti-tTG, IgG-EmA, IgG-anti-dGli) were negative for only 1 patient (Table 1). Applying age-specific cutoffs, 31 of the 34 IgA-deficient patients were positive for IgG-anti-tTG, 25 of 33 for IgG-EmA, and 30 of 34 for IgG-anti-dGli. This corresponds to diagnostic sensitivities of 91.2% (95% CI 76.3%–97.7%), 75.8% (58.8%–87.4%), and 88.2% (72.8%–95.9%), respectively. Applying kit manufacturer cutoffs, 28 of 34 patients were positive for IgG-anti-tTG, 25 of 33 for IgG-EmA, and 30 of 34 for IgG-anti-dGli. This corresponds to diagnostic sensitivities of 82.4% (66.1%–92.0%), 75.8% (58.8%–87.4%), and 88.2% (72.8%–95.9%), respectively.

If only 28 patients with sIgAD under normal diet (Table 1) were considered (applying age-specific cutoffs), 26 of 28 patients were positive for IgG-anti-tTG, 21 of 27 for IgG-EmA, and 26 of 28 for IgG-anti-dGli. This corresponds to diagnostic sensitivities of 92.9% (76.3%–99.1%), 77.8% (58.9%–89.7%), and 92.9% (76.3%–99.1%), respectively. Applying kit manufacturer cutoffs, 24 of 28 patients were positive for IgG-anti-tTG, 21 of 27 for IgG-EmA, and 26 of 28 for IgG-anti-dGli. This corresponds to diagnostic sensitivities of 85.7% (67.9%–94.9%), 77.8% (58.9%–89.7%), and 92.9% (76.3%–99.1%), respectively.

If only 20 CD children with sIgAD under normal diet (Table 1) were considered (applying age-specific cutoffs), 18 patients were positive for IgG-anti-tTG, 15 for IgG-EmA, and 18 for IgG-anti-dGli, with diagnostic sensitivities of 90.0% (68.7%–98.4%), 75.0% (52.8%–89.2%), and 90.0% (68.7%–98.4%), respectively. Applying kit manufacturer cutoffs, 17 patients were positive for IgG-anti-tTG, 15 for IgG-EmA, and 18 for IgG-anti-dGli. This corresponds to diagnostic sensitivities of 85.0% (63.1%–95.6%), 75.0% (52.8%–89.2%), and 90.0% (68.7%–98.4%), respectively.

These results show that the diagnostic sensitivity of IgG-anti-dGli is comparable with that of IgG-anti-tTG for CD in IgA deficiency. Assays of IgG-anti-tTG and IgG-anti-dGli appear important not only for avoiding false-negativity in sIgAD, but also in patients with low IgA concentrations. These assays may also

Table 1. Comparison of different antibody assays in diagnosis of IgA-deficient CD patients.^a

Patient					Anti-dGli, RU/mL		Anti-tTG, RU/mL		EmA, titer	
No.	Age	Sex	Diet	IgA status	IgA	IgG	IgA	IgG	IgA	IgG
1	C ^b	F	N	slgAD	0.4	68.0 ^c	0.3	5.5	Neg	Neg
2	C	F	N	slgAD	0.6	27.2 ^c	0.4	147.3 ^c	Neg	1:320 ^c
3	C	F	N	slgAD	0.5	332.2 ^c	0.5	337.5 ^c	Neg	1:320 ^c
4	C	F	N	slgAD	0.5	51.2 ^c	0.4	368.0 ^c	Neg	1:1000 ^c
5	C	F	N	slgAD	0.7	74.5 ^c	1.2	320.2 ^c	Neg	1:320 ^c
6	C	F	N	slgAD	0.7	216.7 ^c	0.4	460.0 ^c	Neg	1:1000 ^c
7	C	F	N	slgAD	1.0	278.6 ^c	1.2	439.1 ^c	Neg	1:1000 ^c
8	C	M	N	slgAD	0.3	2.6	0.5	5.1	Neg	Neg
9	C	M	N	slgAD	0.6	365.2 ^c	0.6	456.2 ^c	Neg	1:1000 ^c
10	C	F	N	slgAD	0.5	34.2 ^c	0.8	122.9 ^c	Neg	Neg
11	C	F	N	slgAD	0.3	127.4 ^c	0.6	307.3 ^c	Neg	1:320 ^c
12	C	F	N	slgAD	0.6	180.1 ^c	0.2	250.0 ^c	Neg	1:32 ^c
13	C	F	N	slgAD	0.4	488.7 ^c	0.3	406.4 ^c	Neg	1:100 ^c
14	C	F	N	slgAD	0.0	443.9 ^c	0.3	505.0 ^c	Neg	1:320 ^c
15	C	M	N	slgAD	2.0	420.8 ^c	1.3	435.9 ^c	Neg	1:100 ^c
16	C	F	N	slgAD	0.3	14.5	0.3	104.3 ^c	Neg	1:320 ^c
17	C	F	N	slgAD	0.4	312.9 ^c	0.9	374.7 ^c	Neg	1:32 ^c
18	C	F	N	slgAD	0.3	66.2 ^c	0.3	34.8 ^c	Neg	Neg
19	C	F	N	slgAD	0.5	36.1 ^c	0.5	103.8 ^c	Neg	Neg
20	C	F	N	slgAD	1.0	244.3 ^c	0.3	378.3 ^c	Neg	1:32 ^c
21	C	F	N	LowIgA	0.9	412.2 ^c	0.3	371.7 ^c	Neg	1:32 ^c
22	C	F	DT	LowIgA	0.4	0.6	0.5	1.2	Neg	1:100 ^c
23	C	M	DT	LowIgA	0.3	11.3	0.4	360.4 ^c	Neg	1:100 ^c
24	C	F	DT	LowIgA	0.6	154.2 ^c	0.3	398.0 ^c	Neg	1:100 ^c
25	A	F	N	slgAD	1.0	283.1 ^c	0.6	401.0 ^c	Neg	1:1000 ^c
26	A	F	N	slgAD	0.9	290.7 ^c	0.6	373.5 ^c	Neg	1:320 ^c
27	A	F	N	slgAD	0.8	248.9 ^c	0.3	381.6 ^c	Neg	1:1000 ^c
28	A	M	N	slgAD	0.5	194.6 ^c	0.5	232.3 ^c	Neg	1:1000 ^c
29	A	F	N	slgAD	1.2	69.0 ^c	0.7	380.4 ^c	Neg	1:1000 ^c
30	A	M	N	slgAD	0.3	26.2 ^c	0.2	158.8 ^c	Neg	1:320 ^c
31	A	M	N	slgAD	1.1	143.4 ^c	0.8	354.3 ^c	NM	NM
32	A	F	N	slgAD	0.9	481.2 ^c	0.8	56.8 ^c	Neg	Neg
33	A	F	N	LowIgA	0.4	28.0 ^c	0.3	139.8 ^c	Neg	Neg
34	A	F	DT	slgAD	0.1	35.2 ^c	0.1	7.4 ^c	Neg	Neg
Overall diagnostic sensitivity, %										
Age-specific cutoffs					0.0	88.2	0.0	91.2	0.0	75.8
Manufacturer cutoffs					0.0	88.2	0.0	82.4	0.0	75.8

^a Cutoffs for ELISA (95% specificity for children, 95% specificity for adults, manufacturer cutoff) in relative units (RU)/mL: IgA-anti-dGli, 21.2, 17.1, 25.0; IgG-anti-dGli, 15.9, 13.8, 25.0; IgA-anti-tTG, 30.9, 10.4, 20.0; IgG-anti-tTG, 25.5, 4.6, 100.0. Common cutoff for immunofluorescence assays (IgA- and IgG-EmA) is 1:10.

^b C, child; A, adult; N, normal diet; DT, dietary transgression; slgAD, selective IgA deficiency; LowIgA, low IgA concentration; Neg, negative; NM, not measured.

^c Antibody concentrations higher than age-specific cutoff for 95% specificity.

detect IgA-deficient patients in dietary transgressions (Table 1). Among the 6 control subjects with sIgAD (no CD), the concentrations of IgG-anti-tTG and IgG-anti-dGli were within the reference range (data not shown).

Our results show that IgG-anti-dGli are valid markers for CD in IgA deficiency. The high diagnostic sensitivity obtained with the IgG-anti-dGli assay is comparable with results of previous smaller studies on IgA-deficient CD patients (9, 19) and with reports on individual IgA-deficient cases (17, 18) applying another test based on dGli as the antigen.

It is worth mentioning that not only sIgAD can cause false-negative test results in IgA-based assays; they may also occur in patients with low age-specific IgA concentrations, which do not strictly fulfill the criteria of sIgAD.

IgA deficiency does not always cause false-negative IgA-autoantibody concentrations in CD (3, 20). Our IgA-deficient patient group comprised only individuals with low IgA-anti-tTG concentration. This represents a bias, since patients with low total IgA but increased (true-positive) IgA-anti-tTG were not considered. The retrospective nature of our study and the nonsequential character of our data may represent further sources of bias.

The IgG-anti-dGli test has high diagnostic sensitivity not only in IgA-competent but also in IgA-deficient CD patients. This is in contrast to the IgG-anti-tTG assay, which is specific for CD only in IgA deficiency. As recently described (11) in IgA-competent CD children, the 96% diagnostic sensitivity (at 95% specificity) of IgG-anti-dGli is comparable to that of IgA-anti-tTG (also 96%) but substantially higher than that of IgG-anti-tTG (62%). Use of manufacturer cut-offs maintained this relationship (11).

We conclude that increased concentrations of IgG-anti-tTG are informative only after estimation of total IgA. However, IgG-anti-dGli specifically indicate CD irrespective of total IgA concentration. Therefore, a combined evaluation of IgA-anti-tTG and IgG-anti-dGli, as already suggested for IgA-competent CD

(10, 11, 16), seems to be adequate for serodiagnosis of CD irrespective of IgA deficiency and without the need for estimating total IgA concentrations.

Inspection of duodenal biopsy remains the gold standard in CD diagnosis (1). IgA-deficient symptomatic patients with negative serological tests (such as patient 8, Table 1) should undergo duodenal biopsy for evaluation of CD and other intestinal diseases associated with IgA deficiency.

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