

the manifestations of different forms of leprosy through their functional roles in antigen presentation and inhibition of T-cell responses.

Although predisposing major histocompatibility complex alleles may exhibit inefficient antigen presentation, the LYP-Trp620 allele may have a pathogenic role in the hyporesponsiveness of T cells owing to anomalies in early T-cell signaling, resulting in clinical manifestations of leprosy. Contrary to our expectations, a significantly higher number of tuberculoid patients had *PTPN22* 1858CT, suggesting that there may be early T-cell defects in these patients. This results in a compromised immune response to the infectious agent, which manifests in the milder form of the disease. Most healthy people exposed to *M. leprae* are resistant to the infection, and with an effective immune response they do not develop the disease (Bongiorno et al., 2008). Because the CT genotype accounts for only 15–16% of lepromatous and tuberculoid patients, other genes involved in the downregulation of T-cell responses, such as *CTLA-4* and *Foxp3*, should be investigated for additional host factors that may be detrimental in conferring anergy to *M. leprae* antigens in lepromatous leprosy patients.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/jid>

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IgA Anti-Epidermal Transglutaminase Antibodies in Dermatitis Herpetiformis and Pediatric Celiac Disease

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TO THE EDITOR

Recent studies have suggested epidermal transglutaminase (eTG) as the autoantigen of dermatitis herpetiformis (DH) (Sardy et al., 2002) (Donaldson et al., 2007), but the patient cohorts in

published studies on its clinical utility in DH have been small. IgA anti-eTG is present in about 50% of adult celiac disease (CD) (Hull et al., 2008); however, its prevalence in a large cohort of pediatric CD has not been reported.

The primary objective of this study was to confirm and expand on our previously published data, and to determine the clinical utility of IgA anti-eTG in a large cohort of DH patients. Our second objective was to further evaluate the relative prevalence of IgA anti-eTG in a larger cohort of pediatric CD patients.

Abbreviations: Ab, antibody; CD, celiac disease; DH, dermatitis herpetiformis; eTG, epidermal transglutaminase; tTG, tissue transglutaminase

Table 1. Statistical comparison between IgA anti-epidermal transglutaminase (eTG) and other markers for gluten-sensitive enteropathy in 80 retrospective sera from patients with dermatitis herpetiformis and 49 sera from normal adults

| | eTG IgA | tTG IgA | tTG IgG | DGP IgA | DGP IgG |
|------------------------|------------------|------------------|------------------|------------------|------------------|
| % Sensitivity (95% CI) | 71.3 (60.1–80.8) | 48.8 (37.4–60.2) | 2.5 (0.3–8.7) | 61.3 (49.7–71.9) | 46.3 (35.0–57.8) |
| % Specificity (95% CI) | 100 (92.8–100) | 100 (92.8–100) | 100 (92.8–100) | 93.9 (83.1–98.7) | 100 (92.8–100) |
| % PPV (95% CI) | 100 (93.7–100) | 100 (91.0–100) | 100 (15.8–100) | 94.2 (84.1–98.8) | 100 (90.5–100) |
| % NPV (95% CI) | 68.1 (56.0–78.6) | 54.4 (43.6–65.0) | 38.6 (30.1–47.6) | 59.7 (47.9–70.8) | 53.3 (42.6–63.7) |
| AUC | 0.912 | 0.778 | 0.709 | 0.845 | 0.825 |

AUC, area under curve; CI, confidence interval; DGP, deamidated gliadin peptides; NPV, negative predictive value; PPV, positive predictive value; tTG, tissue transglutaminase.

Table 2. Serology results for serial blood draws from a single DH patient on a strict gluten-free diet

| | eTG IgA | tTG IgA | tTG IgG | DGP IgA | DGP IgG |
|-------------------|---------|---------|---------|---------|---------|
| Pre Dx | 76 | 209 | 1 | 210 | 90 |
| 60 days post Dx | 14 | 58 | 2 | 44 | 75 |
| 12 months post Dx | 2 | 12 | 1 | 7 | 6 |

DGP, deamidated gliadin peptides; DH, dermatitis herpetiformis; Dx, diagnosis; eTG, epidermal transglutaminase; tTG, tissue transglutaminase.

12 Units or greater for IgA anti-eTG=positive; 20 Units or greater IgA and IgG anti-tTG and DGP=positive.

The patient did not take dapson.

Serum from the following cohorts was assessed for IgA antibodies (Abs) against eTG and for traditional markers associated with gluten-sensitive enteropathy (that is, tissue transglutaminase (tTG) and deamidated gliadin peptides, IgA and IgG) for comparison: 80 retrospective adult DH patients drawn during their initial clinical evaluation (all on a normal diet), 50 prospective adult DH patients drawn post-diagnosis (7 on a normal diet and 43 on some level of gluten restriction), 54 pediatric CD patients drawn during their initial clinical evaluation (all on a normal diet; 26 males, 1.2–17.9 years, mean=7.7 years; 28 females, 1.3–18.6 years, mean=8.5 years), and 49 adult and 77 pediatric normal controls. DH was diagnosed by characteristic granular IgA staining of the dermis of perilesional skin by direct immunofluorescence, and CD was diagnosed by positive duodenal biopsy and/or positive serology. All CD patients with negative biopsy were positive by serology (IgA anti-endomysial Ab and anti-tTG). There were no DH patients with IgA deficiency (<7 mg per 100 ml). Two of the pediatric CD patients had partial IgA deficiency (7–68 mg per 100 ml).

Serum IgA Ab against eTG (human recombinant) was measured semi-quantitatively by enzyme immunoassay as per the manufacturer's (Immundiagnostik Bensheim, Germany) product insert. As this assay has not yet been approved in the United States for *in vitro* diagnostic use in DH, a cutoff value of 12 Units (+5 SD above the mean) was established for this study on the basis of the IgA anti-eTG values in our normal controls. Serum IgA and IgG Abs against tTG (human red blood cells) and deamidated gliadin peptides (synthetic) were measured semi-quantitatively by enzyme immunoassay as per the manufacturer's (INOVA Diagnostics, San Diego, CA) product insert. These assays have been approved by the food and drug administration for *in vitro* diagnostic use in gluten-sensitive enteropathy. The cutoff values (<20 Units=negative; all assays) recommended by the manufacturer were used for statistical analysis. Sensitivity, specificity, positive and negative predictive values, and the area under the receiver operating characteristic curve were calculated for each assay. Ninety-five percent confidence intervals were also computed for sensitivity, specificity, and

positive and negative predictive values. All statistics were generated using SAS software, version 9.1 of the SAS system for Windows (SAS institute Inc., Cary, NC).

While identifying patients with DH on a normal diet, IgA anti-eTG performed better than any other single marker associated with gluten-sensitive enteropathy (Table 1). The sensitivity of IgA anti-eTG was lower (60.0%) in our cohort of prospective DH patients, which is likely attributed to their gluten restriction and/or treatment. When considering both retrospective and prospective DH patients, there were 28 (21.5%) with IgA anti-eTG⁺/IgA anti-tTG⁻ results, but only 1 (0.8%) having IgA anti-eTG⁻/IgA anti-tTG⁺ results. A negative result for IgA anti-tTG in a patient suspected of having DH, however, does not rule out the diagnosis. These results show that about 20% of DH patients will be negative for IgA anti-tTG Abs, but positive for IgA anti-eTG, and only rare patients are positive for IgA anti-tTG and negative for IgA anti-eTG.

We did not have enough clinical information on patients in the prospective DH cohort to correlate levels of IgA anti-eTG with disease parameters

(degree and duration of gluten restriction or dapsone/sulfapyridine dose); however, future studies should attempt to correlate levels of IgA anti-eTG with parameters of disease activity, including degree and duration of gluten restriction, and dapsone/sulfapyridine dose. The patient presented in Table 2 shows that the levels of each Ab assay decreases over time with adherence to a gluten-free diet. Although definitive conclusions cannot be made from one patient, these results suggest that the levels of IgA against eTG correlate with dietary gluten intake. Prospective studies should be designed to evaluate the levels of IgA anti-eTG in DH patients over time after initiation of a gluten-free diet.

IgA anti-eTG was present in only 11.1% of pediatric CD, which is significantly lower than that reported in adult CD (~50%) (Hull *et al.*, 2008). These results are similar to our previously published data showing a low prevalence of IgA anti-eTG in pediatric CD patients. This occurred in the setting of significantly elevated concentrations of IgA anti-tTG (90.7%). The majority of the six pediatric CD patients with IgA anti-eTG⁺ results showed low titers (13, 13, 14, 15, 20, and 96 Units) and all were duodenal biopsy positive (1 of 18 Marsh 3a (5.6%), 1 of 15 Marsh 3b (6.7%), and 4 of 16 Marsh 3c (25.0%)). All six pediatric CD patients were also positive for IgA anti-tTG (6 of 6), for IgA anti-deamidated gliadin

peptides (6 of 6), and for IgG anti-deamidated gliadin peptides (5 of 6). We will follow-up pediatric CD patients with IgA anti-eTG⁺ results to find out whether they develop symptoms of DH.

In conclusion, IgA anti-eTG was more sensitive in detecting DH than any other marker associated with gluten-sensitive enteropathy and its prevalence is significantly lower in pediatric CD than that which has been reported in adult CD. In a patient suspected of having DH, the present data support testing for IgA anti-eTG, which may help in screening and monitoring the response to a gluten-free diet. We then recommend a biopsy of uninvolved, perilesional skin in an area of grouped vesicles or erosions for direct immunofluorescence, which is the gold standard for diagnosis.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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The Absence of BRAF, FGFR3, and PIK3CA Mutations Differentiates Lentigo Simplex from Melanocytic Nevus and Solar Lentigo

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TO THE EDITOR

Lentigo simplex (LS) is a benign skin lesion preferentially observed in younger people, although it may occur at any age. The lesion measures a few milli-

meters in diameter, is brown to black, and is clinically indistinguishable from a melanocytic nevus. Histopathologically, LS shows a moderate elongation of the epidermal rete ridges and basal

hyperpigmentation. The number of melanocytes in the basal epidermal layer may be slightly increased. In contrast to LS, solar lentigo displays markedly elongated rete ridges and profound actinic elastosis in the dermis. It has been proposed that LS may

Abbreviations: LS, lentigo simplex