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INVESTIGATIVE REPORT

Small Bowel Transglutaminase 2-specific IgA Deposits in Dermatitis Herpetiformis

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Dermatitis herpetiformis (DH) is an extraintestinal manifestation of coeliac disease. Untreated coeliac disease patients are known to have transglutaminase 2 (TG2)-targeted IgA deposits in the small bowel mucosa. To evaluate whether similar intestinal IgA deposits are also present in DH and whether the deposits disappear with gluten-free diet, 47 untreated and 27 treated DH patients were studied. Seventy-nine percent of untreated and 41% of the treated DH patients had TG2-specific IgA deposits in the small bowel, and the presence of the deposits showed a significant association with the degree of small bowel villous atrophy ($p<0.001$). Other coeliac-disease related inflammatory markers were also investigated, and the density of small bowel mucosal intraepithelial $\gamma\delta^+$ T cells was increased in 91% of untreated and 73% of treated DH patients. The results show that the majority of untreated DH patients have similar gluten-dependent TG2-specific IgA deposits in the small bowel mucosa as coeliac disease patients. ***Key words: dermatitits herpetiformis; coeliac disease; IgA deposit; transglutaminase 2; intraepithelial lymphocytes.***

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Dermatitis herpetiformis (DH) is an intensively itching blistering skin disease, which is currently recognised as an extraintestinal manifestation of coeliac disease (1). Already in 1966 it was demonstrated that DH patients have coeliac-type enteropathy (2), and soon thereafter it was also reported that the rash responds to a gluten-free diet (GFD) treatment (3). The majority of DH patients have villous atrophy in the small bowel mucosa identical to coeliac disease (4), and the remainder show signs of inflammation with increased density of $\gamma\delta^+$ intraepithelial lymphocytes (IELs) as in coeliac disease (5). Moreover, coeliac disease and DH share similar genetic background, and these 2 conditions often occur in the same families (6) or in monozygotic twins (7). The diagnosis of coeliac disease is based on small bowel biopsy showing villous atrophy (8, 9), and that of DH on the demonstration of granular immunoglobulin A (IgA) deposits in the papillary dermis by direct immunofluorescence (IF) (10).

A typical feature in coeliac disease and DH is the presence of circulating IgA-class autoantibodies against transglutaminase 2 (TG2) (11, 12). Evidence suggests that coeliac autoantibodies are produced in the small bowel mucosa (13–15). Serum coeliac autoantibodies are known to occur in the untreated stage of the disease and disappear during the GFD treatment. Moreover, untreated coeliac patients have shown almost invariably deposited IgA in the small bowel mucosa. This mucosal autoantibody has proven to be directed against TG2 (13), and furthermore, these deposits are disease specific (16, 17) and seem to disappear during GFD treatment (18). Small bowel IgA deposits have been found previously in children with DH (19) but it is currently not known whether these are directed against TG2 as in coeliac disease. Instead, it has been shown that IgA in DH skin is directed against TG3 but not TG2 (20).

The aim of this study was to investigate whether DH patients have coeliac-type IgA deposits directed against TG2 in the small bowel. We further examined the presence of other coeliac disease-related inflammatory markers such as densities of $CD3^+$ and $\gamma\delta^+$ IELs in the small bowel mucosa of DH patients.

MATERIALS AND METHODS

Patients with dermatitis herpetiformis

This study comprised 47 untreated and 27 GFD treated DH patients investigated at the Departments of Dermatology, Tampere and Helsinki University Hospitals. The mean age was 44 years in the untreated and 50 years in the treated DH group (Table I). The diagnosis of DH was based on the clinical picture of the rash and the presence of pathognomonic granular IgA deposits in the papillary dermis of uninvolved skin detected with direct IF (10). Forty-five percent (5 out of 11) of untreated DH patients with available data had abdominal symptoms such as diarrhoea or flatulence and 27% had anaemia or weight loss as a manifestation of malabsorption. At the time of the diagnosis, 69% (11 out of 16) of treated DH patients had suffered from abdominal symptoms and 44% from malabsorption. Almost all of the DH patients in our area adhere to GFD and about

Table I. *Demographic data, and intestinal and serum findings in the untreated and gluten-free diet treated patients with dermatitis herpetiformis (DH)*

	DH untreated ($n=47$)	DH treated ($n=27$)
Male, *n* (%)	27 (57)	16 (59)
Age, years, mean (range)	44 (17–74)	50 (30–75)
Small bowel mucosal finding, *n* (%)*		
Subtotal villous atrophy	18/43 (42)	–
Partial villous atrophy	17/43 (39)	1/27 (4)
Normal	8/43 (19)	26/27 (96)
Small bowel mucosal TG2-specific IgA deposits present, *n* (%)**	37/47 (79)	11/27 (41)
Small bowel mucosal $CD3^+$ IEL density increased, *n* (%)	16/23 (70)	11/26 (42)
Small bowel mucosal $\gamma\delta^+$ IEL density increased, *n* (%)	21/23 (91)	19/26 (73)
Serum coeliac antibody-positive, *n* (%)*	16/19 (84)	0/26 (0)

Statistically significant difference between two study groups (*$p<0.001$, **$p=0.002$).
TG2: Transglutaminase 2; IEL: intraepithelial lymphocyte.

60% consume oats in their diet (21). In this study all treated DH patients were on a strict GFD and a median duration of the diet was 7 years (range 2–35 years). None of the treated DH patients were taking dapsone and all but one were free of skin symptoms. The study protocol was approved by the ethics committee of Tampere University Hospital and informed consent was obtained from all study participants.

Small bowel mucosal morphology and intraepithelial lymphocytes

All 47 untreated DH and 27 GFD-treated patients underwent oesophago-gastroduodenoscopy and 7 forceps biopsy specimens were taken from the distal part of the duodenum. Five of these were processed, stained with haematoxylin and eosin and studied under light microscopy. The villous height-crypt depth ratios (Vh/CrD) were determined from several well-oriented biopsy samples from multiple sites in order to detect patchy forms of villous atrophy. Vh/CrD >2 was considered normal, Vh/CrD 0.9–2.0 represented partial villous atrophy and Vh/CrD <0.9 subtotal villous atrophy.

Two small bowel biopsy specimens were freshly embedded in optimal cutting temperature compound (OCT, Tissue-Tec, Miles Inc, Elkhart, IN), snap-frozen in liquid nitrogen and stored at –70°C. Immunohistochemical stainings were carried out on 5 µm-thick frozen sections. $CD3^+$ IELs were stained with monoclonal antibody Leu-4 (Becton Dickinson, San Jose, CA) and $\gamma\delta^+$ IELs with TCRγ antibody (Endogen, Woburn, MA). Positive IELs were counted with a 100× flat field light microscope objective throughout the surface epithelium; at least 30 fields measuring 1.6 mm in epithelial length were counted and IEL density expressed as cells/mm of epithelium was estimated. The reference values were set at 37 cells/mm for $CD3^+$ IELs and 4.3 for $\gamma\delta^+$ IELs (22). In our laboratory the correlation coefficients for intraobserver variation for $CD3^+$ and $\gamma\delta^+$ IELs were 0.95 and 0.98, and those for interobserver variation 0.92 and 0.98, respectively. Evaluations of the specimens and calculations of the IELs were carried out by one investigator without prior knowledge of DH treatment.

Small bowel mucosal TG2-specific IgA deposits

Small bowel mucosal TG2-specific IgA deposits were investigated from frozen small bowel sections as previously described (13). From each patient, 6 unfixed, 5 µm-thick sections from frozen small bowel specimens were processed, 3 for investigation of IgA deposits and 3 for double-colour labelling for both IgA and TG2. IgA was detected by direct IF as described by Korponay-Szabo et al. (13). In deposit positive samples a clear subepithelial IgA deposition was found below the basement membrane along the villous and crypt epithelium and around mucosal vessels (13). Sections were further double-stained for human IgA (green) and for TG2 (red) to confirm that coeliac-type IgA deposits co-localised with TG2 (13). The occurrence of the IgA deposits was graded semiquantitatively according to their intensity along the basement membrane in the villous-crypt area as follows: negative, weak (+), moderate (++), and strong positive (+++). In cases where the intensity was patchy, it was graded from different areas and the mean value was given. All evaluations were carried out blindly without knowledge of DH history or laboratory findings. The correlation coefficient for both intraobserver and interobserver variations for the detection of presence or absence of TG2-specific IgA deposits have both been 0.98 in our laboratory (23).

Serum coeliac autoantibodies

Serum IgA-class endomysial antibodies (EmA, primate-type reticulin) (24) and reticulin antibodies (ARA, rodent-type reticulin) (25) were determined by an indirect IF method using human umbilical cord (EmA) and rat kidney and liver sections (ARA) as antigens, respectively; a serum dilution of $1:\geq 5$ was considered positive in both. EmA and ARA are both directed against TG2, and in our laboratory ARA and EmA tests have proved to be virtually identical (26). In this study these antibodies are referred as serum coeliac autoantibodies.

Statistics

Quantitative data were expressed as means and ranges. Statistical differences between study groups were evaluated using the Pearson chi-square test, Fisher's exact test or Mann-Whitney *U*-test, as appropriate. $p<0.05$ was considered as statistically significant. Spearman's rank correlation was used to measure statistical dependences of the variables. All calculations were performed with SPSS (version 12.0.1).

RESULTS

Thirty-five (81%) untreated DH patients showed villous atrophy in their small intestinal mucosa (Table I). Overall, 42% had subtotal, 39% partial villous atrophy and 19% normal villous architecture. In the GFD-treated DH group small bowel mucosal morphology was normal in 96% of the patients (Table I). The only patient with partial villous atrophy was free of skin symptoms and had no serum coeliac autoantibodies.

Thirty-seven out of 47 (79%) untreated DH patients had TG2-specific IgA deposits in their small bowel mucosa (Table I, Fig. 1A, Fig. 2). The intensity of the deposits was either strong or moderate in 30 (81%) patients. In the GFD-treated DH group, 11 (41%) had IgA deposits, and the intensity was weak in all (Table I, Fig. 1A). The median duration of GFD in the treated group was 15.0 years in deposit positive patients and 5.5 years in deposit negative patients, but the difference was not statistically significant ($p=0.148$).

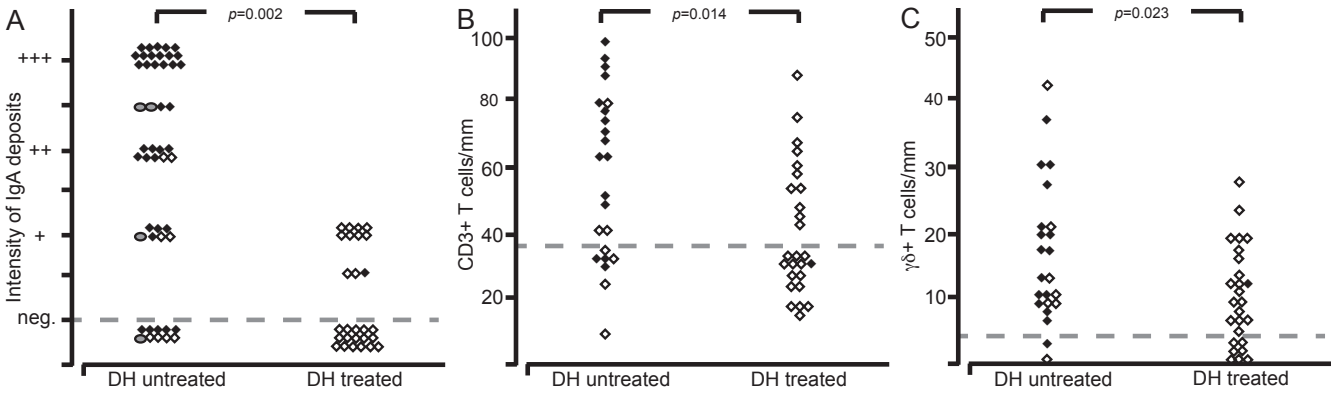

Fig. 1. Intensities of small bowel mucosal transglutaminase 2-specific IgA deposits in untreated ($n=47$) and gluten-free diet treated ($n=27$) dermatitis herpetiformis (DH) patients (A). Densities of $CD3^+$ intraepithelial lymphocytes (B) and $\gamma\delta^+$ intraepithelial lymphocytes (C) in the small bowel mucosa of untreated ($n=23$) and gluten-free diet treated ($n=26$) dermatitis herpetiformis (DH) patients. Open diamonds denote DH patients with normal small bowel villi and filled diamonds patients with villous atrophy and ellipses patients without small bowel morphological result.

Altogether 69% (31 out of 45) of IgA deposit positive patients with reliable morphological results (treated and untreated) evinced some degree of small bowel mucosal villous atrophy; 17 had subtotal and 14 partial villous atrophy. In the 25 patients with no TG2-specific IgA deposits villous architecture was normal in 20 (80%) cases, 5 (20%) had partial villous atrophy and none subtotal villous atrophy. Overall, the presence of TG2-specific IgA deposits showed significant association with the degree of small bowel villous atrophy ($p<0.001$).

$CD3^+$ and $\gamma\delta^+$ IEL densities were available from 23 untreated DH patients, and for 70% and 91% of the patients the densities were increased, respectively (Table I, Fig. 1B and C). In the GFD-treated DH patients 73% (19 out of 26) of patients had elevated densities of $\gamma\delta^+$ IELs. The mean density of these cells was statistically significantly lower ($p=0.023$) in the treated DH group (9.8 cells/mm) compared to the untreated study group (16.8 cells/mm). Similarly, the mean density of $CD3^+$ IELs was significantly ($p=0.014$) lower in the GFD treated DH group (40 cells/mm) than in the untreated group (57 cells/mm). There was a statistically significant correlation between the densities of $CD3^+$ and $\gamma\delta^+$ IELs ($p<0.001$), but the increased densities of these cells showed no significant association with the presence of TG2-specific IgA deposits. Of the untreated DH patients with normal small bowel villous architecture, 50% (4 out of 8) had TG2-specific IgA deposits, 42% (3 out of 7) had increased densities of $CD3^+$ cells and 86% (6 out of 7) increased densities of $\gamma\delta^+$ cells.

Serum coeliac autoantibodies were positive in 84% of the untreated DH patients and in none of the GFD-treated DH patients ($p<0.001$, Table I). All 3 seronegative untreated DH patients had TG2-specific IgA deposits in the gut.

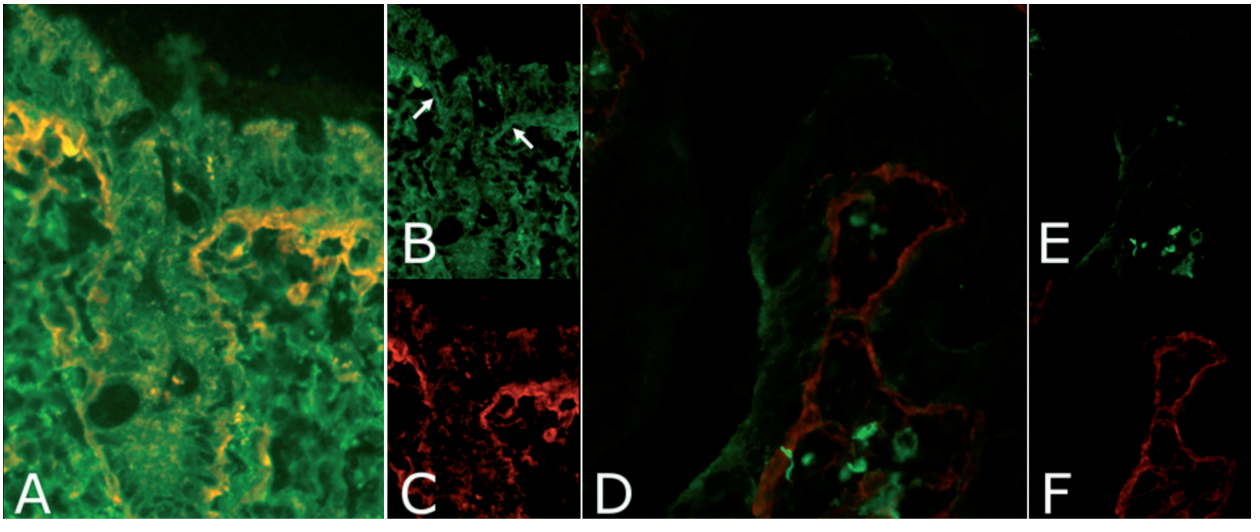

Fig. 2. Subepithelial coeliac-type small bowel mucosal IgA deposits (B, green, arrow) and transglutaminase 2 (TG2; C, red) in untreated dermatitis herpetiformis (DH) patient. Yellow-colour in composite picture (A) indicates colocalisation of coeliac-type IgA deposits and TG2. In patient without IgA deposits (E) colocalisation (yellow) of IgA (E) and TG2 (F) was not detected in the composite picture (D).

DISCUSSION

This study showed in a large patient material that the majority of untreated DH patients show coeliac-type autoimmune reaction against TG2 in the small bowel mucosa. TG2-specific IgA deposits were found in 79% of the patients and most of them presented with subtotal or partial villous atrophy. However, this percentage in DH was lower than previously reported (90–100%) in untreated coeliac disease (16–18, 27). In the present DH study it was further documented that similarly to coeliac disease, the intensity of the TG2-specific IgA deposits in the gut seems to diminish or disappear during the GFD treatment. It is, however, noteworthy that the disappearance of the IgA deposits during GFD treatment was a time-consuming process. Even after a median of 7 years on the strict GFD 41% of the DH patients were still deposit positive though serum autoantibodies were negative and all but one patient had normal small bowel mucosa. Similarly to the TG2-specific IgA deposits in the gut, the cutaneous IgA deposits are known to disappear slowly from the skin of GFD-treated DH patients (28, 29), but unfortunately in the present study we were not able to examine the presence or absence of these deposits.

Since the first description of intestinal TG2-specific IgA deposits in the small bowel (13) there have been several studies showing sensitivity figures approaching 100% in untreated coeliac disease (16–18). Besides detecting classical coeliac disease with villous atrophy, the presence of intestinal IgA deposits have had a predictive value in early stage and latent coeliac disease (30). Moreover, it has been shown that extra-intestinal TG2-specific IgA deposits can occur in untreated coeliac disease e.g. in the liver (13). However, studies focusing on small intestinal autoimmune reaction in DH are sparse. Karpati et al. (19) showed already in 1988 with direct IF examination that 11 out of 12 DH children had IgA deposits in their proximal jejunum. Korponay-Szabo et al. (13) showed in 2004 that the intestinal IgA deposits are directed against TG2 in coeliac disease. Their study also included 11 untreated DH patients of whom 7 had intestinal TG2-specific IgA deposits. Before the present study there has been no additional information on the TG2 targeted intestinal deposits in DH. In contrast, the possible role of TG3 as the autoantigen in DH skin has been examined more thoroughly. Sardy et al. (20) showed that in DH IgA in the papillary dermis is directed against TG3, and they further described that the deposited complexes did not contain TG2. In addition, patients with DH have been shown to produce two circulating IgA antibody populations against TG3: one that binds exclusively TG3, and the other which cross-reacts with both TG2 and TG3 (31). The cross-reactive TG3 antibodies have also been found in coeliac disease patients, but their levels, or avidity for TG3, seems to be lower than in the patients with DH (20, 31–33). Therefore it has been proposed that TG3 rather than TG2 is the autoantigen in DH, while TG2 is the dominant antigen for coeliac disease. In addition to skin, TG3 has been found in the small intestine of mouse tissue (34). However, we are not aware of any human studies looking at the immune response against TG3 in the small intestine. In this study we were also unable to examine whether the present DH patients would have small bowel mucosal deposits against TG3 in addition to TG2-specific IgA deposits.

In DH the degree of small bowel mucosal villous atrophy is often milder than in coeliac disease, and previous studies have shown that approximately 20% of untreated DH patients have normal villous architecture in the intestine (4, 5, 35). Consistently, there is a larger proportion of autoantibody seronegative patients in DH compared to coeliac disease (36, 37). In the present study 19% of untreated DH patients had normal villous architecture in the small bowel mucosa, but other signs of coeliac disease-related inflammation were present. Half of these patients had TG2-specific IgA deposits in the small bowel, and as many as 86% showed increased densities of $\gamma\delta^+$ T cells. Overall, these cells were still elevated in 73% of the patients on a long-term GFD. Since the density of $\gamma\delta^+$ T cells decreases after introduction of GFD, but typically remains elevated compared to healthy controls, it has been suggested that these cells might have a regulatory potential in coeliac disease (38) and thus also in DH.

To conclude, in this study we showed that 79% of untreated and 41% of GFD-treated DH patients had coeliac-type autoimmune reactivity against TG2 in their small bowel mucosa. The presence of TG2-specific IgA deposits was shown to have a significant association with the degree of small bowel villous atrophy and thus appeared more often in association with severe intestinal damage. Furthermore, 91% of untreated DH patients had elevated densities of $\gamma\delta^+$ IELs in the small bowel mucosa, and these cells were still elevated in 73% of DH patients on a long-term GFD treatment.

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The authors declare no conflict of interest.

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