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2016

Hervonen , K , Salmi , T T , Ilus , T , Paasikivi , K , Vornanen , M , Laurila , K , Lindfors , K , Viiri , K , Saavalainen , P , Collin , P , Kaukinen , K & Reunala , T 2016 , ' Dermatitis Herpetiformis Refractory to Gluten-free Dietary Treatment ' , Acta Dermato-Venereologica , vol. 96 , no. 1 , pp. 82-86 . <https://doi.org/10.2340/00015555-2184>

<http://hdl.handle.net/10138/160248>

<https://doi.org/10.2340/00015555-2184>

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CLINICAL REPORT

Dermatitis Herpetiformis Refractory to Gluten-free Dietary Treatment

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Dermatitis herpetiformis (DH) is a blistering skin disease, which is regarded as an extra-intestinal manifestation of coeliac disease. Refractory cases of coeliac disease, that do not respond to a gluten-free diet and which carry an increased risk of lymphoma, are well-known in coeliac disease. To determine whether refractory cases of DH with active rash and persistent small bowel atrophy occur we analysed our series of 403 patients with DH. Seven (1.7%) patients, who had been on a gluten-free diet for a mean of 16 years, but who still required dapsone to treat the symptoms of DH, were identified. Of these, one patient died from mucinous adenocarcinoma before re-examination. At re-examination skin immunoglobulin A (IgA) deposits were found in 5/6 refractory and 3/16 control DH patients with good dietary response. Small bowel mucosa was studied at re-examination from 5 refractory and 8 control DH patients and was normal in all 5 refractory and 7/8 control DH patients. One refractory DH patient died from adenocarcinoma, but no lymphoma developed in any of the patients. This study documents for the first time refractory DH, in which the rash is non-responsive to a gluten-free diet, but the small bowel mucosa heals. This differs from refractory coeliac disease, in which the small bowel mucosa does not heal on a gluten-free diet. Key words: dermatitis herpetiformis; coeliac disease; small bowel mucosa; gluten-free diet; dapsone.

Accepted Jun 15, 2015; Epub ahead of print Jun 18, 2015

Acta Derm Venereol 2016; 96: 82–86.

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Dermatitis herpetiformis (DH) is an itchy, blistering autoimmune skin disease most often affecting the elbows, knees and buttocks (1). Diagnosis of DH is based on the clinical picture and demonstration of granular immunoglobulin A (IgA) deposits in the papillary dermis (2). Patients with DH evince small bowel mucosal villous atrophy or, at least, coeliac-type inflammatory changes (3–6). DH and coeliac disease share the same genetic background, having a strong association with HLA-DQ2 (7). Both conditions often occur in the same

families (8) and even in monozygotic twins (9). In DH, both the rash and enteropathy respond to a gluten-free diet (GFD) (10, 11) and DH is currently considered a cutaneous manifestation of coeliac disease. It takes several months on a GFD until the DH rash clears, and therefore patients with an active rash require additional treatment with dapsone (4,4-diaminodiphenylsulfone). The initial dose is usually 25–50 mg/day and, on a strict GFD, it takes approximately 2 years until dapsone can be stopped (11–13).

We have prospectively collected a large series ($n=483$) of patients with DH since 1970. Follow-up showed that 98% of the patients adhered to a GFD (14). However, despite long adherence to an apparently strict GFD, a small proportion of patients with DH need to continue treatment with dapsone to control the active rash (12, 13). In coeliac disease there exists a subgroup of patients in whom clinical symptoms and small bowel villous atrophy do not recover on a strict GFD; the condition is called refractory coeliac disease (15). This is usually accompanied by severe symptoms, malabsorption, osteoporosis and a risk of intestinal lymphoma (15–17). The term “refractory DH” has not been used previously in the literature and the occurrence of this condition remains obscure. The aim of this study was therefore to analyse our series of 483 DH patients to identify all refractory cases, i.e. those in whom the rash does not recover on a strict GFD. A further aim was to examine whether patients with refractory DH have persistent small bowel villous atrophy and a risk of complications similar to subjects with refractory coeliac disease.

METHODS

Patients

Since 1970 we have prospectively collected and followed up all patients with DH detected at the outpatient clinic of the Department of Dermatology of Tampere University Hospital (14). All patients with DH in a defined area are diagnosed in this unit, since the frozen skin biopsies required for the diagnosis are not taken elsewhere. In each patient the diagnosis of DH had been based on the clinical picture and on the demonstration of granular IgA deposits in the papillary dermis. Upper intestinal endoscopy with small bowel biopsy had been performed on approximately 75% of the patients (14, 18), after which all

had been advised to adhere to a GFD. In addition, dapsone had been started in patients with an intensive rash, and 65% of all patients had used it (14). The patients had been followed up at the out-patient clinic at 3–6-month intervals for at least 1–2 years or longer, until the rash was controlled by the GFD alone.

Until 2010 our series consisted of 483 patients with DH, of which 403 were alive. In 2013 we retrospectively analysed the records of all patients, to determine which patients had not responded to a GFD as expected. The DH patients were classified as refractory when they had been on a GFD for at least 3 years, but still needed dapsone, at least 75 mg/week, to control the rash. For each suspected refractory case 2 control patients with DH were selected, who were of the same sex and who had been diagnosed within 2 years of the index patient. They all had a good response to a GFD, i.e. no rash or dapsone use during the last 3 or more years on a strict diet. All refractory and control subjects with DH were invited to participate at the re-examination.

The study protocol was approved by the ethics committee of Tampere University Hospital (R12267). All subjects provided written informed consent.

Skin symptoms and immunofluorescence biopsy

The presence or absence of typical DH rash was examined in every refractory and control patient. Dapsone treatment was stopped if no skin symptoms were seen. A 4-mm punch biopsy was taken from normal-appearing perilesional skin and, when there was no rash, from normal-appearing forearm skin. The biopsy specimens were embedded in optimal cutting temperature compound (OCT, Tissue-Tec, Miles Inc., Elkhart, IN, USA), snap-frozen in liquid nitrogen and stored at -70°C until use. Direct immunofluorescence was performed and IgA deposits in the upper papillary dermis were graded as strongly (+++), moderately (++) or weakly (+) positive, as previously described (19).

Dietary assessment

A dietician evaluated adherence to a GFD in the refractory and control DH patients by personal inquiry and via a 3-day food record with additional questions specifically designed to uncover hidden exposure to gluten.

Antibody and HLA measurements

A commercially available enzyme-linked immunosorbent assay (ELISA) was used to measure serum IgA antibodies to epidermal transglutaminase (TG3; Immunodiagnostic, Bensheim, Germany) and tissue transglutaminase (TG2; Celikey; Phadia, Freiburg, Germany). The optimal cut-off point for positivity was ≥ 25 AU/ml for TG3 and ≥ 3 AU/ml for TG2 antibodies (20). Serum IgA class endomysial antibodies (EmA) were determined using an indirect immunofluorescence (IIF) method with human umbilical cord as substrate; a dilution of 1:5 or more was considered positive.

Human leukocyte antigen (HLA) DQB1*02 and DQB1*0302 alleles were determined in the refractory DH patients with the SSP™ DQB1 low-resolution kit (Olerup SSP AB, Saltsjöbaden, Sweden). The single nucleotide polymorphism rs2187668 tagging the DQ2.5 haplotype (DQA1*05:01-DQB1*02:01) was further genotyped from the patients by the TaqMan genotyping assay, as described earlier (21).

Upper intestinal endoscopy, small-bowel mucosal morphology, intraepithelial lymphocytes and analysis of intestinal T-cell clonality

All study subjects were offered upper intestinal endoscopy at the re-examination, but this was voluntary. During the endoscopy, 7–8 small bowel mucosal biopsy specimens were taken from the distal part of the duodenum, and 4 of these were pro-

cessed, stained with haematoxylin and eosin and studied under light-microscopy. Villous-height to crypt-depth ratios were determined; ratios of 2.0 or more were considered normal (22).

Two small bowel biopsy specimens were freshly embedded in OCT (Tissue-Tec), snap-frozen in liquid nitrogen and stored at -70°C . Immunohistochemical staining of CD3⁺ and $\gamma\delta^{+}$ intraepithelial lymphocytes (IELs) was carried out on 5- μm -thick frozen sections and reference values were set at 37 cells/mm for CD3⁺ IELs and 4.3 for $\gamma\delta^{+}$ IELs (6).

Small bowel mucosal TG2-specific IgA deposits were investigated from frozen small bowel sections. From each patient, unfixed, 5- μm thick sections from frozen small bowel specimens were processed for investigation of IgA deposits. IgA was detected by direct immunofluorescence, as described by Korponay-Szabo et al. (23).

Small bowel mucosal biopsies from patients with refractory DH were subjected to analysis of intestinal T-cell clonality according to a PCR protocol (24). DNA was extracted from paraffin-embedded small-bowel mucosal biopsy specimens with NucleonHT kit (Amersham-Pharmacia, Biotech, Uppsala, Sweden). Each sample was analysed for T-cell receptor gamma gene rearrangements using primers V γ I+ V γ III/IV+J γ 1/2 and V γ I+ V γ III/IV+JP γ 1/2, then the products were run on 10% polyacrylamide gels. Samples giving rise to 1 or 2 fragments of expected size were regarded as monoclonal. Jurkat cell DNA was used as a positive control for monoclonality.

Gastrointestinal symptoms, bone mineral density, body mass index and laboratory parameters

Gastrointestinal symptoms were evaluated with the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire, which comprises 15 items describing abdominal pain, gastro-oesophageal reflux, indigestion, diarrhoea and constipation (25). Bone mineral density of refractory DH patients was measured in the lumbar spine and both femoral necks by dual-energy X-ray absorptiometry. Scores between -1.0 and -2.4 indicate osteopaenia and -2.5 or less osteoporosis. Body mass index (BMI) was calculated as weight per square of height (kg/m^2).

The laboratory values measured from the patients with refractory DH were: blood haemoglobin (reference values: men 134–167 g/l; women 117–155 g/l), free thyroxine (11–22 pmol/l) and serum dapsone concentration (4–20 $\mu\text{mol}/\text{l}$).

RESULTS

Frequency of refractory DH and dietary features before re-examination

Altogether, 16 (4.0%) of 403 patients with DH needed to continue treatment with dapsone to control the rash after adhering to a GFD for at least 3 years. Twelve patients participated at re-examination. A thorough dietary assessment revealed that 2 patients had regular lapses in their GFD, and a further 3 patients experienced no flare-up of rash when dapsone was withdrawn. The remaining 7 (1.7%) patients, 2 women and 5 men, by definition, had refractory DH. The mean age at diagnosis was 30 years in the refractory patients and 33 years in the 17 control patients ($n=13$) (Table I). Median duration of skin symptoms before diagnosis of DH was 9 (range 4–384) months in the refractory patients and 12 (range 1–60) months in the control patients. The mean daily

Table I. Demography, small bowel findings, daily dose of dapsone, duration of gluten-free diet (GFD) and use of oats in the diet in 7 refractory and 17 sex- and age-matched control patients with dermatitis herpetiformis (DH)

	Patients with refractory DH	Control patients with DH
Males, n (%)	5 (71)	14 (82)
Age at diagnosis, mean (range)	30 (12–51)	33 (7–60)
Subtotal or partial villous atrophy at diagnosis, n (%)	5/6 (83)	16/17 (94)
Serum coeliac antibody ^a positive at diagnosis, n (%)	6/6 (100)	11/12 (92)
Dapsone dose after diagnosis, mg, mean (range)	38 (12.5–50)	40 (25–100)
Duration of GFD before re-examination, years, mean (range)	16 (3–36)	23 (5–39)
Oats in the diet, n (%)	3 (43)	13 (76)
Malignancies before re-examination, n (%)	1 (14)	3 (18)

^aSerum IgA-class endomysium, tissue transglutaminase or/and reticulin antibodies.

dose of dapsone after the diagnosis was 38 mg in the refractory and 40 mg in the control patients (Table I).

Mean duration of GFD treatment before re-examination was 16 years in the refractory patients and 23 years ($p=0.20$) in the control patients (Table I). Two (29%) refractory and 3 (18%) control patients had been non-compliant for some time at the beginning of the GFD treatment. Three (43%) refractory and 13 (76%) control patients regularly included oats in their diet.

One refractory patient with DH died just before re-examination, from metastatic mucinous adenocarcinoma, which, according to immunological studies (CDX-2 positive immunostaining), probably originated from the intestine. Of the control patients with DH, 1 had carcinoid tumour of the colon, 1 had metastatic neuroendocrine carcinoma, probably originating from the gastrointestinal tract, and 1 had thyroid carcinoma. Regarding other autoimmune manifestations, 1 of the patients with refractory DH (patient 7) had hypothyreosis. Of the control patients with DH, 1 had psoriasis and 1 ankylosing spondylitis.

Rash, cutaneous IgA deposits and dietary treatment at re-examination

We had 6 refractory DH patients at re-examination since one refractory DH patient died at the beginning of the study. At re-examination the mean dose of dapsone

in these patients with refractory DH was 42 mg/day and 1 patient used sulfasalazine 1–2 g/day due to dapsone hypersensitivity (Table II). Median serum dapsone concentration was 2.8 (range 0–3.5) $\mu\text{mol/l}$. All 6 refractory patients presented with typical DH rash, whereas no rash was seen in the control patients. Five refractory (83%) and 3 control patients (19%) showed cutaneous IgA deposits, all with weak or moderate fluorescence (Tables II and III).

Dietary assessment revealed that 2 patients with refractory DH had minor lapses in their otherwise strict GFD. One patient (patient 3, Table II) had a few lapses once a year during a short holiday abroad, and another patient (patient 4, Table II) had twice inadvertently eaten food containing gluten. Three (18%) control patients with DH had also minor lapses in their strict GFD; they had consumed beer or buns that contained gluten a couple of times in a year with no symptoms.

Serology and HLA findings at re-examination

At re-examination all 6 patients with refractory DH had no TG2 or TG3 antibodies, but 1 had a borderline positive EmA titre (Table II). Of the DH controls 2 had low levels of TG3, but none had TG2 and EmA antibodies. All 6 refractory DH patients studied carried HLA DQ2, 2 of them also HLA DQ8.

Small bowel mucosal findings and gastrointestinal symptoms at re-examination

All 5 refractory and 7/8 (88%) control DH patients had normal small bowel mucosal architecture (Tables II and III). The only patients with refractory DH who refused gastroscopy had undergone the procedure 16 years earlier when on a GFD and, at that time, his small bowel mucosa was normal. Of the DH controls, 7 had

Table II. Duration of gluten-free diet (GFD), dapsone dose and cutaneous, small bowel and serological antibody findings in 7 patients with refractory dermatitis herpetiformis

Sex/age at diagnosis, years	GFD years	GFD strict at present	Dapsone dose at diagnosis/at present (mg/day)	Rash/skin IgA deposits at present	Small bowel histology at diagnosis/at present	Serology at present		
						TG3-ab	TG2-ab	EmA
F/44	25	Yes	25/sulfasalazine 1–2 g	+++	SVA/normal	Neg	Neg	Neg
M/42	3	Yes	50/50	+++	SVA/normal	Neg	Neg	Neg
M/22	21	Yes ^a	50/50	+++	PVA/normal	Neg	Neg	Neg
M/19	4	Yes	50/50	++	PVA/normal	Neg	Neg	Pos
M/12	9	Yes	12.5/50	+++	Normal/normal	Neg	Neg	Neg
M/20	36	Yes	25/12.5	+/-	SVA/nd	Neg	Neg	Neg
F/51	12	Yes	50/40	+/nd	nd/nd	nd	nd	nd

^aMinor faults less often than once a month.

++: moderate; +: weak; -: negative; nd: not done; SVA: subtotal villous atrophy; PVA: partial villous atrophy; TG3-ab: epidermal transglutaminase antibodies; TG2-ab: tissue transglutaminase antibodies; EmA: endomysium antibodies.

Table III. *Body mass index, dapsone dose, IgA deposits in the skin, and small bowel and serological findings in the refractory and controls patients with dermatitis herpetiformis (DH) on a strict gluten-free diet at re-examination*

	Patients with refractory DH <i>n</i> = 7	Control with DH <i>n</i> = 17
Body mass index, mean (range)	29 (24–32)	26 (21–32)
Daily dose of dapsone, mg, mean (range)	42 (12.5–50)	0
IgA deposits in the skin, <i>n</i> (%)	5/6 (83)	3/16 (19)
Small bowel findings		
Normal mucosal histology, <i>n</i> (%)	5/5 (100)	7/8 (88)
Villous-height to crypt-depth ratio, mean (range)	2.6 (2.6–2.7)	3.2 (2.9–3.9)
Increased density of $\gamma\delta$ + IEL, <i>n</i> (%)	2/3 (67)	6/8 (75)
Serum antibodies positive, <i>n</i> (%)		
Epidermal transglutaminase (TG3)	0	2 (12)
Tissue transglutaminase (TG2)	0	0
Endomysium (EmA)	1 (17)	0

IEL: intraepithelial lymphocytes; EmA: endomysial antibodies.

normal villous architecture and 1 had partial villous atrophy (Table III).

CD3⁺ and $\gamma\delta$ + IEL densities and small bowel mucosal IgA deposits were available for 3 refractory and 8 control DH patients. CD3⁺ IELs were increased in 2 and 4, and $\gamma\delta$ + IELs in 3 and 6 patients, respectively (Table III). None of the refractory or responsive DH patients had IgA deposits in the small bowel mucosa. Three patients with refractory DH were analysed for intestinal T-cell clonality, but none showed monoclonal T-cell receptor gamma gene rearrangements.

The gastrointestinal symptoms measured by GSRS were the same in the refractory (total score; mean 1.9, range 1.6–2.5) and control DH patients (mean 1.9, range 1.1–3.4). Bone mineral density measurement showed osteopaenia in 2 of the 6 patients with refractory DH, but none of them had osteoporosis. All 6 patients with refractory DH had normal blood haemoglobin and serum free thyroxine levels.

DISCUSSION

This study showed that refractory DH exists, but is a rare condition, as only 7 out of 403 (1.7%) patients met the criteria of active rash that was not responding to a strict GFD. Two patients who were initially suspected to have refractory DH were found to have marked lapses in the GFD, and an additional 3 patients on a strict GFD could stop dapsone without re-appearance of the rash. Previously, Garioch et al. (13) described 3 (7%) patients in their DH series who did not respond to a strict GFD and who still required dapsone to control the rash. These patients had adhered to a GFD for 4 years or longer and all had normal small bowel mucosa. In the present study, although the rash did not respond, the small bowel mucosa was normal in all 5 patients with refractory DH who underwent upper intestinal

endoscopy at re-examination. This is an important finding, showing that refractory DH is different from the well-known refractory coeliac disease in which small bowel mucosa does not recover on a GFD (15–17).

The frequency of refractory DH in the present study was low (1.7%). The frequency of refractory coeliac disease was even lower (0.3%) in a recent study in Finland (26). Earlier studies of coeliac disease have found markedly higher frequencies of refractory coeliac disease and have shown that its subgroup with abnormal IELs bears a high risk for intestinal lymphoma (15–17). Lymphomas are also known to occur in DH (27, 28). Importantly, however, no lymphoma or abnormal IELs were found in the present patients with refractory DH, although one patient with refractory DH died from metastatic adenocarcinoma most probably originating from the intestine. No other obvious malignancies or complications were seen in these patients, indicating that refractory DH is a benign condition that differs from refractory coeliac disease.

At diagnosis all patients with refractory DH in the current study had pathognomonic cutaneous IgA deposits. Furthermore, all 6 patients with refractory DH studied carried the predisposing HLA-DQ2, which is carried by 95–100% of patients with DH in general (7). In agreement with the presence of rash, 5 of the 6 patients with refractory DH had IgA deposit in the papillary dermis at re-examination. Three (18%) of the control patients also showed IgA deposits, although they had been asymptomatic for a mean of 8 years on a strict GFD. The slow disappearance of IgA deposits from DH skin even after adherence to a strict GFD for several years has also been noted in earlier studies (13, 19, 29).

It can be argued that, in the patients with refractory DH in the current study, the most obvious explanation for the poor GFD response with regard to the rash would be ongoing inadvertent consumption of gluten. Indeed, this has been shown to be the reason in a proportion of non-responsive patients with coeliac disease (30). However, in the present study an experienced dietician evaluated the strictness of adherence to the GFD, but did not find any dietary lapses in the patients with refractory DH. The fact that their small bowel mucosa had recovered, even though the villous-height to crypt-depth ratio was rather low, and TG2, TG3 and EmA antibodies were normal also supports good adherence to the GFD.

It is possible that the rash in the present patients with refractory DH was sensitive to even minute amounts of gluten hidden in their GFD. A strict GFD may contain traces of gluten, which may inhibit mucosal recovery in a proportion of patients with coeliac disease (30). There are also some reports suggesting that a few DH patients would react to dietary antigens other than gluten, such as cow's milk (31, 32). In this study we did not find any such food antigens on careful dietary assessment of the patients with refractory DH. A trial with an elemental

diet, i.e. a diet containing defined amounts of free amino acids and short-chain polysaccharides, would have been of interest. This diet has shown a rapid effect on the activity of the rash in DH patients who have previously eaten a normal gluten-containing diet (33, 34), but patients refractory to a strict GFD have not been examined.

The present study indicates that patients with refractory DH differ from those with refractory coeliac disease by showing a clear response to a GFD in the small bowel mucosa and occurrence of circulating coeliac-type antibodies. However, the rash remains active in patients with refractory DH, and cutaneous IgA deposits are still present. Thus, the presence of IgA deposits is a marker of continuous cutaneous activity in patients with refractory DH. Epidermal transglutaminase co-localizes with IgA deposits, suggesting that this enzyme could be an initiating factor for cutaneous inflammation leading to blister formation in DH (35, 36). Further research will reveal whether epidermal transglutaminase activity or any other specific biomarker predict the development of refractory DH.

In conclusion, in this large DH series we found 7 (1.7%) patients in whom the rash, but not the small bowel mucosa, was non-responsive to a strict GFD treatment, and termed the condition refractory DH. The patients with refractory DH did not develop any complications or lymphoma, as refractory coeliac disease is known for, but a larger series is needed to draw definite conclusions.

ACKNOWLEDGEMENTS

This study was financially supported by the Competitive State Research Financing of the Expert Area of Tampere University Hospital (grants 9P008, 9N062, 9R034, 9R018) and Seinäjoki Central Hospital (VTR16), the Academy of Finland, the Sigrid Juselius Foundation and Seppo Nieminen Fund.

The authors declare no conflicts of interest.

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