Dermatitis herpetiformis (DH) is an itchy, blistering skin disease with sites of predilection at the elbows, knees and buttocks. Although DH is mostly asymptomatic, all patients exhibit small bowel villous atrophy or at least coeliac-type inflammatory changes. Deposition of immunoglobulin A (IgA) in the papillary dermis is a key diagnostic feature of DH. Epidermal transglutaminase (TG3) is the antigen for IgA deposited in the skin, and tissue transglutaminase (TG2) is the antigen for IgA deposited in the small bowel mucosa. Clinically silent, but immunologically active coeliac disease in the gut appears to result in IgA TG3 antibody complexes aggregated into DH skin. The prevalence of DH in northern Europe is high (30–75/100,000), but its incidence is decreasing, possibly due to increased recognition of subclinical coeliac disease. The rash and small bowel heal on a gluten-free diet, which is a life-long treatment. The risk of non-Hodgkin’s lymphoma is increased, but in patients with DH who adhere strictly to a gluten-free diet long-term prognosis is excellent. Key words: dermatitis herpetiformis; coeliac disease; gluten-free diet; transglutaminase autoantibodies; immunoglobulin A deposits.

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Dermatitis herpetiformis (DH) was first described as a clinical entity by Louis Duhring in 1884, and was associated with coeliac disease (CD) in 1966 when enteropathy was discovered in the small bowel of DH patients (1, 2). Subsequently, the blistering rash with sites of predilection on the elbows, knees and buttocks was found to respond to a gluten-free diet (GFD) (3, 4). Further evidence of the relationship between DH and CD came from immunogenetic and family studies. Both diseases were found to have the same strong association with human leukocyte antigen (HLA) DQ2, which is carried by up to 100% of patients with DH (5, 6). Moreover, DH and CD cluster in the same families, and monozygotic twins (1 with DH and the other with CD) have been reported (7, 8).

Demonstration of granular immunoglobulin A (IgA) deposits in the uninvolved skin is an easy way to diagnose DH, whereas small bowel biopsy is needed to confirm the diagnosis of CD (9–11). In both diseases patients have IgA class circulating antibodies, first described to reticulin, then to endomysium (EmA) and, finally, to tissue transglutaminase (TG2; 12, 13). The breakthrough in CD research was the finding by Schuppan and co-workers in 1997 that tissue transglutaminase (TG2) enzyme, which is present in the gut mucosa, was the auto-antigen (14). In 2002 Sárdy et al. (15) presented evidence that epidermal transglutaminase (TG3) was an auto-antigen for IgA deposited in DH skin. Thereafter, IgA TG2 deposits have been shown to occur in the small bowel mucosa of most untreated patients either with CD or DH (16, 17).

Several expert reviews (18–22), 2 national guidelines (23, 24), a continuous medical examination (25), and a clinical practice article (26) have been published on DH in recent years. The present review focuses on the latest research findings and provides further evidence that DH is a specific skin manifestation of CD.

IMMUNOPATHOGENESIS OF DERMATITIS HERPETIFORMIS

The IgA deposits in the papillary dermis of DH skin have long been suspected to derive from the gut. Following discovery of the gluten-sensitive enteropathy, Seah et al. (27) proposed, in 1971, that IgA originates from the gut in gluten-antigluten immune complexes. These are then trapped in the skin as a result of cross-reactivity with deposited reticulin antibodies. Although gluten-antigluten immune complexes could be found in the serum of patients with DH, studies did not reveal any gluten or gluten antibodies in the skin (28). In 2002, Sárdy et al. (15) demonstrated that the antigen for deposited IgA was TG3 enzyme. They used dual immunostaining for the presence of IgA, and showed that TG3 and IgA co-localized. This important finding was confirmed by Donaldsson et al. (29). Sárdy et al. (15) also showed that, although patients with CD also presented with IgA class TG3 antibodies, the antibodies in patients with DH recognized TG3 selectively and with high avidity. TG3 and TG2 are closely related and show a high degree of sequence conservation, mostly within enzymatically relevant domains (20). Therefore, cross-reactivity of the antibodies against TG3 and TG2 is not surprising. The ability of TG2 to deamidate and cross-link gluten peptides is essential for the production
of TG2 autoantibodies in CD. TG3 forms gluten peptide complexes less efficiently, which could be a reason for the different auto-antibody response in DH (30). Whether the high affinity IgA antibodies to TG3 in patients with DH arise against TG3 as a primary antigen or are the result of epitope spreading is still an open question, because TG3 protein has not been detected in the small bowel similarly to the TG2 enzyme (15, 20). An immunopathogenesis of DH, starting from subclinical CD in the gut and evolving to immune complex deposition of high avidity IgA TG3 antibodies together with TG3 enzyme in the papillary dermis, is shown in Fig. 1.

One important point is that, in normal skin, TG3 is expressed in the keratinocyte layers and not in the papillary dermis where the IgA deposits are located in DH (10, 15, 29). Hence, the IgA precipitates could be immune complexes containing TG3, which accumulate specifically in the papillary dermis (20). Supporting this, TG3 deposits have also been observed in cutaneous vessels in DH skin (31). Recently, Taylor et al. (32) showed that TG3 present in IgA aggregates in DH skin is enzymatically active and can bind soluble fibrinogen. This fits well with an earlier study showing fibrinogen at the same site as the IgA deposits in the uninvolved skin (33). Moreover, evolving DH blisters show marked fibrin deposition and upregulation of urokinase type plasminogen activator, suggesting enhanced fibrinolysis (34, 35). The blistering rash in DH has sites of predilection at the knees, elbows and buttocks, although IgA aggregates are also deposited in sites that are never involved in lesion formation (10, 29). The most likely explanation for this unique distribution of the rash involves the influence of local factors, such as pressure and stretching (Fig. 1). It is possible that direct activation of TG3 in dermal aggregates by mechanical force, similarly to TG2 activation in vascular walls, could be an initiator leading to blister formation (36). This would result in release of fibrinogen from the aggregates (32, 33), which, besides being a clotting factor, is an inflammatory protein capable of attracting T cells, neutrophils and macrophages, all of which have been shown to influx into the developing DH lesions (34, 37).

One interesting question is why IgA deposits persist in DH skin in patients on a GFD long after the rash has become asymptomatic and circulating TG3 auto-antibodies have disappeared from the serum (38–40). In a recent study (41) we found 3 patients with DH with IgA deposits, despite the fact that they had been asymptomatic on a strict GFD for a mean of 8 years. The reason for the unexpectedly long persistence of IgA TG3 aggregates seems to be the tight binding to the extracellular matrix of the papillary dermis. Active cross-linking is further substantiated by the observation that TG3 retains at least part of its enzymatic activity in DH skin (32). In contrast to the long time taken for IgA deposits to disappear after withdrawal of gluten, these seem to reappear more rapidly, within one year on gluten challenge (42). Further gluten challenge studies, focusing on the reappearance of IgA TG3 aggregates in the skin and TG2 aggregates in the small bowel, would provide important knowledge about the initial events in the immunopathogenesis of DH.

**CLINICAL PRESENTATION AND DIAGNOSIS OF DERMATITIS HERPETIFORMIS**

DH can appear at any age. The age of the youngest patient in our Tampere series is 3 years and the oldest 84 years (43). Mean age at diagnosis of DH was 43 years, both in

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**Fig. 1.** Immunopathogenesis of dermatitis herpetiformis starting from subclinical coeliac disease in the gut. Small bowel mucosa: gliadin peptides are modified by tissue transglutaminase (TG2) enzyme and recognized by human leukocyte antigen (HLA) DQ2/8-positive antigen presenting cells after which B cells/plasma cells produce immunoglobulin A (IgA) antibodies to gliadin peptides and TG2. Blood: circulating IgA class antibodies to gliadin, TG2 and epidermal transglutaminase (TG3) are present. High-avidity TG3 antibodies may arise from TG2 antibodies by epitope spreading. Uninvolved skin: immune complexes consisting of IgA TG3 antibodies and TG3 enzyme are deposited in the papillary dermis. Stretching/pressure, or possibly other factors, activate deposited TG3 enzyme, which is capable of binding fibrinogen. This and/or other factors attract inflammatory cells, such as T lymphocytes and polymorphonuclear leucocytes (PMNs), to influx into the papillary dermis. These cells secrete inflammatory mediators, such as various cytokines and proteases, which finally cause subepidermal blister formation.
men and women, but it has increased significantly during recent years. Similar mean ages have been reported in DH series from Europe, North America and Asia. Recent DH series from Italy (44) include many children, and the mean age of the patients is only 32 years. It is possible that DH appears in childhood more often in southern than northern Europe, since in Finland childhood DH is rare, comprising only 4% of all patients (45). Males slightly or markedly predominate in adults with DH (Table I), whereas the opposite is true in children (45, 46) and in CD (11, 47).

The typical sites of predilection of DH are the elbows, knees and buttocks (Fig. 2). In addition, the upper back, abdomen, groin, axillae, scalp and face can be affected, but oral lesions are rare (48). The rash is polymorphic with small blisters (Fig. 2). These are, however, often eroded and crusted because of intense itch and scratching. Palmar or acral purpuric lesions may appear on the hands (49). The presentation and activity of the rash varies greatly from patient to patient, but complete remission is infrequent on a normal, gluten-containing diet.

The clinical picture is often highly suggestive of DH although, linear IgA disease is always a diagnostic problem (50). The symptoms and signs of mild DH are easily masked if the patient has a concomitant itchy skin disorder, such as atopic dermatitis (45). The burning itch felt during the development of blisters is, however, usually severe enough to raise suspicion of DH. The ideal method for diagnosis of DH is a direct immunofluorescence biopsy of unaffected skin in close proximity to an active lesion. This reveals pathognomonic granular IgA deposits at the dermo-epidermal junction (Fig. 2), and the diagnosis of DH should not be made without this finding (10, 18, 19).

SMALL BOWEL AND SEROLOGICAL FINDINGS IN DERMATITIS HERPETIFORMIS

Patients with DH rarely present with abrupt gastrointestinal symptoms or signs of malabsorption (18, 19, 51). Consistent with CD, approximately 70% of patients with DH have villous atrophy and crypt hyperplasia in small bowel mucosal samples from upper gastrointestinal endoscopy (18, 19, 51; Table I). The remaining patients have markers of early-stage CD, such as increased density of gamma/delta positive intraepithelial T lymphocytes (52, 53). Furthermore, in 1988, Kárpáti et al. (54) showed that children with DH had IgA deposits in the proximal jejunum. In 2004, Korponay-Szabó et al. (16) reported that the intestinal IgA deposits were directed against TG2, in both CD and DH. Subsequent studies showed that almost all untreated patients with CD and 80% of patients with DH have TG2-targeted IgA deposits in the small bowel mucosa, and that these deposits are gluten-dependent (17, 55).

Patients with untreated CD or DH present with circulating IgA autoantibodies. Anti-reticulin antibody test was the first CD-specific test and the EmA test the second (12, 56). When TG2 was identified as the auto-antigen in CD, an enzyme-linked immunosorbent assay (ELISA) method was established for detecting IgA-class TG2 antibodies in the serum (13, 14). TG2 antibody ELISA test has proven highly sensitive and specific for CD. In DH TG2 antibodies are found at a somewhat

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Table I. Comparison of dermatitis herpetiformis (DH) and coeliac disease (CD)

<table>
<thead>
<tr>
<th></th>
<th>DH</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Slightly more males</td>
<td>Females predominate</td>
</tr>
<tr>
<td>Age at onset</td>
<td>Mainly adults</td>
<td>Children and adults</td>
</tr>
<tr>
<td>1st-degree relatives with CD or DH</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>HLA DQ2</td>
<td>95–100%</td>
<td>95%</td>
</tr>
<tr>
<td>IgA deposits in the skin</td>
<td>100% (by definition)</td>
<td>0%</td>
</tr>
<tr>
<td>Small bowel villous atrophy</td>
<td>70%</td>
<td>100% (by definition)</td>
</tr>
<tr>
<td>IgA deposits in bowel mucosa</td>
<td>79%</td>
<td>100% (by definition)</td>
</tr>
<tr>
<td>IgA TG3 antibodies in serum</td>
<td>86%</td>
<td>24%</td>
</tr>
<tr>
<td>IgA TG2 antibodies in serum</td>
<td>86%</td>
<td>92%</td>
</tr>
<tr>
<td>IgA EmA antibodies in serum</td>
<td>89%</td>
<td>95%</td>
</tr>
<tr>
<td>Prognosis on a gluten-free diet</td>
<td>Excellent</td>
<td>Increased all-cause and lymphoma mortality</td>
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</tbody>
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*Salminen et al. (17), *Reunala et al. (40), *Hervonen et al. (62), *Tio et al. (66).

HLA-DQ2: human leukocyte antigen DQ2; IgA: immunoglobulin A; TG3: epidermal transglutaminase; TG2: tissue transglutaminase; EmA: endomysium.
lower percentage than in CD, and positive findings are confined mostly to patients with small bowel villous atrophy (57). The majority of patients with untreated DH also have circulating antibodies against TG3, whereas the frequency is much lower, up to 24%, in patients with CD (40, 58, 59; Table I). In patients with DH adhering to a GFD IgA antibodies to TG3 decrease in parallel with TG2 and EmA antibodies (40). This indicates that the measurement of TG3 antibodies does not offer any advantage over the widely used TG2 antibody assay for monitoring GFD treatment.

GLUTEN-FREE DIET AND LONG-TERM PROGNOSIS OF DERMATITIS HERPETIFORMIS

A GFD is the treatment of choice for patients with DH, leading to healing of the rash and small bowel enteropathy (3, 4, 38). However, it takes several weeks to months for the rash to respond to a strict GFD and, therefore, 65% of our patients also start dapsone (4,4'-diaminodiphenylsulfone) treatment. The initial daily dose is 25–50 mg, which causes rapid relief of itching and the rash subsides within 2–3 days. If there is no effect, the dose is increased to 100 mg daily. Dapsone has a dose-related risk for haematological side-effects, such as methaemoglobinaemia and haemolysis, but these are rare in doses below 100 mg daily.

Patients on a GFD were previously advised to avoid wheat, rye, barley and oats. At present they can consume oats, which has been shown to be non-toxic (60, 61). Long-term follow-up of our patients with DH showed that 98% adhered to the GFD, 72% of them strictly (62). The reason for this excellent compliance appears to be regular visits to the specialist outpatient clinic run by experienced dermatologists, for at least 1–2 years or longer, until dapsone could be stopped. Recently, we analysed whether some of our patients with DH could be non-responsive to a strict GFD (41). We found 7 (1.7%) patients who still used dapsone for active rash, although they had been on a strict GFD for a mean of 16 years. In contrast to the rash, the small bowel mucosa had recovered. This indicates that the condition in DH is different from refractory CD, which is associated with various complications and occurrence of intestinal lymphoma (63). The rash in DH reappears on gluten challenge (42), and there is general agreement that adherence to a GFD should be lifelong. There are, however, some studies suggesting that a few children and adults with DH may go into remission and tolerate gluten (64, 65).

CD is known for increased risk for all-cause mortality and non-Hodgkin’s lymphoma mortality (66). Recently, we analysed the mortality rate in our prospectively collected cohort of 476 patients with DH (62). The patients were followed up for a total of 9,079 person years and almost all of them adhered to a GFD. Unexpectedly, the standardized mortality rate (SMR 0.70) was significantly reduced compared with the general population. Previously, Lewis et al. (67) studied 846 patients with DH in Nottingham, UK, and found a slightly, but non-significantly, reduced mortality rate (hazard ratio 0.93). However, one-third of their patients had no data on adherence to a GFD, which could be a reason for the non-significant mortality rate.

In DH the risk of non-Hodgkin’s lymphoma is significantly increased (up to 10 times), but following a GFD for more than 5 years seems to be protective (68–70). In agreement with this, we found in our recent DH series (62), in which almost all patients adhered to a GFD, a significantly increased lymphoma mortality rate during the first 5 years of follow-up, but not thereafter. A significantly reduced mortality rate due to cerebrovascular diseases (SMR 0.38) was also observed, which might be related to the GFD or to the lower level of smoking in patients with DH.

CONCLUSION

DH is relatively common, especially among people in northern Europe and in Utah, USA (43, 71, 72). It also occurs in South America, but is extremely rare in Asia, and appears to be non-existent among native people in Africa due to low consumption of wheat and absence of gluten. A recent increase in DH since the 1990s in Finland and the UK, with a simultaneous rapid increase in CD (43, 71, 72), fits our hypothesis that clinically silent CD is a prerequisite for the development of DH (18, 81). This large pool of undiagnosed, and mostly subclinical, CD seems to be the basis from which DH evolves. In support of this theory, we have seen patients who initially developed CD, then followed or did not follow a GFD, and finally developed DH (79). Moreover, patients with DH frequently have coeliac-type dental enamel defects (80), which develop early in childhood as a result of malabsorption or immune alteration caused by undiagnosed CD. The decreasing incidence of DH since the 1990s in Finland and the UK, with a simultaneous rapid increase in CD (43, 71), fits our hypothesis that clinically silent CD is a prerequisite for the development of DH (18, 81).

The rash, with IgA deposits in the skin, is the main feature that differentiates DH from CD, whereas small bowel findings are generally similar in both conditions. That TG3 enzyme is the auto-antigen for IgA deposits in DH skin and TG2 for IgA deposits in coeliac mucosa are important observations (15–17, 29). Whether IgA TG3 aggregates in DH skin are involved in the initial events of blister formation is unknown. Granular IgA deposits are, however,
the key diagnostic feature of DH that differentiates this blistering disease from all other dermatological disorders. The treatment of choice for DH is a GFD and, if carefully followed, the long-term prognosis is excellent (62).

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