Acta Derm Venereol 2015; 95: 917–922

REVIEW ARTICLE

Dermatitis Herpetiformis: Pathognomonic Transglutaminase IgA Deposits in the Skin and Excellent Prognosis on a Gluten-free Diet

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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.***

Accepted Jun 3, 2015; Epub ahead of print Jun 10, 2015

Acta Derm Venereol 2015; 95: 917–922.

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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

 doi: 10.2340/00015555-2162
 ISSN 0001-5555

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 autoantibodies 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

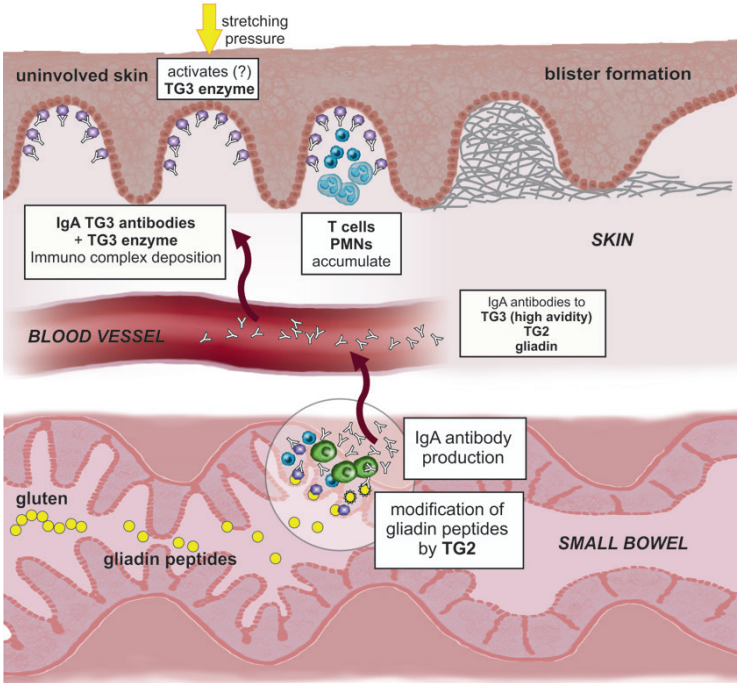

Fig. 1. Immunopathogenesis of dermatitis herpetiformis starting from subclinical coeliac disease in the gut. *Small bowel mucosa:* gliadin peptides are modified by tissue transglutaminase (TG2) enzyme and recognized by human leukocyte antigen (HLA) DQ2/8-positive antigen presenting cells after which 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).

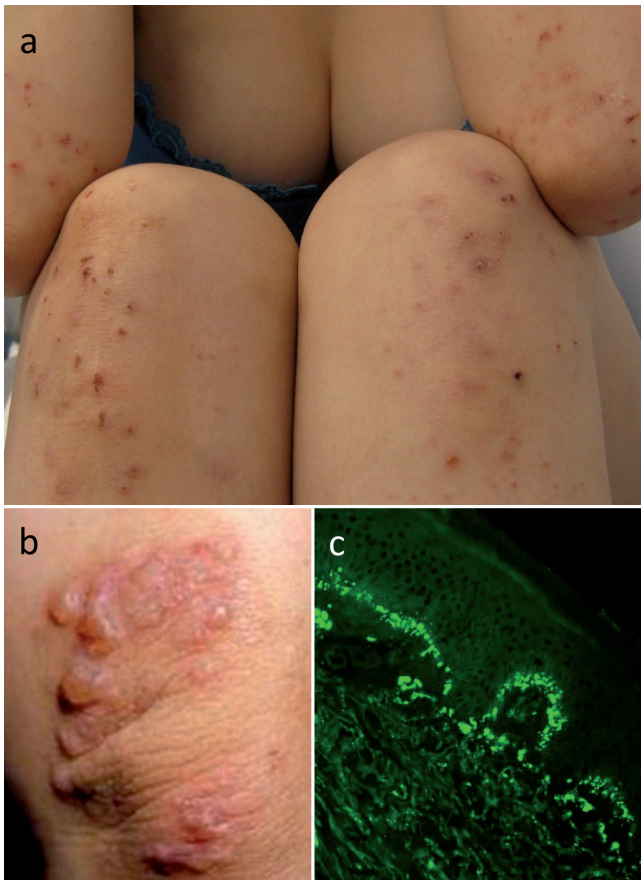

Fig. 2. Dermatitis herpetiformis. (a) Polymorphic rash with excoriated blisters on the elbows and knees. (b) Typical small blisters on the elbow. (c) Granular immunoglobulin A (IgA) deposits at the dermo–epidermal junction. Direct immunofluorescence examination of uninvolved skin.

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

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

	DH	CD
Sex	Slightly more males	Females predominate
Age at onset	Mainly adults	Children and adults
1st-degree relatives with CD or DH	Yes	Yes
HLA DQ2	95–100%	95%
IgA deposits in the skin	100% (by definition)	0%
Small bowel villous atrophy	70%	100% (by definition)
IgA deposits in bowel mucosa[a]	79%	95–100%
IgA TG3 antibodies in serum[b]	86%	24%
IgA TG2 antibodies in serum[b]	86%	92%
IgA EmA antibodies in serum[b]	89%	95%
Prognosis on a gluten-free diet	Excellent[c]	Increased all-cause and lymphoma mortality[d]

[a]Salmi et al. (17), [b]Reunala et al. (40), [c]Hervonen et al. (62), [d]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 HLA DQ2 (73–76). Two recent studies of DH, the first from Finland with 477 patients (43) and the second from the UK with 1,160 patients (71) found prevalences of 75/100,000 and 30/100,000. Interestingly, the prevalence of DH in the UK is 8 times lower than for CD (71). In Finland both diseases appeared at approximately the same frequency in the 1980s, whereas at present the prevalence of DH is 6 times lower than that of CD (43, 77). Recent serological screening studies have documented that the prevalence of CD is as high as 1%, thus for every patient identified 7–8 remain undiagnosed (11, 47, 78). 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).

ACKNOWLEDGEMENTS

The authors would like to thank nurses Sanna Sällinen and Tiina Kallio for their help in running the specialist outpatient clinic for the patients with DH. Prof Raimo Suhonen provided the blister photograph of DH. Tiina Rauhavirta, PhD, is acknowledged for her help in preparing the diagram about immunopathogenesis of DH. The study was financially supported by the Competitive Research Funding of Tampere University Hospital (grant 9N062).

REFERENCES

1. Marks J, Shuster S, Watson AJ. Small-bowel changes in dermatitis herpetiformis. Lancet 1966; 2: 1280–1282.
2. Fry L, Keir P, McMinn RM, Cowan JD, Hoffbrand AV. Small-intestinal structure and function and haematological changes in dermatitis herpetiformis. Lancet 1967; 2: 729–733.
3. Fry L, Seah PP, Riches DJ, Hoffbrand AV. Clearance of skin lesions in dermatitis herpetiformis after gluten withdrawal. Lancet 1973; 1: 288–291.
4. Reunala T, Blomqvist K, Tarpila S, Halme H, Kangas K. Gluten-free diet in dermatitis herpetiformis. I. Clinical response of skin lesions in 81 patients. Br J Dermatol 1977; 97: 473–480.
5. Spurkland A, Ingvarsson G, Falk ES, Knutsen I, Sollid LM, Thorsby E. Dermatitis herpetiformis and celiac disease are both primarily associated with the HLA-DQ (alpha 1*0501, beta 1*02) or the HLA-DQ (alpha 1*03, beta 1*0302) heterodimers. Tissue Antigens 1997; 49: 29–34.
6. Balas A, Vicario JL, Zambrano A, Acuña D, García-Novo D. Absolute linkage of celiac disease and dermatitis herpetiformis to HLA-DQ. Tissue Antigens 1997; 50: 52–56.
7. Reunala T. Incidence of familial dermatitis herpetiformis. Br J Dermatol 1996; 134: 394–398.
8. Hervonen K, Karell K, Holopainen P, Collin P, Partanen J, Reunala T. Concordance of dermatitis herpetiformis and celiac disease in monozygous twins. J Invest Dermatol 2000; 115: 990–993.
9. van der Meer JB. Granular deposits of immunoglobulins in the skin of patients with dermatitis herpetiformis. An immunofluorescent study. Br J Dermatol 1969; 81: 493–503.
10. Zone JJ, Meyer LJ, Petersen MJ. Deposition of granular IgA relative to clinical lesions in dermatitis herpetiformis. Arch Dermatol 1996; 132: 912–918.
11. Gujral N, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. World J Gastroenterol 2012; 18: 6036–6059.
12. Hällström O. Comparison of IgA-class reticulin and endomysium antibodies in coeliac disease and dermatitis herpetiformis. Gut 1989; 30: 1225–1232.
13. Dieterich W, Laag E, Schöpper H, Volta U, Ferguson A, Gillett H, et al. Autoantibodies to tissue transglutaminase as predictors of celiac disease. Gastroenterology 1998; 115: 1317–1321.
14. Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med 1997; 3: 797–801.
15. Sárdy M, Kárpáti S, Merkl B, Paulsson M, Smyth N. Epidermal transglutaminase (TGase 3) is the autoantigen of dermatitis herpetiformis. J Exp Med 2002; 195: 747–757.
16. Korponay-Szabó IR, Halttunen T, Szalai Z, Laurila K, Király R, Kovács JB, et al. In vivo targeting of intestinal and extraintestinal transglutaminase 2 by coeliac autoantibodies. Gut 2004; 53: 641–648.
17. Salmi TT, Hervonen K, Laurila K, Collin P, Mäki M, Koskinen O, et al. Small bowel transglutaminase 2-specific IgA deposits in dermatitis herpetiformis. Acta Derm Venereol 2014; 94: 393–397.
18. Reunala TL. Dermatitis herpetiformis. Clin Dermatol 2001; 19: 728–736.
19. Fry L. Dermatitis herpetiformis: problems, progress and prospects. Eur J Dermatol 2002; 12: 523–531.
20. Kárpáti S. Dermatitis herpetiformis: close to unravelling a disease. J Dermatol Sci 2004; 34: 83–90.
21. Zone JJ. Skin manifestations of celiac disease. Gastroenterology 2005; 128: S87–91.
22. Kárpáti S. Dermatitis herpetiformis. Clin Dermatol 2012; 30: 56–59.
23. Caproni M, Antiga E, Melani L, Fabbri P. Guidelines for the diagnosis and treatment of dermatitis herpetiformis. J Eur Acad Dermatol Venereol 2009; 23: 633–638.
24. Ingen-Housz-Oro S, Joly P, Bernard P, Bedane C, Prost C. Dermatitis herpetiformis. Guidelines for the diagnosis and treatment. Ann Dermatol Venereol 2011; 138: 271–273.
25. Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis. Part II. Diagnosis, management, and prognosis. J Am Acad Dermatol 2011; 64: 1027–1033.
26. Jakes AD, Bradley S, Donlevy L. Dermatitis herpetiformis BMJ 2014; 348: g2557.
27. Seah PP, Fry L, Hoffirand AV, Hollborow EJ. Tissue antibodies in dermatitis herpetiformis and coeliac disease. Lancet 1971; 2: 834–836.
28. Katz SI, Strober W. The pathogenesis of dermatitis herpetiformis. J Invest Dermatol 1978; 70: 63–75.
29. Donaldson MR, Zone JJ, Schmidt LA, Taylor TB, Neuhausen SL, Hull CM, et al. Epidermal transglutaminase deposits in perilesional and uninvolved skin in patients with dermatitis herpetiformis. J Invest Dermatol 2007; 127: 1268–1271.
30. Stamnaes J, Dorum S, Fleckenstein B, Aeschlimann D, Sollid LM. Gluten T cell epitope targeting by TG3 and TG6; implications for dermatitis herpetiformis and gluten ataxia. Amino Acids 2010; 39: 1183–1191.
31. Preisz K, Sárdy M, Horvath A, Kárpáti S. Immunoglobulin, complement and epidermal transglutaminase deposition in the cutaneous vessels in dermatitis herpetiformis. J Eur Acad Dermatol Venereol 2005; 19: 74–79.
32. Taylor TB, Schmidt LA, Meyer LJ, Zone JJ. Transglutaminase 3 present in the IgA aggregates in dermatitis herpetiformis skin is enzymatically active and binds soluble fibrinogen. J Invest Dermatol 2015; 135: 623–625.
33. Haffenden GP, Blenkinsopp WK, Ring NP, Wojnarowska F, Fry L. The potassium iodide patch test in the dermatitis herpetiformis in relation to treatment with a gluten-free diet and dapsone. Br J Dermatol 1980; 103: 313–317.
34. Reitamo S, Reunala T, Konttinen YT, Saksela O, Salo OP. Inflammatory cells, IgA, C3, fibrin and fibronectin in skin lesions in dermatitis herpetiformis. Br J Dermatol 1981; 105: 167–177.
35. Airola K, Vaalamo M, Reunala T, Saarialho-Kere UK. Enhanced expression of interstitial collagenase, stromelysin-1, and urokinase plasminogen activator in lesions of dermatitis herpetiformis. J Invest Dermatol 1995; 105: 184–189.
36. Huelsz-Prince G, Belkin AM, VanBavel E, Bakker EN. Activation of extracellular transglutaminase 2 by mechanical force in the arterial wall. J Vasc Res 2013; 50: 383–395.
37. Garioch JJ, Baker BS, Leonard JN, Fry L. T lymphocytes in lesional skin of patients with dermatitis herpetiformis. Br J Dermatol 1994; 131: 822–826.
38. Garioch JJ, Lewis HM, Sargent SA, Leonard JN, Fry L. 25 years' experience of a gluten-free diet in the treatment of dermatitis herpetiformis. Br J Dermatol 1994; 131: 541–545.
39. Fry L, Haffenden G, Wojnarowska F, Thompson BR, Seah PP. IgA and C3 complement in the uninvolved skin in dermatitis herpetiformis after gluten withdrawal. Br J Dermatol 1978; 99: 31–37.

40. Reunala T, Salmi TT, Hervonen K, Laurila K, Kautiainen H, Collin P, et al. IgA antiepidermal transglutaminase antibodies in dermatitis herpetiformis: a significant but not complete response to a gluten-free diet treatment. Br J Dermatol 2015; 172: 1139–1141.
41. Hervonen K, Salmi T, Ilus T, Paasikivi K, Vornanen M, Laurila K, et al. Dermatitis herpetiformis refractory to gluten free dietary treatment. Acta Derm Venereol 2015: Jun 18 [Epub ahead of print].
42. Leonard J, Haffenden G, Tucker W, Unsworth J, Swain F, McMinn R, et al. Gluten challenge in dermatitis herpetiformis. N Engl J Med 1983; 308: 816–819.
43. Salmi TT, Hervonen K, Kautiainen H, Collin P, Reunala T. Prevalence and incidence of dermatitis herpetiformis: a 40-year prospective study from Finland. Br J Dermatol 2011; 165: 354–359.
44. Antiga E, Verdelli A, Calabrò A, Fabbri P, Caproni M. Clinical and immunopathological features of 159 patients with dermatitis herpetiformis: an Italian experience. G Ital Dermatol Venereol 2013; 148: 163–169.
45. Hervonen K, Salmi TT, Kurppa K, Kaukinen K, Collin P, Reunala T. Dermatitis herpetiformis in children: a long-term follow-up study. Br J Dermatol 2014; 171: 1242–1243.
46. Ermacora E, Prampolini L, Tribbia G, Pezzoli G, Gelmetti C, Cucchi G, et al. Long-term follow-up of dermatitis herpetiformis in children. J Am Acad Dermatol 1986; 15: 24–30.
47. Mooney PD, Hadjivassiliou M, Sanders DS. Coeliac disease. BMJ 2014; 348: g1561.
48. Patinen P, Hietanen J, Malmström M, Reunala T, Savilahti E. Iodine and gliadin challenge on oral mucosa in dermatitis herpetiformis. Acta Derm Venereol 2002; 82: 86–89.
49. Tu H, Parmentier L, Stieger M, Spanou Z, Horn M, Beltraminelli H, et al. Acral purpura as leading clinical manifestation of dermatitis herpetiformis: report of two adult cases with a review of the literature. Dermatology 2013; 227: 1–4.
50. Smith EP, Zone JJ. Dermatitis herpetiformis and linear IgA bullous dermatosis. Dermatol Clin 1993; 11: 511–526.
51. Gawkrodger DJ, Blackwell JN, Gilmour HM, Ridkind EA, Heading RC, Barnetson RS. Dermatitis herpetiformis: diagnosis, diet and demography. Gut 1984:25: 151–157.
52. Savilahti E, Reunala T, Mäki M. Increase of lymphocytes bearing the gamma/delta T cell receptor in the jejunum of patients with dermatitis herpetiformis. Gut 1992; 33: 206–211.
53. Järvinen TT, Kaukinen K, Laurila K, Kyrönpalo S, Rasmussen M, Mäki M, et al. Intraepithelial lymphocytes in celiac disease. Am J Gastroenterol 2003; 98: 1332–1337.
54. Kárpáti S, Kosnai I, Török E, Kovacs JB. Immunoglobulin A deposition in the jejunal mucosa of children with dermatitis herpetiformis. J Invest Dermatol 1988; 91: 336–339.
55. Koskinen O, Collin P, Lindfors K, Laurila K, Mäki M, Kaukinen K. Usefulness of small-bowel mucosal transglutaminase-2 specific IgA deposits in the diagnosis and follow-up of celiac disease. J Clin Gastroenterol 2010; 44: 483–488.
56. Ladinser B, Rossipal E, Pittschieler K. Endomysium antibodies in coeliac disease: an impoved method. Gut 1994; 35: 776–778.
57. Dieterich W, Laag E, Bruckner-Tuderman L, Reunala T, Karpati S, Zagoni T, et al. Antibodies to tissue transglutaminase as serologic markers in patients with dermatitis herpetiformis. J Invest Dermatol 1999; 113: 133–136.
58. Jaskowski TD, Hamblin T, Wilson AR, Hill HR, Book LS, Meyer LJ, et al. IgA anti-epidermal transglutaminase antibodies in dermatitis herpetiformis and pediatric celiac disease. J Invest Dermatol 2009; 129: 2728–2730.
59. Borroni G, Biagi F, Ciocca O, Vassallo C, Carugno A, Cananzi R, et al. IgA anti-epidermal transglutaminase autoantibodies: a sensible and sensitive marker for diagnosis of dermatitis herpetiformis in adult patients. J Eur Acad Dermatol Venereol 2013; 27: 836–841.
60. Hardman CM, Garioch JJ, Leonard JN, Thomas HJ, Walker MM, Lortan JE, et al. Absence of toxicity of oats in patients with dermatitis herpetiformis. N Engl J Med 1997; 337: 1884–1887.
61. Reunala T, Collin P, Holm K, Pikkarainen P, Miettinen A, Vuolteenaho N, et al. Tolerance to oats in dermatitis herpetiformis. Gut 1998; 43: 490–493.
62. Hervonen K, Alakoski A, Salmi TT, Helakorpi S, Kautiainen H, Kaukinen K, et al. Reduced mortality in dermatitis herpetiformis: a population-based study of 476 patients. Br J Dermatol 2012; 167: 1331–1337.
63. Rubio-Tabia A, Murray JA. Classification and management of refractory celiac disease. Gut 2010; 59: 547–557.
64. Bardella MT, Fredella C, Trovato C, Ermacora E, Cavalli R, Saladino V, et al. Long-term remission in patients with dermatitis herpetiformis on a normal diet. Br J Dermatol 2003; 149: 968–971.
65. Paek SY, Steinberg SM, Katz SI. Remission in dermatitis herpetiformis: a cohort study. Arch Dermatol 2011; 147: 301–305.
66. Tio M, Cox MR, Eslick GD. Meta-analysis: coeliac disease and the risk of all-cause mortality, any malignancy and lymphoid malignancy. Aliment Pharmacol Ther 2012; 35: 540–551.
67. Lewis NR, Logan RF, Hubbard RB, West J. No increase in risk of fracture, malignancy or mortality in dermatitis herpetiformis: a cohort study. Aliment Pharmacol Ther 2008; 27: 1140–1147.
68. Lewis HM, Reunala TL, Garioch JJ, Leonard JN, Fry JS, Collin P, et al. Protective effect of gluten-free diet against development of lymphoma in dermatitis herpetiformis. Br J Dermatol 1996; 135: 363–367.
69. Hervonen K, Vornanen M, Kautiainen H, Collin P, Reunala T. Lymphoma in patients with dermatitis herpetiformis and their first-degree relatives. Br J Dermatol 2005; 152: 82–86.
70. Grainge MJ, West J, Solaymani-Dodaran M, Card TR, Logan RF. The long-term risk of malignancy following a diagnosis of coeliac disease or dermatitis herpetiformis: a cohort study. Aliment Pharmacol Ther 2012; 35: 730–739.
71. West J, Fleming KM, Tata LJ, Card TR, Crooks CJ. Incidence and prevalence of celiac disease and dermatitis herpetiformis in the UK over two decades: population-based study. Am J Gastroenterol 2014; 109: 757–768.
72. Smith JB, Tulloch JE, Meyer LJ, Zone JJ. The incidence and prevalence of dermatitis herpetiformis in Utah. Arch Dermatol 1992; 128: 1608–1610.
73. Clarindo MV, Possebon AT, Soligo EM, Uyeda H, Ruaro RT, Empinotti JC. Dermatitis herpetiformis: pathophysiology, clinical presentation, diagnosis and treatment. An Bras Dermatol 2014; 89: 865–875.
74. Ohata C, Ishii N, Hamada T, Shimomura Y, Niizeki H, Dainichi T, et al. Distinct characteristics in Japanese dermatitis herpetiformis: a review of all 91 Japanese patients over the last 35 years. Clin Dev Immunol 2012: 562168.
75. Zhang F, Yang B, Lin Y, Chen S, Zhou G, Wang G, et al. Dermatitis herpetiformis in China: a report of 22 cases. J Eur Acad Dermatol Venereol 2012; 26: 903–907.
76. Hall RP, Clark RE, Ward FE. Dermatitis herpetiformis in two American blacks: HLA type and clinical characteristics. J Am Acad Dermatol 1990; 22: 436–439.
77. Collin P, Huhtala H, Virta L, Kekkonen L, Reunala T. Diagnosis of celiac disease in clinical practice: physician's alertness to the condition essential. J Clin Gastroenterol 2007; 41: 152–156.
78. Fasano A, Catassi C. Clinical practice. Celiac disease. N Engl J Med 2012; 367: 2419–2426.
79. Salmi TT, Hervonen K, Kurppa K, Collin P, Kaukinen K, Reunala T. Coeliac disease evolving into dermatitis herpetiformis in patients adhering to normal or gluten-free diet. Scand J Gastroenterol 2015; 50: 387–392.
80. Aine L, Mäki M, Reunala T. Coeliac-type dental enamel defects in patients with dermatitis herpetiformis. Acta Derm Venereol 1992; 72: 25–27.
81. Reunala T. Dermatitis herpetiformis: coeliac disease of the skin. Ann Med 1998; 30: 416–418.