

An Exception Within the Group of Autoimmune Blistering Diseases: Dermatitis Herpetiformis, the Gluten-Sensitive Dermopathy

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KEYWORDS

- Dermatitis herpetiformis • Gluten sensitivity • IgA precipitate
- Transglutaminase autoimmunity

Dermatitis herpetiformis (DH) is special among the classic autoimmune blistering skin diseases when considering its dermatologic symptoms, associated diseases, and pathomechanisms. The granular IgA precipitates present at the tips of the papillary dermis of the patients, an observation made by van der Meer in 1969 in Groningen,¹ proved to be pathognomonic for the disease. Contrary to other autoimmune blistering diseases, whereby tissue-bound and serum autoantibodies bind the same target molecule in the skin, no circulating IgA has been detected in DH sera reacting with normal tissue components of the sub-basal membrane zone or any other connective tissue particles within the healthy papillary dermis. The antigenicity of skin-bound IgA remained unknown for 3 decades, until 2002, when epidermal transglutaminase (TG3) was identified by the author's research group as its main antigen, an enzyme never detected in that area of the normal skin.² It has also been confirmed that DH patients have serum IgA autoantibodies to TG3. This article focuses on the clinical data concerning DH, rather than its detailed pathomechanism.

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SKIN SYMPTOMS AND DISEASE MANAGEMENT

DH can start at any age; rarely, it can be present in toddlers or in the very elderly, but the mean onset is generally in young adulthood or middle age. It is a chronic, very pruritic skin disease, characterized by 1- to 3-mm large papules, seropapules, vesicles, crusted erosions, and excoriations (**Fig. 1**). Rarely, larger blisters can also develop. The lesions heal with hypopigmentation or hyperpigmentation. In young patients, urticarial plaques might be the predominant skin symptoms (**Fig. 2**). The severe pruritus and scratching can result in extended lichenification (**Fig. 3**). In the majority of cases DH is a polymorphic skin disease, and only rarely presents as a bullous dermatosis.³⁻⁵ Specific symptoms, not always present, are purpura on the fingers and toes, which alone may focus attention on the diagnosis (**Fig. 4**).

DH has a typical distribution of the skin symptoms; these are, in order of frequency (strongly supported by the author's personal observations): 1, elbows and knees; 2, buttock; 3, shoulders, middle line of the back, and scapula; 4, scalp; 5 (rarely), purpura on the fingers and toes (see **Figs 1-4**).^{3,4}

Although severe DH is almost a continuous disease with some fluctuation in the severity and itch, it might also present as a relatively mild lichenification, with alternating



Fig. 1. Grouped polymorphic eruption above the elbows in dermatitis herpetiformis. Red arrow indicates the best site for a lesional biopsy for routine histology, and the blue arrow the best site for a perilesional biopsy for direct immunofluorescence.

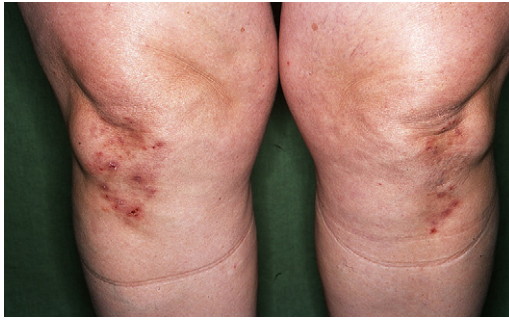


Fig. 2. Note the symmetric crusted erosions above the knees.

remissions and relapses: a few patients have skin disease only for a few days between long symptom-free periods. The symptom-free periods may only be in the warmer months when it is sunny. By contrast, in some DH patients sweating may induce disease progression in hot weather. There are patients who, without a gluten-free diet or other medication, remain free of skin symptoms for at least 6 months, in so-called spontaneous remission.⁶ One must bear in mind that the underlying celiac disease (CD) and the possibility for further secondary disease development will persist. Spontaneous remissions are rare, but might develop and may last for years, life-long, or just for a short



Fig. 3. Skin along the gluteal cleft is commonly involved in dermatitis herpetiformis: eczema-like chronic, livid erythema and mild lichenification without vesicles and crusts.



Fig. 4. Purpura on the fingers in dermatitis herpetiformis, a rare but specific sign.

time. Pruritus can precede the skin symptoms and rarely also challenge the otherwise symptom-free time of the patients.

Untreated DH can be a life-long disease with variable severity. Associated uncontrolled diabetes, autoimmune diseases, underlying tumors, and iodine challenges might induce permanent very severe skin symptoms. During pregnancy the disease may improve, but in some cases it is worse. The reason for iodine sensitivity of DH patients is unknown, but is common. A possible relationship with thyroid diseases also remains unraveled. The sensitivity can be proved by patch testing, but iodine-containing drugs also flare up the disease. One of the author's young patients underwent a thyrotoxic crisis together with a severe DH flare-up after one short visit to a salt cave suggested for her as a "natural therapy."

DIAGNOSIS CONFIRMATION

Diagnosis should be made by histologic and direct immunofluorescence (IF) analysis of the skin. The former sample should be taken from the lesional skin, the latter from perilesional, close to symptom-free tissue. On urticaria like lesions the presence of IgA, C3, and eventually IgM and IgG vasculitis is commonly associated with granular IgA and C3 staining of the dermis.⁷ In the serum the presence of circulating IgA endomysial antibodies (EMA) or tissue transglutaminase (TG2) autoantibodies should be checked by indirect IF and by enzyme-linked immunosorbent assay (ELISA), respectively. The sensitivity and specificity of these tests are very high for CD, between or above 90% to 95%, whereas for DH it is less: about 75% to 90%. Serum samples from autoimmune diseases as well as sera from normal individuals treated by heat or pH shift might show nonspecific TG2 reactivity.^{8,9} The TG3 antibodies (ELISA) are also gluten dependent and slowly disappear under gluten-free diet (GFD), but later than the EMA or TG2. TG3 antibodies are more commonly present in DH than in CD patients, and in DH patients they have higher avidity and affinity.^{2,10,11} An upper gastro-duodenoscopy and a small bowel histology is strongly advised to visualize and document the upper part of the gastrointestinal and to analyze the initial jejunal histology, due to its strong association with CD.^{3,4}

Enteropathy and Malabsorption

The majority (75%–90%) of DH patients have an associated small bowel disease, a latent or silent CD. It persists and without treatment leads to malabsorption, which may induce secondary diseases: microcytic or macrocytic anemia due to iron, folate, or B12 deficiency, caries, alopecia due to zinc deficiency (see also dental problems), and early or very severe osteoporosis. Weight loss but also weight gain is possible,

with unfavorable body mass index (BMI). Most patients have no typical gastrointestinal symptoms, but symptoms may include any of the following: diarrhea, constipation, bloating, abdominal discomfort or pain, and secondary lactose intolerance. Similarly to other gluten-sensitive enteropathy (GSE) patients, in DH patients with severe insulin-dependent diabetes, because of malabsorption the diabetes will be controlled only under a combined, strict GFD and diabetic diet. In childhood short stature, delayed development and puberty, or a high BMI might indicate the underlying GSE. Dental enamel defects, and mineralization disturbances of permanent and deciduous teeth may be evident. Half of DH patients have celiac-type permanent-tooth enamel defects, milder than those described for severe celiac disease, and secondary severe caries or early tooth loss is also more common.^{3-6,12,13} Although the skin can go into spontaneous remission,³⁻⁶ the underlying CD and the possibility for further secondary disease development persist.

OTHER ASSOCIATED DISEASES

Autoimmune Diseases

Due to the high frequency of associated autoimmune diseases, the author recommends screening and following the patients for autoimmune thyroiditis, type 1 diabetes (anti-islet AB), lupus erythematosus, Sjögren syndrome, vitiligo, primary biliary cirrhosis, pernicious anemia, and alopecia areata.¹⁴ Screening the family for DH, CD, and autoimmune diseases is suggested.

Neurologic Associations

Gluten sensitivity presenting with ataxia (gluten ataxia) is approximately one-quarter of the sporadic idiopathic cerebellar ataxia, the single most common cause of the disease.¹⁵

Rarely, gluten-induced axonal and demyelinating neuropathy, and myopathies have also been identified. In the central nervous system epilepsy, myoclonus, dementia, and multifocal leukoencephalopathy were detected in patients with GSE.¹⁶

Tumors

Long-lasting GSE is significantly more commonly associated with jejunal adenocarcinomas and lymphomas. Enteropathy-associated T-cell lymphomas encompass about 1% of the non-Hodgkin lymphomas, and these usually have a very poor prognosis. Other lymphomas, such as B or cutaneous lymphomas, have also been described. The relative risk of any lymphoma in untreated CD and DH is significantly enhanced, while a risk reduction is well documented under strict GFD.¹⁷⁻¹⁹

Other Disease Associations

Iodine sensitivity (cause is unknown), selective immunoglobulin A deficiency (more common also in CD), Down syndrome, and Turner syndrome have been reported.^{3,4}

GENETIC BACKGROUND AND FAMILY SCREENING

There is no difference between CD and DH patients: HLA could be a nonspecific diagnostic marker for both diseases. Ninety-five percent of DH patients are HLA DQ2 positive with DQA1*0501/DQB1*0201; DQA1*0501/DQB1*0202; DRB1*03/DRB1*05/07 alleles, while 5% of them are HLA-DQ8 positive and carry the DQA1*0301/DQB1*0302, DRB1*4 alleles.^{6,20} Asiatic races lack this HLA pattern, therefore DH and CD are rare and in these patients because this association cannot be detected.

There are a few patients reported from Japan with only epidermal but not with tissue TG autoantibodies.²¹

GSE is more common among the family members of DH patients. Therefore it is strongly suggested to screen the first-degree and second-degree relatives for the presence of tissue TG antibodies (or EMA) to identify latent or silent forms of gluten sensitivity.²⁰

TREATMENT

A strict, long-lasting (according to current knowledge life-long) GFD is the most advisable treatment for DH patients, which is healthy and seems to prevent the development of lymphomas and diseases associated with gluten-induced enteropathy and malabsorption.^{3–5} The GFD should be maintained in DH patients who become free from skin symptoms while on the diet. Also, patients with spontaneous regression need to take the diet because the GSE persists. The skin symptoms rarely disappear even under a strict GFD within a few weeks, and commonly persist for months or for a year. Gastroenterological and dietician consultations are necessary.

A secondary lactose intolerance might accompany the GSE, and in these cases a temporary lactose-gluten-free diet combination is advised.

In severe or insulin-resistant diabetic patients, only the combination of low-carbohydrate diet and GFD seems to be effective, because severe diabetes can be only stabilized if the enteropathy is reversed and the absorption is normalized. Low iodine intake like iodine-free salt, avoidance of fruit of mer (eg, shellfish), and GFD might be necessary for DH cases with iodine sensitivity. A dose of 50 to 150 mg dapsone per day could be a quick help for severe skin symptoms, because all DH patients react well to this medication. Dapsone, however, has no effect on the underlying GSE, nor on the secondary malabsorption and the enhanced risk of lymphomas. Dapsone may induce peripheral neuropathy and in glucose-6-phosphate-deficient patients, hemolysis. Rarely, it may be toxic to the bone marrow or might induce drug hypersensitivity syndrome. A high-dose vitamin C supplementation is suggested with dapsone to reduce methemoglobinemia.¹² In the first months of dapsone treatment blood counts, including reticulocyte counts, and bilirubin and liver enzyme values should be repeatedly determined. For more detailed information on dapsone, see the article elsewhere in this issue. Sunshine or ultraviolet A are beneficial for the skin symptoms and may keep mild cases in good condition, but cannot be considered as a sole treatment (personal observation by the author). In GFD refractory cases, patients should be screened for underlying diseases, particularly for tumors.¹³

DISEASE PATHOGENESIS: CLINICAL RELEVANCE

When and how the tolerance to alimentary gluten is lost in DH patients is not known exactly. The presence of IgA antibodies against gliadin and TG2 in the circulation prove the activity of enteropathy or a too short or improper diet adherence, therefore they should be regularly monitored. The major difference between CD and DH is the presence of skin symptoms, and the IgA precipitates in the papillary skin that may persist for years even in symptom-free patients. Furthermore, only in DH skin a pathologic epidermal TG3 is also deposited, colocalizing there with the granular IgA staining.^{2,22,23} TG3-IgA immune complexes can be also detected in the small vessels of the papillary dermis.⁷ These data show that DH can be considered as a gluten-induced immune-complex disease of the skin developing in some patients suffering from milder CD. The presence of cutaneous immune complexes also explains the purpura on the fingers and toes. The gluten-induced skin and small bowel pathology develops

Table 1**Dermatitis herpetiformis is a multidisciplinary disease: a guideline summary for patient care**

Skin	Skin histology (lesional) and direct IF for papillary IgA (perilesional)
Serum	Detect IgA to TG2 (ELISA) or endomysium (EMA, indirect IF), and TG3 (ELISA). Total serum IgA level
Gut	Gastroenterology consult: endoscopy/small bowel biopsy for H&E and IgA
Family	Screen the first- and second-degree relatives for gluten-sensitive diseases by IgA-TG2 antibody test (ELISA)
Associations	Autoimmune diseases, osteoporosis, enamel deficiencies, and neurologic symptoms. Correct the symptoms of malabsorption
Diet	Dietician consult; healthy, strict GFD; control the patients following the titer of serum IgA to TG2 or EMA. SLOW improvement! (months). Relapses indicate diet failure or tumor
Follow-up	Regular checkup for associated diseases. Be aware of the rare possibility of lymphoma development in patients under gluten-containing diet

Abbreviations: ELISA, enzyme-linked immunosorbent assay; EMA, endomysial antibodies; GFD, gluten-free diet; H&E, hematoxylin and eosin; IF, immunofluorescence; TG, transglutaminase.

only in genetically determined individuals who carry specific HLADQ8 or DQ2 haplotypes (see earlier discussion).

Although an interesting animal model of a gluten-sensitive skin disease was presented in HLA-DQ8 transgenic NOD mice, and this animal model demonstrated well the role of HLA molecules in gluten-induced immunologic reactions, a DH similar TG3 autoimmunity could not be reproduced.²⁴ It is likely that there are additional genetic or environmental factors that might contribute to gluten-dependent TG autoimmunity.^{25,26}

MANAGEMENT OF DH

Management of DH will be discussed in more detail in the next issue, but a summary guideline is given in **Table 1**.

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