**Review Article**

# A Review on Dermatitis Herpetiformis

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**ABSTRACT**

Dermatitis herpetiformis (DH), or Duhring's disease, is a chronic blistering skin condition, characterised by blisters filled with a watery fluid. Despite its name, DH is neither related to nor caused by herpes virus: the name means that it is a skin inflammation having an appearance similar to herpes.

DH was first described by Dr. Louis Adolphus Duhring in 1884. A connection between DH and gluten intolerance (celiac disease) was recognised in 1967, although the exact causal mechanism is not known.

The age of onset is usually about 15-40, but DH can also affect children and the elderly. Men and women are equally affected. Estimates of DH prevalence vary from 1 in 400 to 1 in 10000. It is most common in patients of northern European ancestry, and is associated with the HLA-DQ2haplotype along with celiac disease and gluten sensitivity.

Dermatitis herpetiformis sufferers usually experience their rashes in the same location every time. The rash might be continuous, or it might come and go.

Before the actual dermatitis herpetiformis rash breaks out, your skin may itch in that location, or it might feel as if it's burning. The rash itself usually includes reddened skin plus multiple small, pimple-like bumps, which contain a clear liquid.

The dermatitis herpetiformis bumps usually take several days to heal (during which time new bumps usually appear nearby), and once healed, will leave behind small purple marks that last for weeks or months. People with long-standing dermatitis herpetiformis usually have continuously reddened skin where their rash occurs.

Dermatitis herpetiformis, an itchy, stinging, blistering skin rash, occurs when your skin reacts to gluten antibodies circulating in your system. Some people call dermatitis herpetiformis a "gluten rash" or a "celiac disease rash" because it occurs in conjunction with celiac disease.

The purpose of present review is to summarize pathophysiology, clinical manifestations, diagnosis and treatment of dermatitis herpetiformis.

**Keywords:** Clinical manifestations, diagnosis, Introduction, pathophysiology, treatment for dermatitis herpetiformis

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## INTRODUCTION

Dermatitis herpetiformis (DH), described over 100 years ago, is a life-long blistering skin disease that can appear at any age. Dapsone controls the rash effectively and has been used for over 50 years in the treatment of DH. Major landmark in their search of DH was 30 years ago the discovery of granular IgA deposits in the upper papillary dermis[1], and further differentiation of an autoimmune disorder termed now as linear IgA disease from DH [2-4]. The finding of mostly asymptomatic gluten-sensitive enteropathy, that is, celiac disease [5], and the observation that in all patients with DH the rash also responds to gluten free diet (GFD) treatment [6-7], have had an important impact on our understanding of DH as a part of the spectrum of celiac disease. [8-9]. An immunogenetic link, HLA-DQ2, joins DH and celiac disease also tightly together [10-11]. A novel hypothesis of autoimmune pathogenesis of celiac disease consists of deamidation of wheat gliadin by tissue transglutaminase, binding to HLA-DQ2 and its recognition by gut T cells with

subsequent production of epithelial damaging cytokines, matrix degrading enzymes, and also IgA autoantibodies against tissue
trans-glutaminase [12–14]. In DH, a clinically silent but immunologically active celiac, disease in the gut could produce IgA antibodies cross reacting with the connective tissue in the skin, a hypothesis presented already for 30 years ago. [15] In contrast to the major progress made in the characterization of the target antigens in various autoimmune blistering disorders, such as pemphigus, pemphigoid, and linear IgA disease, one of the main goals in the research on Dis still to resolve the enigma of IgA deposition in the skin, what is the antigen, and does IgA have any role in blister formation.

**PATHOPHYSIOLOGY**

Dermatitis herpetiformis is a disease of the skin caused by the deposition of IgA in the papillary dermis, [16] which triggers an immunologic cascade, resulting in neutrophil recruitment and complement activation. Dermatitis herpetiformis is the result of an immunologic response to chronic stimulation of the gut mucosa by dietary gluten [17].

An underlying genetic predisposition to the development of dermatitis herpetiformis has been demonstrated. Both dermatitis herpetiformis and celiac disease (CD) are associated with an increased expression of HLA-A1, HLA-B8, HLA-DR3, and HLA-DQ2 haplotypes. Environmental factors are also important; monozygotic twins may have dermatitis herpetiformis, celiac disease, and/or gluten-sensitive enteropathy with variable symptomatology.

The leading theory for dermatitis herpetiformis is that a genetic predisposition for gluten sensitivity, coupled with a diet high in gluten, leads to the formation of IgA antibodies to gluten-tissue transglutaminase (t-TG), which is found in the gut. These antibodies cross-react with epidermal transglutaminase (e-TG) [18]. eTG is highly homologous with tTG. Serum from patients with gluten-sensitive enteropathy, with or without skin disease, contains IgA antibodies to both skin and gut types [19].Deposition of IgA and epidermal TG complexes in the papillary dermis cause the lesions of dermatitis herpetiformis.

In patients with gluten-sensitive enteropathy, levels of circulating antibodies to tissue and epidermal transglutaminase have been found to correlate with each other, and both appear to correlate with the extent of enteropathy [20].

Co-localized IgA and eTG deposits have been demonstrated in the papillary dermis in patients with dermatitis herpetiformis and, to lesser extent, in healthy skin of gluten-sensitive enteropathy patients [21].eTG has not been demonstrated in normal papillary dermis, suggesting it is part of the circulating complex that is deposited in the papillary dermis, rather than originating from the papillary dermis.

Cutaneous IgA deposits in dermatitis herpetiformis have been shown to function in vitro as a ligand for neutrophil migration and attachment. Although IgA deposition is pivotal for disease, an increased serum IgA is not necessary for pathogenesis; in fact, case reports describe dermatitis herpetiformis in patients with a partial IgA deficiency [22]. When the disease is active, circulating neutrophils have a higher level of CD11b and an increased ability to bind IgA. The characteristic histologic finding of dermatitis herpetiformis is neutrophil accumulation at the dermoepidermal junction, frequently localizing to the papillary tips of the basement membrane zone.

Collagenase and stromelysin 1 may be induced in basal keratinocytes either by cytokines released from neutrophils or by contact with keratin from damaged basement membrane matrix. Stromelysin 1 may contribute to blister formation.

One study found levels of E-selectin mRNA expression in normal-appearing skin of patients with dermatitis herpetiformis to be 1271 times greater that that of controls [23]. Additionally, the same study observed increased soluble E-selectin, IgA antitissue transglutaminase antibodies, tumor necrosis factor-alpha, and serum interleukin 8 (IL-8) levels in patients with dermatitis herpetiformis, providing further evidence of endothelial cell activation and a systemic inflammatory response as part of the pathogenic mechanism of the disease.

Mild local trauma may also induce the release of cytokines and attract the partially primed or activated neutrophils, which is consistent with the typical location of dermatitis herpetiformis lesions on frequently traumatized areas, such as the knees and elbows.

Deposits of C3 also may be present in a similar pattern at the dermoepidermal junction. The membrane attack complex, C5-C9, also has been identified in perilesional skin, although it may be inactive and not contribute to cell lysis [24].

A recent study showed an increased expression of disintegrin and metalloproteinase (ADAMs) 8, 10, 15, and 17 in lesional skin of patients with dermatitis herpetiformis compared with controls. The high affinity of ADAMs for the basement membrane led the authors to hypothesize a role in blister formation in dermatitis herpetiformis [25].

Hormonal factors may also play a role in the pathogenesis of dermatitis herpetiformis, and reports describe dermatitis herpetiformis induced by treatment with leuprolide acetate, a gonadotropin-releasing hormone analog [26].Androgens have a suppressive effect on immune activity, including decreased autoimmunity, and androgen deficient states may be a potential trigger for dermatitis herpetiformis exacerbation. Exacerbation of dermatitis herpetiformis by oral contraceptives has also been reported.

Apoptosis may contribute to the pathogenesis of epidermal changes in dermatitis herpetiformis, and research demonstrates a markedly increased apoptotic rate within the epidermal compartment in dermatitis herpetiformis [27]. In addition, Bax and Bcl-2 proteins are increased in the dermal perivascular compartment and Fas proteins showed epidermal staining in dermatitis herpetiformis lesions.

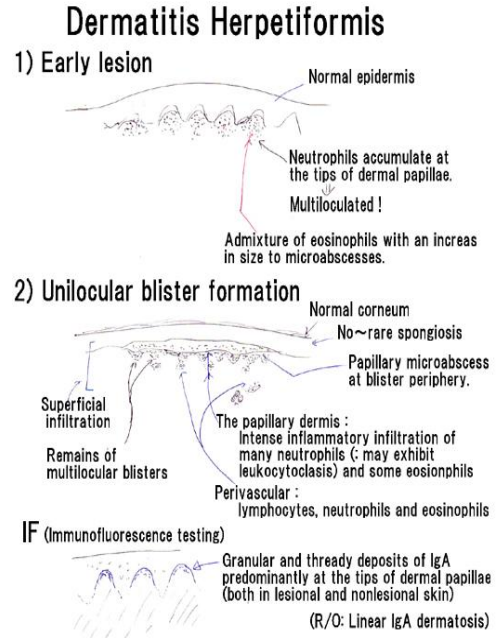
**CLINICAL MANEFASTATIONS [28]:**

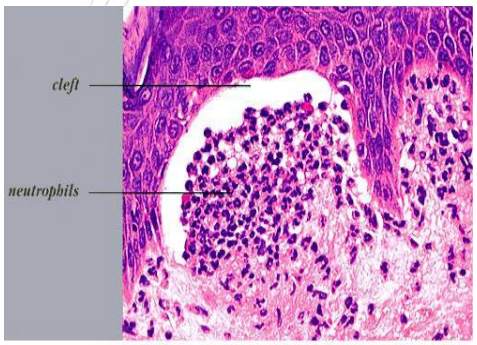
DH is an intensely itchy bullous rash. It characteristically affects extensor surfaces, particularly the scalp, buttocks, elbows and knees. However, lesions can occur on any area of skin.

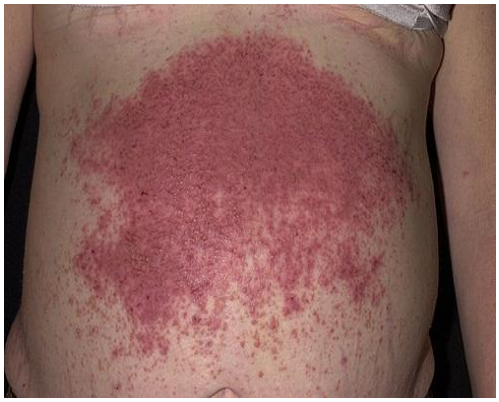
The lesions are papules and blisters, up to 1 cm in diameter, which are extremely itchy. They arise on normal or reddened skin. Burning, stinging and intense pruritus can precede the appearance of new lesions.

The severity can vary from week to week.

Lesions rarely resolve without specific treatment.



There may also be symptoms of coeliac disease.

Investigations [29]

Skin biopsy

This is usually necessary to confirm the diagnosis. The microscopic appearance of DH is characteristic:

The blister is subepidermal.
Inflammatory cells group in the dermal papillae.
Direct immunofluorescence reveals IgA immunoglobulin in dermal papillae.
Blood tests[30]
These may show abnormalities due to gluten enteropathy; for example:

- Mild anaemia
- Folic acid deficiency
- Iron deficiency

Coeliac disease can usually be detected by autoantibody testing:
IgA anti-tissue transglutaminase or IgA endomysial antibodies are highly specific and sensitive for untreated coeliac disease. They are also relevant to DH patients. IgA-epidermal transglutaminase 3 is likely to be the most specific immunocomplex in DH[31-32].
Note that these tests can be falsely negative if the patient:
Is already on a gluten-free diet.
Has selective IgA deficiency, which is more common in coeliac disease patients than in the general population.Therefore it may be advisable to measure serum IgA levels to identify cases of IgA deficiency; or to test for IgG endomysial antibodies or IgG-tissue transglutaminase levels[33].

- A small proportion of patients with coeliac disease are tissue transglutaminase antibody-negative (0.4% in one series) and some are endomysial antibody-negative[34-35].Detection rates may be improved by combining both test[36]

Other possible investigations

- A novel serological assay using deamidated gliadin-analogous fusion peptides (GAF3X) showed high diagnostic sensitivity in DH patients with coeliac disease[37]
- Histocompatibility antigen typing: HLA-DR-DQ genotyping is expensive but techniques are being developed to make this more cost-effective in the diagnosis of coeliac disease[37].
- Small bowel biopsy (may appear normal if on a gluten-free diet, or due to skip lesions in the bowel)[38]

**DIAGNOSIS** [39-40]

- Erythema multiforme
- Herpes gestationis
- Linear IgA bullous dermatosis[42]
- Eczema
- Neurotic excoriations
- Papular urticaria
- Scabies
- Transient acantholytic dermatosis Management[41]

A strict gluten-free diet is important in order to:
Reduce the medication needed to control skin symptoms. It may be possible to discontinue dapsone when on a gluten-free diet for sufficient time.
Reduce the associated enteropathy, improve nutrition and bone density.
Possibly, reduce the risk of developing other autoimmune conditions and intestinal lymphoma.
**TREATMENT:**
Dapsone is first choice and reduces the itch within a day or two. Cautions and blood monitoring requirements should be noted.
For those intolerant or allergic to dapsone, the following may be used:
Sulfapyridine
Ultrapotent topical steroids
Systemic steroids
Ciclosporin, colchicines, heparin, tetracycline and nicotinamide are other treatments that have been tried with some benefit.
Avoid drugs which exacerbate DH. These may include NSAIDs (though ibuprofen seems safe) and iodides.
Complications and associated conditions [43]
Virtually all DH patients have coeliac disease, although it may be unnoticed [44].
Complications may arise from problems associated with coeliac disease. These include:
Neurological problems - ataxia (gluten ataxia), peripheral neuropathy, epilepsy
Cardiac problems- pericarditis and cardio-myopathy
Osteoporosis and poor dental enamel
Reduced fertility and recurrent miscarriage
Abnormal LFTs
Aphthous ulcers
Possibly, other autoimmune conditions: thyroid disease, insulin-dependent diabetes mellitus, autoimmune hepatitis, Addison's disease, atrophic gastritis and alopecia [45]

Non-Hodgkin's lymphoma - affects <1% of DH patients
There may be a slightly increased risk of other cancers [46]
Some of these problems may be improved by a gluten-free diet.

**MANAGEMENT:**

- o Gluten-Free Diet
- o Dapsone
- o Alternative Temporary Therapies

Like celiac disease, DH is a chronic autoimmune condition triggered by the consumption of gluten, and can only be treated through a lifelong gluten-free diet [47-48]Skin contact with gluten containing foods and products has not been shown to cause DH outbreaks.
While a strict gluten-free diet will eventually eliminate both granular IgA deposits in the skin and the outward signs and symptoms of DH - it may take several weeks, even months, for skin to completely heal.
As a result, Dapsone oral medication is often prescribed to help eliminate the uncomfortable DH symptoms until the gluten-free diet takes full therapeutic effect.
Dapsone is used to suppress both symptoms and additional outbreaks, but cannot be used as an alternative treatment to the gluten-free diet.
In general, itching and new lesions will begin to subside within 48-72 hours of starting Dapsone.
While well tolerated in 90% of patients, [49] Dapsone does possess a variety of serious side effects. As a result, this therapy must be properly prescribed and vigilantly monitored by a doctor.
Symptoms like nausea and upset stomach are often reported, so taking Dapsone with food is recommended for those who experience these problems. Flu-like symptoms, fatigue and sensitivity to light are also common problems. More serious side effects include anemia, headaches, kidney damage, and peripheral neuropathy.
As a result, your doctor will most likely prescribe Dapsone in smaller doses when first starting out, and then increase the amount taken overtime.

Remission
DH has been known, in some cases, to go into remission, [50] whether or not patients are adhering
to a gluten-free diet. Research indicates that DH remission is both spontaneous and only experienced in a very small percentage of patients (about 12%).
[51] However, patients diagnosed with DH should NOT abandon a gluten-free diet at anytime, regardless of any apparent remission.

**CONCLUSION**

DH is a chronic waxing and waning cutaneous manifestation of CD associated with gluten sensitivity. It presents on extensor surfaces with intensely pruritic papulovesicles, with excoriations and crusting and a corresponding neutrophilic infiltration of dermal papillae and granular IgA deposits on direct immunofluorescence. Serologic test for eTG provides the highest sensitivity and good specificity when compared to tTG and anti-endomysium antibodies, although biopsy is still needed for definitive diagnosis. Generally, DH has a good prognosis with combined initial therapy of GFD and dapsone, usually progressing to dose reduction after a few months. Close monitoring for dapsone toxicities and autoimmune conditions associated with DH is indicated. An inter-professional team involving a dermatologist and dietician, as well as potentially a gastroenterologist and rheumatologist is ideal.

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