# Dermatitis herpetiformis

## Part I. Epidemiology, pathogenesis, and clinical presentation

Diana Bolotin, MD, PhD, and Vesna Petronic-Rosic, MD, MSc
*Chicago, Illinois*

Dermatitis herpetiformis (DH) is an autoimmune disease that is linked to gluten sensitivity and has a clear relationship to celiac disease. Both conditions are mediated by the IgA class of autoantibodies and the diagnosis of DH is dependent on detection of granular deposits of IgA in the skin. There is an underlying genetic predisposition to the development of DH but environmental factors are also important. Typically, young adults present with excoriations only, as the severe pruritus effectively destroys any primary lesions. Based upon our experience with DH and a comprehensive literature review, we provide an update of DH epidemiology, pathophysiology, and clinical presentation. (J Am Acad Dermatol 2011;64:1017-24.)

***Key words:*** autoimmune bullous disease; blister; celiac disease; dermatitis herpetiformis; gliadin; gluten-sensitive enteropathy; human leukocyte antigen—DQ2; human leukocyte antigen—DQ8; transglutaminase.

Dermatitis herpetiformis (DH) was initially described by Louis Duhring in 1884.[1] Recent progress in understanding the pathogenesis of this disease has led to improved treatment. Linking gluten sensitivity to DH led to the adoption of the gluten-free diet as a key component of treatment. DH is an autoimmune disease, a finding that is strongly supported by landmark studies revealing the granular deposition of immunoglobulin in the skin.[2,3] The immunologic basis of DH shows a clear relationship to celiac disease (CD). Both conditions are mediated by the immunoglobulin A (IgA) class of autoantibodies. Tissue transglutaminase (tTG) is the major autoantigen targeted in CD, and epidermal transglutaminase (eTG) is the autoantigen most closely linked to DH. IgA anti-eTG is the most sensitive serologic marker for DH. Many details about the immunologic basis and pathogenesis of DH are still emerging in the literature. Part I of this series will focus on the epidemiology, pathophysiology, and presentation of DH.

**CAPSULE SUMMARY**

- Dermatitis herpetiformis is a multifactorial disease with strong genetic and autoimmune influences
- All patients with dermatitis herpetiformis have gluten intolerance
- Hypothyroidism is the most common autoimmune condition associated with dermatitis herpetiformis

## EPIDEMIOLOGY

### Key points

- **Dermatitis herpetiformis is most prevalent in patients of Northern European descent**
- **Men have a higher prevalence of dermatitis herpetiformis than women**

A number of epidemiologic studies have elucidated the incidence and prevalence of DH. Most of these studies focus on individuals of Northern European heritage, both in Europe and the United States, in whom this disorder is most common. Studies in these populations performed in the late 1970s to early 1980s report a prevalence range from 1.2 to 39.2 per 100,000 people and an incidence range of 0.4 to 2.6 per 100,000 people per year.[4-8] In addition, a population-based study performed in Utah in 1992 documented a prevalence of 11.2 per 100,000 people and an incidence of 0.98 per 100,000 people per year, and both rates are comparable to studies performed in Europe.[8] Because the population of Utah has a high proportion of people with Northern European ancestry, the concordance of this finding with previous studies is not surprising. The reported incidence of DH is also comparable to that reported for other immunobullous diseases, such as bullous pemphigoid and pemphigus vulgaris.[9]

A few studies in Asian populations have shown that DH is very rare among this group and even rarer among African Americans. In fact, so few cases have been described that no larger population-based studies have been reported in these ethnic groups.[10,11] Although DH was not considered a familial condition for many years, that view is now changing because a number of genetic studies and epidemiologic reports have recorded familial cases of DH.[12-14] The prevalence and presentation of DH varies geographically. Northern Europe appears to have the largest number of cases overall, but DH with onset in childhood tends to be more common in Mediterranean countries.[15] This may be related to differences in diet or to a genetic predisposition within these populations.

Males have a higher prevalence of DH.[8] In fact, most population-based studies to date have found male to female ratios ranging from 1.5:1 to 2:1.[8] Interestingly, the opposite is true of the prevalence of CD, with female to male ratios ranging from 2:1 to 4:1.[16,17]

Most patients report the onset of symptoms during the warmer months of the year, any time from spring to late summer.[8] Whether this finding is related to the pathophysiology of the condition is unclear. The time of onset of DH is variable, with the most common age range at presentation being 30 to 40 years old; however, the age at diagnosis varies widely from infancy to the geriatric population.[8,15] Childhood DH is rare, and for many years it was grouped with the diagnosis of linear IgA bullous dermatosis of childhood. Therefore, the true prevalence of childhood DH is not well characterized.

## PATHOGENESIS

### Key points

- **A strong genetic predisposition to dermatitis herpetiformis exists among affected families**
- **Human leukocyte antigen–DQ2 and human leukocyte antigen–DQ8 are associated with**

From the Section of Dermatology, The University of Chicago.
Funding sources: None.
Reprint requests: Vesna Petronic-Rosic, MD, MSc, Section of Dermatology, The University of Chicago, 5841 S Maryland Ave, MC5067, Chicago, IL 60637. E-mail: vrosic@medicine.bsd.uchicago.edu.
0190-9622/$36.00

**dermatitis herpetiformis in humans and animal models**

- **Gliadin modified by tissue transglutaminase, the major autoantigen in celiac disease, has a higher affinity for antigen-presenting cells expressing human leukocyte antigen−DQ2**
- **Epidermal transglutaminase appears to be the dominant autoantigen in dermatitis herpetiformis**

The pathophysiology of DH likely involves a complex interplay between autoimmune factors, such as human leukocyte antigen (HLA) predisposition, genetics, and environment. Both gluten sensitivity and DH have a strong genetic component, as revealed by a number of case studies in monozygotic twins. More recently, a prospective study of six monozygotic twin pairs revealed a concordance rate of 0.91, a figure much higher than expected for a complex inheritance trait.[18] These studies, while suggestive, are confounded by small sample size, which limits statistical analysis. In addition to twin studies, a population-based analysis of first-degree relatives revealed that the incidence of CD and DH among first-degree relatives was almost 15 times higher than that in the general population.[19] Up to 18% of patients with DH in this study had a first-degree relative with either DH or gluten intolerance.[19] These findings emphasize that genetic factors likely play an important role in the pathogenesis of DH, an observation that is both intriguing and clinically useful in counseling patients and families with this condition.

One gene that has been found to be genetically linked to CD and weakly to DH in some populations is myosin IXB (MYO9B) on chromosome 9p13.[20-23] This linkage was not present in every population studied, but the possible role of MYO9B in the pathogenesis of CD and DH suggested by these findings is interesting.[24] MYO9B functions in cell signaling and regulation of the actin cytoskeleton dynamics, thereby regulating cell integrity and the permeability of the gut barrier. It has been suggested that increased permeability of the intestine may allow more gluten penetration, and that a subsequent immunologic triggering results in clinically overt CD or DH. Additional genetic and biochemical studies are needed to evaluate this hypothesis.

Two recent genome-wide association studies of CD found an association between CD and genomic variants at the interleukin-2 (IL-2) to IL-21 region, regulator of G-protein signaling 1 (RGS1), IL-12A, IL-18 receptor protein (IL18RAP), cluster of chemokine receptor 3 (CCR3), T cell activation GTPase-activating protein (TAGAP), and SH2B3 protein.[25,26] The functional significance of these genes in CD development and any relationship to DH is unclear.

Predisposition to developing DH has also been reported with respect to HLA loci. A close association between DH and HLA-DQ2 or HLA-DQ8 has been noted in a number of studies.[27,28] In one study comparing 50 patients with DH to 290 healthy controls, 86% of the affected patients carried the HLA-DQ2 allele (compared to 25% of the controls), with the majority of the remaining cases associated with HLA-DQ8.[27] Murine models have confirmed the association, with HLA-DQ8$^+$ transgenic mice developing gluten sensitivity similarly to humans.[29] Of interest, mice engineered with an HLA-DQ8$^+$ transgene alone lacked skin manifestations of gluten sensitivity.[28,29] However, a murine model that combined HLA-DQ8 expression in a nonobese diabetic (NOD) mouse model mouse background (a classic murine model of autoimmunity) with a trigger for inflammation resulted in recapitulation of DH skin findings upon a gluten challenge.[28] The mice with a genetic predisposition, a tendency for autoimmunity, and an inflammatory trigger developed clinical, histologic, and immunofluorescence evidence of DH, again confirming that complex gene−environment interaction is probably necessary for development of this condition.[28]

The immunologic basis for development of DH is intimately linked with the pathogenesis of gluten intolerance and CD.[14,15,30,31] tTG is the major autoantigen for CD.[32] The tTG protein is a primarily cytoplasmic, calcium-dependent enzyme that catalyzes crosslinks between glutamine and lysine protein residues.[33] Its biologic functions vary widely, from stabilization of the cytoskeleton and extracellular matrix via protein polymerization, the regulation of cell matrix adhesion and cell migration, and proliferation via the effects on integrin-dependent cell signaling.[14,33,34] tTG is ubiquitously expressed in many tissues. In the skin, it is found in basal keratinocytes and dermal capillaries.[35] In the small bowel, tTG expression colocalizes with IgA deposition seen in CD.

Transglutaminase plays a central role in the pathogenesis of gluten intolerance. First, tTG modifies the alcohol-soluble fraction of gluten known as gliadin into an efficient autoantigen with stronger affinity for HLA-DQ2 on antigen-presenting cells, resulting in T cell stimulation and the ensuing inflammatory response.[30,33,34,36,37] In addition, protein−protein cross-linking results in tTG−gliadin complexes that also generate a robust autoantibody response.[33,34,36,37] The subsequent inflammation leads to intestinal damage and villous atrophy clinically present in CD.

Because the initial neutrophilic infiltrate in DH is within the dermal papillae, most investigators

assumed the vesicles formed below the lamina densa. This was supported by electron microscopic (EM) studies. However, immunomapping has confirmed that the subepidermal cleft is, in fact, within the lamina lucida.[38] This discrepancy may be related to papillary dermal edema, which can simulate a sublamina densa cleft. In addition, EM studies are limited by the minute area of tissue examined, making it more likely to miss clefts within the lamina lucida.

The pathogenic autoantibodies in both CD and DH are predominantly of the IgA class, although IgG can be seen and becomes important in patients with gluten sensitivity and IgA deficiency.[33,39] The hallmark finding in DH is granular deposition of IgA within the tips of the dermal papillae and along the basement membrane as seen on direct immunofluorescence of perilesional skin.[14,15,31,39-42] The deposition of IgA is thought to trigger an inflammatory response that, in turn, results in a predominantly neutrophilic infiltrate and skin vesiculation.[15,31,39]

Circulating IgA and/or IgG anti-tTG and antigliadin antibodies are found in patients with active CD. However, in patients with DH, eTG appears to be the dominant autoantigen, and it colocalizes with IgA deposits in the skin.[14,15,39-42] eTG is homologous to tTG within the enzymatically active domains.[35,43] The main function of eTG in the epidermis involves cross-linking and the maintenance of cornified envelope integrity.[43,44] The expression of eTG is more restricted than tTG, and is primarily seen in the epidermis, small intestine, brain, and testes.[44] Patients with DH appear to have both IgA antibodies that are specific for eTG and IgA antibodies that react with both eTG and tTG.[42] Although the main autoantigens differ between CD and DH, one study showed that they share common conserved epitopes, further linking the two diseases.[40,42] The majority of children with CD have higher levels of anti-tTG than eTG IgA antibodies compared to adults with either CD or DH.[40,45] Adult patients, conversely, have higher levels of anti-eTG IgA.[40] Given that the onset of DH is usually in adulthood, this brings up the question of whether children with subclinical CD may develop intermolecular epitope spreading to involve eTG, resulting in development of DH as adults.[40] This hypothesis, and the mechanism for development of anti-eTG antibodies later in life, remains to be investigated.

Whether the IgA anti-eTG antibodies are the central pathogenic factor in DH is still in question. Circulating levels of IgA anti-eTG were found to be more sensitive than IgA anti-tTG in identifying DH.[45,46] In one patient, IgA anti-eTG titers were shown to correlate with adherence to a gluten-free diet, raising the possibility that this may be a useful tool for monitoring disease in the clinical setting.[45] Another recent investigation revealed that only about 50% of patients with DH were positive for IgA anti-eTG.[40] This would imply that other pathogenic factors may be involved.[40] A passive transfer model of DH has not yet been established, and the presence of IgA deposits does not seem to correlate with disease activity.[40,47] Skin deposits of IgA immune complexes disappear in patients maintained on a gluten-free diet (GFD) and reappear with rechallenge, again linking the pathophysiology of DH to gluten sensitivity.[47]

As with any multifactorial disease, lifestyle factors modify the pathogenesis of DH and gluten sensitivity. Iodine use and iodine-containing diets (such as shellfish) have been reported to induce flares of DH.[48] Recently, the exacerbation of DH was shown to occur after exposure to triiodomethane-containing material used during dental procedures.[49] Tobacco may also impact DH severity. In two small analyses of adults, smoking rates were found to be lower among patients diagnosed with DH.[50,51] A similar finding was reported for patients with CD alone, suggesting a protective role for smoking in CD similar to that seen in ulcerative colitis.[52-54] Whether the immunomodulation induced by smoking would have a protective effect on DH is unclear. Additional studies are necessary to determine if nicotine treatment may be a management option for these conditions.

## CLINICAL FEATURES

### Key points

- **In this highly pruritic condition, the primary lesions of dermatitis herpetiformis (papules and vesicles) are often absent, replaced by erosions and excoriations**
- **Dermatitis herpetiformis has a classic distribution, involving bilateral extensor surfaces, scalp, and buttocks**
- **Mucosal involvement in dermatitis herpetiformis is rare**

The clinical distribution and morphology of skin lesions are the hallmarks of DH.[14,31] Primary lesions of DH are grouped erythematous papules surmounted by vesicles. Because of the intense pruritus associated with this condition, patients often scratch all the vesicles and therefore may present with only erosions and excoriations.[55] The eruption is symmetrically distributed on the extensor surfaces of the upper and lower extremities, elbows, knees, scalp, nuchal area, and buttocks (Fig 1). The face and groin may also be involved (Fig 1). Generally, lesions heal

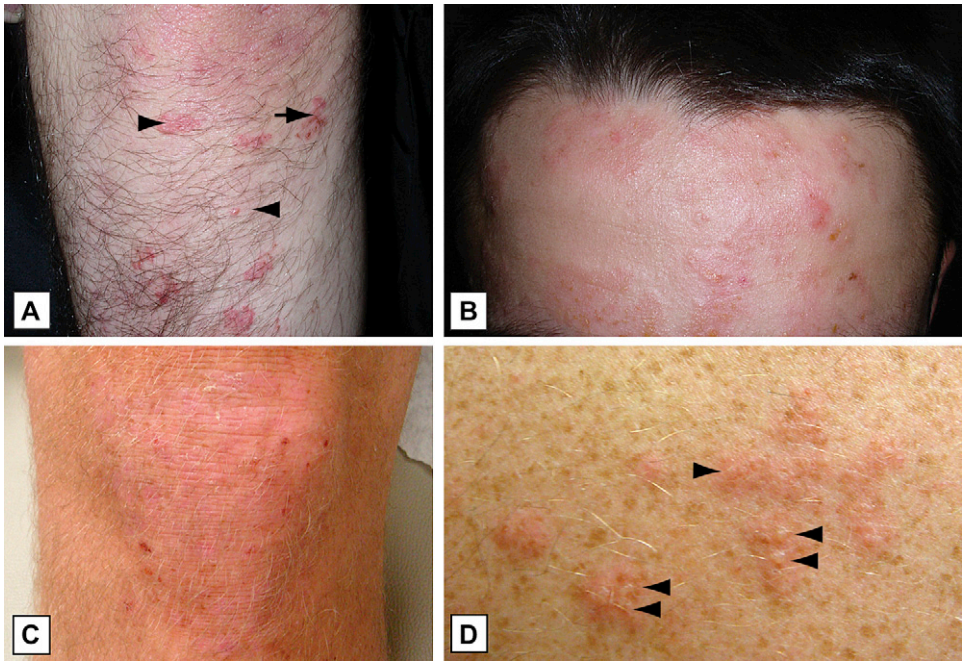


**Fig 1.** **A**, Erythematous papules and plaques on the elbow. Excoriations (*arrow*) and scattered intact vesicles (*arrowheads*) are also noted. **B**, Edematous, erythematous papules and plaques on the forehead and scalp (photograph courtesy of Dr M. Nikolic). **C**, Excoriations with hemorrhagic crusts on the knee. **D**, Grouped vesicles (*arrowheads*) on an erythematous base on the back (photograph courtesy of Dr B. Ortel).

without scarring, although significant postinflammatory pigment changes can occur. Because DH is more commonly seen in patients of Northern European descent, there are only a few reports detailing the clinical presentation of DH in darker-skinned individuals.[10,11] In general, the clinical presentation in patients with darker skin types is similar to that seen in whites.

DH should be differentiated from other bullous skin disorders, such as linear IgA bullous dermatosis (LABD) and bullous pemphigoid. Urticaria, atopic, nummular or contact dermatitis, and scabies infestation should be considered in the differential diagnosis. LABD in particular may have a similar clinical presentation to DH. However, a "crown of jewels" configuration of lesions and large bullae are characteristic for LABD. Biopsy specimens for histopathologic evaluation and direct immunofluorescence testing and an oil preparation for scabies will allow for a prompt and accurate diagnosis.

An uncommon skin manifestation of DH is palmoplantar purpura. This finding is more common in children, but a number of adult cases have been described.[39,56-60] Clinically, petechiae are present on the palms and/or soles. No involvement of the dorsal surface of the hands or feet has been reported. The dominant hand often appears more involved, suggesting trauma as an etiologic factor.

Mucosal involvement is rarely seen in DH.[31] Most studies reporting oral lesions lack confirmation by direct immunofluorescence testing of the oral mucosa. DH-associated conditions, such as CD and autoimmune connective tissue diseases, may cause oral ulceration independently, thereby complicating assessment of the cause of mucosal findings in patients with DH. Despite these limitations, a few reports describe oral lesions in the context of an established DH diagnosis. They include vesicles, erythematous macules, and erosions on the mucosa (Fig 2), including the tongue.[31,61] These may be accompanied by soreness or a burning sensation. It is important to note, however, that CD alone has been associated with both oral aphthosis and mucosal ulceration.[31,62-64] Therefore, the relationship of these oral findings to DH is still unclear.

Finally, dental abnormalities have been described in patients with CD and in patients with DH.[14,62,64] Enamel defects in permanent teeth are seen in both childhood and adult CD and DH.[65,66] Horizontal grooves, defects in enamel color, and large enamel pits (Fig 2) are the most common dental findings in patients with DH.[64-66] Delayed eruption of teeth was also noted in some children.[64] One study showed that first-degree relatives of patients with CD often had enamel defects themselves, suggesting a pathophysiologic link between CD and enamel defects.[67]

**Fig 2.** Multiple erosions of the lower lip mucosa (*arrowheads*). An enamel pit is present on the left lower canine (*arrow*).

The pathogenesis of dental findings seen in CD and DH is uncertain.

## ASSOCIATED DISORDERS

### Key points

- **Dermatitis herpetiformis is a cutaneous form of gluten sensitivity**
- **A wide range of autoimmune disorders are associated with dermatitis herpetiformis, but hypothyroidism is the most common**
- **Patients with dermatitis herpetiformis may have a higher risk of non-Hodgkin lymphoma, particularly enteropathy-associated T-cell lymphoma**

DH is considered the cutaneous manifestation of gluten sensitivity. Despite this, the majority of patients with DH have clinically silent or mild gastrointestinal CD and show improvement of cutaneous manifestations of CD on a GFD.[12,14,18,27,35,55] In fact, isolated iron deficiency may be the only indicator of CD in a patient with DH.[14,68] Because underlying CD may cause atrophic gastritis, pernicious anemia may also be the sole finding in patients with DH.[69]

A number of autoimmune conditions have a close association with DH. There is an increased prevalence of thyroid disease and presence of thyroid microsomal antibodies in patients with DH.[69-71] Hypothyroidism is more common than hyperthyroidism.[70] Increased age and thyroid microsomal antibodies are associated with a higher risk of thyroid disease.[70] The prevalence of type I diabetes (IDDM) is also increased in patients with DH and their first-degree relatives.[69,72] The prevalence of IDDM ranges from 2.3% to close to 5% among patients with DH, which is similar to that in CD but much higher than what is reported for the general population.[69,72-74]

Rarely, Addison disease is found in association with DH.[69,75] A number of cases and series have also documented the cooccurrence of vitiligo and DH.[14,69,70,76,77] Of note, alopecia areata, known to be associated with vitiligo and IDDM, was also reported in association with DH.[69,73] Lastly, autoimmune connective tissue diseases reportedly have a higher prevalence among DH patients.[69] These include Sjögren syndrome, rheumatoid arthritis, and lupus erythematosus.[69,73,78] Whether GFD reduces the risk of developing autoimmune conditions in patients with DH is unknown.

Patients with CD have an increased risk of osteoporosis and fracture.[79,80] However, although DH belongs in the spectrum of CD, studies to date have not identified an increased risk of fracture or bone abnormalities in patients with DH.[81,82] Although this may be attributed to the comparatively mild clinical features of CD seen in most patients with DH, additional studies with larger patient numbers are needed to draw definitive conclusions.

While patients with DH do not appear to have an increase in mortality related to malignancies, a number of studies have revealed a higher risk of non-Hodgkin lymphoma.[15,31,83-86] First-degree relatives of patients with DH do not have an increased incidence of lymphoma, not solely enteropathy-associated T-cell lymphoma, as is traditionally thought to be the case in CD, but also B-cell lymphoma, which may occur both in and outside the gastrointestinal tract as a nodal or extranodal disease.[15,84] It remains unclear whether compliance with a GFD is protective against the development of lymphoma in patients with DH.[15,31,83,84,87]

We thank Christopher R. Shea, MD, for his helpful comments on this article.

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