Dermatitis herpetiformis

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Creation date: November 2003
Update: February 2005

Scientific editor: Professor Benvenuto Giannotti

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Summary
Dermatitis herpetiformis (DH) is a subepidermal bullous disease characterized by chronic recurrence of itchy, erythematous papules, urticarial wheals and grouped vesicles that appear symmetrically on the extensor surfaces, buttocks and back. Children and young adults are mostly affected. Prevalence is estimated to be about 10 to 39 cases/100,000/year, with incidence ranging from 0,9 (Italy) to 2,6 (Northern Ireland) new cases/100,000/year. The disease is the cutaneous expression of a gluten-sensitive enteropathy identifiable with celiac disease. The clinical and histological pictures of both entities are quite similar. Granular IgA deposits at the dermo-epidermal junction, neutrophils and eosinophils together with activated CD4+ Th2 lymphocytes are supposed to represent the main immune mechanisms that co-operate in the pathogenesis of the disease. A strict gluten withdrawal from diet represents the basis for treatment.

Keywords
autoimmune bullous diseases, celiac disease, tissue transglutaminase, anti-endomysium antibodies, anti-tissue transglutaminase antibodies, gluten sensitivity, dapsone.

Disease name and synonyms
- Dermatitis herpetiformis (DH),
- Duhring-Brocq disease,
- Duhring's dermatitis.

Definition
DH is an autoimmune subepidermal blistering disease characterized by chronic and recurrent eruptions of erythematous, urticarial, papular, vesicular and bullous lesions. Granular IgA deposits at the dermal papillae represent the immunological marker of the disease, that is strictly associated with a gluten-sensitive enteropathy (GSE), indistinguishable from celiac disease (CD).[1]

Prevalence

DH is relatively more frequent than the autoimmune bullous dermatoses belonging to the bullous pemphigoid group. Its prevalence is estimated to be about 10 to 39 cases/100,000, with incidence ranging from 0,9 (Italy) to 2,6 (Northern Ireland) new cases/100,000/year.

Males are affected slightly more frequently than females[2] The disease is less frequent in Blacks.[3] Dermatitis herpetiformis occurs mainly between the age of 20 and 55, but is occasionally seen in children, usually after the age of 5.[4]

Clinical manifestations

The onset of DH may be acute or gradual, and pruritus is usually the first and predominant symptom. Early lesions are pleomorphic, consisting of itchy, erythematous papules and urticarial wheals that appear symmetrically on the extensor surfaces, buttocks, back, rarely on the face. Small grouped vesicles progressively develop on plaques of erythema but they rapidly erode/are excoriated, evolving into crusts and erosions. Rarely bullae 1-2 cm in diameter can be seen.[5] Oral lesions, detectable in about 50% of patients, mainly consist of mucosal redness, ulcerations, atrophy in tongue or oral blisters. Pain or a burning sensation may accompany these lesions.[7]

Moreover, enamel defects are found in about 80% of childhood DH cases and approximately 50% of adult DH cases,[8] with slight structural alterations and typical horizontal grooves.

A specific enteropathy occurs in 100% of patients with DH.[3] Bowel disease (celiac disease) is gluten-sensitive and responds to a withdrawal of wheat and other gluten-containing grains from the diet. In most affected adults, enteropathy may be present histologically but not patent clinically, whereas if presenting in childhood it commonly goes into spontaneous remission during adolescence.[6]

The clinical symptoms vary greatly, depending on the length of small intestine involved. Malabsorption can cause diarrhea, steatorrhea, foul-smelling flatus, abdominal pain, weight loss and weakness. Not uncommonly, no or minimal intestinal symptoms are observed, and the disease manifests itself instead as an isolated deficiency state of various vitamins or minerals (anemia due to iron or folate deficiency, bone pain or pathological fractures secondary to impaired absorption of vitamin D and calcium).[6]

Differential diagnosis

In view of the persistent pruritus that resists topical treatment, early DH has to be distinguished from other itching dermatoses like scabies, prurigo, atopic dermatitis. When vesico-bullae are present, erythema multiforme must be excluded, as well as some other autoimmune bullous diseases with particular regards to bullous pemphigoid, linear IgA dermatosis and non-autoimmune bullous conditions, such as transient acantholytic dermatosis (Grover's disease). Clinical doubts can be sometimes eliminated only by direct immunofluorescence (DIF) performed on perilesional healthy skin.

Etiopathogenesis

DH and CD are both gluten-sensitive diseases with a common immunogenetic background. They share a strong association with class II histocompatibility locus antigens DR3 and DQW2 and with the alleles DQA1*0501 and B1*0201 of chromosome 6.[10] Currently, immunopathological mechanisms leading to blister formation and bowel damage in DH are partially known. The discovery in 1967 by Cormane[11] of granular deposits of IgA at the dermo-epidermal junction (DEJ) in the skin of affected patients represents a cornerstone in our understanding of the pathogenesis of DH. However the way IgA are deposited and the structures to which they bind are still debated. It has been demonstrated that IgA detected in DH skin contain both γ and k chains, indicating that they are polyclonal. Besides the IgA1 are the predominant subclass and only in few cases J chains and secretory component can be detected suggesting these immunoglobulins may not have a mucosal origin.[12]

Furthermore, circulating IgA1 autoantibodies to endomysium (EMA) can be detected in both DH (95% of patients in our series) and celiac disease; these antibodies are closely linked to the degree of intestinal abnormalities and are direct indicators of the patients' adherence to a gluten-free regimen (GFD), since their frequency decreases to 18% after a six-month diet.

In 1997, Dieterich *et al.*[13] identified tissue transglutaminase (tTG) as the unknown endomysial autoantigen in CD. This enzyme belongs to the transglutaminase (TG) family, which in man consists of nine distinct proteins present in a wide variety of cell lines and showing conservation of certain enzimatically relevant domains. tTG is synthesized by a broad spectrum of cell types but is usually retained in intracellular compartments. An abundant extracellular release of cytosolic tTG, mainly by lamina propria mononuclear or mesenchymal cells, follows the damage of the intestinal epithelium after gluten ingestion. It has also been demonstrated that tTG accepts dietary gliadin as a preferred substrate catalyzing the formation of gliadin-gliadin cross-links as well as

the incorporation of gliadin into complexes with other proteins and tTG itself. The antigenic neo-epitopes thus created may initiate an immune response in genetically susceptible individuals, finally directed both to gliadin and tTG.[13]

Recently, a positive correlation of IgA anti-tTG levels with semiquantitative EMA titers was demonstrated in both CD and in DH.[14,15] Celiac patients with early mucosal changes, represented by increased intraepithelial lymphocytes, had low EMA titers and slightly raised IgA anti-tTG antibodies. On the contrary IgA anti-tTG showed high values in those patients with biopsy-proven CD and strong EMA reactivity.[14,16]

Moreover, recent findings by Sardy et al.[17] demonstrated that epidermal transglutaminase (eTG or TG3) is the major autoantigen recognised by IgA antibodies deposited in lesional skin of DH. Cross-reacting antibodies to tTG and eTG may be expected as a result of high degree of sequence conservation among members of the TG family. Hence, it is postulated that IgA autoantibodies against tTG cross-react with eTG in the skin. With continued gliadin exposure, specific cross-reacting antibodies with high affinity to eTG and low affinity to tTG may develop among patients who will go on to acquire DH. It is still unknown, however, whether these antibodies develop against eTG as the primary antigen or occur as a consequence of "molecular mimicry".

Nowadays, in addition to the proven role of autoantibodies (that can fix complement, inducing recruitment and activation of neutrophils) an increasing body of experimental evidence supports the participation of cell-mediated immunity and of perivascular infiltrate (mainly composed by CD4+ T lymphocytes together with a varying number of neutrophils and eosinophils) in the initiation and perpetuation of autoimmune response of DH. In fact, the presence of IgA deposits in uninvolved skin supports the hypothesis that in the generation of DH lesions not only the IgA antibodies and triggering of the complement cascade could be implicated, but also the cellular infiltrate which, through a Th2-cell-mediated immune response, is presumably involved in recruiting polymorphonuclear leukocytes.[18,19]

Management – treatment

The therapy for DH is based on strict gluten withdrawal from diet, which may not be simple to achieve, since gluten-containing cereals are ubiquitous in processed foods and it is difficult to avoid gluten in restaurant foods. The patient must be educated and motivated by the physician.

Dapsone (diaminodiphenylsulphone) is the most widely used drug for DH before diet-related improvement. Starting dose is 100 mg daily, but every effort should be made to reduce it to a maintenance of 25-50 mg daily, because dose-dependent methemoglobinaemia and hemolytic anemia are serious adverse effects of this drug.[20]

In patients intolerant of dapsone, sulphapyridine or sulphamethoxypyridazine can be substituted.

Although systemic corticosteroids are generally ineffective, topical steroids may be helpful in lessening pruritus.

Diagnostic criteria – methods

In typical cases the diagnosis of DH can be made relying on 3 main elements:

- Clinical features (pleomorphic and itchy erythematous papules, urticarial wheals and vesico-bullae predominantly located on the extensor surfaces, buttocks and back).

- Histological picture (subepidermal bullae, eosinophil and neutrophil micro-abscessual accumulation within dermal papillae).

- Circulating anti-endomysium (EMA) and anti-tTG IgA antibodies. (these last yielding a sensitivity of 89.1% and a specificity of 97.6%).[21]

- DIF of perilesional skin demonstrating granular deposition of IgA in the basement membrane zone, at top of dermal papillae. (sensitivity: 90%; specificity: 96%).[21]

Provocation or exacerbation by potassium iodide either by mouth or by patch test is not specific for DH and is now considered outmoded.

The diagnosis is confirmed ex juvantibus by the early and excellent response to therapy with dapsone.

Gluten-sensitive enteropathy can be diagnosed by jejunal biopsy (villous atrophy, hyperplasia of criptae and mononuclear infiltration of the lamina propria).

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