Review article

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Dermatitis herpetiformis

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Summary

Dermatitis herpetiformis (DH) is a cutaneous manifestation of coeliac disease (CD), which causes an itching and blistering rash, typically on the elbows, knees and buttocks. DH and CD share a similar genetic background, small bowel mucosal alterations, and an autoimmune response against tissue transglutaminase in the serum and small bowel. DH is typically diagnosed during adulthood, and it is slightly more common among males than females. The incidence of DH seems to be decreasing, in contrast to the detected four-fold increase in the incidence of CD. In addition to typical clinical picture, diagnosis of DH relies on the demonstration by direct immunofluorescence of pathognomonic granular IgA deposits in the papillary dermis. Circulating tissue transglutaminase antibodies support the diagnosis, but their absence does not exclude DH. Obtainment of small bowel mucosal biopsies is not necessary when DH is diagnosed, but if performed, the majority of patients are found to have villous atrophy, and even those with normal villous architecture evince CD-type inflammation. The treatment of choice in DH is a strict, life-long adherence to a gluten-free diet (GFD). In addition to alleviating the symptoms of DH and healing the small bowel mucosal damage, a GFD increases the quality of life for patients, and decreases the risk for lymphoma in DH. Further, the mortality rate of patients with DH treated with a GFD seems to be lower than that of the general population. However, as changing to a GFD has a rather slow effect on the DH rash, patients with severe skin symptoms should additionally be treated with dapsone medication.

This review article is based on a presentation given at the British Society for Medical Dermatology blistering skin diseases meeting 2019.

Introduction

Dermatitis herpetiformis (DH) is a cutaneous manifestation of coeliac disease (CD), in which gluten induces an itchy, blistering rash in genetically susceptible individuals with the human leucocyte antigen (HLA) DQ2 or DQ8 haplotypes. As the same alleles predispose to both DH and CD, these two conditions often occur in the same families, and even monozygotic twins with both phenotypes exist: one with DH and the other with CD.[1,2] Approximately 75% of the patients with DH have evidence of small bowel mucosal villous atrophy at diagnosis, and the remainder have CD-type inflammation.[3] However, obvious gastrointestinal symptoms are considered rare in DH, and some type of abdominal symptoms occur in approximately one-third of patients at diagnosis.[4] Furthermore, characteristic of both, DH and CD is an autoantibody response against tissue transglutaminase (TG)2 in the serum and small bowel mucosa.[3]

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Epidemiology

The highest reported prevalence of DH to date has been 75 per 100 000,[5] and recent studies have shown that

currently approximately 13% of patients with CD have DH.[5,6] Interestingly, even though the incidence of CD has shown to increase four-fold during recent decades, it seems that the incidence of DH is decreasing; in recent studies from Finland[5] and the UK,[6] the incidence of DH was 2.7 and 0.8 per 100 000 person-years, respectively, Furthermore, in contrast to CD, DH is slightly more common among males than in females, and even though DH can appear at any age, it is more rarely diagnosed during childhood compared with CD.[5,6]

Diagnosis

DH diagnosis is based on typical clinical picture and demonstration of IgA deposition in papillary dermis. The predilection sites for the DH rash are elbows, knees and buttocks, and the rash is polymorphic with vesicles, papules and macules.[7] However, because of scratching, the vesicles are often broken and only erosions and crusts are seen, which makes differentiation from other pruritic skin diseases, such as urticaria, atopic dermatitis and scabies, more difficult. Therefore, diagnosis should always be verified by perilesional skin biopsy and direct immunofluorescence examination.[8] The pathognomonic finding for DH is granular IgA in the papillary dermis, and epidermal transglutaminase (TG3) has been identified as the target for this immune response in DH skin.[9].

Histopathological analysis of lesional skin biopsy is not necessary for diagnosis, as the findings are not invariably specific for DH. Small bowel mucosal biopsies are not mandatory for DH diagnosis either: even though the severity of the mucosal damage varies between patients with DH, it seems not to have any effects on the long-term prognosis.[10]

ELISA-based IgA-class TG2 antibody test should be the first-line serological test used when DH or CD is suspected. Antigliadin antibodies are no longer used because of their lack of specificity, and even though endomysial antibodies have comparable reliability for DH and CD as TG2 antibodies, the indirect immunofluorescence-based endomysial antibody test is more laborious and subjective in the interpretation. Serum TG2 antibodies have shown to correlate with the degree of small bowel mucosal damage in DH,[11] and they are less prevalent in DH than in CD. Therefore, the presence of circulating TG2 antibodies supports the diagnosis, but their absence does not exclude DH. Interestingly, it has been documented that, in addition to skin, the majority of patients with DH have circulating antibodies against the autoantigen of DH, i.e. TG3.[12] However, TG3 antibodies also exist occasionally in the serum of patients with CD without any skin symptoms.[13] Hence the specificity of TG3 antibodies for DH is yet to be confirmed, and this antibody test is not currently used in clinical practice.

Treatment

The treatment of choice for all patients with DH is a strict life-long gluten-free diet (GFD), as the rash and the small bowel villous atrophy are both gluten-dependent.[3] In a GFD, wheat, rye and barley are excluded from the diet, but the majority of patients with DH tolerate oats.[14] However, a strict GFD is not easy to maintain and a dietitian should be consulted at the beginning of the treatment. The rash in DH responds slowly to the diet and it usually takes several months until the rash totally disappears. Therefore, patients with widespread, active rash should be given additional treatment with dapsone, which is known to relieve the itch and the rash in DH in a few days; however, it has no effect on the enteropathy. Dapsone is usually well tolerated, but it has some potential dose-dependent haematological adverse effects, including haemolysis and methaemoglobinaemia, and it can also cause agranulocytosis. The initial dose of dapsone in DH is 25–50 mg/day, but the dose can be increased up to 100 mg/day if needed. Once the rash is controlled, the dose of dapsone should be tapered gradually to a minimum maintenance level and finally discontinued when the rash is controlled on a GFD alone. However, a small proportion of patients with DH have active DH rash despite adherence to a strict GFD for several years. This condition is called refractory DH, and according to the only study published to date,[15] refractory DH has shown to occur in approximately 2% of patients with DH. The patients with refractory DH in that study had followed a strict GFD for a mean of 16 years, but they still needed dapsone to control the ongoing skin symptoms. However, the small bowel mucosa had recovered in all of the patients and none had developed lymphoma, indicating that refractory DH is different from refractory CD, in which the small bowel mucosa does not heal on a GFD and the risk of lymphoma is increased. Nonetheless, dietary lapses, either voluntary or accidental, are a far more common reason for ongoing skin symptoms in patients with DH following a GFD, thus dietary consultation is essential.

In addition to clearance of the rash and healing of the enteropathy, GFD treatment also increases the quality of life in DH, which has shown to be decreased at the time of the diagnosis.[4] Further, adherence to GFD for > 5 years seems to protect against lymphoma, the risk of which is known to be increased up to 6–10-fold at diagnosis.[16,17] In CD the risk of bone

fractures is known to be increased, but according to the only study published to date,[18] the fracture risk seems not to be increased in GFD-treated DH.

Long-term prognosis

Several studies have also reported an increased mortality rate in CD, whereas there are studies showing significantly reduced mortality rates in patients with DH compared with the general population.[19,20] In these studies, > 95% of the patients with DH adhered to a GFD, which may explain the excellent prognosis. Interestingly, a few studies have reported that a minority of patients with DH have been able to return to a normal gluten-containing diet without a disease relapse.[21,22] Nonetheless, according to current conception, GFD should be life-long in all individuals with DH, and it offers an excellent prognosis for individuals with DH.

Learning points

- DH is a cutaneous manifestation of CD.
- The typical clinical presentation of DH is an itchy papulovesicular rash on the elbows, knees and buttocks.
- The pathognomonic finding for DH is granular IgA in papillary dermis detected by direct immunofluorescence.
- Levels of serum TG2 antibodies are typically, but not invariably, increased at the time of diagnosis of DH.
- Small bowel biopsies are not necessary for diagnosis of DH, but if taken, CD-type villous atrophy or inflammation is present in all patients.
- The treatment of choice in DH is strict life-long adherence to a GFD.

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CPD questions

Learning objective

To gain up-to-date knowledge on the pathology and treatment of dermatitis herpetiformis.

Question 1

What is the target of dermal IgA deposition in dermatitis herpetiformis?

(a) Gliadin.
(b) Endomysium.
(c) Tissue transglutaminase.
(d) Epidermal transglutaminase.
(e) BP180.

Question 2

What serum antibody test should be used as the first-line test in dermatitis herpetiformis?

IgA-class gliadin antibodies.
IgA-class endomysial antibodies.
IgA-class tissue transglutaminase antibodies.
IgG-class tissue transglutaminase antibodies.
IgA-class epidermal transglutaminase antibodies.

Question 3

Which of the following statements about gastrointestinal tract involvement in dermatitis herpetiformis (DH) is correct?

The majority of patients with DH have abdominal symptoms at diagnosis.
Approximately 25% of patients with DH have small bowel mucosal villous atrophy at diagnosis.
Approximately one-third of patients with DH do not have small bowel mucosal changes characteristic of coeliac disease.
The degree of small bowel mucosal damage has no effect on the long-term prognosis of DH.
The degree of bowel inflammation correlates with the skin disease.

Question 4

Which of the following statements about dapsone treatment in dermatitis herpetiformis (DH) is correct?

All patients with DH need treatment with dapsone after diagnosis.
Dapsone has a rapid effect on the DH rash.
Dapsone heals the small bowel mucosal damage in DH.
Dapsone has haematological adverse effects, which are idiosyncratic and not dose-dependent.
Dapsone has no anti-inflammatory properties.

Question 5

Which of these options is *not* a currently known beneficial effect of a gluten-free diet in dermatitis herpetiformis (DH)?

It heals the DH rash.
It heals the small bowel mucosal damage.
It increases the quality of life.
It decreases the risk for lymphoma.
It reduces cardiovascular mortality.

Instructions for answering questions

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