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Introduction and AIMS

Short Definition in Layman Terms

Dermatitis herpetiformis is the skin manifestation of coeliac disease. The trigger of both diseases is known; ingestion of gluten in certain HLA phenotypes (HLA-DQ8 or HLA-DQ2) leading to an autoimmune reaction characterized by IgA autoantibodies against tissue transglutaminase (tTG) and later in DH patient against the epidermal transglutaminase (eTG).

Dermatitis herpetiformis (DH) is the specific skin manifestation of coeliac disease (CD) caused by the digestion of gluten in HLA-DQ2 or HLA-DQ8 individuals

Didactical Questions; Cross Section of Questions to Prime the Readers' Interest

How can you diagnose DH? What would you see in the histopathological section? How can you make de difference between other autoimmune and immunological diseases? In this section the focus is on the clinical differential diagnostics and work up of patients suspected for DH.

Learning Objectives

After reading this chapter you will be able to differentiate dermatitis herpetiformis from other pruritic dermatoses and to recognize the classic clinics of DH. You will be able to perform and interpret the immunological tests, to make a treatment algorithm and to manage patients with DH.

Case Study: Part 1

41-year-old male patient presented with itchy papules, blisters on knees, elbows, shoulders and lower back for 3 years. He had no mucosal involvement, nor digestive tract symptoms. He was non-atopic, family history reported no skin disease or other problems. There was no medicine administered before.

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Facts and Figures

Definitions and Classification

Dermatitis herpetiformis is the cutaneous manifestation of coeliac disease, both disease are the different phenotype of glutens sensitive disease (GSD). This means that in both diseases gluten is the trigger that in certain susceptible HLA phenotypes provokes autoimmune reaction. An autoantibody population against tTG characterizes CD. As gluten sensitivity is obligate to develop in DH, also DH patients have tTG autoantibodies, however with low affinity. Moreover patient with DH develop another autoantibody population against the eTG [1].

Epidemiology

Due to its genetic background DH has a different prevalence geographically. DH is most common in patients with North-European origin. Studies report a prevalence of 1.2 to 39.2 per 100,000 people, with an incidence range of 0.4 to 2.6 per 100,000 people per year. DH is rare in the Asian population and even more rare in African Americans. Familial cases were reported. Male female ratio is 1.5:1 to 2:1. Interestingly an opposite female predominance is known in CD. The onset of the disease is variable; mostly in the fourth decade, but childhood and geriatric cases are not rarity. The childhood onset is more reported in the Mediterranean area [2].

DH is most common in patients with North-European origin

Pathogenesis

There is a strong genetic predisposition for DH. In patients with HLA-DQ2 and/or HLA-DQ8 phenotype an autoimmune reaction develops after the ingestion of gluten (Fig. 20.1). First, tTG modifies gliadine, the alcohol-soluble fraction of gluten to an antigen, which binds to the HLA-DQ2/HLA-DQ8 molecule to evoke cellular and humoral (anti-gliadine antibodies) immune reactions. Moreover the tTG-bound gliadine serves also as a strong antigen producing excessive autoantibody production against the enzyme complex (tTG antibodies). This humoral and cellular immune reaction leads to inflammation and damaging of the gut mucosa, resembling changes seen in CD [2].

The subclinical gluten sensitivity is obligate to develop DH. eTG and tTG share common epitopes within the enzymatically active domain. It is hypothesized, that epitope spreading is the suspected mechanism after the development of the new autoantibody population targeting the eTG. This is supported by the facts that children have mainly CD with high levels anti-tTG and low levels of anti-eTG compared with adults. Moreover CD mainly develops in childhood whereas DH is the disease of adults. Suggesting that the epitopes spreading needs time to take place [2].

The circulating IgA autoantibodies against eTG in DH target epidermal transglutaminase, a protein playing role in the formation of the cornified envelop of the epidermis. In DH skin eTG is co-localized with IgA at the BMZ in the papilla tips supporting that eTG is the autoantigen of DH [1]. However it remains to be elucidated whether there are true circulating IgA-eTG immune complexes in DH, since deposits of IgA and eTG in the dermal vessel are seen frequently (Fig. 20.2) [3] clinically corresponding with the digital purpura in DH (Fig. 20.3) [4].

In DH skin eTG is co-localized with IgA at the EBMZ in the papillary tips supporting that eTG is the autoantigen of DH

Diagnosis Paths

History and Physical Examination

The classic clinical presentation of DH is a very itchy polymorphous skin eruption comprising erythema, urticarial plaques, papules, vesicles, excoriations and purpura sometimes in herpetiform configuration. The lesions are distributed typically on the extensor surfaces of the body; knees, elbows (Fig. 20.4), shoulders, in the so-called vertical distribution (Fig. 20.5). Large blister are rarely seen. The disease has a fluctuating course driven mostly but not always by gluten ingestion, improves under UV light (seasonal flare-ups). There are known associations with autoimmune thyroid disease and other autoimmune diseases [4].

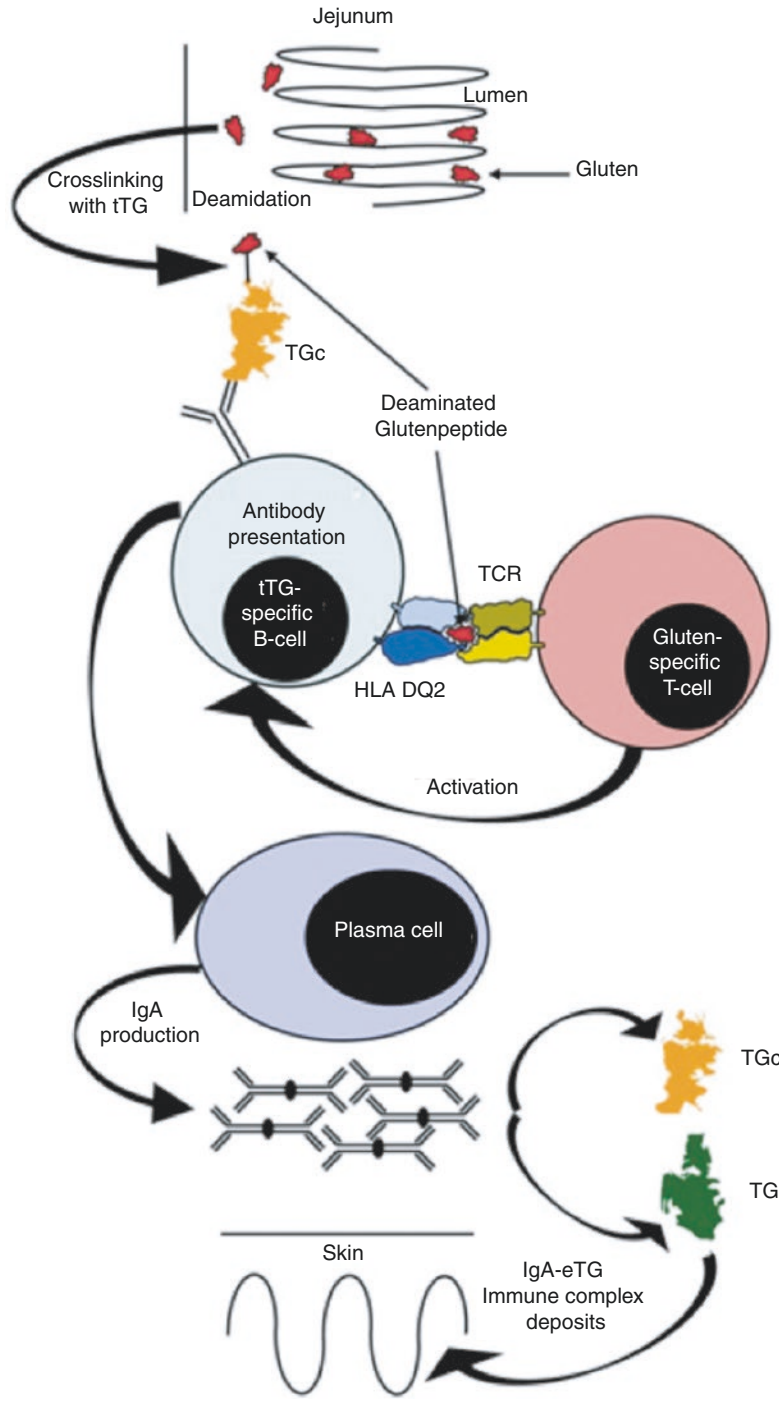

Fig. 20.1 Diagram of the hypothetical pathogenesis of DH. Incomplete metabolized gluten peptides are deaminated in the gut and covalent crosslinked with TGc (=tTG). The gluten peptide TGc-complex induces a anti-TGc, and anti-TGe autoimmune response by glutenpeptide specific T-cells, which activate a TGc-specific B-cells. The subsequently produced IgA autoantibodies, which crossreact with TGe, are deposited as TGe-immune complexes in the dermis. *TZR* T-cell receptor. Reprinted from Sardy and Tieze with permission from Springer Science and Buisness Media

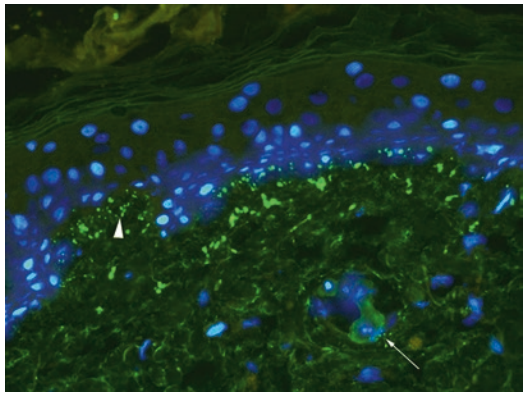

Fig. 20.2 DIF of DH shows granular depositions below the basement membrane zone (arrowhead) and in the walls of dermal blood vessels (arrow)

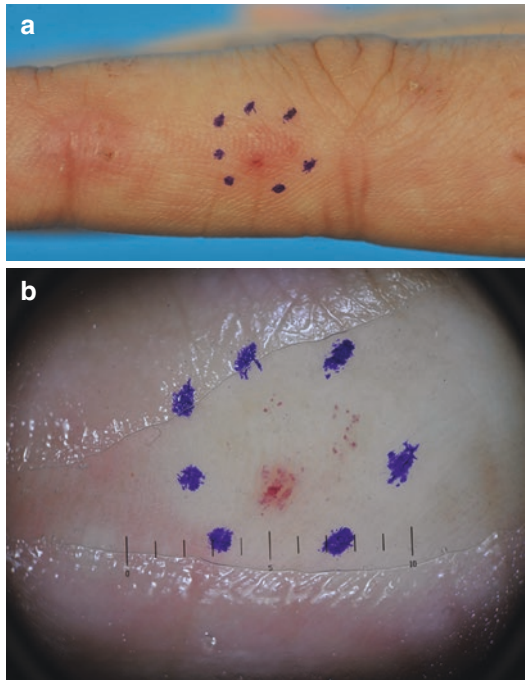

Fig. 20.3 (**a**) Digital purpura in dermatitis herpetiformis. (**b**) Dermoscopy reveals coagulated capillaries

General Diagnostics

The histological picture is unique in DH. Routine histology in DH shows infiltration of neutrophils at the dermo-epidermal junction just above the papilla tips, called microabscesses (Fig. 20.6).

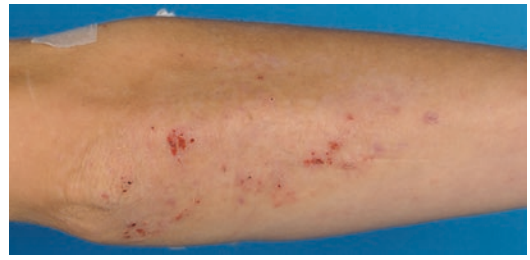

Fig. 20.4 The extensor surface of the elbow is a predilection place in DH, and preferable side for IF biopsy

Specific Diagnostics

On direct immunofluorescence (DIF) granular deposits of IgA at the dermal papilla tips or along the BMZ is seen (Fig. 20.2), mostly representing the location of the neutrophils on the routine histology (Fig. 20.6). On indirect immunofluorescence (IIF) on monkey oesophagus IgA binding is seen on the smooth muscle layer corresponding with the endomysium (EMA positivity, Fig. 5.3a). The major antigen of EMA is tTG [4]. In the blood IgA anti-tTG is positive. However patients with IgA deficiency can also develop CD as well DH resulting in autoantibodies from the IgG class. Therefore simultaneous measurement the IgA levels is mandatory for diagnostics.

DIF shows granular IgA deposits along the BMZ. On monkey esophagus EMA positivity is seen representing autoantibodies against tTG

Case Study: Part 2

Routine laboratory examination showed no abnormality. On histopathological examination subepidermal blister forming with neutrophil microabcesses at the dermal papilla tips were seen. On direct immunofluorescence granulair deposits of IgA (2+) and complement (C3C 1+) were seen at the BMZ. On indirect immunofluorescence on monkey esophagus anti-EMA positivity (1+) was seen.

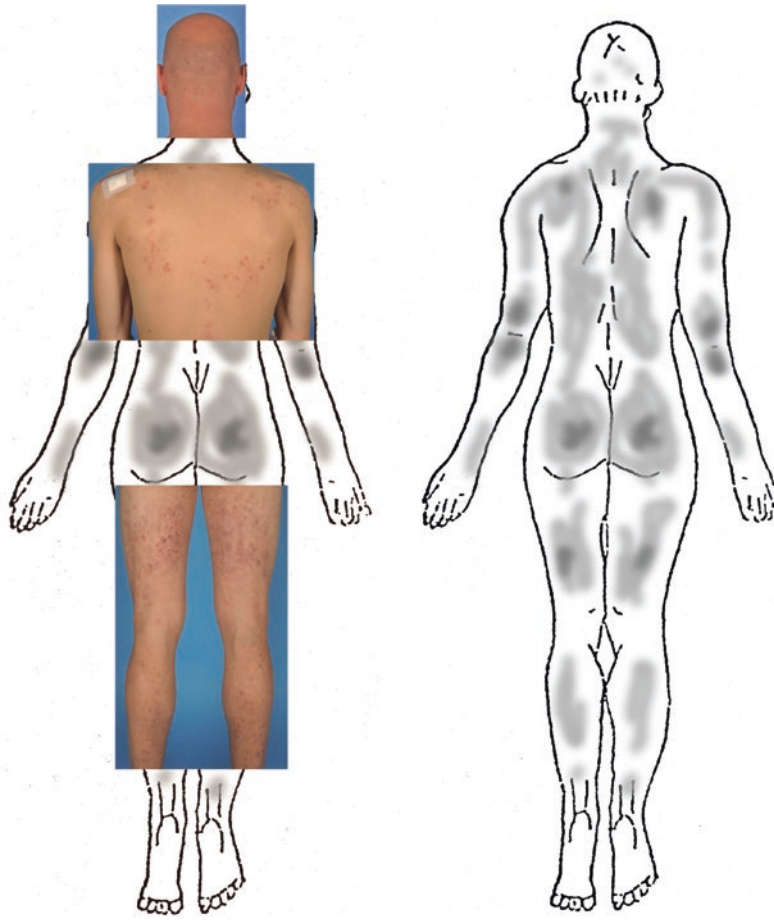

Fig. 20.5 The vertical distribution of skin lesions at the backside of the body typical for DH

Treatment Tricks

Initial Treatment and Escalator

Gluten free diet (GFD) is the first choice of treatment (Table 20.1). Every patient with DH should be informed about this, however consistent adherence on GFD is difficult. Patient with symptoms of celiac disease should be referred to gastroenterologists. Patient without gut symptoms can be managed primary at dermatologists. Since most patients with DH have mild CD, denying of GFD is acceptable as long as they are carefully monitored for sign of malabsorption, anemia, vitamin B12-deficiency, osteoporosis, and thyroid dysfunction.

Patients with severe CD may develop enteropathy associated T-cell lymphoma (EATL). Since patients with DH—per definition—do not develop severe CD, they do not develop EATL, and therefore do not have to be warned for the possibility of developing intestinal lymphoma.

Unfortunately the effect of GFD takes time. The skin rash disappears in months after the ces-

sation of gluten, and gluten re-challenge causes flare-up of the disease within days.

To achieve quick improvement of itch, patients need dapsone as medication at the beginning of the therapy. Dapsone, a member of the sulfonamide antibiotics, is the first line medical treatment for DH. Dapsone inhibits the diapedesis of neutrophils and migration to the EBMZ bound IgA in a dose dependent manner [5]. Dapsone can be started with 50 mg per day. Administration of dapsone reduces the itch promptly within 48 h. Glucose-6-phosphate dehydrogenase deficiency should be excluded within the first week of treatment and prior to raising the dosage of dapsone.

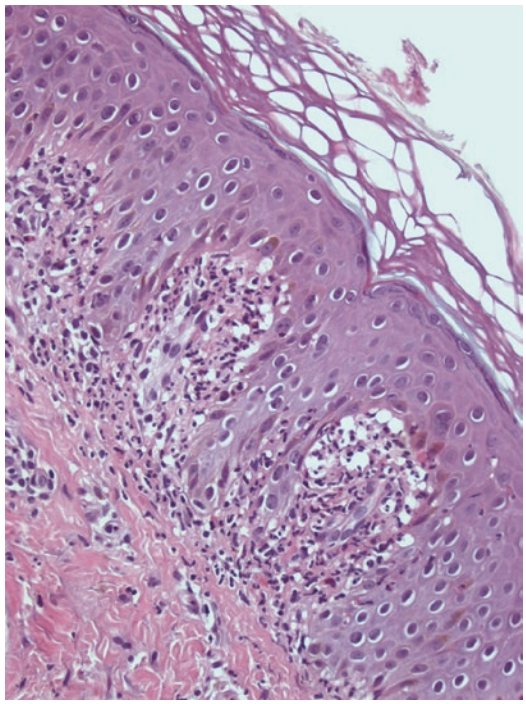

Fig. 20.6 Histopathology of DH shows neutrophil microabcesses in the dermal papillae

Table 20.1 Gluten free diet

Foods to avoid	Foods allowed
Grains and starches • Wheat • Kamut • Rye • Barley • Oats • Many cereals	Grains and starches • Tapioca • Soybean • Potato • Buckwheat • Quinoa • Rice • Corn • Coconut flour • Almond meal flour

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Follow-Up and Tapering

Hemolysis is obligate during dapsone treatment, and is dose dependent. It is compensated by reticulocytosis. During the dapsone treatment patient should be carefully monitored for excessive hemolysis: drop in the hemoglobin concentration with 1g/dL, insufficient elevation of reticulocytes, lactate dehydrogenase above 225 U/L and total bilirubin above 17 μmol/mL For methemoglobinaemia arterial concentrations of metHb should be measured regularly. Agranulocytosis and dapsone hypersensitivity syndrome are the most feared idiosyncratic side effects of dapsone. When remission is achieved, dapsone can be tapered to the minimal effective dose. If the patient constantly adheres to GFD the dosage of dapsone can be further reduced or even stopped (see box below).

Case Study: Part 3

After excluding glucose-6-phosphat dehydrogenase (G6PD) deficiency patient received dapsone orally. The initial dose was 50 mg per day, which was increased up to 75mg daily after one week under blood controls. Follow-up and tapering

Pharmacology of Dapson [6]

Oral availability is as high as 86%, so it is administered exclusively orally. During its metabolisms in the liver two metabolites are produced: via acetylation the non-toxic metabolites acetyl and diacetyl dapsone and via N-hydroxylation the potentially toxic hydroxylamine. The latter reaction occurs on the cytochrome P450 enzyme-complex (CYP450), so medicines competing these enzymes can influence the production of the toxic metabolites [6]. Table 20.2 shows the medicines influencing the CYP450.

The side effects of dapsone are either dose-dependent or dose-independent.

- Dose-dependent side effects:
  - **Methemoglobinemia.** The development of methemoglobinemia is the direct effect of the toxic metabolite hydroxylamine, which transforms the hemoglobin to MetHB, which binds and release less oxygen. Clinical symptoms of methemoglobinemia are due to the lack of oxygen in the tissues (Table 20.3).
  - **Hemolysis.** It is an indirect effect of hydroxylamine and related on oxygen free radicals. Moreover addition of cimetidine can reduce the concentration of hydroxylamine. Interestingly G6PD-deficient patients are less susceptible to methemoglobinemia, and more susceptible to hemolysis due to decrease in NAPDH formation in the erythrocytes.
- Dose-independent side effects.
  - **Agranulocytosis** is idiosyncratic, thought that hydroxylamine binds in the bone marrow to the myeloprecursor cell to inhibit their maturation. Typically fever with neutropenia appears 1 to 3 months after the first dose of dapsone.
  - **Dapsone hypersensitivity syndrome (DHS)** with fever, rash and organomegaly (lymphadenopathy, hepato-splenomegaly) with elevated erythrocyte sedimentation rate and liver enzymes. The interval is much shorter 1 up to 6 weeks after the first dose.

Table 20.2 Medications inducting and inhibiting cytochrome P450 (CYP450) [7]

Inhibitors of CYP450	Inductors of CYP450
• Diltiazem • Itraconazol • Ketoconazol • Metronidazole • Omeprazol • Paroxetine • Fluoxetine • Amitryptilline • Cimetidine • Haloperodol • Eryhtromycine • Clarythromycine • Ritonavir	• Glucocorticosteroids • Rifampycine • Carbamazepine • Phenobarbital • Phenytoine

Table 20.3 Clinical symptoms of methemoglobinemia [8]

% of total hemoglobin[a]	Symptoms
<10%	None
10–20%	Cyanotic discoloration of the skin
20–30%	Anxiety, headache, tachycardia, lightheadedness
30–50%	Fatique, confusion, dizziness, tachypnea, tachycardia
50–70%	Coma, seizures, arrhythmias, acidosis
>70%	Death

[a]Assumes hemoglobin = 15 g/dL. Patients with lower hemoglobin concentrations may experience more severe symptoms for a given percentage of metHb level

Review Questions

1. What is the trigger of DH?
   a. Gluten
   b. Gliadin
   c. Reticulin
   d. Drugs
2. Which HLA loci are associated with DH and CD?
   a. HLA-DQ8
   b. HLA-B51
   c. HLA-DQ2
   d. a+c are correct
3. Which are the typically involved areas on the body in DH?
   a. Backside of body
   b. Mucosal surfaces
   c. Palms and soles
   d. Front side of body
4. First line medication of DH is
   a. Systemic corticosteroids
   b. Gluten free diet
   c. Doxycycline
   d. Dapsone
5. Which is allowed in the gluten free diet?
   a. Wheat
   b. Potato
   c. Rye
   d. Barley

Answers

1. a.
2. d.
3. a.
4. d.
5. b.

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