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GUIDELINES

S2k guidelines (consensus statement) for diagnosis and therapy of dermatitis herpetiformis initiated by the European Academy of Dermatology and Venereology (EADV)

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Abstract

Introduction Dermatitis herpetiformis (DH) is a chronic, pruritic, gluten-induced skin disorder characterized by subepidermal granular IgA deposition and a variable degree of enteropathy identical to that seen in coeliac disease. So far, there has been no European consensus about the management of DH.

Methods The guidelines were created by small subgroups of a guideline committee consisting of 26 specialists from various medical fields and one patients' representative. The members of the committee then discussed the guidelines and voted for the final version at two consensus meetings. The guidelines were developed under the support of the European Academy of Dermatology and Venereology (EADV) and in collaboration with the European Dermatology Forum (EDF).

Results The guidelines summarize evidence-based and expert-based recommendations (S2 level) for the management of DH (see Appendix).

Conclusion These guidelines will improve the quality of management of DH and support dermatologists in their diagnostic and therapeutic decisions.

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Conflict of interest

None declared.

Funding source

The EADV supported and funded the development of these guidelines.

Introduction

Dermatitis herpetiformis (DH)

Definition Dermatitis herpetiformis (DH) is a chronic, polymorphic, pruritic, gluten-induced skin disorder characterized by subepidermal granular IgA deposition and a variable degree of enteropathy identical to that seen in coeliac disease (CD). DH can be thus regarded as a special, distinct form of CD with combined intestinal and cutaneous manifestations.

History The term DH was first proposed by Louis Adolphus Duhring, a dermatologist in Philadelphia, in 1884.[1] He described a chronic skin disease characterized by intense pruritus and polymorphic skin lesions. Systemic involvement and association with CD was first reported by Marks *et al.*[2] in 1966 who observed small intestinal mucosal lesions in DH. In 1967, Cormane[3] detected immunoglobulins at the dermal-epidermal junction in patients with DH and 2 years later, van der Meer identified this immunoglobulin as IgA.[4] Subsequently, Chorzelski and coworkers separated linear IgA disease from DH on the basis of different findings by direct immunofluorescence microscopy in 1979. Four years later, they also published that sera from patients with DH and CD show IgA autoantibodies to endomysium.[5] In 1990, Kárpáti *et al.*[6] analysed the cutaneous immunoglobulins at the ultrastructural level, but only Dieterich *et al.*[7] could identify tissue transglutaminase (TG2) as the autoantigen of anti-endomysium antibodies in 1997. Six years later, Sárdy *et al.*[8] identified epidermal transglutaminase (TG3) as the main autoantigen of DH.

Genetic background DH is strictly associated with human leukocyte antigen (HLA)-DQ2 or HLA-DQ8. Approximately 85% of Caucasian patients with DH carry HLA-DQ2, and the majority of the remaining 15% carry HLA-DQ8.[9–11] In Japan, a variant with similar cutaneous manifestation but without association with CD was identified; it is characterized by the rare occurrence of gluten sensitive enteropathy, the absence of HLA-DQ2 and HLA-DQ8, and a high frequency of fibrillar IgA deposits in the papillary dermis without a strict association with autoimmune diseases or lymphomas.[12] Beside the genetic predisposition, differences in diet and high gluten consumption are also important provoking factors in the development of the disease.

Epidemiology DH is a rare disease, its prevalence has been reported to be between 10 and 75 per 100 000 habitants, the incidence rate lies between 1 and 3.5.[13] It is very rare in Asian populations and less common among African-Americans. Most of the studies focus on individuals of Northern European ancestry, both in Europe and the United States, in whom this disorder is most common. Although the adult onset of the disease is most prevalent in Northern Europe, it seems that the development of the DH in childhood is more frequent in Mediterranean countries.[14,15] The highest prevalence of 75.3 and incidence of 3.5 per 100 000 people were reported in Finland.[13] The prevalence of DH in Utah was 11.2 per 100 000 in 1987, the incidence was 0.98 per 100 000 people per year.[16] Similar data were reported by Smith *et al.*[17] from the UK with incidence rate of 1.2 per 100 000 persons per year. The comparable data in the population of Utah based on the high proportion of people in the state with Northern European ancestry. During the period 1991–2010, the mean incidence rate was 0.142 per 100 000 persons in Serbia.[18] In many countries, no data are available; it is presumably much less frequent in most European states. Based on recent investigations, there is an increasing incidence of CD, but in contrast to this finding, the incidence of DH decreased in both Finland and UK during the 1990s.[13,16]

Although CD is more common in females, males have a higher prevalence of DH. Overall, the male:female ratio in DH is

3:2, but females predominate under 20 years of age (male:female = 2:3). The mean age at diagnosis of the patients increased continuously during the last decades.[19]

Coeliac disease (CD)

Definition CD is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically (mainly HLA) susceptible individuals, characterized by the presence of a variable combination of gluten dependent clinical manifestations, coeliac-specific antibodies, HLA-DQ2 or DQ8 haplotypes and enteropathy.[20]

In CD, gluten ingested from wheat, rye and barley induce T lymphocyte activation, production of autoantibodies against type-2 (tissue, cellular) TG2 and small intestinal villous atrophy with crypt hyperplasia.

Common features in CD and DH The same gluten-derived (mainly gliadin) peptides can be triggers of these entities and their presentation to T cells require the presence of HLA-DQ2 or DQ8 alleles. Autoantibodies targeting the same TG2 epitopes are produced during gluten intake, while this autoantibody production stops on a gluten-free diet.

In DH, the full spectrum of gluten-enteropathy can be seen: 25–30% of the patients have preserved villous architecture without (Marsh 0) or with increased number of intraepithelial lymphocytes (Marsh I), crypt hyperplasia (Marsh II), but in up to 70–75% of DH patients moderate to severe villous atrophy with crypt hyperplasia (Marsh IIIA-C) is present at diagnosis.[21] DH patients presenting initially with normal intestinal villous structure developed villous atrophy upon gluten challenge.[22,23] Further, DH and CD patients have similarly deposited IgA-TG2 immune complexes in the small bowel irrespective of the structural mucosal alterations.[23,24] Both gastrointestinal and skin manifestations of DH are responsive to a strict and long-term gluten-free diet. The gluten intolerance is definitive and life-long in both CD and DH and there is no spontaneous cure.

Manifestations of DH and CD without visible skin lesions can alternate in the same person during different periods of life[25] or in first degree relatives.[26]

Aims, methods

Development of the guidelines

The aim of this project was to standardize diagnostics and therapy of dermatitis herpetiformis with support of the European Academy of Dermatology and Venerology (EADV) and in cooperation with the European Dermatology Forum (EDF). The chairperson of the guideline committee invited experts from many centres and countries including dermatologists, dermatohistopathologists, (paediatric) gastroenterologists and patient organizations. To achieve a broad consensus, a total of 27 participants from all over the world were included. All participants of the guideline committee agreed to develop consensus-based (S2k) guidelines, which is based on the directions of the Association of the Scientific Medical Societies in Germany (AWMF; https://www.awmf.org/en/clinical-practice-guidelines/awmf-guidance/cpg-development.html). Prior to a Consensus Conference, each of the invited authors submitted a preliminary draft of a selected topic, based on an Internet research of relevant medical databases and a literature survey. The draft was reviewed and commented by all members of the guideline committee prior to the Consensus Conference.

The following 17 members of the guideline committee were present at the first Consensus Conference held on 24–25 May, 2019 in Budapest, Hungary: Emiliano Antiga, Marzia Caproni, Dipankar De, Marian Dmochowski, Kossara Drenovska, Anna Görög, Ágnes Kinyó, Tünde Koltai, Ilma Korponay-Szabó, Angelo Valerio Marzano, Aikaterini Patsatsi, Christian Rose, Miklós Sárdy, Martin Shahid, Soner Uzun, Francesco Valitutti, Snejina Vassileva. Two members were paediatric gastroenterologists (I. Korponay-Szabó and F. Valitutti), one member was the representative of Association of European Coeliac Societies (T. Koltai), one member was dermatopathologist (C. Rose), and all other members were dermatologists. Some chapters could not be discussed and some others needed modifications, thus a second Consensus Conference was organized on 13 June 2019 in Milan, Italy, with the participation of 10 members from the same committee (Emiliano Antiga, Marzia Caproni, Kossara Drenovska, Claudio Feliciani, Ágnes Kinyó, Angelo Valerio Marzano, Aikaterini Patsatsi, Miklós Sárdy, Jane Setterfield, Martin Shahid).

The Consensus Conferences were moderated neutrally and with regard to all relevant topics and questions, voting was performed with three possible outcomes (for, against, abstention). The results were immediately noted into the guideline manuscript. The members of the committee who were unable to be present at the Consensus Conference could vote and make comments after the preparation of the manuscript.

These guidelines are valid until 30 June, 2024.

In order to standardize recommendations throughout this document, the following expressions for the grade (level) of recommendation in Table 1 were used consequently. For better visualization, levels are also labelled with colour-coded arrows. The consensus levels are visualized by representative pie charts as shown in Table 2.

Conflicts of interest

Conflicts of interest are summarized in Table 3. Only conflicts of interest *related to these guidelines* are given. The EADV yielded financial support for the Consensus Meeting (travel expenses, accommodation, catering, organization and editorial costs).

Diagnostics

The diagnostics of DH consists of a few basic procedures shown in Table 4. These procedures may be expanded by a few others if

Table 1 Grades (levels) of recommendation in these guidelines

Grade (level) of recommendation	Syntax
Very strong recommendation, it is practically obligatory	It is necessary
Strong recommendation (some exceptions are acceptable)	It is recommended
Less strong recommendation (one has to consider it but exceptions are not rare)	Should be considered
Weak recommendation (it is allowed but it is not recommended as a rule)	May be considered
Rejection (not recommended)	It is not recommended or it is contraindicated

Table 2 Levels of consensus in these guidelines

Level of consensus	Symbol
Strong consensus (agreement of >95% of participants)	
Consensus (agreement of >75-95% of participants)	
Agreement of the majority (agreement of 50-75% of participants)	

needed. It is necessary that only symptomatic therapy is prescribed until all diagnostic steps are done, because both gluten-free diet (GFD) and dapsone treatment can modify or even falsify diagnostic results.

As DH has a genetic background, it is recommended that all genetically related family members are screened for the presence of DH or CD.

Cutaneous manifestations Dermatitis herpetiformis is clinically manifested by intensely pruritic polymorphic papulovesicular eruption affecting the skin on the extensor body surfaces (Fig. 1).[27] Itching and burning sensation is often the initial sign of the disease.[28–32] Cutaneous lesions that appear afterwards are usually grouped together in a 'herpetiform' fashion and tend to have a symmetric distribution with predilection for elbows, knees, shoulders, back and buttocks, generally in areas most exposed to mechanical forces. Other less commonly affected sites are the scalp, the posterior nuchal area, and the hairline. Due to their pruritic nature, primary lesions are often 'masked' by less specific manifestations, such as excoriations, erosions and crusts. Thus, the localization of skin lesions is more important for clinical suspicion than the elementary lesions. The Nikolsky's sign is negative. Cutaneous lesions tend to heal without scarring, although post-inflammatory hyper-, or hypopigmentation may

Medical history

Medical history

It is recommended that the medical history includes mainly

- The relevant family history
- The time and duration of persistence of lesions and symptoms
- The skin symptoms, i.e. itching, burning, stinging
- The gastrointestinal symptoms, i.e. chronic, relapsing abdominal pain, diarrhoea, constipation, loss of weight, nausea, bloating, etc
- Gastrointestinal medical history to search for signs for malabsorption, coeliac disease and associated diseases
- Anticipated pregnancy because of the risk of maternal anaemia, neonatal hyperbilirubinemia and haemolytic anaemia related to dapsone
- Medical history of any autoimmune or immune-mediated associated diseases, particularly Hashimoto thyroiditis, insulin-dependent diabetes mellitus, pernicious anaemia, etc.

It may be considered that the medical history includes

- assessment of the psychological tolerance to a gluten-free diet and potential side-effects due to treatment, especially dapsone
- evaluation of the impact of the disease on the quality of life

Physical examination

Physical examination

It is necessary that the complete physical examination focuses on the following:

- Cutaneous manifestations
- Oral involvement
- Gastrointestinal complaints, signs of malabsorption or coeliac disease i.e. abdominal distension, pain, evidence of weight loss, peripheral edema, chronic diarrhoea, anaemia, persistent fatigue, steatorrhoea, etc.
- Assessment of associated diseases

Table 3 Conflicts of interest of the members of the guideline committee related to these guidelines

No.	Conflict of interest	Mikló Sárdy	Marian Dmochowski	Enno Schmidt	Marzia Caproni
1	Board membership	No	No	No	No
2	Conflicts of interest of near family members (spouse, children, grandparents)	No	No	No	No
3	Consultancy	No	No	No	No
4	Consulting fee or honorarium	No	No	No	No
5	Employment	No	No	No	No
6	Expert testimony	No	No	No	No
7	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, etc.	No	No	No	No
8	Grant	No	No	Euroimmun	No
9	Grants/grants pending	No	No	No	No
10	Patents (planned, pending or issued)	Issued patent on the human TG2 ELISA.	No	No	No
11	Payment for development of educational presentations	No	No	No	No
12	Payment for lectures including service on speakers bureaus	No	No	No	No
13	Payment for manuscript preparation	No	No	No	No
14	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
15	Royalties	No	No	No	No
16	Stocks/stock options	No	No	No	No
17	Travel/accommodations/meeting expenses related to these guidelines	No	Yes	No	No
18	Others	No	No	No	No
	Conflict of interest	**Angelo Valerio Marzano**	**Dipankar De**	**Soner Uzun**	**Christian Rose**
1	Board membership	No	No	No	No
2	Conflicts of interest of near family members (spouse, children, grandparents)	No	No	No	No
3	Consultancy	No	No	No	No
4	Consulting fee or honorarium	No	No	No	No
5	Employment	No	No	No	No
6	Expert testimony	No	No	No	No
7	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, etc.		No	No	No
8	Grant	No	No	No	No
9	Grants/grants pending	No	No	No	No
10	Patents (planned, pending or issued)	No	No	No	No
11	Payment for development of educational presentations	No	No	No	No
12	Payment for lectures including service on speakers bureaus	No	No	No	No
13	Payment for manuscript preparation	No	No	No	No

Table 3 *Continued*

	Conflict of interest	Angelo Valerio Marzano	Dipankar De	Soner Uzun	Christian Rose
14	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
15	Royalties	No	No	No	No
16	Stocks/stock options	No	No	No	No
17	Travel/accommodations/meeting expenses related to these guidelines	No	No	No	No
18	Others	No	No	No	No
No.	**Conflict of interest**	**Savas Yayli**	**Hervonen Kaisa**	**Ilma Korponay-Szabó**	**Anna Görög**
1	Board membership	No	No	No	No
2	Conflicts of interest of near family members (spouse, children, grandparents)	No	No	No	No
3	Consultancy	No	No	No	No
4	Consulting fee or honorarium	No	No	No	No
5	Employment	No	No	No	No
6	Expert testimony	No	No	No	No
7	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, etc.	No	No	No	No
8	Grant	No	No	No	No
9	Grants/grants pending	No	No	No	No
10	Patents (planned, pending or issued)	No	No	Patent on whole blood rapid trasglutaminase antibody test licenced by Tampere University to Labsystems Oy	No
11	Payment for development of educational presentations	No	No	No	No
12	Payment for lectures including service on speakers bureaus	No	No	No	No
13	Payment for manuscript preparation	No	No	No	No
14	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
15	Royalties	No	No	Yes, from rapid test	No
16	Stocks/stock options	No	No	No	No
17	Travel/accommodations/meeting expenses related to these guidelines	No	No	No	No
18	Others	No	No	No	No
No.	**Conflict of interest**	**Cassian Sitaru**	**Claudio Feliciani**	**Aikatarini Patsatsi**	**Ines Lakos Jukic**
1	Board membership	No	No	No	No
2	Conflicts of interest of near family members (spouse, children, grandparents)	No	No	No	No
3	Consultancy	No	No	No	No
4	Consulting fee or honorarium	No	No	Principia Biopharma, Jannsen, Leo, Novartis, Abbvie, Lilly, UCB, Genesis Pharma - Greece	No
5	Employment	No	No	No	No
6	Expert testimony	No	No	No	No

Table 3 *Continued*

No.	Conflict of interest	Cassian Sitaru	Claudio Feliciani	Aikatarini Patsatsi	Ines Lakos Jukic
7	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, etc.	No	No	No	No
8	Grant	No	No	No	No
9	Grants/grants pending	No	No	No	No
10	Patents (planned, pending or issued)	No	No	No	No
11	Payment for development of educational presentations	No	No	No	No
12	Payment for lectures including service on speakers bureaus	No	No	No	No
13	Payment for manuscript preparation	No	No	No	No
14	Provision of writing assistance, medicines, equipment or administrative support	No	No	No	No
15	Royalties	No	No	No	No
16	Stocks/stock options	No	No	No	No
17	Travel/accommodations/meeting expenses related to these guidelines	No	No	No	No
18	Others	No	No	No	No
No.	**Conflict of interest**	**Tünde Koltai**	**Francesco Valitutti**	**Teea Salmi**	**Kossara Drenovska**
1	Board membership	No	No	No	No
2	Conflicts of interest of near family members (spouse, children, grandparents)	No	No	No	No
3	Consultancy	No	No	No	No
4	Consulting fee or honorarium	No	No	No	No
5	Employment	No	No	No	No
6	Expert testimony	No	No	No	No
7	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, etc.	No	No	No	No
8	Grant	No	No	No	No
9	Grants/grants pending	No	No	No	No
10	Patents (planned, pending or issued)	No	No	No	No
11	Payment for development of educational presentations	No	No	No	No
12	Payment for lectures including service on speakers bureaus	No	No	No	No
13	Payment for manuscript preparation	No	No	No	No
14	Provision of writing assistance, medicines, equipment or administrative support	No	No	No	No
15	Royalties	No	No	No	No
16	Stocks/stock options	No	No	No	No
17	Travel/accommodations/meeting expenses related to these guidelines	No	No	No	Yes
18	Others	No	No	No	No

Table 3 *Continued*

No.	Conflict of interest	Snejina Vassileva	Ágnes Kinyó	Jernej Dolinsek	Emiliano Antiga
1	Board membership	Yes	No	No	No
2	Conflicts of interest of near family members (spouse, children, grandparents)	No	No	No	No
3	Consultancy	No	No	No	No
4	Consulting fee or honorarium	No	No	No	No
5	Employment	No	No	No	No
6	Expert testimony	No	No	No	No
7	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, etc.	No	No	No	No
8	Grant	No	No	No	No
9	Grants/grants pending	No	No	No	No
10	Patents (planned, pending or issued)	No	No	No	No
11	Payment for development of educational presentations	No	No	No	No
12	Payment for lectures including service on speakers bureaus	No	No	No	No
13	Payment for manuscript preparation	No	No	No	No
14	Provision of writing assistance, medicines, equipment or administrative support	No	No	No	No
15	Royalties	No	No	No	No
16	Stocks/stock options	No	No	No	No
17	Travel/accommodations/meeting expenses related to these guidelines	Yes	No	No	No
18	Others	No	No	No	No

No.	Conflict of interest	Martin Shahid	Jane Setterfield	Giuseppe Cianchini
1	Board membership	No	No	No
2	Conflicts of interest of near family members (spouse, children, grandparents)	No	No	No
3	Consultancy	No	No	No
4	Consulting fee or honorarium	No	No	No
5	Employment	No	No	No
6	Expert testimony	No	No	No
7	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, etc.	No	No	No
8	Grant	No	No	No
9	Grants/grants pending	No	No	No
10	Patents (planned, pending or issued)	No	No	No
11	Payment for development of educational presentations	No	No	No
12	Payment for lectures including service on speakers bureaus	No	No	No
13	Payment for manuscript preparation	No	No	No
14	Provision of writing assistance, medicines, equipment or administrative support	No	No	No
15	Royalties	No	No	No
16	Stocks/stock options	No	No	No

Table 3 *Continued*

No.	Conflict of interest	Martin Shahid	Jane Setterfield	Giuseppe Cianchini
17	Travel/accommodations/meeting expenses related to these guidelines	Yes	No	No
18	Others	No	No	No

Table 4 Basic diagnostic procedures

If DH is suspected, the following basic diagnostic procedures are necessary
1. Medical history
2. Physical examination
3. Histopathology from a skin lesion
4. Direct immunofluorescence (DIF) microscopy
5. Serological examinations (indirect immunofluorescence (IIF) microscopy or ELISA
6. Gastroenterological assessment

occur. In patients with darker skin types, the clinical presentation is similar to that seen in Caucasians.[15,33]

Acral purpurae and petechiae are a common cutaneous finding among DH patients and may even represent the initial manifestation of the disease.[27,34–38] Haemorrhagic skin lesions affect mostly the fingers and the toes (digital purpura). As purpuric changes may be small and hard to detect, it should be considered to perform acral dermoscopy during physical examination (Fig. 2).

Rare DH presentations include isolated facial involvement, exclusively macular lesions, leukocytoclastic vasculitis-like appearance, palmoplantar keratosis, urticarial lesions or lesions mimicking prurigo.[28,39] Manifestations in unusual areas may be observed due to tight garments, belts, shoe edges, other chronic mechanical irritation or local inflammation.

Oral manifestations Mucosal involvement is rarely observed in DH and may be accompanied by subjective complaints, such as dryness, soreness or burning sensation.[15,31] On physical examination, some vesicles, erosions, or erythematous macules on the oral mucosa or tongue may be detected.[15,29,31,40,41] DH patients with gastrointestinal manifestations tend to have more pronounced oral manifestations than patients with skin lesions alone.[40]

Besides, some dental abnormalities have been described in patients with DH. These present mainly as enamel defects in permanent teeth both in children and adults.[15,23,42,43] Horizontal grooves, pits, or discoloration are the most common dental findings in patients with DH.

Gastrointestinal and other manifestations Gastrointestinal complaints may be part of the clinical spectrum of DH, although their presence is less frequent than in CD.[15] Small bowel involvement is often clinically asymptomatic despite the detection of histologic abnormalities in the gut. The minority of DH patients

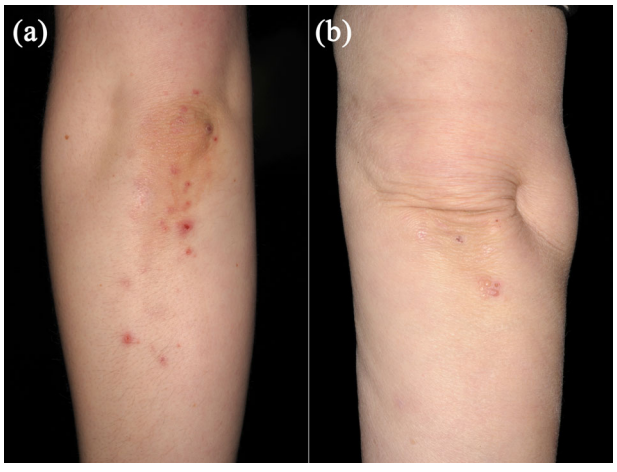


Figure 1 Clinical manifestation of DH. (a) excoriated, red, grouped urticarial papules and (b) grouped vesicles over the elbow.

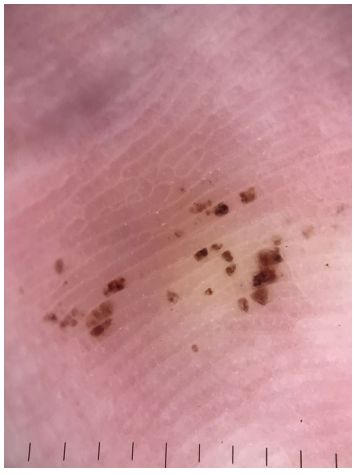
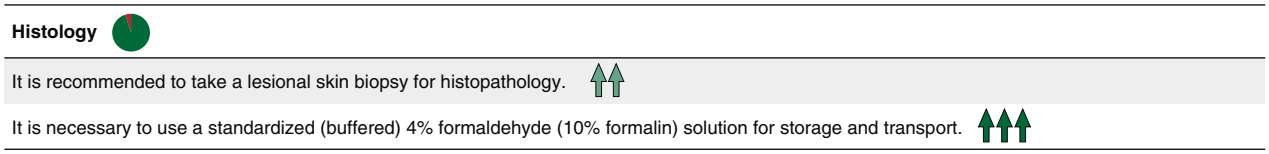


Figure 2 Clinical manifestation of acral petechiae using dermoscope on the finger of a DH patient. The bleedings can be so small that they are invisible for the unaided eye.

(15–20%) who develop gastrointestinal symptoms present with the signs of transient or chronic diarrhoea, constipation, abdominal bloating, cramping, pain, loss of weight and/or muco-cutaneous pallor.[44] Malabsorption, iron deficiency and reduced growth rates in children have also been reported. Other extraintestinal manifestations of CD (infertility, liver disease, nephropathy, neuropathy, cerebellar ataxia etc.) can also occur.

Assessment of associated diseases Besides the evaluation of coeliac manifestations, an assessment for thyroid disease, malignancies (lymphoma and leukaemia) and diabetes is recommended.[45–47] Other diseases that may occur with increased frequency in patients with DH include Addison's disease, vitiligo, alopecia areata and several other autoimmune diseases.[48]

Histology



It is recommended that a 4–5 mm lesional punch biopsy is taken. An intact vesicle or small erosions on inflamed skin can be completely excised. Larger blisters are very rare but if biopsied, it is recommended that a small amount of perilesional skin (approximately ¼ of the biopsy) is taken to prevent the blister roof from floating off during processing.

The histopathological hallmarks of DH are accumulation of neutrophils, so called neutrophilic microabscesses, in the dermal papillae. Oedema of the dermal papillae is frequently found and subepidermal splitting is present in fully developed lesions. In the blister cavity, fibrin and polymorphonuclear cells are present with predominant neutrophils and nuclear dust. Variable numbers of eosinophils may be admixed. A similar cellular infiltrate can be found in the upper dermis. In older lesions, unspecific findings with lymphocytic infiltration, fibrosis and ectatic capillary blood vessels can be observed.[49]

Histopathological findings alone do not allow the differentiation of DH from other autoimmune bullous disorders such as linear IgA disease, bullous pemphigoid, anti-p200/ laminin γ1 pemphigoid or the inflammatory variant of epidermolysis bullosa acquisita.

Direct immunofluorescence microscopy

DIF microscopy is the gold-standard laboratory procedure in diagnosing DH; i.e. it is necessary to perform it in any individual suspected to have DH. Perilesional, uninvolved skin, similarly to other autoimmune blistering dermatoses showing cutaneous lesions, is the optimal biopsy site for DIF microscopy.[50] In addition, the biopsy site is recommended to be at a predilection site.

DIF can be visualized in cryosections with short arc mercury lamp-operated microscopy, blue light-emitting diode technology-operated microscopy or laser scanning confocal microscopy.[51] The main DIF findings are consistent with microgranular or micro-granular-fibrillar IgA deposits at the tips of the dermal papillae, and microgranular IgA deposits along the dermo-epidermal junction (DEJ).[44,52,53] The papillar deposits are often arranged in vertical lines resembling falling snow. However, with serial sectioning of the tissue, up to seven patterns can be seen since combinations of the three main patterns have been described.[52] In about 30% of Japanese patients, a fibrillar deposition of IgA could also be found.[10] There are data supporting both IgA_1 and IgA_2 forming cutaneous deposits in DH, although IgA_1 predominates.[54]

In addition to deposition along the DEJ, IgA deposits have been reported in the vessels of papillary (and occasionally reticular) dermis. Less frequently, IgA granules are detectable in the elastic fibres, in the arrector pili muscles, fibres around hair follicles and in the basement membrane of sweat glands and ducts.[55] Microgranular IgA deposits can occasionally be detected along the basement membrane of the hair follicles (Fig. 3).

Infrequently, patients show granular deposition exclusively of complement factor 3 (C3) at the DEJ in absence of IgA, IgG or IgM. Recently, a case series of 20 patients showing such findings have been reported.[56] The authors proposed the term 'granular C3 dermatosis' to describe them, but due to non-specificity, it could encompass various diseases (such as DH, cutaneous gluten sensitivity, non-DH dermatoses in CD patients) rather than a distinct clinical entity.

DH patients very often show deposits of fibrinogen or fibrin at the sites of IgA precipitates.[57–60] This is a typical finding but it can only confirm diagnosis in the case of typical IgA deposits. Fibrinogen testing by DIF microscopy does not have a relevant diagnostic value.

False positivity of DIF microscopy may infrequently occur when CD patients with non-DH skin diseases, such as contact eczema, tinea or psoriasis are examined by DIF microscopy, because IgA deposits in patterns typical for DH can be detected even in CD patients' healthy skin.[61,62]

False negativity of DIF microscopy is also possible very rarely. It can occur due to technical reasons (e.g. usage of formalin-containing transport medium, inappropriate biopsy procedure) or a

DIF microscopy

DIF microscopy is the gold-standard laboratory procedure in diagnosing DH; i.e., it is necessary to perform it in any individual suspected to have DH.

It is recommended that the biopsy site for DIF microscopy is a perilesional uninvolved area at any predilection site (e.g., gluteosacral area).

It is necessary to use a transport medium designed for DIF microscopy not containing formalin.

sensitivity issue since granular IgA deposition may be scarce or patchy. False negativity can be found even if repeated biopsies are performed at different times.[45,63–65] In such rare cases, other findings may support DH diagnosis (see chapter 3.7).

Serological examinations

The two major types of circulating IgA antibodies in DH allow the testing of anti-gliadin, anti-deamidated gliadin, anti-endomysium, anti-TG2 and -TG3 antibodies for diagnostic and therapy monitoring purposes. Two major methods are currently in use: IgA-based indirect immunofluorescence (IIF) microscopy and ELISAs.

IgG-antibody-based tests are generally either not sensitive or specific enough for diagnosis in patients with normal serum IgA levels, while IgG-based assays are useful for the diagnosis in CD patients with selective IgA deficiency. Although it has been reported that DH with partial IgA deficiency does exist, total IgA deficiency in DH is not possible and therefore, IgG-based tests are only useful in exceptional cases.

Indirect immunofluorescence (IIF) microscopy

IIF microscopy is used for qualitative and semi-quantitative detection of endomysial antibodies (EMA) in the sera of CD and DH patients. Advantages of an IIF test is that it is suitable for both screening and diagnostics, but it is laborious, and specially trained personnel is needed for the somewhat subjective evaluation.

For detection of IgA EMA, cryosections of monkey oesophagus are recommended where a reticular, honeycomb-like endomysial staining pattern around smooth muscle fibres can be seen (Fig. 4). The sections can be produced individually or commercially, either on traditional glass slides or as parts of biochips. Also other substrates may be considered (e.g. human

Background

There are circulating IgA antibodies directed against two different transglutaminase isoenzymes (TG2 and TG3)

Only IgA-antibody-based serological immunoassays (IIF microscopy or ELISAs) play a significant role in diagnostics of DH

Serological examinations are recommended (indicated) in the following clinical situations:

- Establishment of first diagnosis, especially if DIF microscopy cannot be performed or it is repeatedly inconclusive
- Monitoring of dietary adherence during follow-up (only TG2-based quantitative immunoassays are suitable)
- Differential diagnosis

Definition

Indirect immunofluorescence microscopy is used for qualitative and semi-quantitative detection of endomysial antibodies (EMA) in the sera of DH and CD patients

Method for EMA (IIF microscopy)

For detection of IgA EMA, cryosections of monkey oesophagus are recommended, but also other substrates may be considered (e.g., human umbilical cord or appendix or rabbit oesophagus).

umbilical cord, normal human appendix, monkey uterus or rabbit oesophagus); the substrate needs to have smooth muscle fibres. When liver or spleen are used, the antibody binding pattern to tissue TG2 is called reticulin antibodies,[66,67] and it is similarly useful as EMA if a primate or human tissue is used.

EMA are found in only approx. 60–90% of untreated DH patients;[68–70] however, specificity is nearly 100%. In contrast, the sensitivity and specificity of this assay for CD lies between 83–100% and 98–100%, respectively.[71,72] In children, sensitivities are usually higher than in adults.

The semiquantitative EMA test and the quantitative TG2 ELISA do measure the same parameter and do not differ significantly in terms of sensitivity and specificity, hence it is recommended to perform one of them but not both since the autoantigen is the same. Still different accessibility and exposure of the TG2 epitopes may slightly differ and may cause discrepant results at low titres. Current European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines recommend TG2 ELISA as the first-line test[20], because it is available more universally in general practice and it is more quantitative. EMA is rather used as a confirmatory test due to its high specificity. EMA test may also be included in biochips. Reticulin and jejunal antibodies are not any more in routine use. Traditional indirect IF testing on rat tissues (liver, heart) was less sensitive as rodent TG2 has one coeliac epitope less than human TG2.

TG2, TG3 and gliadin ELISAs *TG2 antibody measurement by ELISA or other automated immunoassays.*

Recombinant human TG2 antigens with valine at position 224 display higher sensitivity (up to 95% in DH)[68] and give less false positive reactions in other diseases than previously used guinea pig TG2 antigens. Only kits based on proper calibration curve with multiple points provide numerical values proportional to serum antibody concentrations and only within their measurement range. Values above the upper calibrator are not reliable unless measured from appropriate dilutions (otherwise correctly given as >100 or >highest calibrator). Since calibrators are different human serum samples used in different kits, the numeric results for the same sample may differ when measured by different commercial kits. Therefore, it is important to apply the same testing method when measuring decrease of antibodies on diet.

Higher serum TG2 antibody concentrations correlate with more severe villous atrophy in DH patients.[68] High levels of anti-TG2 ≥10 times of the upper limit of normal are reliable non-invasive markers of Marsh II-III enteropathy both in CD and DH,[20] and thus in children, such TG2 antibody results replace small bowel biopsy in proving villous atrophy (also see section Intestinal diagnostics).

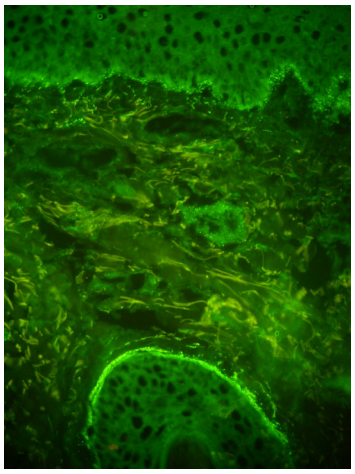


Figure 3 Simultaneous microgranular IgA deposits along the dermo-epidermal junction and the basement membrane of hair follicle of perilesional skin in DH (DIF microscopy, 400× magnification).

TG2 antibodies

Circulating IgA antibodies against TG2 are specific markers of gluten-induced enteropathy in DH and CD patients.
Their assessment is recommended in each patient. ↑↑

Test requirements

It is recommended that clinical tests use human TG2 antigen and the results are calculated based on a calibration curve. ↑↑
Reports are recommended to indicate the antibody concentration in numeric values, the name of the test kit and the upper limit of normal. ↑↑
For monitoring the effect of the gluten-free diet, the same test kit is recommended to be used as initially. ↑↑

Interpretation of TG2 ELISA and other TG2-based immunoassays

TG2 positivity alone is not sufficient for the diagnosis of DH as false positivity may occur. However, it has a high positive predictive value.
TG2 negativity does not exclude the possibility of DH.

Use of EMA or a TG2-based immunoassay

It is necessary that at least one serological test is performed if DH is suspected. ⇑⇑⇑

IIF microscopy (EMA test) and TG2-based immunoassays (e.g., TG2 ELISA) do not differ significantly, hence it is recommended to perform one of them but not both. ⇑⇑

It is recommended that commercially available, quality-controlled assays are used. ⇑⇑

TG3 antibodies. TG3 (epidermal TG) is part of the IgA deposits in the DH skin, and the majority of DH patients have circulating antibodies against TG3. While TG3-specific antibodies are good markers of DH and sometimes can be detected even in DH patients without TG2 antibodies, they also occur in a substantial fraction of CD cases without visible skin lesions. The TG3-specific reactivity increases with age in CD patients.[8]

Interpretation of TG3 ELISA

The use of a TG3 ELISA may be considered in addition to the TG2 test. ⇑
TG3 positivity alone is not sufficient for the diagnosis of DH as it may be positive also in CD. However, it has a high positive predictive value.
TG3 antibody negativity in serum does not exclude the possibility of DH.

Gliadin antibodies. As gliadin peptides are presented to T cells after deamidation by TG2, current gliadin antibody tests usually apply deamidated gliadin peptides as antigens. Although this test has been supposed to be more specific and sensitive than measurement of antibodies against native gliadins, the peptides are not standardized, most are proprietary and new evidence search shows that adding this test to TG2 antibody rather decreases diagnostic specificity for CD without considerably increasing sensitivity. In fact, anti-deamidated gliadin antibodies do not predict CD when TG2 antibodies are not detectable.[73] They frequently occur in healthy persons and in unrelated disease conditions. Anti-gliadin and anti-deamidated gliadin antibodies of IgA class have even less accuracy than those of IgG class. Thus, the use of anti-deamidated gliadin antibodies for diagnosis of CD is not recommended by the recently published guidelines of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition.[20]

Several studies investigated anti-deamidated gliadin antibodies in DH showing that they have in general a slightly higher sensitivity and a slightly lower specificity than anti-TG2 antibodies in patients with DH.[74–79] Thus, detection of antibodies against deamidated gliadin may be considered in the diagnostic workup for DH, but such assays are not recommended as primary tests.

Gliadin antibodies

Antibodies against gliadin or deamidated gliadin are not recommended to be used as primary tests in the diagnostic workup for DH or CD. ⇓

Intestinal diagnostics

Small bowel assessment

It is recommended that small bowel biopsy is performed in DH patients to evaluate the degree of enteropathy. ⇑⇑

At least four specimens from the distal duodenum and at least one from the duodenal bulb should be considered to take by oesophagogastroduodenoscopy. ⇑

In children with very high levels of serum TG2 antibodies (≥10 times above the upper limit of normal) confirmed by EMA positivity from a separate blood sample, enteropathy can be diagnosed even without biopsy.[20]

Since absorption tests have low sensitivity, these tests are not recommended. The absorptive capacity of the small bowel is much higher than actually used, therefore only very severe reduction of the villous surface leads to abnormal values. However, low iron stores (low serum ferritin level) can be an indication of malabsorption, but it is much less often seen in DH than in CD with similar degree of small bowel abnormality.

The direct evaluation of the small bowel structure is commonly done from biopsy specimens from the distal part of the duodenum. Taking more specimens, among them at least one from the duodenal bulb, increases the sensitivity to detect villous abnormalities. It is necessary that specimens for routine histology are fixed in formaldehyde and embedded in paraffin. It is necessary that specimens meant to detect coeliac antibody deposition in the small bowel are processed unfixed and frozen for DIF microscopy.

The small bowel structure is assessed according to the Marsh stages (0-III), where Marsh III is assigned to samples with villous atrophy (qualitative assessment). Marsh stages can only be judged from well-oriented samples and it is necessary that diagnostic conclusions are drawn from samples of sufficient quality.

DIF microscopy reveals TG2-targeted antibody deposition also in the architecturally normal intestinal mucosa of DH patients with only few exceptions, indicating that almost all DH cases have systemic gut involvement with at least low grade enteropathy.

Although the diagnosis of DH can be proven by DIF microscopy of the skin alone, assessment of the small bowel condition is useful for planning the treatment strategy and making clear to the patient and the managing staff that DH is not only a skin problem.

Diagnostic criteria for DH

Diagnostic criteria for DH 

The diagnosis of DH can be made if both major diagnostic criteria are fulfilled:
1. Clinical manifestation compatible with DH
2. Positive DIF microscopy

If the clinical manifestation is incompatible, no diagnosis can be made. If DIF mic-roscopy result is repeatedly negative, but the clinical manifestation is typical for DH, the diagnosis of DH can be supported by the *combination of the following minor criteria*:

- Traditional histology is compatible with DH
- At least one serological test of high diagnostic value (TG2, TG3, or EMA) is positive
- Duodenal biopsy shows evidence for CD
- The result of HLA testing is compatible with DH
- Positive iodine patch test or oral iodine challenge
- Swift response to dapsone (partial recovery within 1 week of 100 mg daily)
- Response to a long-term gluten-free diet

In case of contradictory or incompatible findings, it is recommended that the patient is referred to a referral centre specialized for DH. It is necessary that contradictory examinations are repeated.

Ancillary laboratory examinations

HLA haplotypes genotyping Due to the associated CD, the characterization of the HLA haplotypes as a major genetic risk factor may be considered also for the diagnosis of DH in selected clinical constellations.[44] The most important genetic risk factor for CD is indeed the presence of HLA-DQ heterodimers DQ2.5 (encoded by alleles A1*0501 and B1*0201 in cis, DQ2.2 (A1*0201 and B1*0202)/DQ7 (A1*0505 and B1*0301) also known as DQ2 in trans) and DQ8 (encoded by alleles A1*0301 and B1*0302).[80–82] The presence of HLA-DQ2 (~95%) and HLA-DQ8 (~5%) provides a sensitivity of close to 100% and a very high negative predictive value (>99%) for CD and DH. Thus, in a person lacking the relevant disease-associated alleles, CD is virtually excluded. However, as shown in a large cohort of patients with CD in a prospective study, the addition of HLA-DQ typing to serological investigations, including TG2 ELISA and EMA, did not improve the accuracy of the diagnosis compared with the use of the serological tests alone. Because HLA-DQ2 is present in up to 30% of the Caucasian population, HLA-DQ2 typing has a rather low positive predictive value of about 12%.[83] Therefore, in agreement with the current guidelines for the diagnosis of CD and DH,[20,44,84–86] HLA-DQ2/DQ8 typing is not recommended to be used routinely in the diagnosis of DH. Nevertheless, HLA-DQ2/DQ8 testing may be considered as an extension of the basic diagnostic programme for DH to effectively exclude the disease in selected clinical situations, including but not limited to those detailed in Ref. 43 and chapter 4.

However, current PCR methods often investigate only the SNP-s of the common alleles of DQ2.5, DQ2.2 and DQ8 (which is cheaper than traditional typing), so variant DQ2 or DQ8 alleles in certain populations may give false negative results. Therefore, the negative predictive value of such results is not so strong as earlier anticipated. Moreover, recent observations show that incomplete alleles and DQ9 also confer risk in rare patients.[87] In line with this, DR4 or DR9 (effectively associated with DQ8 and DQ9, respectively) were described in 13/14 Japanese DH cases with granular IgA deposition in the skin.[10]

Screening for co-morbidities

Several conditions, including autoimmune diseases such as thyroidopathies, diabetes mellitus type 1, Addison disease, and multiendocrine syndromes, as well as lymphoproliferative diseases and hyposplenism were shown to have an increased prevalence in patients with CD and DH.[45,88–91] Among them, subclinical thyroid disease is most common and testing is relevant, thus it should be considered that all patients with DH are screened for thyroid disease (at least by measuring TSH).[43] As lymphoproliferative disease is less prevalent in DH than in CD, routine evaluation of lymphoma is not recommended unless there is clinical suspicion.

HLA haplotypes genotyping

HLA-DQ2/DQ8 typing is not recommended routinely in the diagnosis of DH. ↓

Indication for HLA-DQ2/DQ8 testing

HLA-DQ2/DQ8 positivity does not confirm DH and testing may be considered to exclude DH or CD in selected clinical situations due to its high negative predictive value. ↑

Thyroid disease

It should be considered to assess thyroid function and thyroid autoimmunity at diagnosis and during follow-up. ↑

Cardiovascular risk factor assessment

It has been shown that the diet of coeliac patients is based on the regional food preparation traditions and styles.[92] Gluten free products frequently have higher levels of lipids, sugar and salt to improve food palatability and consistency which may result in excessive consumption of hypercaloric and hyperlipidic foods to compensate dietetic restriction in patients with DH. This may have a negative impact on cardiometabolic risk factors such as obesity, serum lipid levels, insulin resistance, metabolic syndrome and atherosclerosis.[92–97] In addition, dapsone treatment may have severe side effects in patients having cardiovascular disease.

Therefore, in males above 40 and females above 50 years of age, medical history should also focus on cardiovascular risk factors (such as smoking, hypertension, diabetes, hyperlipidaemia and hyperuricaemia), and basic cardiovascular assessment (such as ECG, ultrasound examination of main arteries, referral to a cardiologist, etc.) should be considered both initially and during follow-up if clinically indicated.

Other autoimmune diseases

Testing for other autoimmune diseases may be considered and adequate examinations should be performed accordingly depending on the clinical situation. ↑

Cardiovascular risk factors

Cardiovascular risk factors should be considered at diagnosis and during follow-up if clinically indicated. ↑

Evaluation of malabsorption

Evaluation of blood cell counts, serum ferritin level and the nutritional state should be considered. ↑
Further examinations depend on the clinical situation.

Evaluation of malabsorption

Malabsorption resulting in anaemia, weight loss as well as vitamin- and mineral-deficiencies characterize classical CD and are still highly prevalent in patients with newly diagnosed CD.[98,99] Therefore, appropriate nutritional assessment at the initial diagnosis of DH will provide a base for nutritional advices and follow-up in patients with DH.[43] This is why assessment of nutritional state should be considered. The incidence of asymptomatic CD-related deficiencies or autoimmune diseases is low in patients with normal nutrition at diagnosis,[100] still low iron stores (low ferritin) may be often detected even in absence of anaemia. The best evaluation of the absorption status is histological assessment of the small intestinal villous structure by biopsy. Other so called absorption tests (D-xylose test, H_2 breath test) are not sensitive enough to detect enteropathy, thus they are not recommended routinely. In adults, DEXA scan can assess bone mineral density and low level can indicate malabsorption, but in DH, it is not indicated routinely. However, in paediatric patients its use is discouraged as no clinical predictors for low mineral density are available[101] and the normal mineral density will be obtained once the diet is started.[102]

Blood cell counts and serum ferritin determination should be considered, other laboratory screening is not recommended in this group.

Other non-laboratory examinations

Other non-laboratory examinations
Routine bone mineral density measurements are not recommended at the time of DH diagnosis.
Quality of life assessments are not routinely recommended but individually suggested when DH is diagnosed.

The bone mineral density (BMD) has been shown to be decreased in untreated CD,[103] and further, increased bone fracture risk is associated with CD.[104] However, although scarcely studied, it seems that BMD is less affected in untreated DH compared to CD,[105,106] and the fracture risk in DH has been comparable to that in the general population.[107] Therefore, there is no need for routine BMD measurements when DH is diagnosed.

The quality of life (QoL) of DH patients seems to be impaired at the time of the diagnosis and the presence of abdominal symptoms and female gender has been linked to even more reduced QoL. Adherence to a GFD has been shown to improve the QoL to the level of healthy controls within the first year of gluten-free dietary treatment.[108] Current evidence about QoL in DH is, however, insufficient to recommend routine QoL investigations, and DH-specific health related QoL questionnaires are lacking. Hence, at the moment the necessity of QoL assessments with generic or dermatological QoL instruments should be considered on the individual level.

Differential diagnostics

DH should be differentiated from each cutaneous condition with itching, excoriated, blistering or eroded rash. The most important such conditions are autoimmune bullous diseases, thus they will be presented in a separate section.

Autoimmune bullous diseases

DH has to be differentiated from linear IgA bullous dermatosis and prototypic autoimmune bullous skin diseases, particularly bullous pemphigoid and epidermolysis bullosa acquisita.[109,110]

Main differential diagnoses for DH: autoimmune bullous diseases
• Linear IgA dermatosis • Bullous pemphigoid • Anti-laminin γ1 pemphigoid • Epidermolysis bullosa acquisita • Bullous systemic lupus erythematosus • Pemphigus herpetiformis • IgA pemphigus

Linear IgA bullous dermatosis (LABD) Linear IgA bullous dermatosis is a rare autoimmune blistering disease that occurs in both children and adults. LABD may mimic DH in terms of clinical presentation. However, the 'string of pearls' configuration of the vesicles, that is regarded as hallmark of LABD, and possible occurrence of large blisters in LABD are clues differentiating the two conditions. Besides, predilection sites of LABD are generally different from those of DH including the trunk, followed by the

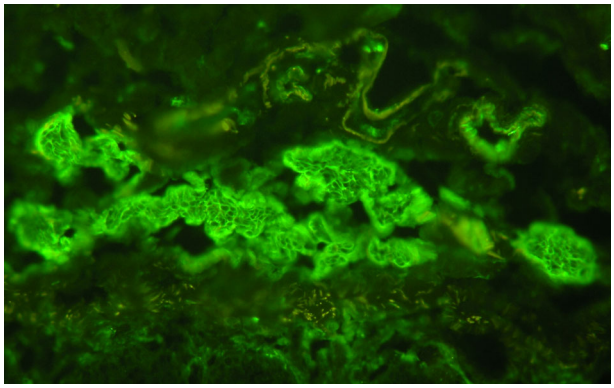


Figure 4 Positive EMA test. IgA antibodies show typical honeycomb-like, endomysial staining with IIF microscopy on a monkey oesophagus section (80× magnification).

legs, face with main involvement of the perioral region, and anogenital region.[111] Furthermore, disease-specific mucosal involvement, presenting with vesicles, erosions and erythematous macules, is seen in DH[31,40] much more rarely than in LABD.[112] On the other hand, autoimmune connective tissue diseases may be independently associated with oral manifestations, making difficult to distinguish the latter from strictly DH-related mucosal features.

Histology may be similar in DH and LABD. Conversely, DIF microscopy shows granular, fibrillar or punctate IgA deposits predominantly visible at the top of dermal papillae in DH,[31] whereas in LABD, linear IgA deposits along the DEJ are considered the hallmark of the disease.[111] In addition, IIF microscopy is positive for linear IgA along the basement membrane in approximately 30% of LABD patients[113] and its sensitivity increases using the salt-split skin technique reaching nearly 80% and 50% of positivity in children and in adults, respectively.[112] On the other hand, circulating IgA autoantibodies against TG2 are typically detected in DH.[28,114]

Bullous pemphigoid (BP) Each manifestation of bullous pemphigoid (BP), especially vesicular, urticaria-like, nodular or eczema-like presentations, may mimic DH. However, BP usually occurs in the elderly population unlike DH and is not associated with CD. From a histopathological point of view, the inflammatory infiltrate in BP mainly consists of lymphocytes and eosinophils,[115] while in DH, neutrophilic microabscesses are characteristic at the top of the dermal papillae.[116] Furthermore, DIF microscopy in BP typically reveals linear deposits of IgG and C3 along the DEJ, while ELISA shows the presence of circulating anti-BP180 and/or anti-BP230 antibodies at different titres.[115]

Anti-laminin γ1 pemphigoid Anti-laminin γ1 pemphigoid (formerly anti-p200 pemphigoid) is a rare subepidermal autoimmune blistering disease that occurs more frequently in the middle-aged and may clinically resemble to DH. It generally manifests as erythematous plaques and tense blisters on the trunk as well as palms and soles, accompanied by itching; mucous membrane involvement is present in 20% of cases. Differentiation from DH is allowed by a combination of clinical and immunopathological features, notably the detection of serum IgG autoantibodies against the laminin-γ1 chain on immunoblot or immunoprecipitation.[109]

Epidermolysis bullosa acquisita (EBA) Similarities in terms of cutaneous manifestations exist between DH and EBA. In the classic variant of EBA, vesicular and blistering lesions typically occur at the sites of trauma, possibly mimicking the agminated configuration of DH lesions but generally lacking the rigorously symmetrical distribution of the latter one. The rarer BP-like presentation of EBA may in some cases recall the clinical picture of DH but in the first one there is usually associated mucous membrane involvement, notably of the oral cavity. Unlike DH, vesiculobullous lesions of EBA heal leaving often superficial scars and milia. Eventually, IIF microscopy on salt-split skin displays linear IgG deposits along the floor of the bulla and ELISA reveals the presence of autoantibodies against collagen VII, which is the target autoantigen in EBA.[115]

Bullous systemic lupus erythematosus (BSLE) Bullous systemic lupus erythematosus (BSLE) is a rare presentation of lupus erythematosus usually occurring in SLE patients that may share clinical and histopathological features with DH. However, DH can be differentiated from the bullous variant of lupus by the presence of laboratory markers of gluten sensitivity and the absence of serum immunological findings such as antinuclear and other autoantibodies. Furthermore, BSLE is hallmarked by IgG and IgM deposits at the basement membrane zone, allowing this condition to be easily differentiated from DH, where only IgA deposits are detected.[117] Similarly to EBA, IIF on salt-split skin displays dermal binding of IgG anti-BMZ antibodies and ELISA is positive for autoantibodies against collagen type VII.

Pemphigus herpetiformis Pemphigus herpetiformis may be regarded as another possible differential diagnosis of DH. It is clinically characterized by a vesiculobullous eruption with arcuate, urticarial and circinate plaques with peripheral vesicles mainly involving the trunk. However, skin biopsies demonstrate focal intraepidermal split with acantholysis, eosinophilic spongiosis and intraepidermal IgG and C3 deposits with an intercellular pattern using DIF microscopy.[110]

Rarely, CD can be associated with autoimmune bullous diseases different from DH (e.g. EBA).[118]

Non-autoimmune diseases

Main differential diagnoses for DH: non-autoimmune diseases

- Atopic dermatitis and other types of eczema
- Multiple folliculitis
- Nodular or subacute prurigo
- Scabies
- Arthropod bite reactions (papular urticaria, strophulus)

Due to its polymorphic clinical presentation, DH can be misdiagnosed as other chronic pruritic non-autoimmune dermatoses including atopic dermatitis, scabies, papular urticaria (insect bite reactions), impetigo in children, and other forms of eczema, nodular or subacute prurigo, folliculitis, urticaria and erythema multiforme in adults.[15,44] Moreover, other diseases have been reported to mimic the clinical appearance of DH.

Atopic dermatitis and other types of eczema need to be differentiated since they can present with itchy, grouped papulo-vesicles. The localization of the lesions is usually different since the eczematous lesions are more flexural in contrast to more common extensor involvement in DH. The differentiation may be difficult in children with atopic dermatitis if the lesions are limited to the extensors. The differential diagnosis of nummular eczema presenting as grouped, itchy papulo-vesicles may be very challenging.

Prurigo presents as excoriations as is often seen in DH, though the lesions are generally distinct and not grouped as in the latter. Scabies may present as pruritic papules and excoriations, but the lesions are generally discrete except in crusted scabies where oozy crusted lesions may localize on the extensors as in DH and create diagnostic confusion. Papular urticaria can present as itchy urticarial papules/vesicles on the exposed parts of extremities but the lesions are generally discrete. Erythema multiforme may occasionally resemble DH; though the lesions are generally non-itchy and usually localized at palms and soles, there may be grouped tiny vesicular lesions on erythematous base on the elbows and knees. Polymorphic light eruption may have itchy grouped papulo-vesicles, but the lesions are associated with photosensitivity, in contrast to DH.

DH can occasionally present as acral purpura[37] and may be clinically confused with thrombocytopenic purpura, though the lesions are not strictly acral in the latter. There are stray reports of chronic urticaria,[119] bullous prurigo pigmentosa,[120] Grover's disease[121] and bullous rheumatoid neutrophilic dermatitis[122] having clinical resemblance with DH.

Although clinical observation alone is not sufficient for the diagnosis, the localization and burning itch experienced during the development of blisters is usually severe enough to raise suspicion of DH.[8,43] Nevertheless, the presence of granular IgA deposits at the dermal papillae found in perilesional skin of patients with DH is the clue to make the differential diagnosis.[44]

It has been reported recently that CD patients with inflammatory skin diseases different from DH may present granular IgA deposits at the dermal papillae,[61] and the latter may be present even in CD patients without any cutaneous involvement.[62] Therefore, in patients with CD, DIF findings alone may be not enough to make a differential diagnosis with DH, and more weight should be given to clinical presentation, histopathological examination, as well as response to a gluten free diet.[61]

Finally, in the last years, skin manifestations of non-coeliac gluten sensitivity have emerged as a novel diagnostic challenge in patients with gluten intolerance, since they can clinically resemble DH and can be associated with similar intestinal symptoms.[123,124] In these cases, however, DIF microscopy and serologic testing for anti-transglutaminase antibodies are negative, making the differential diagnosis easier.

Therapy

Therapeutic options recommended in DH

Main option:
- Lifelong gluten-free diet +/- dapsone

Additional options:
- Sulfasalazine
- Potent topical corticosteroids
- Antihistamines

Therapeutic decisions

A lifelong gluten-free diet with or without dapsone is the main option for treatment of DH; other therapies are significantly less beneficial. The only causative treatment option is a lifelong gluten-free diet (GFD). It is necessary in each case. It should be started, however, only after completing all diagnostic examinations.

All other options are for symptomatic therapy of the skin findings and pruritus. They do not act on any internal organ

manifestation of DH; consequently, they are not recommended to replace the GFD. They should be considered only if (i) the symptoms are not tolerable by the patient, (ii) the skin involvement is severe, (iii) the patient does not accept a GFD or is unable to adhere to it, (iv) the disease does not respond to a correct GFD. The most efficient drug for symptomatic treatment is dapsone. Its effect can be observed already within 3–4 days (this swift response supports the diagnosis). Other symptomatic therapy options, such as sulfasalazine, potent topical corticosteroids and antihistamines, are significantly less efficient and may be considered only if dapsone is contraindicated, not tolerated or the patient does not give consent to its use.[28,125]

In the next chapters, the above mentioned therapies will be described in detail.

Gluten-free diet

Dietary treatment of DH

It is necessary that all patients with DH follow a strict and lifelong gluten-free diet (GFD).

It is recommended that patients with suspected DH do not start a GFD before completing all diagnostic examinations.

A strict and lifelong gluten-free diet (GFD) is the treatment of choice in DH. It is associated with the relatively rapid resolution of coeliac gastrointestinal signs and symptoms, clearance of circulating IgA autoantibodies and the lower risk of developing lymphomas promoted by chronic antigenic stimulation.[126] However, the resolution of the skin lesions is slower and can take several months or even years (on average, 2 years).[127] Deposited IgA autoantibodies may stay in the dermis for up to a decade even under a strict GFD. Further benefits of a GFD are proper mineralization of bones, improved quality of life and prevention of refractory DH.[126] For further information on a GFD, please refer to the recently published ESPGHAN guidelines.[20]

Regulations on GFD in Europe

- Gluten-free labels guarantee safety for DH and CD consumers, whereas foods labelled as "very low gluten content" are not suitable for these patients
- Hidden gluten contamination should be avoided as it is easy to reach toxicity thresholds

Gluten provides structure and elasticity to bakery products.[128] A GFD encompasses the elimination of wheat, rye, barley, triticale, khorasan wheat (also known as kamut®) and spelt from the diet, i.e. bread, pasta, baked goods, cereal-derived beverages such as beer, etc.[129]

Oat can be safely recommended nowadays for coeliac patients if it is not contaminated with gluten-containing cereals (especially during the harvesting, transportation, storage or production).[130] Prohibited cereals can be substituted by other sources of complex carbohydrates such as rice or corn, some pseudo-cereals, like sorghum, millet, quinoa, or by flours derived from almond, poppy seed, chestnut, coconut, pumpkin seed or sesame, all of which are naturally gluten-free. Other vegetables, legumes, fruits, milk and cheeses, eggs, any kind of meat and fish can be eaten without any restrictions unless contaminated with gluten during the whole technological/storage process.

It is noteworthy to stress that patients should not start with a GFD before they receive the final diagnosis.

Commission Regulation No 41/2009/EC set out for the first-time harmonised rules on the information provided to consumers on the absence of gluten ('gluten-free') in food.[131] Starting from 20th July 2016, European Commission released an update of structured product labelling to consumers: these regulations helped CD and DH patients in identifying gluten and choosing a varied diet when eating inside or outside their home.[132,133]

The statement 'gluten-free' may only be made if the food contains no more than 20 mg/kg of gluten. 'Very low gluten' containing products (<100 mg/kg) are not suitable for CD and DH patients and their consumption should be strongly discouraged. These products comply to EU regulation but they are developed in some countries to address specific dietary needs of gluten-sensitive patients who are not in the CD-DH autoimmune spectrum.

In fact, ingesting even small amounts of gluten may trigger again the disease for DH patients. Safety threshold for gluten traces of <50 mg/day has been established for CD by a double-blind, placebo-controlled trial.[134] Gluten might be hidden in a huge variety of food, such as sauces, coatings for meatballs and fish-fingers. Moreover, the possibility of cross-contamination should be considered when serving meals at home or at restaurants. This may be the consequence of inappropriate storage or shared processing.[135]

GFD: nutritional implications

- It is recommended that DH patients follow a healthy and well-balanced GFD.
- Micronutrient and vitamin supplementation may be considered case-by-case.

Elimination of gluten-containing cereals theoretically exposes to group B vitamin deficiencies as these represent the major source of them.[136] A lower intake of calcium and iron has also been described on a GFD.[137] Similarly, since whole grains deliver a substantial amount of soluble fibres as well, a reduced fibre intake might be an issue.[138]

Dietary counselling should always emphasize the importance of a very wide GFD diet comprising naturally gluten-free food such as vegetables, legumes, fruit and various sources of protein; moreover, the consumption of nutritionally rich gluten-free cereals and pseudo-cereals such as quinoa and amaranth should be encouraged.[139,92]

For a correctly performed GFD, the help of a dietitian is indispensable who can provide a list of products containing primarily gluten or are possibly contaminated. Patients on a diet relying merely on rice and corn as complex sugars are theoretically at higher risk for arsenic and mycotoxin exposure.[140,141] Patients with type I diabetes comorbidity should be wisely informed about the dietary choices as gluten-free products and cereals have a higher glycaemic index which may undermine blood glucose control.[142]

The overweight/obesity epidemics affect CD (and likely DH as well), both as accompanying initial presentation[143–145] and as rebound overweight during follow-up.[146,147] Thus, DH patients on a GFD should be cautioned on the rebound weight gain and should follow a well-balanced normo-caloric diet in order to prevent cardiovascular disease.

After commencing a GFD, micronutrient and vitamin supplementation (iron, vitamin D, calcium, vitamin B) may be considered in some cases depending on the severity of the deficiencies. Data about its benefit are contradictory,[99,148,149] albeit underlying malabsorption in DH/CD is almost always corrected by the sole exclusion diet within 6–12 months and nutritional supplementation is usually not needed on the long run.

Other dietary recommendations

The GFD is the base of the therapy of DH. However, observations showed that excessive iodine intake (e.g. sea food, multivitamin-multimicroelement diet supplements) should be avoided to prevent relapses in patients on an incomplete GFD.[52,150,151]

Dapsone

Dapsone is the drug of first choice for symptomatic DH treatment. Although there are no randomized, controlled trials evaluating its efficacy in DH, except for small case series, there is strong consensus that dapsone is highly effective for DH treatment. Until the gluten-free diet becomes effective (after 6–24 months), dapsone is the most effective treatment for cutaneous manifestations and itching.[44,125] Signs and symptoms of DH usually resolve within 3–4 days of starting dapsone and withdrawal of dapsone results in recurrence within a few days.[44,152,153]

The activity of serum glucose-6-phosphate dehydrogenase (G6PDH) is recommended to be determined prior to dapsone administration. The starting dose can be either low or high depending on the severity of the skin manifestation. If a low starting dose is chosen, it should be 25 mg qd or bid in order to minimize the potential side effects. Then the dose can be increased by 25 mg/day every week up to 200 mg/day until an optimal dose is found that controls the disease; in the maintenance phase, 0.5–1 mg/kg/day can generally control pruritus and prevent the development of new cutaneous lesions.[28,44,125]

Dietary counselling

For a correctly performed GFD, it is necessary to refer all DH patients to a dietitian, especially if there is need for an additional diet due to co-morbidites.

Indications of dapsone treatment in DH patients

Dapsone therapy is recommended in the following clinical situations:

- Intolerable and/or severe skin involvement
- The skin manifestation does not respond to a correct GFD
- The patient does not accept or is unable to adhere to a GFD

In case of severe skin involvement and extreme pruritus, higher starting doses such as 50 mg bid or tid may be considered, if a G6PDH deficiency can be excluded. After clinical remission is reached, the dose should be lowered to the minimal maintenance dose. If no response can be detected within 1 week at a daily dose of ≥150 mg, the diagnosis should be reconfirmed or a change to a different therapy considered. A strict and continuous GFD helps to reduce the dose of dapsone rapidly, and in most patients, dapsone therapy can be completely discontinued.[154,155]

The initial paediatric dose of dapsone should be 1–2 mg/kg PO qd or in two divided doses; the maximum single dose should be 50 mg. The maintenance dose is individual and usually lies between 10–25% of the initially effective dose.

In case of renal impairment, no dose adjustment is needed. In case of hepatic impairment, caution and frequent laboratory follow-up examinations are advised.

Dapsone therapy should be continued until complete remission. In case of relapses, the dose can be temporarily increased by the patient, and if a severe relapse occurred after the drug had been stopped, it can be resumed. It should be kept in mind, however, that a correct GFD is decisive in 100% of the cases and subsequent relapses of the disease are therefore a consequence of a gluten-containing diet. A flare can appear from a few days till up to a few months from the reintroduction of gluten.[44]

Mode of action The mode of action of dapsone is still not understood in each aspect. It shows anti-inflammatory activity by inhibiting neutrophilic and eosinophilic activation and migration. In addition, it prevents tissue destruction by inhibiting myeloperoxidase, an enzyme involved in the neutrophils' respiratory burst which is responsible for the production of toxic oxidants.[156] As a consequence, it acts only in the skin but does not influence other underlying pathologies such as intestinal involvement.

The side effects of dapsone The side effects of dapsone are usually dose dependent, appear to a certain extent in virtually each patient and are generally well tolerated in young or middle-aged patients.[28,44,125,157] However, also idiosyncratic side effects can emerge very rarely. Thus after a detailed baseline evaluation, patients receiving dapsone should be followed up regularly with clinical and laboratory examinations during the treatment (Table 5). Major dose dependent (toxic) side effects are methaemoglobinaemia, haemolytic anaemia (it can appear rapidly within the first days of treatment, but it develops usually over a few weeks), neutropenia, headache, dizziness, weakness, fatigue and gastrointestinal symptoms such as nausea and vomiting.[28,125,158]

These side effects are more frequent in patients with G6PD deficiency, co-morbidities reducing tissue oxygenation, and in the elderly.[116,157] Thus in such cases, lower doses and closer follow-ups are recommended.[31,44,159]

Major contraindications of dapsone

- Glucose-6-phosphate dehydrogenase (G6PDH) deficiency
- Low blood cell counts, especially anaemia or neutropenia
- Any cardiac or pulmonary disease leading to significantly impaired tissue oxy-genation

When methaemoglobinaemia levels are between 20% and 40%, symptoms such as dizziness, headache, tachycardia and

Table 5 Diagnostic examinations under dapsone therapy in DH. In patients with co-morbidities or abnormal laboratory values, more frequent follow-ups, dose reduction of dapsone or interruption of therapy should be considered[14,125,159]CBC, Complete blood cell counts, MetHb, methaemoglobin.

Frequency	Recommended examinations
Baseline	History and clinical review CBC including reticulocyte count Liver function panel Renal function panel Serum G6PD level (if not available, reduced starting dapsone dose is recommended)
First month: weekly Second and third month: every two weeks	History and clinical review CBC including reticulocyte count MetHb if daily dose>150 mg
First three months: every two weeks	Liver function panel Renal function panel
Every third month	History and clinical review including peripheral motor neurological examination CBC including reticulocyte count MetHb if daily dose>150 mg Liver function panel Renal function panel

Table 6 Alternative therapies in DH[164–174]

Treatment modality	Remarks
Sulfasalazine,sulfapyridine, sulfamethoxipyridazine	Less effective than dapsone, variable dosage (1-4 g/day sulfasalazine or 0.25-1.5 g/day sulfamethoxypyridazine). In Europe, sulfapyridine and sulfamethoxipyridazine are only approved for veterinary use.
Tetracycline plus nicotinamide	Tetracycline 500 mg q.i.d. and nicotinamide 500 mg t.i.d.
Colchicine	Its usefulness cannot be judged currently
Cyclosporine	Published dosage in dangerous range (5-7 mg/kg body weight)
Potent topical glucocorticoids	Partially effective, potentially severe side effects upon long-term use
Systemic glucocorticoids	Not recommended due to inefficacy

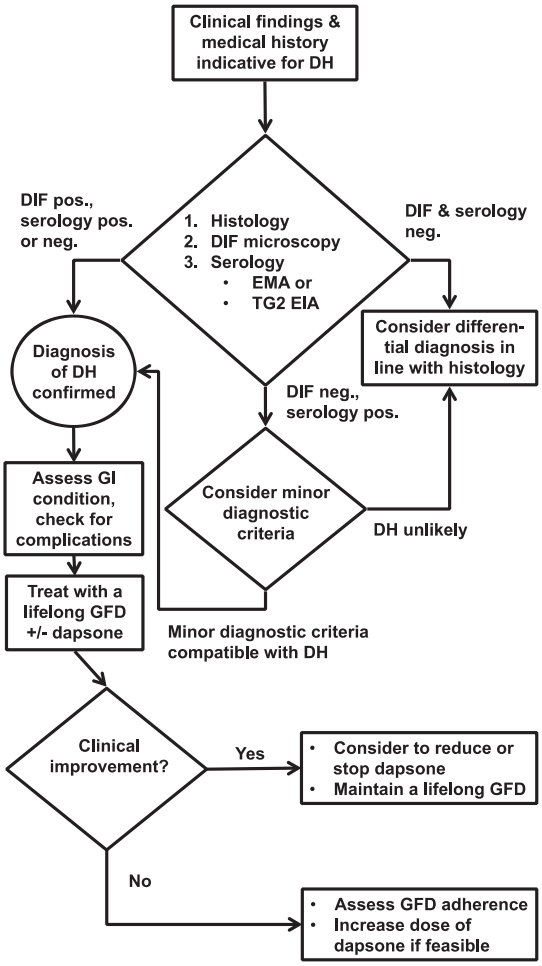


Figure 5 Management of dermatitis herpetiformis (DH). Abbreviations: DIF, direct immunofluorescence microscopy; EMA, endomysial antibodies; TG2 EIA, tissue transglutaminase enzyme immunoassay; GFD, gluten-free diet; GI, gastrointestinal.

weakness may occcur, and this may require dose reduction.[156,159,160] However, above 45% (usually at doses exceeding 200 mg/day) it may become a serious problem with the signs of acidosis, dyspnoea, seizures, arrhythmias and coma.[159,160] Reducing agents such as vitamin C (200 mg tid) and E (400 mg tid) can significantly improve these symptoms. Vitamin C may also be started prophylactically.

Other side effects include a possible idiosyncratic hypersensitivity reaction. Dapsone hypersensitivity syndrome usually appears in the form of a 'drug reaction with eosinophilia and systemic symptoms' (DRESS) within the first 2–6 weeks of treatment, regardless of dosage, and is characterized by the triad of fever, rash (erythematous papules, plaques, pustules and eczematous lesions), and internal organ involvement such as renal and/or hepatic failure.[44,116,157,159,161,162] In addition, pruritus, lymphadenopathy, eosinophilia and photosensitivity may develop. Dapsone syndrome is a rare (estimated 1% of patients) but serious complication requiring both withdrawal of the medication and systemic corticosteroid treatment.[125,159] Hypo- or agranulocytosis may also emerge within the first three months of treatment, hence blood cell counts have to be monitored strictly (Table 5).[125,158,159] Given the rare photo-sensitizing activity of dapsone, a total photo-protection may be needed if clinically indicated. Most side effects appear within the first 3 months. However, peripheral motor neuropathy typically occurs after some years of taking high doses and it may not be reversible after dose reduction or stopping of dapsone.[158,159]

Use of dapsone in special situations Although dapsone can cross the placenta during pregnancy, it is generally considered to be safe for both mother and fetus. It is secreted in breast milk and may cause mild haemolytic anaemia in babies. Dapsone usually does not pose a risk to infants unless they have G6PD deficiency. Dapsone is considered a safe treatment in infants and children at doses of 1–2 mg/kg/day.[157,159]

Other alternatives

Exceptionally, alternative medical treatment may be considered in case of contraindications, unavailability, or inefficacy of dapsone, and/or in case of inadequate control of the disease despite strict adherence to a gluten-free diet. With the exception of a case series,[163] only case reports are available about these alternatives, thus their use is not evidence based and should be restricted to special situations. They are listed in Table 6.

Summary

In summary, if clinical findings and medical history are compatible with DH, histological and serological examinations are necessary (Fig. 5). If the result of DIF microscopy is positive, then the diagnosis of DH can be made. If DIF microscopy is repeatedly negative, but serology is positive, it is recommended to consider minor diagnostic criteria. In case of confirmed DH diagnosis, assessment of GI condition and complications is recommended.

It is necessary to include a lifelong GFD in the treatment. In addition, dapsone therapy is recommended in certain cases. In case of a relapse, it is necessary to check adherence to a GFD. The dose of dapsone is recommended to be adjusted according to the clinical condition including both skin manifestation and laboratory results.

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Appendix

Abstract table

Summary of the strongest recommendations, if DH is suspected↑↑↑
1 Medical history
• the relevant family history
• the time and duration of persistence of lesions and symptoms
• the skin symptoms, i.e. itching, burning, stinging
• the gastrointestinal symptoms, i.e. chronic, relapsing abdominal pain, diarrhoea, constipation, loss of weight, nausea, bloating, etc.
• gastrointestinal medical history to search for signs for malabsorption, coeliac disease and associated diseases
• anticipated pregnancy
• medical history of any autoimmune or immune-mediated associated diseases
2 Physical examination
• cutaneous manifestations
• oral involvement
3 Histopathology from a skin lesion
• lesional skin biopsy
4 Direct immunofluorescence (DIF) microscopy
• DIF microscopy is the gold-standard laboratory procedure in diagnosing DH from a perilesional uninvolved area at any predilection site
• transport medium designed for DIF microscopy not containing formalin
5 Serological examinations (indirect immunofluorescence (IIF) microscopy (EMA test) or TG2 ELISA)
6 Gastroenterological assessment