REVIEW ARTICLE

Guidelines for the diagnosis and treatment of dermatitis herpetiformis

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Abstract

Dermatitis herpetiformis is a rare disease that should be considered the cutaneous expression of a gluten-sensitive enteropathy indistinguishable from celiac disease. Dermatitis herpetiformis is often misdiagnosed and to date no guidelines for the management of dermatitis herpetiformis have been published in Literature. The present guidelines have been prepared for dermatologists by the Group for Cutaneous Immunopathology of the Italian Society of Dermatology and Venereology. They reflect the best data available at the time of preparation and the clinical experience of the authors and the members of the Italian Group for Cutaneous Immunopathology. The diagnosis of dermatitis herpetiformis is established clinically, histologically, immunopathologically and serologically. A gluten-free diet (GFD) is the treatment of choice for patients with dermatitis herpetiformis. Dapsone and/or other drugs should be used during the period until the GFD is effective. In conclusion, the present guidelines provide evidence-based guidance for the diagnosis and treatment of dermatitis herpetiformis.

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Keywords

celiac disease, dermatitis herpetiformis, diagnosis, guidelines, management, therapy

Conflicts of interest

None declared.

Introduction

Dermatitis herpetiformis is an inflammatory cutaneous disease with a chronic-relapsing course, pruritic polymorphic lesions and typical histopathological and immunopathological findings. There is growing evidence that dermatitis herpetiformis should be considered the specific phenotypic cutaneous expression of a gluten-sensitive enteropathy indistinguishable from celiac disease.[1,2] Both dermatitis herpetiformis and celiac disease are multifactorial disorders in which genetic and environmental triggering factors play a crucial role, leading to specific lesions in small bowel and skin, respectively. Strong associations with HLA DQ2 (in 80–90% of patients) and HLA DQ8 (in 10–20% of patients) have been demonstrated in both diseases.[2–4]

Dermatitis herpetiformis usually presents in the third decade, although individuals of any age can be affected. It is predominately a disorders of Caucasians;[5] the incidence was found to be 11.5 per 100 000 in Scotland and ranging form 19.6–39.2 per 100 000 in Sweden.[6,7]

An increased incidence of immunomediated diseases and associated conditions, including lymphoma, has been demonstrated in dermatitis herpetiformis (Table 1).[6,7]

Diagnostic protocol

Specific guidelines, based on the use of few, essential, sensitive and specific criteria, would provide adequate protocols for the diagnosis of the majority of dermatitis herpetiformis patients, leading to the correct treatment and monitoring of the disease.

The diagnosis is established clinically, histologically, immunopathologically [direct immunofluorescence (DIF)] and serologically [IgA anti-tissue transglutaminase antibodies (anti-tTG) and IgA endomisial autoantibodies (EMA); Table 2]. In the presence of a suggestive clinical picture, despite the fact that positive serologic tests result can be supportive of the diagnosis and that some authors have considered anti-tTG as diagnostic,[8] DIF of uninvolved skin remains the gold standard for establishing dermatitis herpetiformis diagnosis.[5,9] Therefore, in case of a negative result, serial sections of the biopsy should be performed and if negative a second biopsy should be taken from surely uninvolved skin and checking that the patient is not on a gluten-free diet (GFD). Moreover, considering that failure to detect IgA is usually technical, DIF testing must be performed in experienced laboratories to minimize both false-positive and false-negative results.

Table 1 Dermatitis herpetiformis/celiac disease–associated conditions

1	Insulin-dependent diabetes mellitus
2	Hashimoto thyroiditis
3	Down syndrome
4	Pernicious anaemia
5	Nephropathies
6	Liver diseases
7	Multiple sclerosis
8	Sjogren's syndrome
9	Lupus erythematosus
10	Rheumatoid arthritis
11	Partial IgA deficiency*
12	Vitiligo
13	Psoriasis

*The presence of IgA is considered essential in the pathogenesis of dermatitis herpetiformis. To date, no cases of IgA deficiency have been reported in dermatitis herpetiformis, but IgA deficiency is found in 2–3% of patients with celiac disease. According to Samolitis et al., dermatitis herpetiformis may develop in patients with partial IgA deficiency, indicating that pathogenetically directed IgA antibodies may be sufficient for cutaneous IgA deposition in this disease.[49]

Table 2 Diagnostic examinations required for dermatitis herpetiformis diagnosis

Clinical picture
Histopathology
DIF
Serological findings (anti-tTG and EMA antibodies)

In our experience, in the very few cases with clinical signs of dermatitis herpetiformis and negative DIF, all the tests needed to make a diagnosis of celiac disease following the current guidelines[10] should be performed. A confirmed diagnosis of celiac disease in a patient with clinical signs of dermatitis herpetiformis would allow to start the main therapeuthical approach for both celiac disease and dermatitis herpetiformis (i.e. GFD). As suggested by some authors, another possibility is to perform an aggressive gluten challenge after a GFD for at least 1 month.[11] This can lead to a flare in lesion formation in about 24 h, thus confirming the diagnosis of dermatitis herpetiformis in patients with negative DIF.[12]

A brief description of the main clinical, histopathological, immunopathological and serological findings of dermatitis herpetiformis is reported below.

Clinical features

Dermatitis herpetiformis presents with diffuse, symmetrical, grouped polymorphic lesions consisting of erythema, urticarial plaques, papules, herpetiform vesiculae and blisters followed by erosions, excoriations and hyperpigmentation.[5,13–15] The most commonly involved sites are the extensor surfaces of the elbows (90%), knees (30%), shoulders, buttocks, sacral region, and face. Itching of variable intensity, scratching and burning sensation immediately preceding the development of lesions are common.[5,13–15] Although small bowel involvement in dermatitis herpetiformis is often asymptomatic in adults, it can be associated with abdominal pain, diarrhoea, iron deficiency and reduced growth rates in children.[5,13–15]

Since clinical presentation of dermatitis herpetiformis is often atypical this diagnosis may not come to mind. The main differential diagnoses in children are atopic dermatitis, scabies, papular urticaria, and impetigo, whereas eczema, other autoimmune blistering diseases (especially IgA linear disease and bullous pemphigoid), nodular prurigo, urticaria and polymorphic erythema should be considered in adults. The clinical course, histopathology and, mainly, DIF will help to establish the diagnosis.[13,15] In Table 3, the main differential diagnoses of dermatitis herpetiformis are reported.

Table 3 Differential diagnosis of dermatitis herpetiformis

Disease	Clinical picture	Clinical localization	Histopathology	Immunopathology
Dermatitis herpetiformis	Typical polymorphic lesions, herpetiformis vesiculae	Extensor aspects of limbs, sacral region and buttocks	Subepidermal blister with NG at papillary tips	Granular IgA at BMZ
Linear IgA dermatitis	Herpetiformis bullae and vesiculae	Peri-orificial regions	Subepidermal blisters with NG infiltration	Linear IgA at BMZ
Bullous pemphigoid	Large, grouped, tense blisters	Proximal limbs, inferior abdomen	Subepidermal blisters with EG infiltration	Linear IgG at BMZ
Papular urticaria	*Popular and pomphoid itching lesions*	*Limbs, trunk*	*Demal oedema, perivascular infiltrate with EG*	*Non typical findings*
Atopic Dermatitis	Eczematous itching lesions	Face and flexural arreas (depending on patient's age)	Acanthosis, spongiosis, lympho-monocytic infiltrate	Non typical findings
Scabies	Cuniculi and polymorphic itching lesions	Interdigital areas, axillae, genital regions, buttocks.	Mixed perivascular infiltrate, sporadically acarus detection	Non typical findings
Urticaria	Itching wheals, angioedema	Diffuse	Demal oedema, perivascular lympho-monocytic infiltrate	Non typical (with exception for urticaria vasculitis)

NG, neutrophil granulocytes; EG, eosinophil granulocytes; BMZ, basement membrane zone.

Histopathology

The typical histopathological features of lesional skin are subepidermal blisters and accumulation of neutrophils and very few eosinophils at the papillary tips.[5,14–16] Histopathology of a dermatitis herpetiformis skin lesion can be evocative, but not diagnostic, and a non-specific histopathologic picture is often documented. Thus, if DIF is positive, a biopsy for histology is not necessary.

DIF

As stated above, DIF of uninvolved skin is the gold standard for the diagnosis of dermatitis herpetiformis.[5] Two different patterns of DIF are possible: (i) granular deposits in the dermal papillae and (ii) granular deposits along the basement membrane. Sometimes, a combination of both patterns, consisting in granular IgA deposition along the basement membrane with accentuation at the tips of the dermal papillae, may be present.[5,13–15]

Serologic findings

Serologic tests, and in particular IgA anti-tTG and EMA testing, have become relatively sensitive and specific tools for initial detection of gluten-sensitive disease and therefore of dermatitis herpetiformis.

Anti-tTG belong to the IgA1 subclass and are directed against tTG antigen. tTG share a 64% homology with epidermal TG, which represents the target autoantigen of dermatitis herpetiformis, as recently demonstrated.[4] Anti-tTG are measured using an enzyme-linked immunosorbent assay (ELISA) and are a useful marker of bowel damage and diet adherence in dermatitis herpetiformis/celiac disease patients.[16] In dermatitis herpetiformis, some authors have demonstrated an IgA anti-tTG specificity higher than 90%, and a sensitivity ranging from 47% to 95%.[8,17–21]

EMA belong to the IgA1 subclass and are directed against primate smooth muscle reticular connective tissue. The detection of EMA is based on an indirect immunofluorescence assay on monkey oesophageous and it is more time-consuming and operator-dependent than the one of anti-tTG ELISA testing.[10] EMA testing have shown a specificity close to 100%, and a sensitivity ranging from 52% to 100% for the diagnosis of dermatitis herpetiformis.[17–22] As for anti-tTG, EMA are usually absent in patients on GFD and thus represent a useful diet-compliance marker in celiac disease/dermatitis herpetiformis subjects.[10,11,13–16]

Other autoantibodies, such as antigliadin antibodies and antireticulin antibodies, are no longer considered a sensitive and specific marker of dermatitis herpetiformis. Their detection predates the previously described serologic tests, but the diagnostic performance is not advantageous compared with that of IgA anti-tTG and EMA.[10]

Interestingly, very recently, it has been shown that tests detecting both antibody isotypes (IgA and IgG) against deamidated synthetic gliadin-derived peptides may be considered as the most reliable serologic tool in order to identify gluten sensitivity in dermatitis herpetiformis patients.[23] However, further studies are required to confirm such findings.

Other tests to be performed in dermatitis herpetiformis patients

Although unnecessary for dermatitis herpetiformis diagnosis, other tests such as small bowel biopsy, HLA testing, screening for autoimmune diseases and associated conditions and evaluation of malabsorption (see Table 6) should be performed in dermatitis herpetiformis patients to have an accurate global assessment of the patient.

Small bowel biopsy

Since dermatitis herpetiformis can be considered the cutaneous counterpart of celiac disease,[1] a proven diagnosis of dermatitis herpetiformis in a patient should be used as diagnostic tool for bowel damage recognition. Accordingly, small bowel biopsy would be unnecessary in dermatitis herpetiformis patients, and diet adherence would be monitored by serological testing and skin lesions observation (as it is known, dermatitis herpetiformis lesions usually recurs within few days after gluten ingestion).[11,12] Indeed, very recently, several Authors have suggested that small bowel biopsy is no longer regarded as mandatory for the diagnosis of celiac disease at least in a subgroup of patients.[24]

HLA haplotypes testing

As in celiac disease, virtually all patients with dermatitis herpetiformis carry either HLA DQ2 or HLA DQ8 haplotypes.[2] Thus, the presence of these alleles provides a sensitivity of close to 100% for dermatitis herpetiformis and a very high negative predictive value for the disease (i.e. if individuals lack the relevant disease-associated alleles, celiac disease is virtually excluded). HLA testing for the relevant DQ alleles can be a very useful adjunct in an exclusionary sense when the diagnosis based on other test results is not clear. In contrast, given the marked prevalence of the celiac disease-associated HLA class II alleles in the general population, the specificity of these alleles for the disease is poor.[16,25]

Screening for autoimmune diseases and associated conditions

Considering the increased incidence of immunomediated diseases and associated conditions, several screening tests should be performed in patients with dermatitis herpetiformis.[22,26] Non-specific antibodies, such as antithyroid peroxidase (in almost 20% of patients), antigastric parietal cells (in 10–25% of patients), antinuclear and anti-Ro/SSA antibodies, should be tested in celiac disease/dermatitis herpetiformis patients. The presence of such antibodies correlates with autoimmune predisposition of celiac disease/dermatitis herpetiformis patients. Furthermore, testing for thyroid disease (TSH, T3 and T4)[27] and for diabetes (glucose)[28] should be performed.

Finally, although in contrast to previous literature,[29,30] a very recent work has shown lack of increased risk of lymphoma in

people with dermatitis herpetiformis in comparison to the general population,[31] it is recommended to pay clinical attention to the potential development of intestinal or extraintestinal lymphoma.

Screening first-degree relatives for celiac disease

Since the incidence of celiac disease is higher in dermatitis herpetiformis/celiac disease patients' relatives, some authors suggested a screening for celiac disease in first relatives of the patients. However, although the utility of testing for celiac disease in symptomatic first-degree relatives is clear, there is currently little evidence to support screening in asymptomatic first-degree relatives.[16]

Therapy

GFD

A GFD is the treatment of choice for patients with celiac disease/dermatitis herpetiformis since both the enteropathy and the cutaneous rash depend on gluten.[32–36] GFD alleviates gastrointestinal symptoms much more rapidly than the rash: it takes an average of 2 years of GFD for complete elimination of the cutaneous lesions, which invariably recurs within 12 weeks after the reintroduction of gluten. IgA antibodies may disappear from the dermal-epidermal junction after many years of a strict GFD. On reintroduction of gluten, IgA deposits reappear in the skin and it is also present when the rash recurs.[32–36]

The cereal species whose proteins are toxic to patients with celiac disease/dermatitis herpetiformis are grasses of the tribe Triticeae, which includes wheat, rye and barley.[32] Although in the past the basis of GFD was the avoidance of all gluten-containing cereals, including wheat, barley, rye, and oats (mnemonic BROW), recently, some authors have demonstrated that oats belonging to the Avenae tribe can be safely consumed by celiac disease/dermatitis herpetiformis patients.[33,34] However, only oats known to be pure and not contaminated in any way with wheat, barley or rye (which is the case of the majority of commercially available oats) can be safely consumed.[5]

Observing 133 dermatitis herpetiformis patients on a long-term GFD, Garioch *et al.* reported the following advantages: reduced or no need for medication, resolution of enteropathy and the correlated malabsorption of essential nutrients (and therefore prevention of alimentary deficiency of iron, vitamin B12 and folate), a general feeling of well-being, protective effects against development of intestinal lymphoma.[29,30,35,36]

Although GFD offers many benefits in the management of dermatitis herpetiformis, it is not easy to realize by many dermatitis herpetiformis patients. A GFD requires scrupulous monitoring of all ingested foods; it is time-consuming and socially restricting. Strict adherence to a GFD requires extensive knowledge of foods and diet, thus consultation with a dietician and involvement in dermatitis herpetiformis support groups are strongly encouraged. In general, patients following a GFD are advised to read carefully all food labels and to avoid products with unfamiliar ingredients. Many food ingredients (i.e. additives, cereal grains, natural and artificial colourings, emulsifiers, excipients, artificial flavourings, malts, hydrolysed plant and vegetable proteins, monosodium glutamate, preservatives, natural and modified food starches, vegetable gum, vinegar) may be derivatives of gluten-containing products. Rottmann provides a detailed list and description of foods permitted and those to be avoided.[37]

More studies are required to determine whether a long-term GFD will decrease the incidence of concurrent autoimmune conditions in patients with dermatitis herpetiformis.

Table 4 Dapsone adverse effects

1 Toxic/Pharmacologic
Metahemoglobinemia
Haemolytic anaemia
2 Idiosyncratic/Allergic
[Dapsone hypersensitivity syndrome]
General malaise
Exanthematous eruption, Stevens–Johnson syndrome/Toxic Epidermal Necrolysis
Photosensitivity
Neurological effects: peripheral neuropathy, optic nerve atrophy, psychosis, headache, nervousness, lethargy, *depression*
Nephropathy: nephritis, renal failure
Hypothyroidism
Gastro-intestinal effects: nausea, vomiting, gastro-intestinal upset

Dapsone

Dapsone represents a valid therapeutic option for dermatitis herpetiformis patients during the 1- to 2-year period until the GFD is effective;[38–45] dosages of 1/mg/kg/day can control itching and blister development.[38–45] Although dapsone does effectively decrease pruritus and inflammatory lesions, patients taking this drug should be strictly monitored (especially for renal and liver function) because of possible severe adverse effects.[38–45] In particular, the commonest side-effect of dapsone is haemolysis and patients should be seen within 2 weeks after starting the drug as haemolysis may be acute in some individuals.

Table 4 presents the main adverse reactions to dapsone, classified as toxic and idiosyncratic. Such adverse effects are usually dose dependent and more common in patients with comorbidity (anaemia, cardiopulmonary disease, glucose-6-phosphate-dehydrogenase deficiency).[38–45] Dapsone can induce a severe hypersensitivity syndrome, consisting of fever, rash, malaise, lymphadenopathy, and varying degrees of visceral involvement, which develops in about 5% of dermatitis herpetiformis patients 2–6 weeks after the beginning of treatment.[38–45]

Table 5 Indications for monitoring

GFD adherence
Possible development of an autoimmune associated disease (despite GFD adherence)
Metabolic alterations (dyslipidemia, non-alcholic steatohepatitis)
Possible development of neoplastic (lymphoma) or non–neoplastic (refractory celiac disease, ulcerative jejunoileitis, collagenosic sprue) complications

Table 6 Item list for routine check-ups

Physical examination
Dietician counselling
Serological laboratory tests (haemochrome, malabsorption evalutation: sideremia and ferritin levels, *mean corpuscular volume*, glucose, thyroid hormones)
Immunological and autoimmune markers (dermatitis herpetiformis–specific and non-specific autoantibodies)

Sulfasalazine and sulphamethoxypyridazine

Sulfasalazine and sulphamethoxypyridazine might provide an effective alternative to dapsone especially when it fail to control the disease or the therapy is complicated by adverse events.[5,46,47] The suggested dosages are of 1–2 g/day for sulfasalazine and of 0.25–1.5 g/day for sulphamethoxypyridazine.[46,47] Both drugs share common adverse effects, including hypersensitivity reactions, haemolytic anaemia, proteinuria and crystalluria; thus, a full blood count with differential and urine microscopy with urinalysis should carried out prior to starting treatment and *monthly* for the first 3 months of therapy, and thereafter once every 6 months. However, the most common adverse effects are nausea, anorexia and vomiting, which can be prevented by prescribing the enteric-coated forms of the drugs.[46,47]

Corticosteroids

While orally administered corticosteroids give poor results, application of potent or very potent topical steroids (especially clobetasol *propionate*) can be useful to decrease pruritus and itching.

Anti-histamines

Although their efficacy is not very high in the treatment of dermatitis herpetiformis, third-generation antihistamines with specific activity on eosinophilic granulocytes, classified as a third-level therapeutic option, may also be used to control pruritus and itching.

Dermatitis herpetiformis monitoring

Follow-up is necessary to confirm the diagnosis by an objective response to a GFD and to detect and manage non-compliance. Patients with dermatitis herpetiformis/celiac disease should be evaluated at regular intervals (i.e. 6 months after diagnosis and then yearly) by a health care team including a physician and a dietician. These visits can be used to assess, by history, a patient's compliance with a GFD, to reinforce the importance of such compliance and to evaluate the possible development of intestinal malabsorption and/or dermatitis herpetiformis–associated conditions (see Table 1). Beyond this, there are no clear guidelines as to the optimal means to monitor adherence to a GFD. In general, monitoring adherence to a GFD with serological investigations (i.e. anti-tTG or EMA) is sensitive for major but not for minor transient dietary indiscretions.[10] Table 5 lists the main targets in monitoring. Follow-up examinations recommended for celiac disease/dermatitis herpetiformis patients are summarized in Table 6.

Conclusions

The aim of the guidelines presented here is to optimize and standardize dermatitis herpetiformis diagnostic procedure and follow-up to give all patients with cutaneous involvement and gluten-intolerance equal opportunity for prompt, correct diagnosis. Furthermore, since dermatitis herpetiformis can be considered 'celiac disease of the skin', we aim to highlight the importance of cutaneous involvement as diagnostic tool for bowel damage recognition.[48] Indeed, when dermatitis herpetiformis diagnosis is well proven, a small bowel biopsy would be superfluous. Once the diagnosis has been achieved, such patients should be able to live serenely with their disease, by virtue of an attentive, routine monitoring of their condition.

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