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Dermatitis Herpetiformis: What Practitioners Need to Know

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Dermatitis herpetiformis (DH) is an autoimmune blistering disorder with a multifactorial etiology associated with a gluten-sensitive enteropathy. A chronic disease with a variable course, it is often exceptionally frustrating for patients; however, with current medical management and lifestyle adjustments, treatment can be highly successful. The prevalence in the United States is approximately 11.2 cases per 100,000 and internationally as high as 75.3 cases per 100,000. Health-related practitioners should be able to appreciate and recognize essential features of this disease. This review highlights distinguishing clinical symptoms and serves to aid the reader in the diagnosis and treatment of DH.

INTRODUCTION

Dermatitis herpetiformis (DH) was first described in 1884 by Dr. Louis Duhring at the University of Pennsylvania.[1] It is an autoimmune blistering disorder associated with a gluten-sensitive enteropathy. The etiology is multifactorial with strong genetic and autoimmune influences.[2] Patients with DH can demonstrate varying degrees of enteropathy. Earlier research has shown that patients with mild celiac disease can have notably increased intraepithelial lymphocyte counts and yet display normal gross intestinal mucosa.[3] The intraepithelial lymphocyte infiltration lessens after one to three years on a gluten-free diet (GFD).[3]

DH clinically presents with erythematous papules, vesicles and excoriations. It is remarkably pruritic, so the vesicles are often excoriated to erosions by the time of presentation to medical practitioners. A gluten-free diet remains the cornerstone of therapy, while dapsone provides the most rapid relief of skin signs and symptoms.

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Epidemiology

In the United States the prevalence of DH is 11.2 cases per 100,000 population.[4] Internationally, the prevalence of DH has been reported as high as 75.3 cases per 100,000 population.[5] Although, women seem to be more frequently affected by celiac disease,[6,7] prevalence studies of DH in the United States have shown a male-to-female ratio of 1.44:1[4] while internationally, the male-to-female ratio is up to 2:1. In one study of patients with gluten-sensitive enteropathy, 16% of the men and 9% of the women had DH.[3,8] DH commonly presents in individuals of Northern European ancestry. It is rare in Asians and persons of African descent due to the shared

Table 1: Clinical Presentation of Dermatitis Herpetiformis

Physical Examination	Lesion Distribution	Typical Symptoms	Diagnosis	Prognosis
Clusters of small clear vesicles atop flesh-colored–to–erythematous papules or plaques, often excoriated	Symmetrical distribution over extensor surfaces: elbows, knees, buttocks, and shoulders Less commonly: oral mucosa, scalp and face	Itching, stinging, burning; rarely asymptomatic	Lesional skin biopsy; direct immunofluorescence of unaffected perilesional skin; serologic testing	Life-long disease requiring long-term management

HLA associations of DH and celiac disease, including DQA1*0501 and B1*-02, which encode HLA-DQ2 heterodimers.[4, 9] Classically, it appears in the second to fourth decade and is a rare occurrence in prepubertal children.[10]

Clinical Presentation (Table 1.)

DH typically presents with clusters of tiny, clear vesicles atop flesh colored or erythematous papules or plaques symmetrically distributed on extensor surfaces of the body such as the elbows, arms, shoulders, knees and buttocks (Fig 1). Progression to a generalized distribution is uncommon. Due to DH's intensely pruritic nature, intact vesicles are rarely seen as patients mechanically disrupt them by scratching. Less commonly, lesions occur on the oral mucosa,[11, 12] scalp and face.[13,-15] DH can also present as digital purpura that resembles a vasculitis. Palms and soles are routinely spared. Symptoms include painful burning, stinging, and variations in the intensity of itching. It is uncommon for it to be asymptomatic. Patients who present with DH may not report any gastrointestinal discomfort or symptoms.[16] Additionally, intestinal biopsy may appear normal due to a number of reasons including as a result of treatment, the biopsy sample being taken from a skip lesion (or an unaffected site), or simply because the intestine may not be affected by the disease.

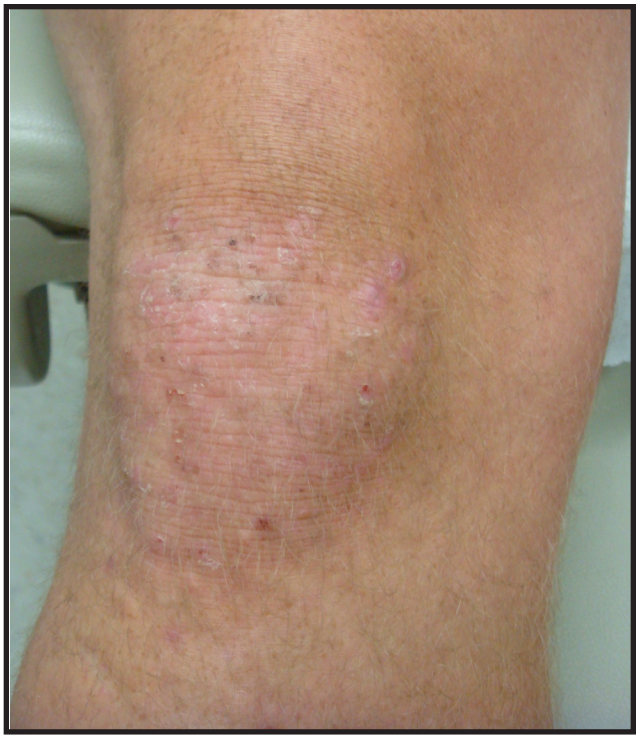

Figure 1.

Diagnosis

The diagnosis of DH is definitively established with a lesional skin biopsy for microscopic evaluation and a perilesional skin biopsy for direct immunofluorescence in patients with clinical manifestation suspicious for the disease. Diagnosis can also be confirmed by a simple blood test for serum markers such as IgA endomysial antibodies, tissue transglutaminase antibody - tTG (IgA), deamidated gliadin peptide antibody - dGP (IgA and IgG) and gliadin assay (IgA and IgG). However, serum markers such as IgA endomysial antibodies are negative in as many as 10-37% of patients with DH.[17] Additionally, many physicians would recommend obtaining tTG for diagnosis; however, because of

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impurities and cross-reactivity, tTG enzyme-linked immunosorbent assay positivity can occur in many autoimmune diseases.[18] All serology positive tests should be confirmed by small bowel biopsy before the patient starts a gluten free diet (GFD) or they might generate negative results.[19]

Characteristically, direct immunofluorescence (DIF) testing demonstrates the presence of granular deposits of IgA in the papillary dermis. DIF testing is highly sensitive and found to be positive in 92.4% of patients.[17] IgA deposits in the skin may be seen with other dermatological conditions including bullous pemphigoid and cicatricial pemphigoid; however, their distribution differs from that of DH. The most likely differential diagnosis is depicted in Table 2.

Serologic testing for circulating antiendomysial antibodies in the sera of DH patients is a less sensitive test compared to DIF and was positive in 40 of the 63 patients tested (63.5%) in one study.[17] Histopathologic examination of lesional skin with hematoxylin and eosin staining shows clusters of neutrophils in the dermal papillae, with fibrin deposition, some eosinophils and papillary dermal edema. Vesiculation due to release of neutrophil lysosomal enzymes can occur in the lamina lucida.[20]

Management

Definitive treatment of DH includes a strict GFD with which the patient can expect some skin improvement in several months, although it may take years for GFD to suffice as the sole treatment. Gluten is found in wheat, rye and barley, as well as their derivatives, and can be a source of contamination even in gluten-free products,[21] thus making complete avoidance challenging. Additionally, a strict GFD may require vitamin and mineral supplementation to avoid nutritional deficiencies.[22] See February 2012 Practical Gastroenterology for a GFD update.

Pharmacotherapy for DH includes dapsone (diaminodiphenyl sulfone) and sulfapyridine. Medical management with dapsone quickly improves skin manifestations and provides rapid symptomatic relief although it has no effects on gastrointestinal pathology.[24] Possible adverse effects of dapsone include hemolytic anemia, methemoglobinemia, agranulocytosis, neuropathy, as well as others. Sulfapyridine may be used in place of dapsone for those who develop severe adverse effects. If a patient fails therapy with dapsone or sulfapyridine, other possible treatments include colchicine,[25] cyclosporine,[26] systemic corticosteroids,[27] and less commonly heparin, tetracycline and nicotinamide.[28] Nonsteroidal anti-inflammatory drugs (NSAIDs) may aggravate symptoms as demonstrated by a small controlled, double-blind cross-over study where nine of the thirteen DH patients that were given indomethacin in addition to dapsone or sulphamethoxypyridazine developed an exacerbation of their rash and pruritis.[29] Therefore, caution should be used in prescribing NSAIDs, however, one study investigating the use of NSAIDs in DH patients demonstrated that ibuprofen may not have an effect on serum dapsone levels and disease activity in DH.[30] A GFD remains the cornerstone of therapy, while dapsone provides the most rapid relief of skin signs and symptoms.[31] An algorithm of the therapeutic approach is presented in Table 3.

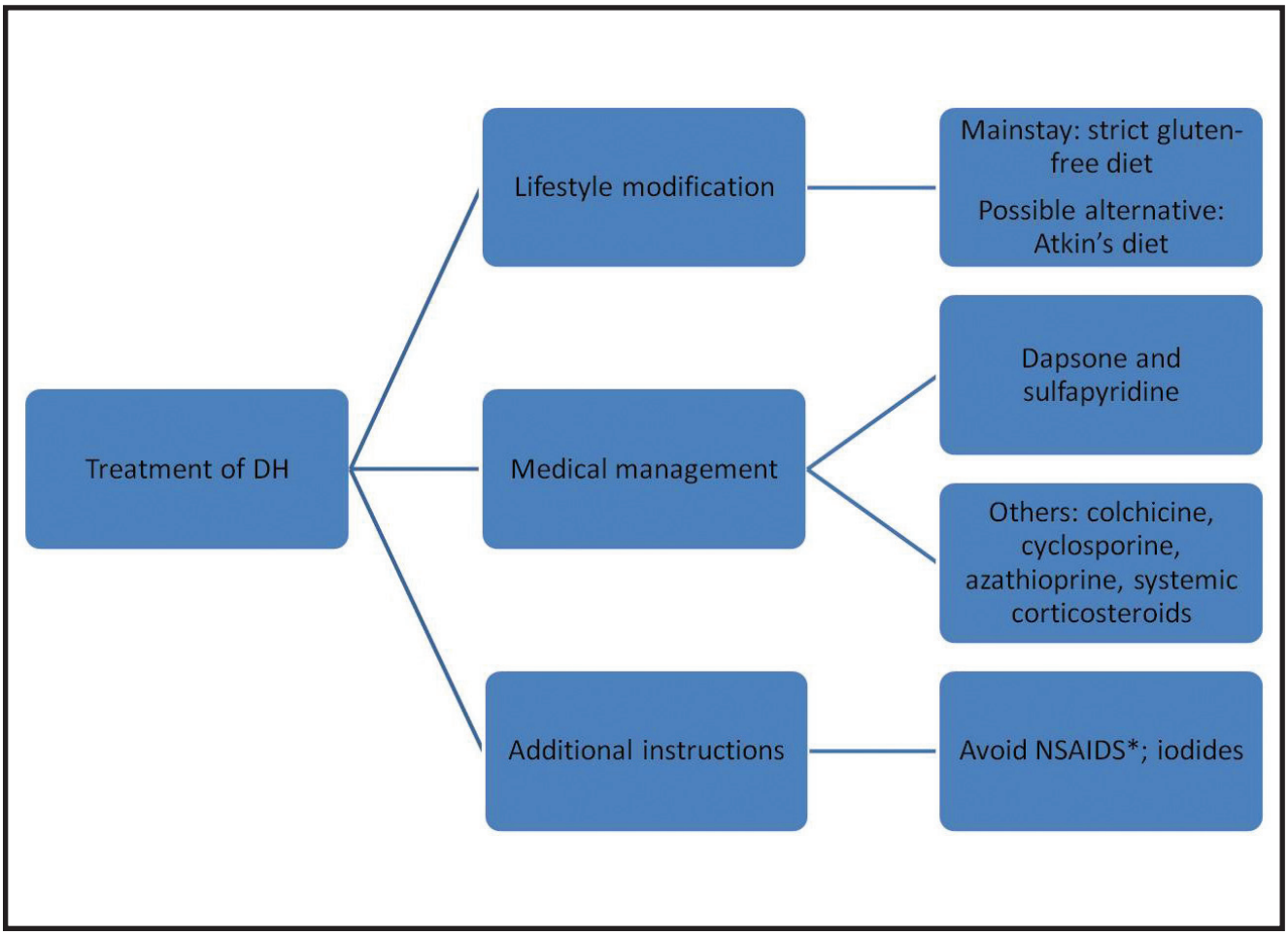
Table 2: Differential diagnoses of Dermatitis Herpetiformis

- Atopic dermatitis
- Papular urticaria
- Bullous pemphigoid
- Erythema multiforme
- Linear IgA dermatosis
- Scabies
- Transient acantholytic dermatosis

Prognosis/ Recommendations

DH is a life-long disease that requires long-term management. Patients can have worsening symptoms of DH with dietary intake of gluten; spontaneous remissions have been reported with its reduction in the diet. In one small study, six of the eight patients demonstrated spontaneous remission with an estimated mean daily intake of gluten below 12 grams.[32] Patients with DH should work with both a gastroenterologist and a dietician for evaluation of a gluten-sensitive enteropathy and formulation of a gluten-free diet to help alleviate future symptomatology.

Table 3: Treatment of Dermatitis Herpetiformis



*Ibuprofen may be acceptable for use [30]

SUMMARY

Although DH is a chronic disease, patients can have exceptional control over clinical symptoms after they have made the necessary lifestyle modifications; specifically, strict adherence to a gluten-free diet and if possible. In addition, medical management may be necessary as dictated by the patient's symptoms. Although medications prescribed strictly for the treatment of DH; namely, dapsone and/or sulfapyridine, have no effect on the underlying gastrointestinal disease, they offer the advantage of rapid symptomatic relief and improvement in skin manifestations. DH patients can be reassured that although this is a chronic and sometimes unpredictable disease, lifestyle adjustments and medical treatment can be highly successful.■

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