

Management of Dermatitis Herpetiformis

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KEYWORDS

- Dermatitis herpetiformis • Management
- Gluten-sensitive enteropathy • Pruritus

Dermatitis herpetiformis (DH) is a severely pruritic cutaneous disease characterized by markedly pruritic, symmetrically distributed papulovesicles that usually affect the extensor surfaces: the scalp (especially the posterior hairline), elbows, knees, back, and buttocks.^{1,2} Histology of skin lesions in DH is characterized by a subepidermal blister with a predominantly neutrophilic infiltrate in the dermal papillary tips,³ although a mixed or even predominantly lymphocytic dermal infiltrate may also be found.^{4,5} Direct immunofluorescence reveals granular deposition of immunoglobulin A (IgA) at the dermal-epidermal junction in both involved and uninvolved skin as well as the oral mucosa.^{6–10} Patients with DH have an associated gluten-sensitive enteropathy (GSE),¹¹ and dietary control is sufficient in abrogating the cutaneous symptoms of DH.^{12,13} The condition is chronic, but it waxes and wanes with no clear triggering factors. This disease tends to be chronic, although approximately 10% to 12% of these patients can go into spontaneous remission.^{14,15}

Epidermal transglutaminase (eTG) or transglutaminase 3 has been identified as the target autoantigen in DH.^{16,17} Serum eTG IgA compared with tissue transglutaminase IgA and IgG was more sensitive in detecting GSE.¹⁸ These serologic studies, however, should not be used to confirm the diagnosis of DH because the presence of IgA anti-eTG has a sensitivity for diagnosis of DH of only 70%. Furthermore, dietary intake seems to correlate with eTG IgA; that is, avoidance of gluten resulted in the gradual decrease of antibody levels.

TREATMENT

The 2 major options for the treatment of DH are medical treatment with dapsone or a sulfone drug and dietary treatment by the strict restriction of gluten intake.¹⁹ Medical

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therapy with dapsone results in a rapid clinical improvement of skin findings, but it can be associated with side effects. Furthermore, it does not improve the gastrointestinal pathology in patients with DH.^{20,21} On the other hand, dietary restriction of gluten has been proven to attenuate both the cutaneous and gastrointestinal signs and symptoms of DH.¹³ However, this can be difficult because strict adherence is often required and the improvement of cutaneous symptoms may take weeks if not months.

Gluten-free Diet

Both the skin and the gastrointestinal manifestations of DH are gluten sensitive.^{12,13} Leonard and coworkers²² rechallenged 12 patients whose DH had previously been controlled on a gluten-free diet, and both the rash and the gastrointestinal changes recurred in response to the reintroduction of gluten. As many as 80% of patients with DH are able to stop or reduce their dose of dapsone on a strict gluten-free diet.²³ Those who are able to reduce but not completely eliminate gluten from their diet may see some benefit¹⁵ but not enough to completely control their cutaneous symptoms.^{20,24} Patients with DH treated with a gluten-free diet need at least 5 months before they are able to reduce their dapsone dose and anywhere from 8 to 48 months before they can stop dapsone treatment altogether.^{12,13,23} In some patients, gluten restriction need not be lifelong because long-term remission can occur in as many as 10% to 12% of patients.^{14,15} Bardella and colleagues²⁵ reported that 7 out of 38 patients who reverted to a normal, gluten-containing diet after an average of 8 years of gluten restriction continued to experience remission of their skin and gut disease after a mean follow-up of 12 years. Fry and coworkers²⁰ observed that macroscopic and microscopic small intestinal abnormalities among patients with DH on a gluten-free diet decreased significantly when compared with those who were on a normal diet, including a decrease in intraepithelial lymphocytic infiltration.²⁰ In this same study, they found that the improvement of cutaneous symptoms and gastrointestinal abnormality was directly related to the degree of strictness of the gluten-free diet. The incidence of lymphoma and other malignancies in patients with DH and GSE, although low, has been reported to increase when compared with the normal population.^{26,27} Recent studies, however, have not found a similar increased risk of malignancy.²⁸ The reason for this discrepancy is not clear. It has been suggested that adherence to a gluten-free diet may play a role in moderating the risk of developing a malignancy, but a controlled study has not been done.^{26,29} Van Der Meer and colleagues³⁰ have reported that an elemental diet can lead to the control of the eruption of DH. Kandunice and coworkers³¹ have also shown that an elemental diet is effective at achieving control of DH often within 2 to 4 weeks.³¹ Of interest, this effect seems to be independent of gluten ingestion. These studies suggest that other dietary proteins may also be important in the pathogenesis of dermatitis herpetiformis. IgA deposition in the skin appears to improve, albeit over a course of several years, on a gluten-free diet.^{20,32,33} Fry and coworkers³² noted that only 4 out of 23 patients with DH on a gluten-free diet had complete clearance of IgA deposition in their skin and only after several years. They further described that there was no difference in the quantity of IgA, as assessed by the amount of fluorescence, whether patients were controlled with a gluten-free diet alone, gluten-free diet and dapsone, dapsone alone, or in those in clinical remission. Frodin and coworkers³³ followed 32 patients with DH on either a gluten-free or gluten-reduced diet for 15 to 43 months and, although there was a decrease in the intensity of IgA deposition in the skin of these patients, none had a complete disappearance of cutaneous IgA deposition in spite of a good clinical response. In patients with DH controlled on a gluten-free diet and with clearance of cutaneous IgA deposition, gluten challenge results in the reappearance of cutaneous

IgA deposits within 1 month.²² A more direct immunologic effect of a gluten-free diet is reflected in serum interleukin (IL)-8 levels among patients with DH. Serum IL-8 is elevated in patients with DH, and a gluten-free diet normalizes or reduces the amount of circulating IL-8 in these patients.³⁴ Patients with DH on a gluten-free diet had a decreased mRNA expression of IL-8 compared with those on a normal diet, suggesting that the elevated circulating IL-8 in patients with DH is produced in the intestinal mucosa as a response to gluten.³⁴

Adherence to a gluten-free diet is effective in the majority of patients with DH at controlling the cutaneous manifestations of DH with a resultant decrease or elimination of the need for dapsone therapy. Even patients with DH with a normal initial small-bowel biopsy experience improvement of their rash when placed on a gluten-free diet.³⁵ In addition, a gluten-free diet may prevent or lessen the possibility of an increased risk of lymphoma and other malignancies in patients with DH. Adherence to a gluten-free diet, however, is difficult and requires significant knowledge and strong compliance by patients and their families. Fry and coworkers²⁰ noted that only 23 of 42 patients who thought that they were on a gluten-free diet were actually adhering to a strict gluten-free diet when evaluated by a dietitian. Consultation with a registered dietitian with expertise in gluten-free diets is often extremely valuable in improving patients' compliance with the diet. In addition, several patient groups are extremely useful for patients learning more about the diet (Celiac Sprue Association, csaceliacs.org).

Dapsone

The cutaneous signs and symptoms of DH can often be quickly and adequately controlled by 100 to 200 mg of dapsone with minimal side effects, although there is considerable variability in response.¹⁹ Some patients require as little as 25 mg by mouth daily, whereas others may need up to 400 mg daily. Treatment can be initiated at a dosage of 100 mg daily unless patients have other significant risk factors, such as cardiovascular, pulmonary, or hematologic disease, and those who would likely not tolerate the hemolytic anemia and methemoglobinemia that may result from dapsone therapy. A complete review of the pharmacology and adverse effects of dapsone is beyond the scope of this review and readers are referred to several recent reviews for further information.^{36,37} Most patients with DH will respond to dapsone within 24 to 36 hours of initiating the medication, and withdrawal of dapsone results in recurrence of signs and symptoms within 24 to 48 hours. Treatment with dapsone, however, does not alter gastrointestinal mucosal changes.^{20,21} Furthermore, sulfone treatment does not appear to affect deposition of complement in the skin of patients with DH even when their cutaneous lesions were controlled.³⁸ This finding suggests that the therapeutic effect of dapsone is exerted at the effector cells of the cutaneous pathology; that is, there is neutrophilic infiltration of the skin and not at the initiation of the immunologic response, which is thought to occur when gut mucosa is exposed to gluten. Indeed, dapsone has been demonstrated to interfere with neutrophil chemotaxis³⁹ and the adhesion to antibodies⁴⁰ as well as with the release of IL-8 from keratinocytes.⁴¹

Careful monitoring of the side effects of dapsone is required. Aside from a careful history and physical examination to evaluate the cardiovascular, pulmonary, gastrointestinal, neurologic, and renal status of patients, a baseline complete blood count with differential, renal function test, liver function test, urinalysis, and G6PD level are recommended. Although a complete review of the pharmacology of dapsone is beyond the scope of the review, it is critical that the physician prescribing this drug be aware of the most severe adverse events. All patients will develop a dose-dependent

hemolytic anemia with a resultant decrease in hemoglobin. In addition, some degree of methemoglobinemia will develop in all patients on dapsone, also in a dose-dependent manner. Concomitant administration of cimetidine, 400 mg by mouth 3 times a day, reduces dapsone-induced methemoglobinemia without affecting the clinical response in patients with DH.⁴² Idiosyncratic side effects, including agranulocytosis, and hepatic function abnormalities may also occur. These side effects may be severe, and appropriate monitoring for side effects is essential. Because many of these side effects can be noted early and are reversible, monitoring of complete blood counts should be performed weekly for 1 month, every other week for 1 month, and then at 3- to 4-month intervals. Monitoring of liver and renal function should be performed periodically or as dictated by symptoms. Because many of these side effects are dose related, patients should be told not to adjust dapsone dosage without consulting their physician. Dapsone is also associated with a distal motor neuropathy. This event is relatively rare, but it is reversible and also requires monitoring by clinical examination and nerve-conduction studies as needed. Although dapsone is an extremely effective drug for the control of DH, the potential for toxicity is great and close follow-up is needed. Physicians who prescribe dapsone should be familiar with the pharmacology and adverse effects of the drug.^{36,37} In addition, because of the unfamiliarity of some physicians with the use of dapsone, it is recommended that patients carry cards describing their use of dapsone and the associated adverse effects, including methemoglobinemia and a low-grade hemolytic anemia.

Sulfapyridine and Sulfasalazine

Sulfapyridine is an alternative medical treatment for DH, although less effective than dapsone, and patients are usually controlled with 1 to 2 g by mouth daily. This medication, however, is not readily available in the United States. Sulfasalazine, which is more readily available, is metabolized into 5-amino-salicylic acid (5-ASA) and sulfapyridine. Patients have been reported to respond to 2 to 4 g/d of sulfasalazine.^{43,44} Once sulfasalazine is metabolized in the gut, most of the sulfapyridine is absorbed and excreted in the urine, whereas most of the 5-ASA remains in the gut and is thought to exert a local antiinflammatory effect that makes it useful in the treatment of inflammatory bowel disease.⁴⁵ It is not yet known if sulfasalazine exerts any effect on the gastrointestinal pathology in DH, but in one report of a patient with DH and ulcerative colitis, both the cutaneous and gastrointestinal symptoms improved on treatment with sulfasalazine.⁴⁶

SUMMARY

The major treatment strategies for DH are gluten restriction or medical treatment with sulfones. Control of the cutaneous manifestations, but not the gastrointestinal changes, is rapid with dapsone. In addition to control of the cutaneous signs and symptoms of DH, dietary gluten restriction also induces improvement of gastrointestinal morphology and is possibly protective against the development of lymphoma.

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