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Dermatitis Herpetiformis: An Update on Diagnosis and Treatment

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ABSTRACT

Introduction: Dermatitis herpetiformis is a relapsing skin disease caused by gluten sensitivity, also known as an extraintestinal manifestation of celiac disease. **Methods:** This article was made by reviewing 14 articles related to dermatitis herpetiformis which obtained from Pubmed, Science Direct, and Google Scholar. **Discussion:** Dermatitis herpetiformis is characterized by skin lesions vesicles or exoriated papules intensely itchy or excoriated papules on extensor surfaces, scalp, nuchal area, and buttocks. Dermatitis herpetiformis is primarily diagnosed through direct immunofluorescence of granular IgA deposits. However, modern and recent approaches currently use anti-TG3 antibody levels as the main serological diagnostic marker. Recent studies now confirm strict, long-term gluten free diet as the primary treatment modality. The diet is supplemented with sulfonamides as first line drugs treatment, especially dapsone. Proper diagnosis and management are important to improve the quality of life of the patients. **Conclusion:** Dermatitis herpetiformis is a skin disease related to hypersensitivity which requires comprehensive approach and treatment.

Keyword: Celiac Disease, Dapsone, Dermatitis Herpetiformis, Direct Immunofluorescence, Gluten Free Diet

ABSTRAK

Pendahuluan: Dermatitis herpetiformis, juga dikenal sebagai manifestasi ekstraintestinal penyakit celiac. **Metode:** Artikel ini disusun dengan meninjau 14 artikel berkaitan dengan dermatitis herpetiformis yang didapatkan pada Pubmed, Science Direct, dan Google Scholar. **Pembahasan:** Dermatitif herpetiformis adalah penyakit kulit yang ditandai dengan vesikel yang gatal atau papula yang terkelupas. Dermatitis herpetiformis didiagnosis terutama melalui imunofluoresensi langsung deposit IgA granular. Namun, pendekatan modern saat ini menggunakan antibodi anti-TG3 sebagai penanda diagnostik serologis utama. Studi terbaru sekarang mengkonfirmasi diet bebas gluten jangka panjang yang ketat sebagai modalitas pengobatan utama. Diet dilengkapi dengan sulfonamida sebagai pengobatan lini pertama, terutama dapson. Diagnosis dan penatalaksanaan yang tepat penting untuk meningkatkan kualitas hidup pasien. **Kesimpulan:** Dermatitis herpetiformis adalah penyakit kulit yang berkaitan dengan hipersensitivitas dan membutuhkan pendekatan dan tatalaksana yang komprehensif.

Kata Kunci: Dapson, Dermatitis Herpetiformis, Diet Bebas Gluten, Imunofluoresensi Langsung, Penyakit Seliak

1. Introduction

Dermatitis herpetiformis (DH), a recurrent skin condition brought on by gluten sensitivity, is distinguished by extremely irritating vesicles or excoriated papules. DH is viewed as a celiac disease (CD) extraintestinal manifestation.[1] DH has an incidence of between 0.4-3.5 per 100,000 person-years and a prevalence of between 11.2-75.3 per 100,000. Higher levels are often found in northern European countries. DH prevalence in Finland is 75 cases per 100,000 population. The incidence of DH cases in Scotland and Sweden is 19.6 - 39.2 per 100,000 population per year respectively.[1,2] DH rare in Asian and African races.[1, 3] There are no prevalence reports related to DH in Indonesia. Although it can occur at any age, the most frequent age range

for DH is between 30 and 40, with an average age of 43. There is a male dominance with a ratio of males and females between 1.5-2:1.[1,2]

Similar to celiac disease, the etiopathogenesis of DH involves interactions between genetic, environmental, and immunological variables. The HLA haplotypes DQ2 and DQ8 are closely associated with both DH and celiac disease.[2,3]. An itchy rash on the elbows, extensor areas of the wrists, knees, and buttocks, especially the sacral areas, characterizes the clinical presentation of DH. Small blisters, papules, and erythema make up the polymorphic rash, but due to scratching and itching, erosions, post inflammatory hyperpigmentation, and scaling frequently take center stage in the clinical picture. The location of the rash is fairly common for DH, however each person's level of rash intensity is different.[3,4] Direct immunofluorescence of IgA granular accumulation in the skin papillae and along the cutaneous epidermal junction is used to make the diagnosis.[2] Neutrophilic micro abscesses in the dermal papillae are histological findings in DH lesions in skin biopsies, yet it does not mention DH specifically. Direct immunofluorescence (DIF) continues to be the main method used to make diagnoses. Anti tissue transglutaminase (TG2) along with other autoantibodies can help with illness diagnosis and monitoring, although anti epidermal transglutaminase (TG3) antibody has recently been demonstrated to be an important serological diagnostic. The gluten-free diet (GFD), also referred to as a gluten-free lifestyle, has been shown to improve both celiac disease and DH. Additional medications can be required for recurrent cases, although GFD and dapsone remain the mainstay of therapy.[4]

New alternative therapies such colchicine, methotrexate, heparin, cyclosporin, mycophenolate, tetracycline, nicotinamide, azathioprine, and rituximab have been shown to be effective in treating DH, according to a recent case report.[1] In DH, itching is noticeable and is correlated with general sleep disruption. The quality of life for DH patients can be improved with a proper treatment and diagnosis.[4]

2. Methods

This article was written by reviewing 14 articles which are obtained from several search engines such as Pubmed, Science Direct, and Google Scholar. Article was searched by keywords “Dermatitis Herpetiformis”, “Celiac Disease”, “Gluten Diet”. Articles was screened for relevancy from abstract and publication year between 10 years of publication. Information related to pathophysiology, diagnosis, and treatment of dermatitis herpetiformis was obtained and elaborated in this article.

3. Discussion

3.1 Diagnosis of Dermatitis Herpetiformis

DH affects the extensor surfaces, including the knees, forearms, buttocks, and elbows, and is symmetrically distributed. In addition, the neck, scalp, sacral region, and upper back are frequently impacted. It may also affect the face and lower abdomen. The eruption that develops is typically polymorphic and composed of vesicles, erythematous papules, and urticarial plaques. Many patients have excoriations, crusted papules, and erosions that typically heal without leaving scars. Petechiae, purpura, and mucosal involvement are uncommon in DH. Urticarial plaques, keratosis palmoplantar, and prurigo pigmentosa like lesions are three more unusual clinical manifestations of DH. Patients who have both CD and DH have also been observed to have dental anomalies include enamel flaws and delayed tooth eruption.[1]

The diagnosis of DH can be made using a variety of serological testing. For the early diagnosis of gluten-sensitive illness and DH, serological testing, particularly the anti-tTG lgA examination, is a fairly sensitive and targeted method. The sensitivity range of the enzyme-linked immunosorbent test (ELISA) detects IgA antibody to TG3 is 52% – 100%. The antibodies to endomysium (EMA) and TG2 were less sensitive than anti-TG3 antibodies in diagnosing DH. According to research, CD patients with DH had greater serum levels of anti-TG3 antibodies than CD patients without DH. Serological diagnostics for DH are still being created. In a 2021 study, Ziberna et al. developed a novel ELISA with great diagnostic performance for assessing anti-TG3 antibodies. Additionally, a brand-new bi-analyte immunoblot assay that concurrently detects IgA at TG2 and gliadin in 2021 is useful for diagnosing DH. Anti-TG6, antiGAF3X, and anti-neoepitope TG2 are some more antibodies that are currently being studied. Additionally, it has been discovered that DH patients have significantly higher levels of interleukin-36 (IL-36), but more research is still needed in this area.[1]

Almost all DH patients have the HLA allele DQ8 (10%) or DQ2 (90%). With a high negative predictive value, testing for the HLA haplotypes DQ8 or DQ2 can be used to rule out DH as a diagnosis. A positive test result is useless for DH diagnosis. Consequently, genetic testing for DH is not advised.[5]

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Hematoxylin and eosin (H&E) staining was performed on lesional skin samples from whole vesicles. A biopsy should be performed from intact erythematous skin if no intact vesicles can be observed. Subepidermal vesicles and blisters with an aggregation of neutrophils at the extremities of the dermal papilla are the usual histological abnormalities that can be detected in DH (Figure 1). In order to diagnose DH, a histopathological study is not necessary.[1] Furthermore, in the initial lesion, the upper and middle dermal vessels are surrounded by a lymphohistiocytic infiltrate, as well as some neutrophils and eosinophils. The initial lesions may be indistinguishable from linear IgA disease, bullous eruptions of lupus erythematosus, bullous pemphigoid, or neutrophil-rich forms of acquired epidermolysis bullosa. Immunofluorescence localization and ultrastructural examination of the blister formation sites in DH showed that the blisters formed above the lamina densa, within the lamina lucida. The gastrointestinal symptoms of classic celiac disease are uncommon in patients with DH. However, up to 75 percent of patients with DH had crypt hyperplasia and villous atrophy, according to small intestinal biopsies taken during endoscopy. The long-term prognosis is unaffected by villous atrophy, whether it exists or not (Figure 2) Therefore, regular small bowel biopsies are not necessary.[6]

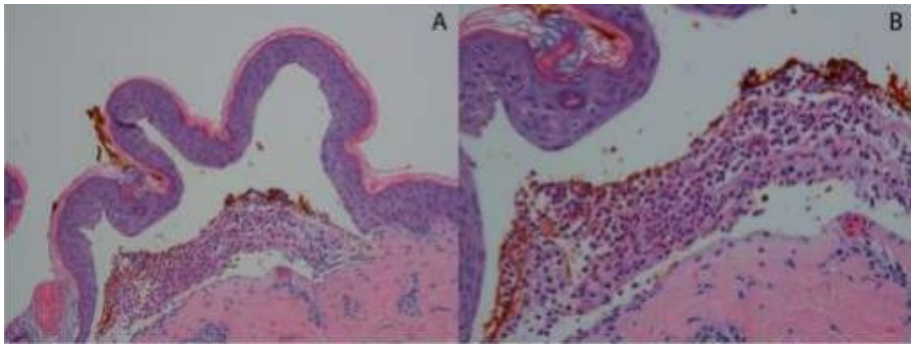

Figure1. Histopathological Findings in DH. Hematoxylin and Eosin Staining of the Sample Demonstrated (A) Subepidermal Separation (H&E x10). (B) Dense Neutrophil Accumulation Forming a Microabscess in the Papillary Dermis (H&E x20).[1]

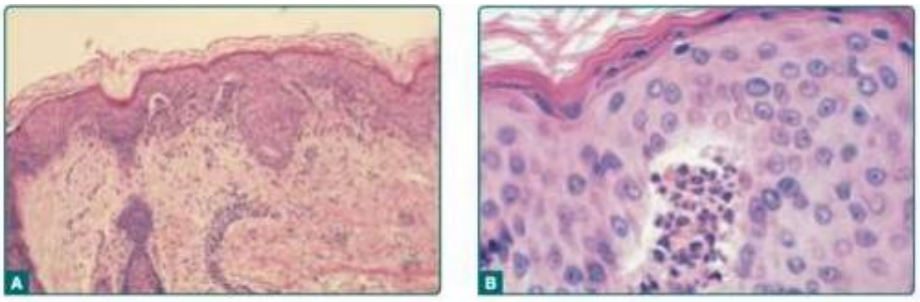

Figure2. Biopsy of the Initial Lesion Shows Collections of Neutrophils and Eosinophils of Papillary Dermal and Subepidermal Vesicles at Low (A) and High (B) Magnifications.[6]

Direct immunofluorescence has the advantage of being cost-effective and is still considered an important procedure for diagnosing DH in the laboratory. In 5% of patients,false-negative immunofluorescence results happen. Granular IgA deposits detected by immunofluorescence assay, along with the necessary clinical features, are sufficient for the diagnosis of DH; however, there was no sign of clinical TG3 precipitating coexistence and DH, indicating that IgA findings are not typical of DH (Figure 3).[7]

The finding of granular IgA deposits in apparently normal skin is the most reliable criteria for the diagnosis of DH. Other immunoglobulins sometimes bind to the skin in the same area as IgA. Furthermore, there is a relationship between DH and increased circulating IgA1-plasmoblasts with skin-homing receptors (CLA) compared to IgA2. The third complement component (C3) is often found in the same location as IgA. The exact location of the IgA deposit on the skin of DH has been studied by immunoelectron microscopy.[6]

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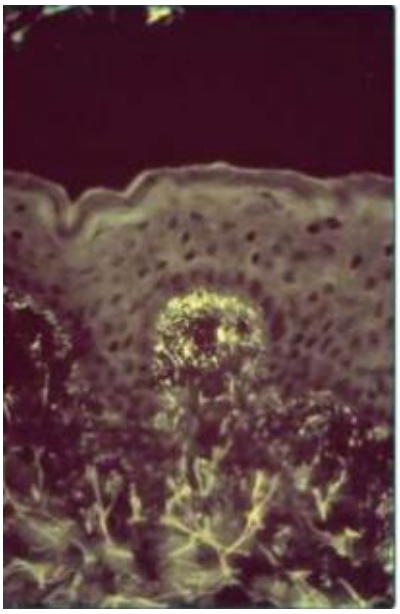

Figure3. Direct Immunofluorescence Shows Papillary Deposits Granular Dermal of Immunoglobulin A.[7]

3.2 Diagnosis Algorithm

Figure 4 shows a suggested diagnostic algorithm based on current research, which includes inquiries and ideas after a DH diagnosis. Because of their greater specificity, anti-TG3 antibodies are favored over anti-TG2 antibodies when diagnosing DH. In addition, the study proposes employing anti-TG2 antibodies as an additional diagnostic tool in situations with ambiguous diagnoses and as a dietary compliance monitor. Additionally, practitioners need to be aware that males typically experience a longer diagnosis delay.[5]

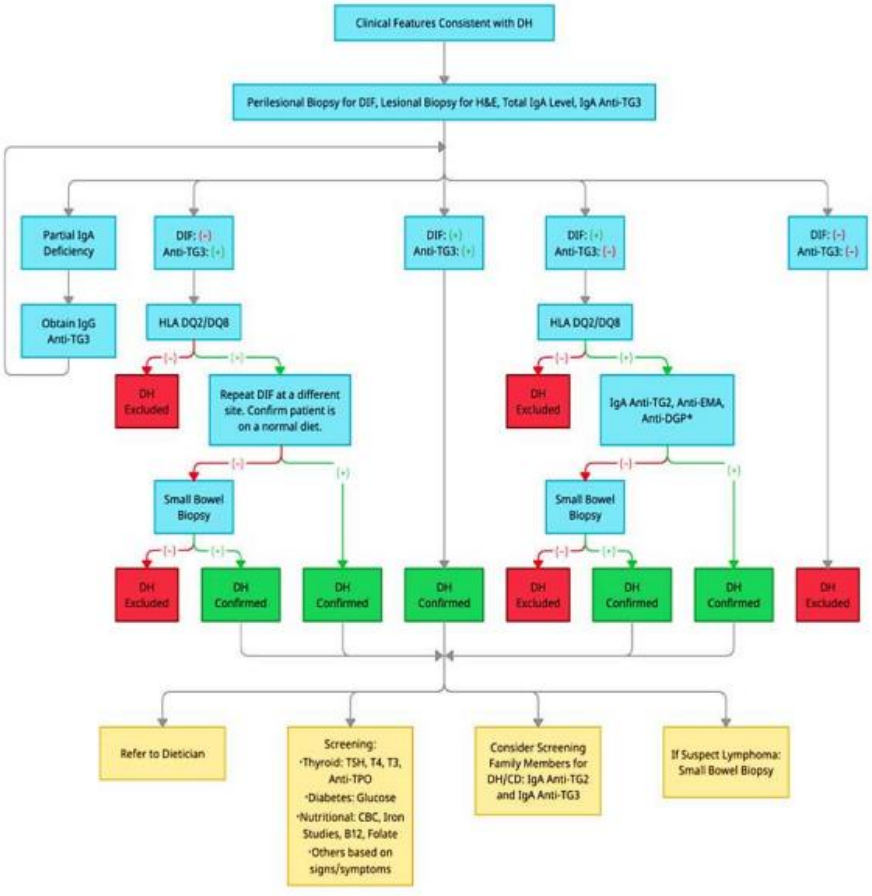

Figure4. Diagnostic Algorithm for Rash Suspected of DH.[5]

3.3 Treatment of Dermatitis Herpetiformis

The initial course of treatment for DH and CD is a lifetime gluten-free diet (GFD). To achieve remission in DH with GFD monotherapy typically takes several months up to a few years. Once the diagnosis has been made, all patients should begin the basic therapy for DH, which is lifetime strict GFD. GFD refers to a lifetime abstinence from all products containing wheat, barley, or rye.[1]

Oats are a food that can help people consume more fiber each day.[5-9] Complete compliance to GFD in DH causes the redness and itching to gradually diminish. Before symptoms disappear, it could take weeks or months, and it often takes two years to completely clear up (Figure 5).[7]

Medication	Dose	Remarks
First Class		
Gluten Free Diet	Not applicable	Strict, lifelong
Dapsone	25-400 mg/day	
Second Class		
Sulfasalazine	1-2 g/day	
Sulfapyridine	1-2 g/day	No longer available in US
Sulfamethoxypyridazine	0.25-1.5 g/day	Through compounding pharmacies
Topical Adjuncts		For local disease control during a flare
Topical Steroids	Various	
Topical 5% Dapsone	BID	Effective for primary facial involvement
Alternatives		Efficacy shown in select case series and reports
Methotrexate	5-25 mg/week	
Colchicine	0.6-2.4 mg/day	
Cyclosporine	3-7 mg/kg/day	Therapeutic dose may be in dangerous range
Heparin	500-1000 U/hr IV or 40 IU SQ	May be given with tetracycline and nicotinamide
Tetracycline	0.5-2 g/day	
Nicotinamide	0.1-1.5 g/day	
Mycophenolate	1 g/day	
Azathioprine	1-2.5 mg/kg/day	
Rituximab	375 mg/m^2	Weekly dose for 4 weeks

Figure5. Treatment Options for DH.[1]

Over 90% of DH patients in Finland who underwent long-term follow-up demonstrated strict adherence to the GFD.[5] Recently, 19 individuals with long-term GFD and asymptomatic DH who undertook a gluten challenge experienced relapses in the skin or small intestine in 95% of cases within a year. This demonstrates that intolerance to gluten is a chronic illness, supporting the need for all DH patients to receive lifelong GFD treatment.[7] Female patients with DH who were treated over an extended period of time had better treatment commitment than male patients, according to Pasternack et al. in Finland.[5]

Dapsone is a sulfone drug with strong anti-inflammatory properties. Dapsone reduced itching and rash in DH within a few days but had no effect on skin enteropathy or IgA deposits. The recommended starting dose of dapsone for adults is 25 to 50 mg/day, and may be raised gradually up to 100 mg/day. In children, the suggested initial dose of dapsone is 0.5 mg/kg/day. Therapy will require approximately of two years with strict GFD. However, response differs, and many patients with GFD need dapsone for longer than this. There may occasionally be hematologic adverse effects, the most frequent of which are methemoglobinemia and dose-dependent hemolysis. Rarely, a patient with prolonged DH using 100 mg of dapsone every day may experience peripheral neuropathy and decreased motor function. Rituximab or sulfasalazine may be helpful. Local DH lesions on the chest and face can be effectively treated with topical 5% dapsone gel.[5, 7-9]

Sulfamethoxypyridazine (0.25-1.5 g/day) and sulfapyridine (1-2 g/day) were previously used, but sulfamethoxypyridazine is no longer accessible, thus other drugs in the sulfonamide class can be administered if the patient cannot handle the adverse effects or there is no improvement from dapsone. Currently, sulfasalazine is the only one commercially available in the US, where the usual recommended dose is 1-2 g/day, but up to 4 g/day may be required [3]. Sulfonamides do not cause the hemolysis that can occur with dapsone. The most common side effects are GI disturbances such as proteinuria and crystalluria. This therapeutic strategy may be employed as well together with dapsone to generate a better response, but patients should also keep themselves properly hydrated throughout treatment.[10]

Other drugs that can be used are superpotent or potent topical steroids to relieve acute symptoms and reduce local lesions in DH, for example clobetasol propionate, dipropionate, or betamethasone valerate. Another treatment that has been proven to be somewhat useful for localized symptoms is dapsone 5% topical. Topical steroids or topical 5% dapsone should not be administered as monotherapy but rather in conjunction with systemic therapy to control local disease during the acute period.[1]

The advantages of alternative medicine have been mentioned in a case study. It is interesting to note that colchicine can be used with a sulfonamide and decreases neutrophil activity. The therapeutic dose needed for cyclosporine, however, may be detrimental to the patient, rendering it ineffective.[10] Nguyen et al. in his case report reported the administration of rituximab as an alternative treatment in DH patients, where several other case reports also indicated that rituximab could assist in achieving clinical and serological remission of DH [10]. Singh et al. reported a patient with severe DH who was treated effectively with a combination of tetracycline and nicotinamide. The two in combination act by suppressing antibody formation and modulating proinflammatory cytokines, and inhibiting inflammatory cell accumulation and T cell activation.[11]

3.4 Quality of Life and Prognosis

DH is a celiac disease skin symptom that is managed with a gluten-free diet. Despite an extended gluten free diet, the itchy, blistering rash usually slowly goes away following abstinence from gluten. The majority of DH patients suffer severe itching, difficulties sleeping, and even gastrointestinal symptoms.[12,14]

DH is a chronic, relapsing disease that can last someone's whole life. However, DH patients who commit strictly to the GFD have a very good prognosis. In 20% of cases, it is feasible to resume a normal diet without relapsing, but it is unknown how these modifications will affect long-term morbidity and death. To get the best prognosis, it is recommended that all DH patients maintain a GFD for the rest of their lives.[13]

4. Conclusion

The majority of DH patients have villous atrophy in the small intestine, making it the most prevalent extraintestinal symptom of celiac disease. DIF is the main method used to diagnose DH, and IgA accumulation in the dermal papillae is basically pathognomonic for this condition. Anti-TG3 antibody levels, however, are currently used as the primary serological diagnostic marker in modern and recent techniques. Strict long-term GFD is currently recognized as the main therapeutic strategy, according to recent studies. Sulfonamide-containing medication, particularly dapsone, are used as a first-line treatment in addition to the diet. To further grasp the particular details in its diagnosis and treatment, DH has to be explored more thoroughly.

5. Acknowledgements

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6. Conflict of Interest

The author declared that there are no conflict of interest in this article.

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