ACHAIKI IATRIKI | 2023; 42(4):175–178

Celiac disease and Dermatitis herpetiformis

Fotios S. Fousekis, Konstantinos H. Katsanos

Abstract

Dermatitis herpetiformis (DH) is a chronic immune-mediated cutaneous disease and an extraintestinal manifestation of celiac disease (CD). It is triggered by gluten exposure in genetically predisposed individuals. DH presents as a pruritic rash with characteristic skin lesions, while atypical clinical manifestations are also possible. Diagnosis involves histopathology, immunofluorescence, and serological testing. DH has a lower prevalence compared to CD, with a higher incidence in men and a broad age range of onset. DH is associated with other autoimmune diseases and an increased risk of non-Hodgkin lymphoma, although a gluten-free diet may offer protective effects. The pathogenesis of DH involves genetic, immunological, and environmental factors. Treatment primarily involves lifelong adherence to a strict gluten-free diet, with dapsone as the main pharmacological therapy. Multidisciplinary management, including regular monitoring and collaboration among various specialists, is recommended. Further research is needed to explore novel treatment options and enhance understanding of the underlying mechanisms. Adherence to a gluten-free diet is essential for symptom resolution and effective disease control of DH and CD.

Key words: *Celiac disease; dermatitis herpetiformis; gluten-free diet; treatment*

INTRODUCTION

DH was first described by Louis Adolphus Duhring in 1884 and is a chronic, polymorphous, pruritic immune-mediated cutaneous disease. DH is considered as one of the most frequent and well-recognised extraintestinal manifestations of celiac disease (CD) and DH is literally referred to as a CD of skin [1]. Both CD and DH are triggered by exposure of dietary gluten in genetically predisposed individuals [2] and both diseases are associated with similar pathogenetic mechanisms.

DH typically presents as a pruritic rash consisting of herpetiform papulovesicular lesions that progress to blisters, erosions, excoriations, and hyperpigmentation on the external surfaces of the body. It mainly affects the elbows, lower limbs (such as the anterior thigh and knee), buttocks, and sacral region, while involvement of the shoulders and scalp is less common. Atypical clinical presentations of DH can include palmar purpura, chronic urticaria, prurigo pigmentosa-like lesions, and pseudovasculitis [3]. Additionally, DH can also affect the oral mucosa, causing aphthous stomatitis [4].

DIAGNOSIS

A diagnosis of CD requires a combination of villous atrophy and lymphocytic infiltration in duodenal biopsies, as well as the detection of celiac-specific antibodies in the serum. Classical symptoms of CD include diarrhoea, abdominal pain, weight loss, anaemia, and flatulence. However, patients with DH, despite having coexisting CD, typically experience milder gastrointestinal symptoms, with signs of malabsorption being rare [5]. While 70% of DH patients exhibit villous atrophy, the remaining patients may have mucosal inflammation indicative of early-stage CD. Importantly, the presence of villous atrophy at the time of DH diagnosis does not affect the clinical recovery of patients on a gluten-free diet [6].

The diagnosis of DH is based on specific findings from direct immunofluorescence and histopathology of skin biopsies, along with the clinical presentation

Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

Received: 15 Jul 2023; Accepted: 17 Oct 2023

and CD diagnosis. Histopathological examination of an erythematous papule typically reveals neutrophilic microabscesses within the dermal papillae, while a vesicle biopsy shows a subepidermal blister [7]. However, these histopathologic findings alone do not allow for differentiation from other autoimmune diseases, such as linear IgA disease, bullous pemphigoid, anti-laminin-1 pemphigoid, or the inflammatory form of epidermolysis bullosa acquisita. The detection of granular IgA either in the dermal papillae or along the dermo-epidermal junction in direct immunofluorescence is considered the gold standard for diagnosis of DH and helps to differential diagnosis between DH and other cutaneous autoimmune diseases [8]. IgA deposition in DH can occur in both involved and uninvolved skin, as well as the oral mucosa. In contrast, CD patients without DH do not show cutaneous IgA deposition. Epidermal transglutaminase (eTG) has been identified as the primary autoantigen target in DH, and the measurement of serum IgA eTG antibodies can effectively distinguish DH from other dermatological conditions [9]. Furthermore, IgA eTG antibodies persist for a longer period in DH patients compared to IgA anti-TG (tissue TG) antibodies in CD patients on a gluten-free diet [10].

EPIDEMIOLOGY

DH is considered a rare disease, and its prevalence varies among countries. The reported prevalence ranges from 1:1,000,000 new cases per year to 59: 100,000 new cases per year [11]. In comparison, the prevalence of CD is higher, affecting approximately 1% of the population, although it also varies geographically. In Europe and North America, CD is diagnosed more frequently, with a prevalence of up to 2% in Finland. Asian countries generally have a lower prevalence of CD. DH can manifest at any age, but the most common age for diagnosis is between 30 and 40 years [12]. However, it is worth noting that DH has been diagnosed in infants as young as 8 months old [13]. Men are more commonly affected by DH, with a male-to-female frequency ratio of approximately 2:1. In contrast, CD appears to occur more frequently in women, with a ratio of approximately 2:1 [14].

ASSOCIATED DISEASES

Several autoimmune diseases have been associated with DH, including rheumatoid arthritis, systemic lupus erythematosus, myasthenia gravis, Sjogren syndrome, autoimmune thyroiditis and sarcoidosis. However, the prevalence of autoimmune disorders in patients with DH is similar to patients with CD only [15]. Additionally, patients with DH may have a higher risk of non-Hodgkin lymphoma, particularly enteropathy-associated T cell lymphoma, but a gluten-free diet may protect against the development of lymphoma [16].

PATHOGENESIS

The pathogenesis of DH is multifactorial and involves a combination of genetic factors, immunological mechanisms, and environmental factors. There is a genetic predisposition with an association to human leukocyte antigens (HLA) DQ2 and DQ8, indicating a potential role of the immune system in the aetiopathogenesis. The closest association is observed with HLA-DQ2 (a combination of the DQA10501 and DQB102 alleles) and DQ8 (a combination of the DQA103 and DQB10302 alleles), present in approximately 85% and 15% of the patients, respectively. Furthermore, patients with DH appear to have a genetic predisposition to developing the condition. A follow-up study on CD and DH revealed that around 20% of patients had affected first-degree relatives, resulting in a prevalence rate of 5.5% among relatives. The annual incidence of CD and DH was found to be 15 times higher compared to the general population [17].

MANAGEMENT

DH and CD are primarily treated with a lifelong gluten-free diet (GFD). Adhering strictly to GFD leads to the resolution of skin and bowel symptoms associated with these conditions. However, in some cases, additional medications such as dapsone, sulfonamides, or steroids may be used temporarily to control symptoms until the diet alone is sufficient. A multidisciplinary approach involving dermatologists, gastroenterologists, dieticians, and other specialists is recommended for managing DH and CD, as it allows for regular assessment of diet adherence, treatment response, side effects, and potential complications [18].

Gluten-free diet

Adherence to a strict GFD is crucial for managing DH. Patients should avoid foods containing gluten, including cereals such as wheat, barley, rye, and malt. Gluten-free foods such as rice, maize, potatoes, and vegetables are safe to consume. Oats can be consumed if they are pure and uncontaminated with gluten. However, most store-bought oat products are typically contaminated,

so they should be avoided. Studies have shown that strict adherence to the GFD reduces the need for medication, improves well-being, and has a protective effect against lymphoma [19].

Dapsone

Dapsone is the primary drug used to treat DH. It has anti-inflammatory and antibacterial properties and provides quick relief from symptoms. Dosing of dapsone may vary, but most patients can be managed with 100-200 mg daily. Hemolysis and methemoglobinaemia are potential side-effects, particularly in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD screening is recommended before starting treatment. Regular monitoring of complete blood count, reticulocyte count, liver and renal function is necessary. Other sulfonamides may be used if dapsone is not tolerated or ineffective [19].

Other medications

In some cases, alternative medications such as methotrexate, colchicine, cyclosporine, heparin, and rituximab may be considered, if GFD and sulfonamides are inadequate. However, more research is needed to evaluate their effectiveness. Biologics targeting IL-1, IL-17, and IL-36 show promise as potential future therapies [20].

Overall, strict adherence to a GFD is essential for managing DH and CD. Dapsone is the mainstay of treatment for DH, with sulfonamides and other medications used as alternatives. Regular monitoring and a multidisciplinary approach are important for assessing treatment response, managing side effects, and addressing complications. Future research is needed to explore additional treatment options and novel therapeutic targets.

CONCLUSION

DH is a chronic immune-mediated cutaneous disease and one of the extraintestinal manifestations of CD. Both conditions are triggered by gluten exposure in genetically susceptible individuals. DH presents as a pruritic rash and can have atypical clinical manifestations. Diagnosis involves a combination of histopathology, immunofluorescence, and serological testing. DH has a lower prevalence compared to CD and can manifest at any age, with a higher incidence in men. Associated autoimmune diseases and an increased risk of non-Hodgkin lymphoma have been observed in DH patients. Pathogenesis involves genetic and immunological factors, and a gluten-free diet is the primary treatment. Dapsone is commonly used to manage DH, with alternative medications considered for refractory cases. Adherence to a gluten-free diet is crucial for symptom resolution and disease control. Close monitoring and a multidisciplinary approach are recommended for effective management of DH and CD. Further research is needed to explore new treatment options and understand the underlying mechanisms of the diseases.

Conflict of interest: *None to declare*

Declaration of funding sources: *None to declare*

Author contributions: *All authors contributed equally to the current work.*

REFERENCES

1. Reunala T. Dermatitis herpetiformis: coeliac disease of the skin. Ann Med. 1998;30(5):416-8.
2. Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, et al. The Oslo definitions for coeliac disease and related terms. Gut. 2013;62(1):43-52.
3. Verdelli A, Corra A, Mariotti EB, Aimo C, Quintarelli L, Ruffo di Calabria V, et al. Skin gluten-related disorders: new and old cutaneous manifestations to be considered. Front Med. 2023;10:1155288.
4. Lahteenoja H, Irjala K, Viander M, Vainio E, Toivanen A, Syrjanen S. Oral mucosa is frequently affected in patients with dermatitis herpetiformis. Arch Dermatol. 1998; 134(6):756-8.
5. Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis. Part I. Epidemiology, pathogenesis, and clinical presentation. J Am Acad Dermatol. 2011;64(6):1017-24; quiz 25-6.
6. Mansikka E, Hervonen K, Kaukinen K, Collin P, Huhtala H, Reunala T, et al. Prognosis of Dermatitis Herpetiformis Patients with and without Villous Atrophy at Diagnosis. Nutrients. 2018;10(5):641.
7. Nicolas ME, Krause PK, Gibson LE, Murray JA. Dermatitis herpetiformis. In J Dermatol. 2003;42(8):588-600.
8. Fry L. Dermatitis herpetiformis. Bailliere›s Clin Gastroenterol. 1995;9(2):371-93.
9. Borroni G, Biagi F, Ciocca O, Vassallo C, Carugno A, Cananzi R, et al. IgA anti-epidermal transglutaminase autoantibodies: a sensible and sensitive marker for diagnosis of dermatitis herpetiformis in adult patients. J J Eur Acad Dermatol Venereol. 2013;27(7):836-41.
10. Rose C, Armbruster FP, Ruppert J, Igl BW, Zillikens D, Shimanovich I. Autoantibodies against epidermal transglutaminase are a sensitive diagnostic marker in patients with dermatitis herpetiformis on a normal or gluten-free diet. J Am Acad Dermatol. 2009;61(1):39-43.
11. Mendes FB, Hissa-Elian A, Abreu MA, Goncalves VS. Review:

dermatitis herpetiformis. An Bras Dermatol. 2013;88(4):594-9.
12. Smith JB, Tulloch JE, Meyer LJ, Zone JJ. The incidence and prevalence of dermatitis herpetiformis in Utah. Arch Dermatol. 1992;128(12):1608-10.
13. Lemberg D, Day AS, Bohane T. Coeliac disease presenting as dermatitis herpetiformis in infancy. J Paediatr Child Health. 2005;41(5-6):294-6.
14. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol. 2012;107(10):1538-44; quiz 7, 45.
15. Reunala T, Collin P. Diseases associated with dermatitis herpetiformis. Br J Dermatol. 1997;136(3):315-8.
16. Lewis HM, Renaula TL, Garioch JJ, Leonard JN, Fry JS, Collin P, et al. Protective effect of gluten-free diet against development of lymphoma in dermatitis herpetiformis. Br J Dermatol. 1996;135(3):363-7.
17. Antiga E, Maglie R, Quintarelli L, Verdelli A, Bonciani D, Bonciolini V, et al. Dermatitis Herpetiformis: Novel Perspectives. Front Immunol. 2019;10:1290.
18. Nguyen CN, Kim SJ. Dermatitis Herpetiformis: An Update on Diagnosis, Disease Monitoring, and Management. Medicina (Kaunas). 2021;57(8):843.
19. Vale E, Dimatos OC, Porro AM, Santi CG. Consensus on the treatment of autoimmune bullous dermatoses: dermatitis herpetiformis and linear IgA bullous dermatosis - Brazilian Society of Dermatology. An Bras Dermatol. 2019;94(2 Suppl 1):48-55.
20. Zebrowska A, Wozniacka A, Juczynska K, Ociepa K, Waszczykowska E, Szymczak I, et al. Correlation between IL-36alpha and IL17 and Activity of the Disease in Selected Autoimmune Blistering Diseases. Mediators Inflamm. 2017;2017:8980534.

Corresponding author:

Konstantinos H. Katsanos
Department of Gastroenterology, University of Ioannina Faculty of Medicine, 45 110 Ioannina, Greece
E-mail: khkostas@hotmail.com