ZWARDOŃ, Jakub, KAPCIAK, Alicja, GÓRNY, Julia, WITAS, Gabriela, HAWAJSKI, Artur, JANKOWSKA, Natalia, KAMIENIECKA, Oliwia, NAJA, Katarzyna, and ŚWIERZYŃSKA, Adrianna. Is a Gluten-Free Diet Sufficient in the Treatment of Duhring's Disease? – A Review. Quality in Sport. 2024;35:56355. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.35.56355
https://apcz.umk.pl/QS/article/view/56355

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 19.11.2024. Revised: 05.12.2024. Accepted: 12.12.2024. Published: 12.12.2024.

Is a Gluten-Free Diet Sufficient in the Treatment of Duhring's Disease?

- A Review

Jakub Zwardoń [JZ]
Medical University of Warsaw
Żwirki i Wigury 61, 02-091 Warsaw, Poland
https://orcid.org/0009-0005-3944-2943
jak.zwa@gmail.com

Alicja Kapciak [AK]
National Medical Institute
of the Ministry of the Interior and Administration
Wołoska 137, 02-507 Warsaw, Poland
https://orcid.org/0009-0000-0655-8820
ala.kapciak@gmail.com

Julia Górny [JG]
Mazovian "Bródnowski" Hospital
Ludwika Kondratowicza 8, 03-242 Warsaw, Poland
https://orcid.org/0009-0008-5363-1590
gornyjulia1@gmail.com

Gabriela Witas [GW]
Western Mazovia Health Center
Limanowskiego 30, 96-300 Żyrardów, Poland
https://orcid.org/0009-0009-2782-6391
gwitas@poczta.onet.pl

Artur Hawajski [AH]
University of Technology and Humanities in Radom
Chrobrego 27, 26-600 Radom, Poland
https://orcid.org/0009-0003-7592-2114
artur.hawajski@gmail.com

Natalia Jankowska [NJ]
University of Technology and Humanities in Radom
Chrobrego 27, 26-600 Radom, Poland
https://orcid.org/0009-0000-3618-6247
nat.jankowska00@gmail.com

Oliwia Kamieniecka [OK]
Medical University of Warsaw
Żwirki i Wigury 61, 02-091 Warsaw, Poland
https://orcid.org/0009-0003-1660-2735
oliwia.kamieniecka@gmail.com

Katarzyna Naja [KN]
Medical University of Warsaw
Żwirki i Wigury 61, 02-091 Warsaw, Poland
https://orcid.org/0009-0008-6513-6984
katarzynanaja99@gmail.com

Adrianna Świerzyńska [AŚ]
University of Technology and Humanities in Radom
Chrobrego 27, 26-600 Radom, Poland
https://orcid.org/0009-0007-1451-3009
ada199805@gmail.com

Abstract

Introduction

Dermatitis herpetiformis is a chronic autoimmune blistering disease characterized by intensely pruritic, symmetrically distributed skin lesions and an association with gluten-sensitive enteropathy. Despite advances in diagnostic methods, delayed diagnosis remains a challenge due to its overlapping features with other dermatoses.

Aim of Study

This study aims to provide a comprehensive overview of the diagnostic methods, associated conditions, and differential diagnosis of dermatitis herpetiformis, focusing on recent advancements in serological, histopathological, and immunological testing.

Material and methods

A comprehensive review of the literature on dermatitis herpetiformis was performed using the PubMed database.

Results and Conclusions

Direct immunofluorescence remains the gold standard in diagnosing dermatitis herpetiformis, revealing granular IgA deposits in the dermal papillae. Histopathological findings are supportive but nonspecific, with early lesions showing subepidermal vesicles and neutrophilic infiltrates. Serological markers, including anti-TG2 and anti-TG3 antibodies, provide valuable diagnostic support but exhibit variable sensitivity. HLA-DQ2/DQ8 haplotypes are present in most dermatitis herpetiformis patients, offering high negative predictive value for exclusion. Associated autoimmune conditions, such as autoimmune thyroid disease and type 1 diabetes, are prevalent, and dermatitis herpetiformis patients face an elevated risk of non-Hodgkin

lymphoma within the first five years after diagnosis. The diagnosis of dermatitis herpetiformis relies on a combination of direct immunofluorescence, serological testing, and clinical features. Increased awareness of dermatitis herpetiformis and its associated conditions is critical for timely diagnosis and management. Advances in immunological and genetic testing may further refine diagnostic accuracy, while screening for associated autoimmune disorders and malignancies remains an integral part of patient care.

Keywords: dermatitis herpetiformis, celiac disease, gluten free diet, direct immunofluorescence, dapsone, sulfonamides

1. Introduction

Dermatitis herpetiformis (DH), also known as Duhring's disease, is a chronic autoimmune blistering disorder considered a specific manifestation of celiac disease (CD) on the skin. It was first described as a clinical entity by Louis Duhring in 1884, characterized by symmetrically distributed, itchy skin lesions (1). These lesions most commonly appear on the extensor surfaces of the elbows, knees, buttocks, and other typical locations such as the nape of the neck and scalp (2).

The etiology and pathogenesis of DH involve a complex interaction of genetic, immunological, and environmental factors. Genetic predisposition, linked to HLA-DQ2 and HLA-DQ8 haplotypes, plays a pivotal role, predisposing individuals to an immune response targeting tissue and epidermal transglutaminases (3). A hallmark feature of DH is the presence of granular deposits of immunoglobulin A (IgA) in the dermis, detectable via direct immunofluorescence testing, which serves as the gold standard for diagnosis (4, 5).

Similar to celiac disease, DH is primarily triggered by gluten consumption- a protein found in grains such as wheat, barley, and rye. Skin lesions and subtle intestinal changes improve with adherence to a strict gluten-free diet (GFD), whereas symptoms recur after gluten reintroduction (6). In addition to dietary management, dapsone is used as an initial treatment to rapidly alleviate pruritus and skin lesions, although long-term use of this drug is not required when the disease is well-controlled with dietary measures (7).

The prevalence of DH is relatively low, and its clinical course can vary significantly between patients. Skin symptoms are often accompanied by mild gastrointestinal manifestations or may be the sole presentation of the disease (8). It is also noteworthy that DH is associated with an increased risk of non-Hodgkin lymphoma within the first few years following diagnosis (9).

The aim of this study is to provide an overview of the current knowledge on the etiology, pathogenesis, clinical presentation, and treatment of Duhring's disease, with particular emphasis on its relationship with celiac disease and the impact of a gluten-free diet on the disease course.

2. Characteristics of Duhring's Disease

2.1.Epidemiology

Duhring's disease is a rare condition that predominantly affects individuals of Caucasian descent. In Europe and the United States, the prevalence of DH ranges from 11.2 to 75.3 cases per 100,000 people, with the highest rates reported in Finland. The annual incidence ranges from 0.4 to 2.6 per 100,000 people (10). DH is extremely rare in African and Asian populations, which can be attributed to the absence of the predisposing HLA-DQ2 and DQ8 haplotypes common in Caucasians and lower wheat consumption in these geographic regions (11). Despite its rarity, DH remains the most common extraintestinal manifestation of celiac disease, with the ratio of CD to DH consistently observed at 8-10:1 across populations (12).

In recent years, a marked decline in new cases of DH has been noted, while the incidence of celiac disease has risen nearly fourfold (13). This increase has been attributed to greater public awareness of mild CD symptoms, advancements in effective serological screening tests, and identification of at-risk groups (14). Epidemiological studies indicate that the rising incidence of celiac disease over recent decades results not only from improved diagnostic capabilities but also from a genuine increase in its frequency (15). The declining incidence of DH, coupled with the rapid rise in celiac disease cases, supports the hypothesis that subclinical, undiagnosed celiac disease is a key predisposing factor for the development of DH (16).

Duhring's disease can occur at any age; however, it is most commonly diagnosed between the ages of 30 and 40, with the mean age of diagnosis being approximately 43 years (10). Over recent decades, there has been a significant increase in the average age of diagnosis, particularly in Finland, where a large cohort study showed that the mean age of DH diagnosis rose from 35 to 51 years in men and from 36 to 46 years in women (13). A similar trend has been observed in celiac disease, which may be related to lower lifetime gluten exposure (17). In children, DH is rare, and its diagnosis can be challenging due to atypical clinical presentations often masked by coexisting skin conditions such as atopic dermatitis (3).

Gender differences are also notable in DH. Among adults with celiac disease, women are more frequently affected, with a female-to-male ratio of up to 3:1. However, in DH, the pattern is

reversed, with men being more commonly affected, and the male-to-female ratio ranging from 1.5:1 to 2:1 (10).

2.2. Etiopathogenesis

The pathogenesis of Duhring's disease involves a complex interplay of genetic, immunological, and environmental factors, with gluten acting as the key triggering agent (18). Similar to celiac disease, HLA-DQ2 and HLA-DQ8 haplotypes play a critical role. HLA-DQ2 is observed in approximately 86% of DH patients (18). In genetically susceptible individuals, gluten consumption leads to intestinal mucosal damage, marking the initial stage of disease development (19).

In the gut, gliadin, which is a component of gluten, serves as a substrate for tissue transglutaminase 2 (TG2), forming covalent complexes known as deamidated gliadin peptides (DGP) (20). These complexes bind to HLA-DQ2/DQ8 on antigen-presenting cells, initiating an immune response. Activated CD4+ T lymphocytes trigger cytokine-mediated damage via Th1 responses, leading to intestinal mucosal injury (21), and Th2 responses, which stimulate the production of IgA antibodies against gliadin, TG2, and endomysium. This immune response is considered pivotal in DH pathogenesis (20).

After prolonged gluten exposure, patients develop IgA antibodies targeting tissue transglutaminase 3 (TG3), which play a central role in disease pathogenesis. These autoantibodies are produced in the small intestine (22) and subsequently form immune complexes that deposit in the dermal papillae (23). In the skin, complement activation and neutrophil infiltration lead to degranulation, release of proinflammatory cytokines-including IL-17 and IL-36 and enzymes such as elastases, which exacerbate inflammation, damage the basement membrane, and cause the formation of characteristic blistering lesions.

Duhring's disease serves as a model autoimmune disorder that can be controlled by eliminating a known triggering factor. Although the gut-skin axis and inflammatory networks in DH are increasingly understood, many aspects of its pathogenesis require further investigation (21).

2.3. Symptoms

Duhring’s disease is characterized by the symmetrical distribution of skin lesions, which primarily appear on extensor surfaces such as the elbows, knees, and buttocks. Lesions may also occur in other areas, including the upper back, neck, scalp, rarely on the face, groin, or oral mucosa. The rash in Duhring’s disease is polymorphic in nature and exhibits typical distribution. Skin changes often manifest as clusters of erythematous papules, urticarial plaques, and vesicles, which may evolve into small, tense blisters filled with serous-hemorrhagic fluid. Rupture of blisters and intense pruritus lead to scratching, resulting in erosions, crusts, and excoriations (24).

In many patients, the healing process of lesions leaves post-inflammatory hypo- or hyperpigmentation; however, scarring rarely occurs (21). The intensity and appearance of the rash may vary among individuals (25), but its characteristic distribution and accompanying severe pruritus are important clinical features raising suspicion of DH (26). Nearly all patients experience intense pruritus, which can significantly lower their quality of life. The absence of

pruritus is rare and strongly argues against the diagnosis of DH, suggesting the need to consider alternative diagnoses (21). Findings from a cohort study involving 159 patients confirmed that almost all participants reported severe itching that negatively affected their daily functioning (27).

In adult patients with Duhring's disease, gastrointestinal symptoms are typically mild and nonspecific. Sudden gastrointestinal complaints or malabsorption symptoms are rare. Most commonly, patients report occasional loose stools, bloating, constipation, or mild gastric discomfort (28, 29). Nevertheless, approximately 75% of individuals with DH exhibit villous atrophy characteristic of celiac disease, although these changes are generally milder than those observed in classical celiac disease (30).

2.4. Long-Term Complications

Due to small intestinal damage and gluten-sensitive enteropathy, patients may experience complications such as nutritional deficiencies, anemia, osteoporosis, stunted growth, or weight loss (28, 29). These complications, however, occur less frequently than in classical celiac disease (3). Duhring's disease significantly increases the risk of developing non-Hodgkin lymphoma, particularly within the first five years after diagnosis. Among patients, B-cell lymphomas are most commonly observed, although T-cell-derived lymphomas may also occur (9).

2.5. Other Triggering Factors

Although gluten is the primary trigger of the disease, increasing evidence suggests that other factors may also induce or exacerbate its symptoms. For instance, potassium iodide, used as an expectorant, has been described as a DH trigger when administered both orally and topically (31). There is also evidence that hormonal factors, particularly those associated with the hypothalamic-pituitary-gonadal axis, may play a role in DH pathogenesis. Cases of the disease have been reported following the use of progesterone-based contraception (32) or therapy with gonadotropin-releasing hormone analogs such as leuprolide acetate (33). Certain medications have also been identified as potential DH triggers. These include cases of disease development during therapy with infliximab, a tumor necrosis factor-alpha inhibitor used for ankylosing spondylitis (34), or ipilimumab, an immunomodulatory drug used in metastatic melanoma treatment (35). Furthermore, instances of DH have been reported shortly after the diagnosis of lung adenocarcinoma and autoimmune pancreatitis in patients without IgA antibodies against tissue transglutaminase or symptoms of celiac disease (36).

3. Diagnosis

The diagnosis of dermatitis herpetiformis is frequently challenging, often leading to delayed recognition of several months, and sometimes even years, from the onset of the initial symptoms. However, in recent decades, this diagnostic delay has been significantly reduced,

largely due to increased awareness of DH and celiac disease within both patient populations and the medical community.

3.1. Direct Immunofluorescence

The gold standard for diagnosing DH remains direct immunofluorescence, which reveals the presence of pathognomonic granular deposits of IgA within the dermal papillae and/or along the dermoepidermal junction (4, 5). First identified in 1969, these IgA deposits are highly specific to DH and form the cornerstone of the diagnostic approach (37). Biopsy samples should be obtained from perilesional skin areas, as these regions exhibit the highest concentration of IgA deposits (38). Importantly, these IgA deposits can persist in the skin for years following the initiation of a gluten-free diet, thus enabling confirmation of the diagnosis without the need for reintroduction of gluten into the diet (39). However, in approximately 5–10% of cases, false-negative results may occur, particularly when the sample is derived from damaged or inflamed skin lesions, or from patients who have adhered to a GFD for an extended period (38, 40). Additionally, DIF may occasionally reveal other immune reactants, such as immunoglobulin G (IgG), immunoglobulin M (IgM), or complement component 3 (C3), but their presence does not alter the diagnostic criteria for DH (4).

3.2. Histopathological Examination

The histopathological features of dermatitis herpetiformis exhibit variability depending on the clinical phase and disease duration. In the early stages, typically within the first two days, subepidermal vesicles and microabscesses are observed in the dermal papillae, with a predominance of neutrophils and few eosinophils (37, 41). In later stages or when lesions are intensely scratched, the histopathological pattern becomes less specific. While these changes are helpful in diagnosing DH, they are not pathognomonic, as they can also be seen in other blistering disorders, such as linear IgA dermatosis. Recent studies suggest a high specificity for histopathological examination (95%), but its sensitivity is lower (75%), limiting its use as a standalone diagnostic tool (42).

3.3. Small Bowel Biopsy

Small bowel biopsy is not routinely required for diagnosing DH, although villous atrophy and crypt hyperplasia are commonly observed in most patients. Characteristic features include intraepithelial lymphocytosis, an increased number of T γδ+ lymphocytes, and the presence of anti-tissue transglutaminase antibodies in the intestinal mucosa (43). However, the degree of mucosal damage does not correlate with long-term prognosis in DH (44). Gastrointestinal symptoms typical of celiac disease are rare, and duodenal biopsy is recommended only in doubtful cases, such as negative direct immunofluorescence results with suspected DH (37, 42). Nearly all DH patients with celiac disease display the presence of HLA-DQ2/DQ8 haplotypes, which can exclude DH in their absence (45). In recent decades, the severity of changes in the small bowel mucosa in DH patients has decreased, further reducing the need for biopsies (43).

3.4. Serology

In DH patients, IgA antibodies against tissue transglutaminase and epidermal transglutaminase are frequently detected. TG2 antibodies, a marker for celiac disease, are primarily found in DH patients with villous atrophy, indicating that their absence does not rule out DH (37). Antibodies against TG3, the main autoantigen in DH, exhibit greater specificity, but their presence has also been reported in patients with celiac disease without skin symptoms. In such cases, lower affinity for TG3 may suggest a reduced risk of developing DH (8). Serological tests, including the measurement of anti-tissue transglutaminase (anti-tTG), anti-endomysium antibodies (anti-EMA), and antibodies against deamidated gliadin peptides, are effective screening tools in diagnostics, with high specificity (>90%) and variable sensitivity (50–95%) (45). Antibodies against epidermal transglutaminase have diagnostic potential, but their presence in celiac patients limits their utility in differentiating DH from other gluten-related dermatoses (46).

3.5. Other methods

HLA-DQ2 or HLA-DQ8 haplotypes are present in the majority of DH patients, but their low specificity makes genetic testing more useful for exclusion, particularly due to the high negative predictive value (21, 47). In certain populations, such as Latin America, up to 10% of celiac patients may lack these alleles (47). While small bowel biopsy is not mandatory in DH diagnosis, it helps assess villous atrophy, especially in cases with positive anti-TG2 antibodies, a celiac marker found in most DH patients with enteropathy (48). On the other hand, anti-TG3 antibodies, the autoantigen of DH, are present in most DH patients and a smaller proportion of celiac patients, though their specificity and reference values remain undetermined, limiting their use in routine diagnostics (49, 50). Modern techniques, such as microbiota and metabolome analysis, represent promising research directions in the context of DH, though further studies are required (24). Dermoscopy can assist in differentiation from other blistering disorders, revealing characteristic features, such as the absence of yellow scales typical of pemphigoid (51).

3.6.Associated Disorders

Autoimmune Diseases

Dermatitis herpetiformis frequently coexists with various autoimmune disorders, most commonly autoimmune thyroid diseases and type 1 diabetes mellitus. Autoimmune thyroid conditions, present in approximately 4.3% of DH patients, tend to develop in older women and can emerge either before diagnosis or during a gluten-free diet regimen (24). Type 1 diabetes is diagnosed in 2.3% of DH patients, typically during childhood or adolescence, and its management can be effectively supported by a concurrent diabetic diet along with the GFD (52). Routine screening for thyroid diseases, including assessments of thyrotropin hormone (TSH), triiodothyronine (T3), tyroxine (T4) levels, and thyroid peroxidase antibodies, as well as screening for type 1 diabetes through glycemia tests, is recommended. Other autoimmune conditions should be diagnosed based on clinical symptoms. Less common but associated conditions include vitiligo, alopecia areata, Sjögren's syndrome, systemic lupus erythematosus, dermatomyositis, rheumatoid arthritis, and pemphigus vulgaris (24).

A particular area of concern is the correlation between DH and pemphigus vulgaris (PV), an autoimmune subepidermal blistering disease. The pathogenesis of PV involves the presence of autoantibodies directed against hemidesmosomal antigens BP180 and BP230 (53). A

retrospective study by Varpuluoma et al. demonstrated a 22-fold increased risk of developing PV in patients with DH, whereas the risk is only doubled in those with celiac disease. The median time for PV onset after DH diagnosis is approximately three years (54).
In younger DH patients, there is a higher prevalence of atopic dermatitis (AD), and studies suggest that the association between AD and autoimmune diseases may help explain this link (55). Given these numerous interdependencies, dermatologists should regularly monitor DH patients for new autoimmune conditions and implement appropriate screening (54).

Neurological Dysfunctions

Gluten sensitivity can occasionally be associated with neurological disorders such as cerebellar ataxia, polyneuropathy, epilepsy, myelopathy, and encephalopathies (39). Although the precise incidence of these conditions in DH patients remains unknown, it is considered to be low. Nevertheless, dermatologists should be aware of this potential link and refer patients for neurological consultations when clinically indicated (56).

Cancers

Patients with DH are at an increased risk of developing non-Hodgkin's lymphoma and gastrointestinal malignancies, as nearly all DH patients also have celiac disease (9). However, unlike patients with celiac disease, the mortality rate in DH patients is not elevated (57). Increased mortality associated with non-Hodgkin's lymphoma has only been observed within the first five years of diagnosis, and this pertains to both T-cell and B-cell lymphomas, with the latter being more common (9).

3.7. Differential Diagnosis

The differential diagnosis of dermatitis herpetiformis includes blistering diseases and pruritic conditions that may present with similar clinical and histopathological features. Among the autoimmune blistering diseases to rule out in DH are linear IgA dermatosis, pemphigoid, and acquired epidermolysis bullosa (58). Other conditions that can be confused with DH based on symptoms include urticaria, atopic dermatitis, eczema, scabies and lichen planus. Symmetrical involvement of the extensor surfaces of the limbs, characteristic of DH, may serve as a helpful diagnostic clue (24). However, definitive diagnosis is confirmed via direct immunofluorescence testing, which reveals IgA deposits in the dermal papillae or at the dermoepidermal junction. Additionally, serum levels of anti-TG2 and anti-TG3 autoantibodies may support the diagnosis in uncertain cases or when other conditions are concomitant (59).

4. Treatment

4.1.Gluten-Free Diet

A gluten-free diet is the first-line treatment for both celiac disease and dermatitis herpetiformis, regardless of the presence of intestinal villous atrophy. It requires the complete elimination of wheat, barley, rye, and gluten-containing products. According to the Food and Drug Administration (FDA), gluten-free foods contain less than 20 ppm of gluten, although in some countries, products with <100 ppm are permitted (21). In most nations, uncontaminated oats

are considered safe for the majority of DH patients, although the potential of oats to induce inflammation dependent on tissue transglutaminase varies among oat varieties (21, 25).

Lifelong adherence to a GFD effectively controls the disease and prevents complications. It promotes the regeneration of the small intestinal mucosa, reduces the need for medication, and alleviates both gastrointestinal and dermatological symptoms. This process is lengthy, with gastrointestinal symptoms typically resolving within 3-6 months, while skin lesions may take up to two years to heal (21). Symptoms invariably recur within 12 weeks following gluten reintroduction (46). GFD adherence improves patients' overall well-being (3); however, it poses challenges due to the meticulous monitoring of product labels, high costs, logistical burdens, and social limitations (7). Reported compliance with GFD among adult CD patients ranges from 36% to 96% (60). Collaboration with dietitians and participation in support groups can facilitate the identification of hidden gluten sources and help maintain dietary adherence.

Over the past two decades, studies have suggested that long-term remission of DH may be achieved in 10–20% of patients, potentially allowing for discontinuation of GFD under strictly controlled conditions (61). However, newer analyses indicate that up to 95% of DH patients who discontinue GFD experience symptom relapse upon gluten re-exposure (62). In light of these findings, current guidelines recommend lifelong adherence to GFD and emphasize the need for further research on the safety of reintroducing gluten-containing diets.

4.2.Pharmacological Treatment

Dapsone

Gastrointestinal symptoms in dermatitis herpetiformis usually resolve within a few weeks of initiating a gluten-free diet. However, skin lesions may persist for months or even years (46). Therefore, pharmacological treatment is often required to manage pruritus and skin changes. Dapsone, a bacteriostatic medication, is the first-line treatment for DH. Its mechanism of action involves inhibiting neutrophil chemotaxis and reducing tissue damage caused by neutrophilic activity in skin lesions (63). Additionally, dapsone blocks the myeloperoxidase cytotoxic system, reduces neutrophil respiratory bursts, and decreases levels of hydrogen peroxide and hydroxyl radicals, thus mitigating eosinophil-induced tissue damage (64).

Dapsone therapy typically lasts 6-24 months until GFD achieves full efficacy (65). While dapsone effectively controls skin lesions, it does not influence enteropathy (7). Therapeutic effects are rapid, with pruritus subsiding within 48-72 hours and skin lesions resolving in days. However, symptoms recur within 24-48 hours after discontinuation (63). Treatment usually starts with low doses (25-50 mg/day) to minimize adverse effects and can be gradually increased to 100-200 mg/day as needed (65). For children, the initial dose is 0.5 mg/kg body weight daily. Alternatively, in patients without significant risk factors, treatment can begin with 100 mg/day, allowing rapid symptom control in most DH patients. The dose should be adjusted

to the lowest effective level. On average, dapsone therapy lasts about two years with strict GFD adherence, but it may be prolonged in cases of inadequate compliance (64, 66).

Before initiating dapsone treatment, comprehensive tests including complete blood count, liver and kidney function tests, and G6PD activity assessment are required. During therapy, regular monitoring is recommended: weekly blood counts for the first month, biweekly for the next 8 weeks, and then every 3-4 months. Liver and kidney function should be monitored biweekly in the first month and subsequently every 3-4 months. In cases of suspected methemoglobinemia or hemolysis, methemoglobin levels or reticulocyte counts should be assessed (46, 63, 67).

Dapsone-related adverse effects are dose-dependent and occur more frequently in patients with comorbidities such as anemia, cardiopulmonary diseases, severe liver disorders, or G6PD deficiency, as well as in those taking drugs that increase the risk of methemoglobinemia (63). Common side effects include hemolysis and methemoglobinemia, particularly significant in G6PD-deficient patients. Vitamin C or E supplementation and cimetidine reduce the risk of methemoglobinemia. In its occurrence, dapsone should be discontinued, and methylene blue administered as rescue therapy (except in G6PD-deficient patients, where vitamin C is used) (68). Hemolysis may vary in severity among all patients, while methemoglobinemia limits oxygen delivery to tissues, potentially causing dizziness, fatigue, and in severe cases, respiratory depression, coma, or death (64). Other adverse effects include headache, malaise, nausea, elevated transaminases, peripheral neuropathy, and agranulocytosis. Dapsone hypersensitivity syndrome, occurring in 0.5–3.5% of cases within 3–20 weeks of treatment, manifests as fever, photosensitivity, rash, gastrointestinal symptoms, and liver injury, which may lead to liver failure in severe cases (46, 63).

Alternative Methods

In cases of dapsone intolerance, sulfonamides such as sulfasalazine, sulfamethoxypyridazine, or sulfapyridine may be used. Recommended doses are 1–2 g/day for sulfasalazine and 0.25–1.5 g/day for sulfamethoxypyridazine. These drugs may cause adverse effects such as gastrointestinal disturbances (nausea, vomiting, anorexia), hemolytic anemia, hypersensitivity reactions, proteinuria, and crystalluria, necessitating monitoring, including blood counts, creatinine levels, and urine analysis, particularly during the first three months of therapy and then every six months (46). For refractory cases or contraindications to conventional therapies, immunosuppressants such as azathioprine, cyclosporine, or rituximab have proven effective (69). Rituximab, used as an adjunctive treatment, may benefit patients unresponsive to traditional methods, including GFD, dapsone, sulfasalazine, or azathioprine (70). Topical dapsone in a 5% gel formulation, available in the United States of America and Canada, can be applied to localized DH lesions, especially on the face and chest, due to its lack of systemic effects (71).

5. **Conclusion**

Dermatitis herpetiformis is a multifaceted condition that bridges dermatology and gastroenterology, requiring a multidisciplinary diagnostic approach. Direct immunofluorescence remains the cornerstone of diagnosis due to its high specificity, complemented by serological markers such as anti-TG3 antibodies and genetic testing for HLA-DQ2/DQ8 haplotypes. While histopathological findings support diagnosis, they are not pathognomonic, emphasizing the importance of integrating clinical and laboratory data. The association of DH with celiac disease and other autoimmune disorders underscores the need for routine screening and vigilant monitoring. Early identification and adherence to a gluten-free diet can prevent long-term complications, including lymphoma and nutritional deficiencies, significantly improving patient outcomes. Emerging diagnostic techniques, such as dermoscopy and microbiota analysis, hold promise for enhancing diagnostic precision. Future research should focus on refining serological testing and exploring the pathophysiological mechanisms linking DH with associated autoimmune and neurological conditions. These advancements will not only optimize patient care but also broaden our understanding of this complex disorder.

Disclosure

Author's contribution

Conceptualization: [JZ], [AK], [JG]
Methodology: [JZ], [AK], [AŚ]
Software: [JZ], [OK], [AK]
Check: [JZ], [AK], [NJ]
Formal analysis: [JG], [GW], [AŚ]
Investigation: [JZ], [JG], [AH]
Resources: [OK], [JZ], [GW]
Data curation: [JZ], [NJ], [KN]
Writing - rough preparation: [JZ], [NJ], [JG], [AH]
Writing - review and editing: [AH], [AŚ], [OK], [KN]
Visualization: [GW], [KN]**,** [NJ]
Supervision: [OK], [AH], [AŚ]
Project administration: [KN]**,** [JZ], [GW]
All authors have read and agreed with the published version of the manuscript.

Funding Statement: No funding was sought or obtained in relation to this review article.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The authors wish to emphasize that they do not express gratitude to any individuals or institutions.

Conflict of Interest Statement: The authors declare no conflicts of interest.

References

1. Duhring LA. Landmark article, Aug 30, 1884: Dermatitis herpetiformis. By Louis A. Duhring. JAMA. 1983;250(2):212-16. doi: 10.1001/jama.250.2.212

2. 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. doi: 10.1016/j.jaad.2010.09.777

3. Collin P, Salmi TT, Hervonen K, Kaukinen K, Reunala T. Dermatitis herpetiformis: a cutaneous manifestation of coeliac disease. Ann Med. 2017;49(1):23-31. doi: 10.1080/07853890.2016.1222450

4. Barnadas MA. Dermatitis Herpetiformis: A Review of Direct Immunofluorescence Findings. Am J Dermatopathol. 2016;38(4):283-8. doi: 10.1097/DAD.0000000000000420

5. Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis. Part II. Diagnosis, management, and prognosis. J Am Acad Dermatol. 2011;64(6):1027-33; quiz 33-4. doi: 10.1016/j.jaad.2010.09.776

6. Leonard J, Haffenden G, Tucker W, Unsworth J, Swain F, McMinn R, et al. Gluten challenge in dermatitis herpetiformis. N Engl J Med. 1983;308(14):816-9. doi: 10.1056/NEJM198304073081406

7. Garioch JJ, Lewis HM, Sargent SA, Leonard JN, Fry L. 25 years' experience of a gluten-free diet in the treatment of dermatitis herpetiformis. Br J Dermatol. 1994;131(4):541-5. doi: 10.1111/j.1365-2133.1994.tb08557.x

8. Savilahti E, Reunala T, Maki M. Increase of lymphocytes bearing the gamma/delta T cell receptor in the jejunum of patients with dermatitis herpetiformis. Gut. 1992;33(2):206-11. doi: 10.1136/gut.33.2.206

9. Grainge MJ, West J, Solaymani-Dodaran M, Card TR, Logan RF. The long-term risk of malignancy following a diagnosis of coeliac disease or dermatitis herpetiformis: a cohort study. Aliment Pharmacol Ther. 2012;35(6):730-9. doi: 10.1111/j.1365-2036.2012.04998.x

10. Graziano M, Rossi M. An update on the cutaneous manifestations of coeliac disease and non-coeliac gluten sensitivity. Int Rev Immunol. 2018;37(6):291-300. doi: 10.1080/08830185.2018.1533008

11. Zhang F, Yang B, Lin Y, Chen S, Zhou G, Wang G, et al. Dermatitis herpetiformis in China: a report of 22 cases. J Eur Acad Dermatol Venereol. 2012;26(7):903-7. doi: 10.1111/j.1468-3083.2011.04204.x

12. Leffler DA, Green PH, Fasano A. Extraintestinal manifestations of coeliac disease. Nat Rev Gastroenterol Hepatol. 2015;12(10):561-71. doi: 10.1038/nrgastro.2015.131

13. Salmi TT, Hervonen K, Kautiainen H, Collin P, Reunala T. Prevalence and incidence of dermatitis herpetiformis: a 40-year prospective study from Finland. Br J Dermatol. 2011;165(2):354-9. doi: 10.1111/j.1365-2133.2011.10385.x

14. West J, Fleming KM, Tata LJ, Card TR, Crooks CJ. Incidence and prevalence of celiac disease and dermatitis herpetiformis in the UK over two decades: population-based study. Am J Gastroenterol. 2014;109(5):757-68. doi: 10.1038/ajg.2014.55

15. Kang JY, Kang AH, Green A, Gwee KA, Ho KY. Systematic review: worldwide variation in the frequency of coeliac disease and changes over time. Aliment Pharmacol Ther. 2013;38(3):226-45. doi: 10.1111/apt.12373

16. Salmi TT, Hervonen K, Kurppa K, Collin P, Kaukinen K, Reunala T. Celiac disease evolving into dermatitis herpetiformis in patients adhering to normal or gluten-free diet. Scand J Gastroenterol. 2015;50(4):387-92. doi: 10.3109/00365521.2014.974204

17. Rampertab SD, Pooran N, Brar P, Singh P, Green PH. Trends in the presentation of celiac disease. Am J Med. 2006;119(4):355 e9-14. doi: 10.1016/j.amjmed.2005.08.044

18. Spurkland A, Ingvarsson G, Falk ES, Knutsen I, Sollid LM, Thorsby E. Dermatitis herpetiformis and celiac disease are both primarily associated with the HLA-DQ (alpha 1*0501, beta 1*02) or the HLA-DQ (alpha 1*03, beta 1*0302) heterodimers. Tissue Antigens. 1997;49(1):29-34. doi: 10.1111/j.1399-0039.1997.tb02706.x

19. Clarindo MV, Possebon AT, Soligo EM, Uyeda H, Ruaro RT, Empinotti JC. Dermatitis herpetiformis: pathophysiology, clinical presentation, diagnosis and treatment. An Bras Dermatol. 2014;89(6):865-75; quiz 76-7. doi: 10.1590/abd1806-4841.20142966

20. Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med. 1997;3(7):797-801. doi: 10.1038/nm0797-797

21. Antiga E, Maglie R, Quintarelli L, Verdelli A, Bonciani D, Bonciolini V, et al. Dermatitis Herpetiformis: Novel Perspectives. Front Immunol. 2019;10:1290. doi: 10.3389/fimmu.2019.01290

22. Hietikko M, Hervonen K, Ilus T, Salmi T, Huhtala H, Laurila K, et al. Ex vivo Culture of Duodenal Biopsies from Patients with Dermatitis Herpetiformis Indicates that Transglutaminase 3 Antibody Production Occurs in the Gut. Acta Derm Venereol. 2018;98(3):366-72. doi: 10.2340/00015555-2849

23. Sardy M, Karpati S, Merkl B, Paulsson M, Smyth N. Epidermal transglutaminase (TGase 3) is the autoantigen of dermatitis herpetiformis. J Exp Med. 2002;195(6):747-57. doi: 10.1084/jem.20011299

24. Salmi T, Hervonen K. Current Concepts of Dermatitis Herpetiformis. Acta Derm Venereol. 2020;100(5):adv00056. doi: 10.2340/00015555-3401

25. Alakoski A, Hervonen K, Mansikka E, Reunala T, Kaukinen K, Kivela L, et al. The Long-Term Safety and Quality of Life Effects of Oats in Dermatitis Herpetiformis. Nutrients. 2020;12(4). doi: 10.3390/nu12041060

26. Collin P, Reunala T. Recognition and management of the cutaneous manifestations of celiac disease: a guide for dermatologists. Am J Clin Dermatol. 2003;4(1):13-20. doi: 10.2165/00128071-200304010-00002

27. Mistry A, Mistry N. Persistent pruritic papulovesicles. Dermatitis herpetiformis. Am Fam Physician. 2014;90(6):407-8.

28.Al-Toma A, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterol J. 2019;7(5):583-613. doi: 10.1177/2050640619844125

29. 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. doi: 10.1590/abd1806-4841.2019940208

30. Reunala T, Kosnai I, Karpati S, Kuitunen P, Torok E, Savilahti E. Dermatitis herpetiformis: jejunal findings and skin response to gluten free diet. Arch Dis Child. 1984;59(6):517-22. doi: 10.1136/adc.59.6.517

31. Haffenden GP, Blenkinsopp WK, Ring NP, Wojnarowska F, Fry L. The potassium iodide patch test in the dermatitis herpetiformis in relation to treatment with a gluten-free diet and dapsone. Br J Dermatol. 1980;103(3):313-7. doi: 10.1111/j.1365-2133.1980.tb07250.x

32. Hassan S, Dalle S, Descloux E, Balme B, Thomas L. [Dermatitis herpetiformis associated with progesterone contraception]. Ann Dermatol Venereol. 2007;134(4 Pt 1):385-6. doi: 10.1016/s0151-9638(07)89198-8

33. Grimwood RE, Guevara A. Leuprolide acetate-induced dermatitis herpetiformis. Cutis. 2005;75(1):49-52.

34. Marakli SS, Uzun S, Ozbek S, Tuncer I. Dermatitis herpetiformis in a patient receiving infliximab for ankylosing spondylitis. Eur J Dermatol. 2008;18(1):88-9. doi: 10.1684/ejd.2007.0323

35. Mochel MC, Ming ME, Imadojemu S, Gangadhar TC, Schuchter LM, Elenitsas R, et al. Cutaneous autoimmune effects in the setting of therapeutic immune checkpoint inhibition for metastatic melanoma. J Cutan Pathol. 2016;43(9):787-91. doi: 10.1111/cup.12735

36. Shigeta M, Saiki M, Tsuruta D, Ohata C, Ishii N, Ono F, et al. Two Japanese cases of dermatitis herpetiformis associated each with lung cancer and autoimmune pancreatitis but showing no intestinal symptom or circulating immunoglobulin A antibodies to any known antigens. J Dermatol. 2012;39(12):1002-5. doi: 10.1111/j.1346-8138.2012.01663.x

37. Fuertes I, Mascaro JM, Bombi JA, Iranzo P. [A retrospective study of clinical, histological, and immunological characteristics in patients with dermatitis herpetiformis. The experience of Hospital Clinic de Barcelona, Spain, between 1995 and 2010 and a review of the literature]. Actas Dermosifiliogr. 2011;102(9):699-705. doi: 10.1016/j.ad.2010.11.007

38. Zone JJ, Meyer LJ, Petersen MJ. Deposition of granular IgA relative to clinical lesions in dermatitis herpetiformis. Arch Dermatol. 1996;132(8):912-8. doi:

39. Hadjivassiliou M, Duker AP, Sanders DS. Gluten-related neurologic dysfunction. Handb Clin Neurol. 2014;120:607-19. doi: 10.1016/B978-0-7020-4087-0.00041-3

40. Alonso-Llamazares J, Gibson LE, Rogers RS, 3rd. Clinical, pathologic, and immunopathologic features of dermatitis herpetiformis: review of the Mayo Clinic experience. Int J Dermatol. 2007;46(9):910-9. doi: 10.1111/j.1365-4632.2007.03214.x

41. Rose C, Brocker EB, Zillikens D. Clinical, histological and immunpathological findings in 32 patients with dermatitis herpetiformis Duhring. J Dtsch Dermatol Ges. 2010;8(4):265-70, -71. doi: 10.1111/j.1610-0387.2009.07292.x

42. Bresler SC, Granter SR. Utility of direct immunofluorescence testing for IgA in patients with high and low clinical suspicion for dermatitis herpetiformis. Am J Clin Pathol. 2015;144(6):880-4. doi: 10.1309/AJCPXIVSR6OZK1HU

43. Mansikka E, Hervonen K, Salmi TT, Kautiainen H, Kaukinen K, Collin P, et al. The Decreasing Prevalence of Severe Villous Atrophy in Dermatitis Herpetiformis: A 45-Year Experience in 393 Patients. J Clin Gastroenterol. 2017;51(3):235-9. doi: 10.1097/MCG.0000000000000533

44. 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). doi: 10.3390/nu10050641

45. Pasternack C, Kaukinen K, Kurppa K, Maki M, Collin P, Hervonen K, et al. Gastrointestinal Symptoms Increase the Burden of Illness in Dermatitis Herpetiformis: A Prospective Study. Acta Derm Venereol. 2017;97(1):58-62. doi: 10.2340/00015555-2471

46. Caproni M, Antiga E, Melani L, Fabbri P, Italian Group for Cutaneous I. Guidelines for the diagnosis and treatment of dermatitis herpetiformis. J Eur Acad Dermatol Venereol. 2009;23(6):633-8. doi: 10.1111/j.1468-3083.2009.03188.x

47. Araya M, Oyarzun A, Lucero Y, Espinosa N, Perez-Bravo F. DQ2, DQ7 and DQ8 Distribution and Clinical Manifestations in Celiac Cases and Their First-Degree Relatives. Nutrients. 2015;7(6):4955-65. doi: 10.3390/nu7064955

48. Dieterich W, Laag E, Bruckner-Tuderman L, Reunala T, Karpati S, Zagoni T, et al. Antibodies to tissue transglutaminase as serologic markers in patients with dermatitis herpetiformis. J Invest Dermatol. 1999;113(1):133-6. doi: 10.1046/j.1523-1747.1999.00627.x

49. Reunala T, Salmi TT, Hervonen K, Laurila K, Kautiainen H, Collin P, et al. IgA antiepidermal transglutaminase antibodies in dermatitis herpetiformis: a significant but not complete response to a gluten-free diet treatment. Br J Dermatol. 2015;172(4):1139-41. doi: 10.1111/bjd.13387

50. Hull CM, Liddle M, Hansen N, Meyer LJ, Schmidt L, Taylor T, et al. Elevation of IgA anti-epidermal transglutaminase antibodies in dermatitis herpetiformis. Br J Dermatol. 2008;159(1):120-4. doi: 10.1111/j.1365-2133.2008.08629.x

51. Sar-Pomian M, Rudnicka L, Olszewska M. Trichoscopy - a useful tool in the preliminary differential diagnosis of autoimmune bullous diseases. Int J Dermatol. 2017;56(10):996-1002. doi: 10.1111/ijd.13725

52. Hervonen K, Viljamaa M, Collin P, Knip M, Reunala T. The occurrence of type 1 diabetes in patients with dermatitis herpetiformis and their first-degree relatives. Br J Dermatol. 2004;150(1):136-8. doi: 10.1111/j.1365-2133.2004.05642.x

53. Maglie R, Hertl M. Pharmacological advances in pemphigoid. Curr Opin Pharmacol. 2019;46:34-43. doi: 10.1016/j.coph.2018.12.007

54. Varpuluoma O, Jokelainen J, Forsti AK, Timonen M, Huilaja L, Tasanen K. Dermatitis Herpetiformis and Celiac Disease Increase the Risk of Bullous Pemphigoid. J Invest Dermatol. 2019;139(3):600-4. doi: 10.1016/j.jid.2018.10.010

55. Kauppi S, Jokelainen J, Timonen M, Tasanen K, Huilaja L. Atopic Dermatitis Is Associated with Dermatitis Herpetiformis and Celiac Disease in Children. J Invest Dermatol. 2021;141(1):191-3 e2. doi: 10.1016/j.jid.2020.05.091

56. Iyer A, Rathnasabapathi D, Elsone L, Mutch K, Terlizzo M, Footitt D, et al. Transverse myelitis associated with an itchy rash and hyperckemia: neuromyelitis optica associated with

dermatitis herpetiformis. JAMA Neurol. 2014;71(5):630-3. doi: 10.1001/jamaneurol.2013.6277

57. Mansikka E, Salmi T, Kaukinen K, Collin P, Huhtala H, Reunala T, et al. Diagnostic Delay in Dermatitis Herpetiformis in a High-prevalence Area. Acta Derm Venereol. 2018;98(2):195-9. doi: 10.2340/00015555-2818

58. Mirza HA, Gharbi A, Bhutta BS. Dermatitis Herpetiformis. StatPearls. Treasure Island (FL)2024.

59. Gorog A, Antiga E, Caproni M, Cianchini G, De D, Dmochowski M, et al. S2k guidelines (consensus statement) for diagnosis and therapy of dermatitis herpetiformis initiated by the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol. 2021;35(6):1251-77. doi: 10.1111/jdv.17183

60. Turchin I, Barankin B. Dermatitis herpetiformis and gluten-free diet. Dermatol Online J. 2005;11(1):6. doi:

61. Paek SY, Steinberg SM, Katz SI. Remission in dermatitis herpetiformis: a cohort study. Arch Dermatol. 2011;147(3):301-5. doi: 10.1001/archdermatol.2010.336

62. Mansikka E, Hervonen K, Kaukinen K, Ilus T, Oksanen P, Lindfors K, et al. Gluten Challenge Induces Skin and Small Bowel Relapse in Long-Term Gluten-Free Diet-Treated Dermatitis Herpetiformis. J Invest Dermatol. 2019;139(10):2108-14. doi: 10.1016/j.jid.2019.03.1150

63. Coleman MD. Dapsone: modes of action, toxicity and possible strategies for increasing patient tolerance. Br J Dermatol. 1993;129(5):507-13. doi: 10.1111/j.1365-2133.1993.tb00476.x

64. Wolverton SE, Remlinger K. Suggested guidelines for patient monitoring: hepatic and hematologic toxicity attributable to systemic dermatologic drugs. Dermatol Clin. 2007;25(2):195-205, vi-ii. doi: 10.1016/j.det.2007.02.001

65. Ghaoui N, Hanna E, Abbas O, Kibbi AG, Kurban M. Update on the use of dapsone in dermatology. Int J Dermatol. 2020;59(7):787-95. doi: 10.1111/ijd.14761

66. Fry L, Seah PP, Riches DJ, Hoffbrand AV. Clearance of skin lesions in dermatitis herpetiformis after gluten withdrawal. Lancet. 1973;1(7798):288-91. doi: 10.1016/s0140-6736(73)91539-0

67. Reunala T, Hervonen K, Salmi T. Dermatitis Herpetiformis: An Update on Diagnosis and Management. Am J Clin Dermatol. 2021;22(3):329-38. doi: 10.1007/s40257-020-00584-2

68. Bilgin H, Ozcan B, Bilgin T. Methemoglobinemia induced by methylene blue pertubation during laparoscopy. Acta Anaesthesiol Scand. 1998;42(5):594-5. doi: 10.1111/j.1399-6576.1998.tb05173.x

69. Antiga E, Caproni M. The diagnosis and treatment of dermatitis herpetiformis. Clin Cosmet Investig Dermatol. 2015;8:257-65. doi: 10.2147/CCID.S69127

70. Albers LN, Zone JJ, Stoff BK, Feldman RJ. Rituximab Treatment for Recalcitrant Dermatitis Herpetiformis. JAMA Dermatol. 2017;153(3):315-8. doi: 10.1001/jamadermatol.2016.4676

71. Cinats AK, Parsons LM, Haber RM. Facial Involvement in Dermatitis Herpetiformis: A Case Report and Review of the Literature. J Cutan Med Surg. 2019;23(1):35-7. doi: 10.1177/1203475418795818