ABSTRACT

Dermatitis herpetiformis (DH) is a chronic and systemic autoimmune disease related to gluten hypersensitivity, characterized by intense itching and a burning sensation. The lesions are polymorphic and predominantly affect the extensor surfaces, such as elbows and knees, as well as the buttocks and scalp, often in a symmetrical manner. It is a cutaneous manifestation typically associated with Celiac Disease (CD). The pathology has a multifactorial origin, involving genetic and dietary factors, and is defined by deposits of immunoglobulin type IgA in the dermal papillae of the skin. Commonly, DH affects individuals of Northern European descent, being uncommon in Asian and African countries. However, in Brazil, there is a lack of extensive studies on the epidemiology of DH. The present study aims to provide an overview of dermatitis herpetiformis, highlighting etiology, epidemiology, pathophysiology, clinical manifestations, diagnostic investigation, and treatment. To achieve this, the literature review involved the search for scientific articles in databases published between 2017 and 2024, as well as other educational materials relevant to elucidate the discussed topic.

RESUMO

A Dermatite Herpetiforme (DH) é uma doença autoimune crônica e sistêmica relacionada à hiper sensibilidade ao glúten, sendo caracterizada por intenso prurido e sensação de queimação. As lesões são polimórficas e afetam, principalmente e de forma simétrica, as superfícies extensoras, como os cotovelos e joelhos, além de nádegas e couro cabeludo. É uma manifestação cutânea associada, geralmente, à Doença Celiaca (DC). É uma patologia de origem multifatorial, incluindo fatores genéticos e dietéticos, sendo definida por depósitos de imunoglobulinas do tipo IgA nas papilas dérmicas da pele. Comumente, atinge indivíduos adultos de ascendência norte-europeia, sendo incomum em países asiáticos e africanos. No Brasil, no entanto, não há estudos amplos sobre a epidemiologia da DH. O presente artigo tem como objetivo apresentar uma visão geral sobre a DH, destacando etiologia, epidemiologia, fisiopatologia, manifestações clínicas, investigação diagnóstica e tratamento. Para tanto, esta revisão bibliográfica contou com busca de artigos científicos em bases de dados, publicadas entre o período de 2017 e 2024, e de outros materiais didáticos que se mostraram relevantes para elucidar o tema abordado.
INTRODUCTION

Dermatitis Herpetiformis (DH), also known as Duhring-Brocq disease, is a chronic and systemic autoimmune disease related to gluten hypersensitivity, characterized by intense itching and a pronounced burning sensation in polymorphic lesions such as erythematous papules, urticarial plaques, clusters of vesicles, and tense blisters. It is a condition that predominantly and symmetrically affects the extensor surfaces — elbows and knees — as well as the buttocks. This condition is considered a cutaneous manifestation of Celiac Disease (CD).

The pathophysiology of DH occurs similarly in patients with CD, as both lesion processes are associated with gluten ingestion and the same immunoglobulins, having a complex origin involving various genetic factors. This results in similar histologies in the small intestine and dermal papillae. However, small intestine involvement does not always occur, as about 80% of individuals with DH do not present gastrointestinal symptoms of CD.

Specific histological characteristics of both skin and small intestine lesions show deposits of circulating IgA antibodies against tissue transglutaminase. The formation of immune complexes with IgA transglutaminases and dermal antibodies stimulates the activation of the complement system and the influx of neutrophils and inflammatory cytokines, resulting in cutaneous lesions. The gold standard diagnosis for DH is made by the presence of IgA deposits at the dermoeipidermal junction, pathognomonic of this condition, through direct immunofluorescence (DIF).

However, one of the major challenges in diagnosing DH is that it is a dermatological finding often confused with other autoimmune bullous diseases, as well as urticaria, scabies, and eczema, making DH a differential diagnosis. Once the diagnosis is confirmed, a strict gluten-free diet must be initiated, serving as a cornerstone for DH treatment and should be maintained for life to ensure the appropriate clinical evolution of both DH and CD, especially because DH can occur as the sole manifestation of CD.

This article aimed to describe and exemplify a comprehensive review of DH, including etiology, epidemiology, pathophysiology, clinical manifestations, diagnostic investigation, and treatment/management.

MATERIAL AND METHODS

This is a literature review on DH with an active search for articles from the following databases: Pubmed/Medline, Latin American and Caribbean Health Sciences Literature (LILACS), Virtual Health Library (VHL), and Scientific Electronic Library Online (SciELO), published between 2017 and 2024, in addition to books and other educational materials outside or within this time frame if necessary to describe historical context, relevant findings, and elucidate the pathology addressed. The research was conducted using the selected descriptors through Health Sciences Descriptors (DeCS): dermatitis herpetiformis, vesiculobullous dermatoses, and celiac disease, combined through the boolean operator AND or NOT. The choice of platforms considered coverage, relevance, affinity, and innovation to the theme. As exclusion criteria, works not in Portuguese, English, or Spanish, as well as works that did not allow full access, duplicated works in the databases, or unrelated to the discussed topic were excluded. A total of 34 works were used in the preparation of this literature review.

This manuscript was translated with the assistance of ChatGPT, an AI language model developed by OpenAI.

RESULTS AND DISCUSSION

Dermatitis Herpetiformis

The DH was first documented over 135 years ago by the American dermatologist Louis...
Duhring\textsuperscript{9} as an itchy, multiform eruption with erythema, blisters, papules, and primarily grouped and well-localized vesicles. At the time, he observed fifteen cases with these manifestations and decided to name it "Dermatitis Herpetiformis" due to the clinical similarity with herpesvirus infection\textsuperscript{8}.

Four years later, the classic symptoms of CD were described by Samuel Gee\textsuperscript{10}. The relationship between DH and CD was found after noticing that celiac enteropathy was a common finding in DH, especially when observing that a gluten-free diet — the treatment of choice in CD — was effective in treating and healing the small intestine mucosa and radically alleviating the DH skin eruption\textsuperscript{11}.

DH is an autoimmune disease causing clusters of intensely itchy, erythematous blisters\textsuperscript{7}. It is caused by sensitivity to gluten — found in barley, wheat, and rye — manifesting on extensor regions, scalp, neck area, and buttocks. It is commonly presented as an extraintestinal manifestation of CD, an inflammatory disease of the small intestine also related to gluten ingestion\textsuperscript{6}.

The pathophysiology of DH is similar to CD as both are multifactorial pathologies involving genetic, immunological, and dietary factors\textsuperscript{7}. Gluten hypersensitivity has a genetic factor, as first-degree relatives of patients with DH and CD have almost 15 times higher risk compared to the general population\textsuperscript{6}. Both DH and CD are closely associated with the HLA-DQ2 and HLA-DQ8 haplotypes\textsuperscript{6}.

These haplotypes are involved in the processing of the gliadin antigen present in gluten. Thus, the immune-mediated reactions of CD pathogenesis initially resemble those of DH\textsuperscript{5}. Tissue transglutaminase (TG2/tTG) present in the intestine is the main autoantigen in CD: it modifies gluten into glutamic acid within gliadin, an alcohol-soluble fraction of gluten, after gliadin absorption in the gastrointestinal lumen\textsuperscript{6}. This modification is significant because gliadin increases its affinity for DQ2 and DQ8 in antigen-presenting cells (APCs)\textsuperscript{6}.

Subsequently, gliadin is also presented to CD4+ T cells, resulting in progressive inflammation and damage to epithelial cells of the mucosa. Additionally, gliadin-modified residues covalently bind to TG2 and are presented to gliadin-specific helper T cells, which in turn stimulate B lymphocytes to produce circulating IgA antibodies directed against TG2. Due to epitope spreading, there is also the formation of IgA autoantibodies against epidermal transglutaminase (TG3/eTG) found in the skin\textsuperscript{8}. In summary, TG3 acts as the main autoantigen in DH, while in CD, this role is played by TG2.

It is currently proposed that DH begins with occult CD as an immune response to intestinal TG2, which later evolves into a response to TG3 in dermal papillae, being a late and progressive finding of CD\textsuperscript{6}. It is worth noting that both CD and DH patients produce anti-TG3 antibodies, but in CD, these antibodies have low affinity for TG3 and do not form immune complexes to be deposited in the skin, unlike high-affinity anti-TG3 antibodies found in DH patients\textsuperscript{8}. This mechanism still needs to be elucidated and comprehensively understood\textsuperscript{8}.

DH diagnosis is established by clinical characteristics, histopathology, serology, and DIF tests, and can be complemented with a biopsy\textsuperscript{6}. Samples for DIF are usually collected from perilesional skin areas because characteristic lesion changes can be lost in damaged tissue. The diagnostic discovery is centered on IgA deposition in the dermal papillae, manifesting in a granular, clumped, dotted, or fibrillar pattern, the latter being more common in individuals of Asian ethnicity\textsuperscript{12}.

Etiology

Although DH has a multifactorial origin, there are some known and determining factors:

Genetics: DH is associated with certain types of HLA, especially HLA-DQ2 and, to a lesser extent, HLA-DQ8. First-degree relatives of celiac and/or DH patients are more likely to be affected by one of the disorders\textsuperscript{12}.

Dietary Factors: DH maintains a close
and direct relationship with gluten, a protein composed of the amino acids glutenin and gliadin found in cereals of the Poaceae family (wheat, rye, and barley) and present in foods such as flour, processed cheese, beer, whiskey, mayonnaise, among others.

Epidemiology

In Brazil, there are no extensive local descriptive studies on the epidemiology of DH, being considered an uncommon disease in the country. However, such epidemiological ignorance may be associated with the lack of research on the theme within the Brazilian reality. It is a more prevalent disease in northern Europe and individuals of northern European descent in the United States, being less common in Asian and African countries. In Sweden, a broad national cohort study observed that the incidence rate of DH was estimated at 0.93 per 100,000 inhabitants — with a 95% confidence interval — with a 1:1 ratio of women to men and an average age at diagnosis of 60.9 years.

It is a cutaneous finding typically observed in adult men, usually during the fourth decade of life, of northern European descent. Asian patients, when presenting the disease, tend to have the characteristic fibrillar pattern. Another relevant point of the pathology is that it does not always present a classic clinical association with CD, and DH can be found in isolation or associated with other autoimmune disorders such as vitiligo and type 1 diabetes. It is important that these patients be screened for other pathologies.

Pathophysiology

The pathophysiology of DH essentially results from a dominant autoimmune response of IgA immunoglobulins to epidermal transglutaminase (TG3) molecules, and the sequence of events that result in inflammation and clinical manifestations has not yet been fully elucidated and understood. However, there are hypotheses that suggest the release of TG3 from keratinocytes to the papillary dermis, for example, so that it can bind to circulating antibodies (IgA) or complexes formed by TG3 and IgA, which are deposited in the skin.

The binding of immune complex deposits of IgA and anti-tTG antibodies with tTG in the dermal papillae promotes the activation of the complement system, influx of neutrophils, release of pro-inflammatory cytokines, and overproduction of matrix metalloproteases. Mononuclear cells, fibroblasts, and intestinal mucosa cells release tTG.

In DH, oxidative stress causes DNA damage to fibroblasts mainly due to gliadin exposure, and such exposure stimulates the binding of tTG to gliadin in the formation of gliadin-protein and tTG immune complexes. It is the immunogenic complex that stimulates the production of IgA antibodies against epidermal transglutaminase.

The simultaneous deamination process of gliadin increases the affinity of tTG for antigen-presenting cells, and as a result, gliadin is recognized by Th1 and Th2 cells. This mechanism increases the secretion of cytokines and tumor necrosis factor-alpha (TNF-α), which promotes damage to the intestinal mucosa. It is believed that the CD response is mainly mediated by Th2, while in DH, it is predominantly by Th1. DH should be treated as a sign of gluten skin hypersensitivity in patients with mild CD who produce high avidity and affinity anti-eTG antibodies.

The constant presence of immune complex deposits in the skin is probably associated with a defect in the Fc receptor of tissue macrophages responsible for the phagocytosis process of damaged cells, cellular debris, and foreign agents. It is characteristic of these cutaneous origin deposits to be displaced to the papillae under the influence of lesions. The activity and expression of the autoantigen epidermal transglutaminase (eTG) can also be the cause for the formation of immune complexes in other organs beyond the intestine and skin, such as in the kidneys in patients with DH and CD.

The presence of IgA deposits, especially of...
the IgA1 class and rarely IgA2, granules, or fibrils in the dermal papillae, is accompanied by IgM, IgG, C3, and fibronectin16, as well as eTG19. Another important finding is the increase in vascular endothelial growth factor (VEGF), which marks vascular permeability. In DH skin biopsies, IgA deposits in the dermal papillae are accompanied by deposits in the vessel walls in 64% of cases5. More research and studies should be conducted to fully understand this pathophysiological mechanism.

Clinical Manifestations

Clinical findings include intensely pruritic cutaneous lesions of chronic course and polymorphic characteristics, symmetrically grouped, and distributed on the extensor surfaces of elbows, knees, sacral, and gluteal regions. However, they can occur in areas of the trunk, back, scalp, armpits, shoulders, and oral mucosa20. These lesions are often replaced by crusty papules, excoriations, and dyschromia due to the subsequent scratching process of the lesion. In children, the main differential diagnoses are atopic dermatitis, scabies, and impetigo. In adults, however, it may be more difficult to differentiate due to urticaria, prurigo nodularis, and especially linear IgA bullous dermatosis, where the difference only occurs in the lesion study by DIF20.

As pruritus is such an important sign, its absence strongly suggests another diagnosis8. Although the lesions are described as multiform, rare formation of petechiae and purpura can occur in palmar and plantar regions, either in conjunction with the classic forms or as the only characteristic presented by DH6. Other uncommon presentations include palmpoplantar keratoses, urticariform plaques, and even dental anomalies and delayed tooth eruption reported in both DH and CD patients6.

Diagnostic Investigation

For diagnosis, a perilesional region sample should be analyzed by direct immunofluorescence, and another sample of the cutaneous lesion — usually an intact vesicle — should be collected for routine histopathological examination1. Serology can also be used to complement the diagnosis6, as well as trichoscopy21, being non-invasive tests.

Direct Immunofluorescence (DIF)

DIF, which recognizes granular IgA deposits at the tips of the dermal papillae, in addition to being the gold standard for DH diagnosis, presents sensitivity of 90% to 95%1. The collected area in DIF is important to minimize the risk of false negatives, reducing the need for biopsy repetition. DIF can be visualized with mercury arc lamp microscopy, blue light-emitting diode technology microscopy, and confocal laser microscopy22. It can observe three main patterns of IgA deposition: microgranular deposits at the tips of the dermal papillae, microgranular-fibrillar or only fibrillar deposits at the tips of the dermal papillae, and microgranular deposits at the dermoepidermal junction22.

Recently, in Japan, a variety of DH with a fibrillar deposition pattern was named, showing that these deposits co-localize with fibrinogen, which is in agreement with the non-fibrillar types of DH and may have epidemiological and pathological significance23. In addition to IgA deposition in dermoepidermal junction regions, the presence of IgA in the vessels and subpapillary dermal vasculature has been reported in DH patients. Even less frequently, this immunoglobulin can be detectable in elastic fibers, the membrane of hair follicles, and the basal membrane of sweat glands22.

Histopathology

Typical histopathological findings include subepidermal vesicle with neutrophils inside and microabscesses in the dermal papillae with relative preservation of the lower tips of the epidermal ridges. However, these findings are not
exclusive to DH and can be observed in other bulbous dermatoses such as bulbous systemic lupus erythematosus. The biopsy is preferably done by hematoxylin and eosin (H&E) staining. If it is not possible to find intact vesicles, the biopsy should be performed on intact erythematous skin. These findings can also be nonspecific in about one-third of DH cases, exhibiting perivascular lymphocytic infiltrate and minimal inflammatory infiltrate in the papillae.

Histological examinations of the small intestine obtained during upper digestive endoscopy are not necessary for the diagnosis of DH. Most untreated DH patients present villous atrophy of the small intestine mucosa due to celiac enteropathy, but at least a quarter of patients present normal villous architecture. However, even without evident damage to the small intestine mucosa, virtually all present some degree of inflammation and/or immune response to gluten due to increased density of intraepithelial lymphocytes and the presence of autoantibodies directed to intestinal TG2. However, regardless of the severity of mucosal damage, there are no effects on the long-term prognosis of DH, which strengthens the dispensability of collecting small intestine tissue for analysis when DH is diagnosed.

Serology

Various serological tests can be used to complement the diagnosis of DH, especially in difficult evaluation cases. Most recognize autoantibodies which can also be used to diagnose CD. Epidermal transglutaminase (TG3) is the main autoantigen in DH. In the United States, the Enzyme-Linked Immunosorbent Assay (ELISA) presents sensitivity ranging from 52% to 100%, and it was observed that detecting anti-TG3 antibodies was more sensitive in the diagnosis of DH than antibodies against TG2 and endomysium. In fact, 38% of patients with biopsy-proven DH were negative for both.

The most specific and accurate serological tests are still under development. According to Zibernia et al. (2020), a new ELISA to measure anti-TG3 antibodies with high diagnostic efficacy was created, as well as a new Western-Blot analytical test that simultaneously identifies IgA for TG2 and gliadin, showing accuracy in DH diagnosis as described by Gornowicz-Porowska et al. (2021). Other tests and antibodies, such as TG6, anti-neoepitope TG2, and anti-GAF3X, as well as significantly elevated interleukin-36 levels in DH compared to other autoimmune bullous diseases, are also being studied.

Differential Diagnosis

Another important point is that due to the multiple and diverse characteristics of DH — sometimes similar to other skin disorders — differential diagnoses for this pathology must be considered. The differential diagnosis should include mainly pruritic vesiculobullous and autoimmune diseases that can share the same clinical symptomatology and even similar histopathological findings with DH. Autoimmune diseases to be considered include linear IgA bullous dermatosis, bullous pemphigoid, acquired epidermolysis bullosa, and erythema multiforme, as well as pruritic diseases — urticaria, atopic eczema, and scabies — which can be confused with DH.

The clinical manifestations of DH are characterized by symmetric involvement of the extensor surfaces, which can guide the diagnosis, with the deposition of IgA in the dermal papillae and/or the dermoeidermal junction identified by DIF being a certain characteristic for diagnosis. However, it is necessary to understand the clinical description of some differential diagnoses of DH as listed in Table 1.

Treatment/Management

Gluten-free diet

The basis of long-term DH treatment is adherence to a totally gluten-free diet, essential
to improve skin changes, treat associated CD, and improve prognosis. It should be managed in consultation with a dermatologist, gastroenterologist, and nutritionist to provide adequate support. Patients are advised to avoid foods derived from cereals such as wheat, barley, rye, and malt. In 2015, the National Health Surveillance Agency (Anvisa) established that all product labels must have the information "contains gluten." If the protein or any possibility of cross-contamination is present, gluten-free foods can be included in the diet. So far, there are no guidelines indicating the transition of well-controlled patients to normal diets, and it is prudent and recommended for DH patients to maintain a gluten-free diet throughout life for better prognosis.

**Pharmacological Therapy**

Adherence to a 100% gluten-free diet can be challenging, and most DH patients require pharmacological intervention for short- and medium-term control, such as the use of dapsone, an important immunomodulator that inhibits neutrophil chemotaxis. It can have hematological side effects such as hemolysis and agranulocytosis, requiring regular blood level monitoring. Additionally, patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to adverse effects of dapsone, and G6PD activity should be checked before treatment. Dapsone does not affect celiac enteropathy, IgA deposition, or lymphoma risk.

Following the therapeutic scheme, together with strict gluten restriction in the diet, the initial dose of dapsone should be 50mg/day with a gradual increase up to 200mg/day — considering G6PD dosage and resolution of the dermatological condition — and the lowest dose necessary to maintain remission should be established and then discontinued when the diet benefits are obtained, usually after 1-2 years. The second line uses sulfapyridine with a recommended dose of 1-2g/day, which has less predictable efficacy compared to dapsone due to variable drug

**Table 1**: Description of the main differential diagnoses of DH.

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Description</th>
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<tbody>
<tr>
<td>Linear IgA Bullous Dermatosis</td>
<td>Autoimmune disease presenting with urticarial papules and blisters and vesicles that may be hemorrhagic, mainly affecting the trunk, face, and legs.</td>
</tr>
<tr>
<td>Bullous Pemphigoid</td>
<td>Autoimmune disease with large, tense, pruritic, and generalized blisters, more prevalent in the elderly and taking days to rupture.</td>
</tr>
<tr>
<td>Acquired Epidermolysis Bullosa</td>
<td>Autoimmune disease marked by serous or hemorrhagic blisters in trauma areas, affecting the back of the hands, feet, and elbows, possibly healing with atrophy and hyperpigmentation.</td>
</tr>
<tr>
<td>Erythema Multiforme</td>
<td>Lesions present in many forms: from red macules to blisters and plaques. An important characteristic of the lesions is their &quot;target&quot; appearance with a darker center and lighter edges.</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Skin eruption characterized by erythematous-edematous lesions and angioedema, mainly on the face, ears, neck, and genitals.</td>
</tr>
<tr>
<td>Scabies</td>
<td>Dermatozoosporosis caused by the mite Sarcoptes scabiei, resulting in grouped erythematous papules with intense itching, mainly in the armpits, interdigital spaces, buttocks, and male genitalia.</td>
</tr>
<tr>
<td>Atopic Eczema</td>
<td>Disease presenting with intense redness and itching, dryness, and scaling of the skin. In more severe cases, blisters or vesicles appear, commonly in skin folds such as elbows.</td>
</tr>
</tbody>
</table>
absorption\textsuperscript{1}, along with topical corticosteroids to improve pruritus\textsuperscript{12}. Finally, tetracycline in combination with nicotinamide can be used as a third line in patients who do not tolerate sulfonamides\textsuperscript{12}.

DH is a gluten-related disorder with great complexity in its clinical presentations, symptomatology, diagnostic possibilities, and associations with other diseases. As a chronic polymorphic skin condition susceptible to being confused with various other skin pathologies, differential diagnosis plays a crucial role in a more accurate prognosis by avoiding symptom aggravation with contraindicated or ineffective drugs. This can be achieved through classic DIF or histopathology techniques or using constantly updated immunological tests such as ELISA and bianalytical Western-Blot. It is essential that this knowledge be disseminated among physicians, especially those not yet widely familiar with this pathology in the Brazilian reality, including non-specialists and Primary Health Care professionals.

In clinical practice, DH is often interpreted and considered a cutaneous manifestation of CD, even in the absence of digestive manifestations and/or histopathological findings indicating small intestine mucosal damage. Therefore, the ideal therapeutic follow-up includes adopting a gluten-free diet, which is effective in controlling, treating, and prognosing skin lesions in the long term. However, it is relevant to consider the use of dapsone as a complementary medication to quickly interrupt manifestations in patients who are not yet on an exclusive diet and can be used until lesions are controlled solely by dietary changes.

This literature review thus facilitates the construction of comprehensive material on the subject, addressing the etiology, epidemiology, and pathophysiology of DH, stimulating and optimizing the diagnosis and management of the disease in medical practice. It is imperative that such a disease is more known, studied, and disseminated in society, in medical courses, and medical practice, respectively, to allow early recognition by physicians and consequently avoid intensification of manifestations and complications of this disease.

REFERENCES


