Dermatitis herpetiformis: pathophysiology, clinical presentation, diagnosis and treatment*

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Abstract: Researches on DH have shown that it is not just a bullous skin disease, but a cutaneous-intestinal disorder caused by hypersensitivity to gluten. Exposure to gluten is the starting point of an inflammatory cascade capable of forming autoantibodies that are brought to the skin, where they are deposited, culminating in the formation of skin lesions. These lesions are vesico-bullous, pruritic, and localized especially on elbows, knees and buttocks, although atypical presentations can occur. Immunofluorescence of perilesional area is considered the gold standard for diagnosis, but serological tests help in cases where it is negative. Patients who follow gluten-free diets have better control of symptoms on the skin and intestine, as well as lower risks of progression to lymphoma. Dapsone remains the main drug for treatment, but it requires monitoring of possible side effects, some potentially lethal.

Keywords: Celiac disease; Dapsone; Dermatitis herpetiformis; Diet, gluten-free; Transglutaminases

INTRODUCTION

Dermatitis Herpetiformis (DH), also known as Duhring-Brocq dermatitis, is a chronic, recurrent disease, secondary to gluten hypersensitivity which main clinical manifestation is the occurrence of a papulovesicular pruriginous rash.[1] Celiac Disease (CD) is the gastrointestinal manifestation of the same etiology and it is characterized by atrophy of the intestinal mucosa secondary to gluten-containing diet. DH patients rarely have gastrointestinal symptoms, but they generally present some degree of intestinal villous atrophy.[2]

DH is characterized by the presence of IgA deposits on top of the dermal papillae and manifests itself mainly on the extensor surface of the limbs, buttocks and scapular area.[3] High incidence of autoimmune diseases and potential complications, including the development of lymphoma have been demonstrated in this dermatosis.[4]

Patients with DH and CD may have the same association with histocompatibility antigens (HLA), the presence of circulating IgA against transglutaminase autoantigens and clinical remission on gluten-free diet.[5]

HISTORY

Dermatologist Louis A. Duhring first described this dermatosis in 1884. It is likely that some cases initially described were of bullous pemphigoid or linear IgA dermatosis bullosa, given the unavailability of better diagnostic tools at that period.[6]

Costello first described, in 1940, the effectiveness of sulfapyridine in a patient with this dermatosis. In 1943 Civatte demonstrated that, in pemphigus, the formation of blisters was intraepidermal, differently from bullous pemphigoid and DH, which present subepidermal alterations.[6]

In the 1950s Pierard described the presence of clusters of neutrophils and eosinophils in the dermal papillae, especially in more recent lesions. In 1969 Van der Meer, in turn, revealed the occurrence of granular IgA deposits in those same locations, which constituted a major milestone for the understanding of this disease and permitted for the first time its differentiation from linear IgA dermatosis bullosa.[7]

Fry described the association with gluten hypersensitivity in 1967, whereas clinical improvement of cutaneous manifestations with gluten deprivation was noted in 1973.[3,8,9]

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In 1978, Strober and Katz elucidated the association between HLA B8/DR3 with CD and DH, and in 1987 Kumar *et al* first noticed the presence of anti-endomysial antibodies in both diseases.[10]

EPIDEMIOLOGY

A relatively rare disease; it is more prevalent in Scandinavian countries and in the UK. Studies conducted in Scotland and Sweden found an incidence of 11.5 and 19.6 affected individuals per 100,000 inhabitants, respectively.[11,12] The higher incidence ever recorded was in Ireland, 1 person for every 300 inhabitants. It affects predominantly Caucasians compared to African-Americans or Asians. In the latter, besides being rare, the disease is characterized by often not being associated with CD, besides the prevalence of fibrillar IgA deposits on direct immunofluorescence, and a different HLA pattern.[3,5,6]

DH may occur at all ages, but most cases affect young adults, between 15 and 40 years old. On gender incidence, males predominate in a ratio of 3:2 compared to females, but in younger individuals this ratio is reversed, with affected females being more prevalent.[3,6]

PATHOGENESIS

Genetic factors:

Studies in monozygotic twins suggest a common genetic basis between DH and CD. Hervonen evaluated 6 pairs of twins, and noted that 3 pairs had DH, and in 2 pairs one twin had DH and the other had CD, and also in just a pair, one twin had DH and the other none of the diseases. Despite the probable similar genetic origin, environmental factors may influence the occurrence of either pathology.[2] Approximately 5% of patients with DH have a sibling with the same pathology, and the percentages for CD are even higher.[7,13]

In both CD and DH, HLA DQ2 or HLA DQ8 alleles are inherited, this being the likely genetic base for the association, which is also observed in animals.[5] The presence of both alleles provide a sensitivity close to 100% with a high negative predictive value, i.e., individuals which do not carry any of the alleles have the diagnoses of CD and DH excluded.[5,7,14]

Triggering factors:

The major environmental factor involved in triggering the disease is exposure to gluten. DH and CD are significant examples of pathologies in which environmental factors participate in the physiopathogeny.[5,15] Gluten is composed of two peptides, gliadin and glutenin, with the disease pathogenesis being linked to gliadin. It can be classified according to its electrophoretic mobility into 4 groups: α, β, δ and λ. The fraction linked to intestinal disease is from the α-gliadin group, and its immunoreactivity is due to the N-terminal.[5] Topical or intradermal application of gluten is not sufficient to trigger typical DH lesions, demonstrating that the development of this disease involves intestinal exposure to gluten.[3]

Immunological response:

a) Transglutaminase family and IgA deposits:

In addition to antibodies directed precisely against gliadin in the intestinal mucosa, the formation of specific antibodies against autoantigens, such as transglutaminases, may also occur. Dieterich et al first described them in 1997, suggesting that this was the primary autoantigen recognized by IgA in CD and DH.[6,16,17]

The transglutaminase family consists of nine different types of proteins expressed in various cell types. Two of them are relevant in DH: tissue transglutaminase (TTG) and epidermal transglutaminase (ETG). TTG is widely distributed in the human body, and is considered a surrogate marker for CD diagnosis. Many authors have demonstrated that TTG's enzymatic activity may be part of the pathogenesis of several diseases such as Huntington's disease, Alzheimer's disease and also CD.[18,19,20]

Sardy *et al* first described ETG in 2002.[21] It is present in keratinocytes and among its functions we highlight the maintenance of stratum corneum's integrity. Also known as transglutaminase 3, it performs its function by connecting the various epidermal structural proteins.[22] TTG is the main antigen for CD antibodies, as ETG is the antigen in DH. Anti-TTG antibodies may, by cross-reaction, recognize ETG, leading to the onset of cutaneous IgA deposits (Figure 1). Between TTG and ETG molecules there is 64% structural homology, which would explain the occurrence of cross-reaction. Serum from patients with CD react against TTG and ETG, whilst those of patients with DH react mainly against ETG.[21,23-26]

In normal subjects ETG is found in more superficial epidermal keratinocytes, and not in the dermoepidermal junction, the main site of IgA deposits.[21] There are two hypotheses to explain this phenomenon. After a trauma, keratinocytes might release ETG that would then deposit in the basement membrane. Circulating antibodies would bind to these autoantigens forming the disease's characteristic deposits in that site.[27] A second hypothesis is the possibility that keratinocytes would release ETG into the blood stream, where it would form immune complexes with IgA, which would then deposit in the dermal papillae.[21] There are reports of IgA nephropathy in patients with DH, reinforcing the latter possibility.[28,29] A study by Donaldson *et al* showed that, in the absence of IgA, ETG is not found in the dermis, which favors the hypothesis of the deposit mechanism.[23,27]

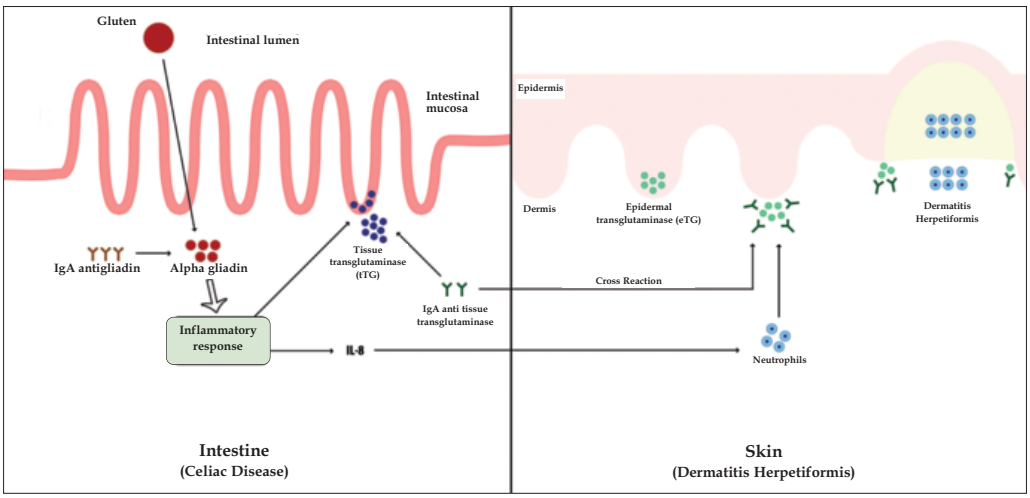

FIGURE 1: Dermatitis Herpetiformis physiopathogenesis

Marietta *et al* demonstrated that IgA anti-TTG and IgA anti-ETG serum levels are dependent of intestinal inflammatory activity, suggesting that the bowel might be the site of formation of these autoantibodies. This same study did not correlate their serum levels with the degree of intestinal atrophy.[24]

Secretory IgA consists of two IgA chains linked by a J chain, with the latter usually being formed by the attachment of two IgA subclasses, called IgA1 and IgA2. Serum IgA is mainly composed of IgA1. IgA deposited on the skin of individuals with DH is predominantly composed of IgA1, with minimal or undetectable IgA2 deposits. While this might suggest that this cutaneous IgA was not originated in the intestinal mucosa, it has been documented that IgA1 is the predominant immunoglobulin in gastrointestinal secretions of patients with DH.[16,30,31]

It was also observed that the TTG could lead to gluten peptide deamidation. These peptides, compared to undeamidated ones, can induce local T lymphocyte activation, initiating the hypersensitive response to gluten.[6,17]

b) The role of interleukin-8:

With the occurrence of intestinal intolerance to gluten, usually in genetically predisposed individuals, the activation of CD4+ T cells located in the mucosa is triggered. Consequently, B-lymphocytes become stimulated and, in turn, start to secrete antibodies directed against α-gliadins and autoantigens. These antibodies are predominantly of the IgA class, however some other classes of antibodies may also be produced.[3,16]

An inflammatory infiltrate, composed of neutrophils, can be found in skin lesions of DH patients, usually in the papillary dermis, the same place where IgA deposits occur.[3] The importance of IL-8 as one of the initiators of the neutrophilic influx has been recently identified and patients with DH have increased serum levels of this substance. The intestinal activity, triggered by gluten in this disease, is primarily responsible for the IL-8 production, whereas patients that are free of cutaneous lesions after the use of dapsone, but do not adhere to the diet, maintain high levels of it. Thus, we conclude that the gluten-free diet also leads to the reduction on the levels of this interleukin.[32]

Certain DH triggers, such as UVB exposure and trauma, have the ability to induce IL-8 production, and thus induce the appearance of cutaneous lesions.[33,34] This interleukin is a potent neutrophil activator, and acts by increasing CD11b expression and decreasing L-selectin expression by these cells, which favors their diapedesis.[5,23,32] IL-8 is expressed in tissues with neutrophil infiltration and its injection into the skin results in the accumulation of neutrophils.[35-37]

However, despite the importance of IL-8, its elevation alone is not able to explain all of DH pathogenesis. Studies with transgenic mice, which expressed IL-8 in the skin, found cutaneous neutrophil infiltrates without evidence of pathological alterations in that topography.[36] Similarly, transgenic mice expressing IL-8 in the intestine had a local increase in neutrophils, without evidence of damage to the intestinal mucosa.[38] These studies suggest that additional local factors are necessary to trigger the production of proteolytic enzymes by neutrophils.[39]

Besides IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF) also starts being produced, especially by the dendritic cells of dermoepidermal junction. It is able to induce the expression of IgA receptors by neutrophils, which are located at the sites where IgA is already deposited.[7] Currently, this point is deemed the probable key to better understanding the pathophysiology of this condition.[16] However, the reason for the appearance of clinical lesions in specific areas such as elbows, knees and but-

tocks is still not fully clarified, since IgA deposits also occur in places where there are no lesions, which emphasizes the influence of local factors.[7]

c) Neutrophilic infiltrate and proteolytic enzymes:

The neutrophilic infiltrate in the papillary dermis is histopathologically translated as Piérard microabscesses and IgA deposits determine their location. The formation of vesicobullous lesions is derived from collagenase and elastase production by neutrophils, which leads to basement membrane destruction.[40] Local keratinocytes and macrophages also start producing important enzymes, such as metalloproteinase collagenase and stromelysin-1 which destruct the extracellular matrix. The latter seems to contribute to the formation of bullous lesions when degrading the basement membrane components such as collagen types IV and VII, and laminin-1. The process leading to the formation of these lesions usually occurs over a 24-hour period.[7]

Studies by Airola *et al* sought to identify the role of these basement membrane-degrading enzymes in self-induced lesions, using 50% potassium iodine in patients with DH. Within 12 hours, even when clinical lesions were not yet visible, it was possible to identify the production of plasminogen activator urokinase by basal keratinocytes. Within 24 hours, the presence of collagenase and stromelysin-1 in these keratinocytes was identified, these enzymes having been produced under the stimulation of plasminogen activator urokinase. At that time, it was possible to verify the destruction of laminin-1 and type VII collagen, essential components for the basement membrane integrity. Besides, laminin-5, a component of anchorage fibrils, responsible for the adhesion of keratinocytes to the basement lamina, was found in keratinocytes at the same period, possibly reflecting the local regenerative response.[41,42]

CLINICAL PRESENTATION:

Lesions appear as grouped vesicles on an erythematous or erythematopapulous base, predominantly on the elbows, knees, and buttocks. More severe cases may present generalized involvement.[26]

Lesions tend to grow in a centrifugal pattern, with vesicles predominating in the periphery (Figures 2A and 2B). The intense pruritus is not related to the extent of disease and promotes the loss of the herpetiform aspect due to multiple abrasions. The disease tends to evolve with periods of remissions, and there is not an efficient method to measure its activity. For this purpose, some studies used the number of lesions presented by the patient and the dose of suppressive medication administered at the time.[3,15]

Petechial or ecchymotic lesions may occur in the palmoplantar regions and are observed more frequently in children. Karpati studied 47 children and showed that 30 of them (64%) had palmar purpuric lesions of a reddish-brown coloration.[26]

DH rarely affects the oral cavity, although IgA deposits frequently occur in this region. Studies demonstrate the difficulty of inducing the appearance of oral lesions with 50% potassium iodine.[43] This involvement, when present, usually occurs especially in areas subject to trauma. Similar patterns of enamel defects in color, roughness, horizontal grooves and punctiform depressions are described in DH and also in CD.[3]

Atypical presentations such as palmoplantar hyperkeratosis, chronic urticaria and prurigo forms are also described.[26]

INTESTINAL INVOLVEMENT:

All patients with DH have intestinal sensitivity to gluten, but only a small proportion of them will present symptoms suggestive of CD. Between 20-30% will present some degree of steatorrhea and less than 10% will have symptoms similar to CD such as diarrhea, cramps, and malabsorption. Reunala *et al* demonstrated that 16% of children with DH had chronic diarrhea and 10% had iron deficiency anemia. One patient in the study had growth deficiency.[11,44,45]

In two thirds of patients with DH there is some degree of villous atrophy in the intestinal mucosa (Figure 3) and one third will have an increased

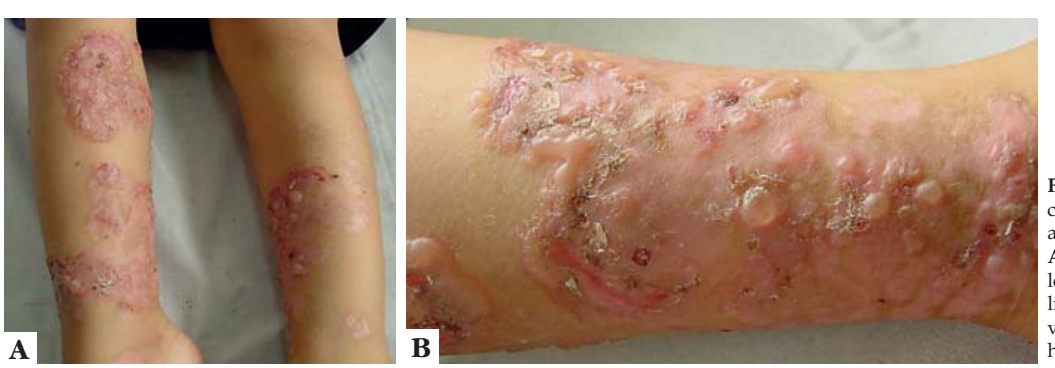

Figure 2: cutaneous lesions in a patient with DH: **A.** Vesico-bullous lesions in lower limbs; **B.** Grouped vesicles on an erythematous base

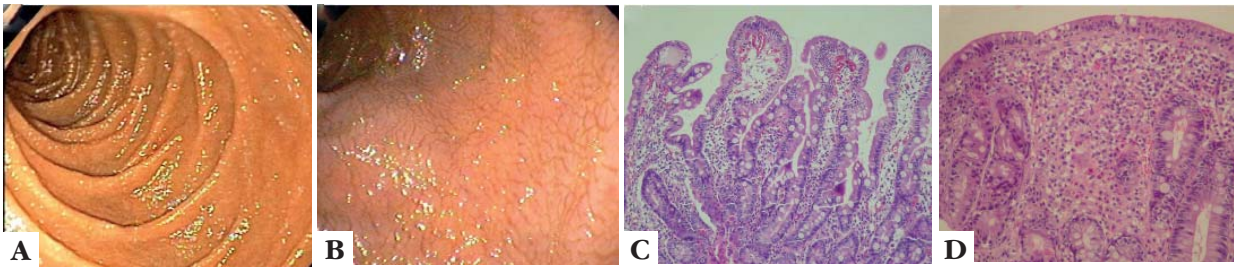

Figure 3: Intestinal involvement due to gluten intolerance. Colonoscopy in a healthy individual **(A)**, and in a patient with CD **(B)** highlight of intestinal villous atrophy. Intestinal histopathology on a healthy individual **(C),** and in a patient with CD **(D)** note the lymphocytic infiltrate and atrophy. The images are a courtesy from Dr. Carlos Floriano de Moraes

intraepithelial lymphocyte count.[6,30] Fry describes that the finding of up to 200 lymphocytes per 1,000 epithelial cells could exclude the diagnosis of DH.[27,46] Both alterations improve noticeably early with adherence to a gluten-free diet.[15]

CORRELATED DISEASES

Reunala *et al* followed 305 patients with DH for 10 years. The study revealed a 10% incidence of autoimmune diseases in patients with this cutaneous condition, particularly autoimmune thyroid diseases, pernicious anemia, gastric atrophy, type I diabetes, systemic lupus erythematosus, Sjoegren disease, sarcoidosis, vitiligo and alopecia areata. [3,47]

Cunningham and Zone evaluated 50 individuals with DH and showed that these patients had a high incidence of hyperthyroidism, hypothyroidism, thyroid nodules / cancer and positivity for thyroid autoantibodies.[10,48,49] Gaspari *et al* demonstrated that the association between Hashimoto's disease and DH was not only due to HLA B8/DR3, common to both diseases, but also to the formation of thyroid autoantibodies triggered by intestinal inflammatory activity in these patients.[49]

Recent studies have shown an association between DH and chronic gastric atrophy. Gastric atrophy may have an autoimmune origin, predominating in the gastric body, or secondary to infection by *Helicobacter pylori*, usually in the gastric antrum. Alakoski *et al* conducted a study with 93 patients with DH and concluded that there was a higher incidence of gastric corpus atrophy and intestinal metaplasia when compared to controls.[50] Primignani *et al* studied 57 cases and found a 30% prevalence of gastric atrophy in patients with DH and 15% in the control group.[51] Other investigators reported even higher rates of gastric atrophy, in 50-70% of patients with DH, and gastric hypochlorhydria in up to 90%.[52-56]

ASSOCIATION WITH LYMPHOMA

Patients with DH / CD are at higher risk of developing lymphoma, ranging from 5.4 to 100 times higher than the general population.[57-59] A study conducted jointly by England and Finland demonstrated the protective effect of a gluten-free diet regarding this complication. In this study, all cases of lymphoma were related to not following the diet or having started it less than 5 years before. The occurrence of lymphoma, especially in the gastrointestinal tract and associated lymph nodes, could be a result of long-term local lymphocyte stimulation, secondary to gluten exposure.[7] The majority of cases are of non-Hodgkin's lymphomas, but B-cell lymphomas and Hodgkin's Disease are also reported. Some studies even found a predominance of B-cell lymphomas.[2,60]

Lewis *et* al evaluated 846 patients with DH, and did not identify an increased risk of malignancies including lymphoma, fractures neither increased overall mortality risk among affected patients.[61]

DIAGNOSIS

DH requires important dietary changes and in most cases the use of medications with potential toxicity.

Direct immunofluorescence performed on healthy skin remains the gold standard for diagnosis. In case of a negative result, one should collect new material, and determine whether the patient is on a gluten-free diet, which could lead to false-negative results.[4]

In patients with clinical signs that are suggestive of DH but with negative direct immunofluorescence, other confirmatory tests such as the dosage of anti-TTG can be used. Another possibility is the confirmation of CD, which warrants the initiation of specific therapy for both diseases. If there is any doubt, some authors also suggest that gluten should be vigorously offered to the patient, which would lead to the appearance of vesicular lesions over a period of 24 hours, supporting the diagnosis.[4]

Considering the high incidence of autoimmune diseases and associated conditions, these patients should undergo a series of tests. Certain antibodies, such as anti-thyroperoxidase antibodies or anti-TPO (positive in 20% of patients), anti gastric parietal cells (positive in 10-25% of patients), ANA, anti-La and

anti-Ro should be measured for all CD or DH patients. Additional tests such as TSH, T3, T4 and fasting glucose levels should also be requested.[4]

Histopathological diagnosis:

A skin fragment for histopathological analysis must be obtained from an erythematous or erythematopapulous area near the vesicle, where neutrophilic microabscesses may be identified. Biopsy performed in vesicular lesions will show subepidermal blisters, making it difficult to differentiate from other bullous diseases with the same cleavage plane.[3]

The collection of neutrophils and also some eosinophils begins in the early stages, before the appearance of vesicles, especially at the top of the dermal papillae. These are Piérard microabscesses, which although very characteristic of this dermatosis, are not pathognomonic. It is also possible, at this stage, to observe the appearance of perivascular inflammatory infiltrates, especially in the superficial and middle areas of the dermis.[3,62,63]

Within 36-48 hours, an increase in the number of eosinophils in the infiltrate is seen in the lesions. Fragments of neutrophils can also be observed. Occasionally, neutrophilic collections may be seen in the epidermis, requiring differentiation from IgA pemphigus, a very rare condition.[62,63]

Edema with the formation of fissures or microvesicles on top of the dermal papillae occurs later. Collagen is degraded resulting in detachment of the epidermis. Multiple vesicles may coalesce forming unilocular blisters, clinically translated as vesicobullae in typical locations (Figure 4A).[1,3]

Warren and Cockerell reported that 37.5% of patients with DH have only lymphocytic infiltrate, papillary dermis fibrosis and vascular ectasia, which may be due to old and very excoriated lesions.[26]

Immunofluorescence:

Because of the possibility of numerous differential diagnoses, it is always desirable to perform direct immunofluorescence. For this purpose, a biopsy should be obtained from perilesional, apparently unaffected skin (up to 1 cm away from the lesion), where proteolytic enzymes did not cause immunoglobulin degradation.[6] The specimen should be kept frozen, avoiding the denaturation of these proteins. The occurrence of IgA deposits along the dermal-epidermal junction and on top of the dermal papillae are the fundamental characteristics of DH (Figure 4B).[1,3,6]

IgA deposits in the dermal papillae may appear with different patterns: granular on the papillary dermis, granular on the basement membrane and fibrillar.[26] Both granular patterns are often associated, so that granular deposits on the basement membrane with accentuation in the dermal papillae may be noted. Kawana and Segawa first described the fibrillar pattern in 1993, with this pattern being found in 50% of patients in Japan. One study with 22 Chinese patients showed that 95.5% had IgA deposits with granular pattern and 4.5% with fibrillar pattern.[23] Although the association between immunofluorescence fibrillar pattern with DH is still debated, it is believed that this pattern is related to some atypical findings, such as lack of HLA-B8/DR3DQ2, absence of circulating autoantibodies and peculiar clinical features like urticariform and psoriasiform lesions.[23,26]

Deposits of complement fraction 3 (C3) in dermal papillae may be present in about 50% of patients.[3] Donald *et al* showed that after two weeks of ingestion of a gluten-containing diet, patients in a previously gluten-free diet showed an increase in C3 deposits on the dermal papillae.[15]

Laboratory diagnosis:

Investigation of anti-TTG and anti-TGE antibodies, antiendomysial antibody and more recently, deamidated anti-gliadin showed good diagnostic, although not always available.

Anti-TTG is elevated in patients with intestinal disease activity and it decreases with the adoption of

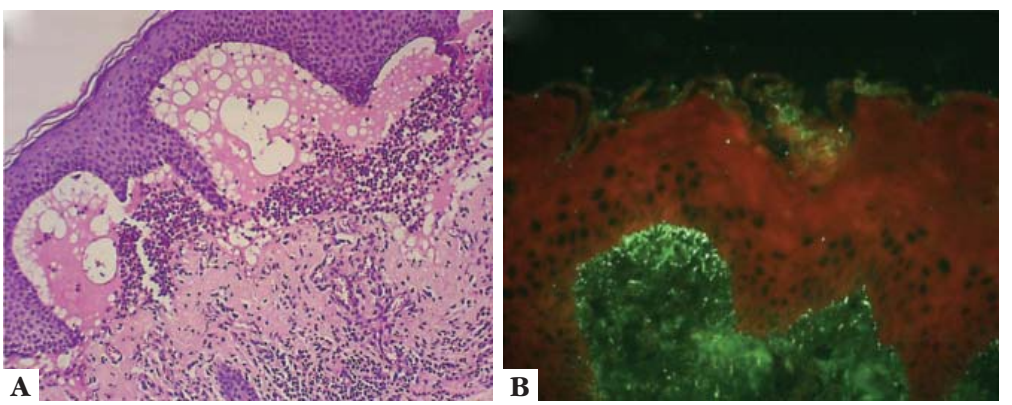

Figure 4: Diagnostic methods in DH: **A.** Skin histopathology showing subepidermal blister with neutrophilic infiltrate in the papillary dermis; **B.** Direct immunofluorescence of skin fragment showing IgA deposits along the dermoepidermal junction and on top of the dermal papillae. The image is a courtesy from Dr. Carlos Floriano de Moraes; B The image is a courtesy from Dr. Valeria Aoki

a gluten-free diet, thus being useful to assess diet adherence.[5,26,64] In general, after two years of dieting, this serological marker disappears.[6] The sensitivity of this antibody for cutaneous disease was 47-95% with specificity over 90%.[4,26,65-69]

Anti-ETG antibody has not yet been approved as a diagnostic tool in the United States. Its sensitivity is 52% in patients with DH, but it may have lower values in the pediatric population.[16,70,71] Nevertheless, other studies show up to 90% sensitivity.[72,73] This divergence may be caused by the different cases severities in each study.[16] This autoantibody may be present in patients with negative anti-TTG. Jaskowski *et al* showed that 20% of patients with DH have negative anti-TTG and positive anti-ETG. Accordingly, it could be used for diagnostic screening and even diet monitoring in patients with suspected DH.[71]

Recently some researchers have suggested the investigation of deamidated anti-gliadin antibody as a possible antigenic marker. This is particularly useful in patients with negative anti-TTG, making it the most reliable marker of gluten susceptibility.[74-76] Its sensitivity ranges between 84 and 90%.[16,77]

The analysis of anti-endomysial antibody in monkey's esophagus has also been useful, with 52-100% sensitivity for the diagnosis of DH and nearly 100% specificity. Similarly to anti-TTG, this marker also becomes absent in patients not exposed to gluten, and it is also used as an indicator of dietary adherence.[4,26]

Other antibodies can also be investigated, such as anti-gliadin antibody (conventional) and antireticulin, but both have lower accuracy compared to the aforesaid.[26] Anti-gliadin and antireticulin antibodies tend to have higher positivity in CD patients compared to those with DH, and this may reflect the lower intestinal inflammatory activity in the cutaneous form of the disease.[6,78]

TREATMENT

The mainstays of DH treatment are the gluten-free diet and drug therapy with sulfonamides or dapsone [3,6,79]

Gluten-free diet:

In 1981 Van der Meer *et al* reported the benefit of a gluten-free diet for patients with DH. Two patients who had improvement of their cutaneous lesions after the institution of a gluten-free diet were evaluated. Later, the patients were able to reduce the maintenance dose of dapsone.[15,80] This same dietary benefit could be seen in another study by the same authors in 1985, when they recorded the resolution of cutaneous lesions in five patients, with the same dermatosis, who followed the diet.[15,81]

A gluten-free diet is considered the treatment of choice for patients with CD / DH, since cutaneous and intestinal manifestations are gluten-dependent, and particularly in DH, because of the cumulative deleterious side effects of the drugs of choice.[3,4] The diet usually provides gastrointestinal benefits much earlier than cutaneous ones; DH improvement can take up to two years to occur if only this therapy is instituted. IgA deposits may take several years to be completely eliminated from the dermoepidermal junction, however the reintroduction of gluten can lead to new deposits and rapid clinical worsening.[4] The offer of gluten is also able to cause C3 deposits.[15]

Among other benefits of this diet, we can mention the protective effect against the development of lymphomas of the gastrointestinal tract, a benefit which is usually seen after 5 years of dieting, and also the recovery of the intestinal mucosa with consequent improvement of malabsorption in those patients with this symptom.[3,4,6,44] More long-term studies are needed to evaluate if the diet decreases the incidence of associated auto-immune diseases.[4]

After a variable period of time, most patients receiving drug treatment often experience a gradual reduction and even discontinuation of medication. The mean time to dapsone interruption is 25 months. Despite the importance of following the diet, patient compliance can be quite difficult, thus nutritional monitoring and, if possible, participation in support groups are reccomended.[3] Patients with CD / DH should be instructed to carefully read food labels and avoid unknown ingredients, since many of these may be gluten derivatives.[4]

Cereal species that are toxic to patients with CD and DH belong to the *Triticeae* family, among which are wheat, barley and rye. Oat belongs to another family, called *Avenae*. Proteins that are toxic to DH patients are rich in proline and glutamine, known as prolamins. Oat-derived prolamin is called oat avenin, and it has a lower proline content compared to wheat, barley and rye. The content of oat avenin is 5-15%, with gliadin content in wheat (wheat prolamin) being approximately 40%. One study showed that 2.5 grams of avenin (equivalent to 300 grams of oat) consumed by DH patients who were clinically controlled with dieting, produced no deleterious effect on the skin or intestine, and neither formation of anti-endomysial, antireticulin or anti-gliadin antibodies.[4,6] However, oats may be contaminated by wheat during the milling process or by the rotation technique used in agriculture crops. Thus, the ingestion of oats can be recommended to patients, provided they can ensure the sources purity.[3,4,6,7]

Kadunce demonstrated some degree of clinical improvement with the use of elemental diets, even in the presence of gluten, putting the latter's role in perspective.[15]

Pharmacological treatment:

Dapsone is the drug of choice in the treatment of DH, with sulfapyridine as the alternative therapy. The mechanism of action of dapsone is not fully elucidated, but it seems to block chemotaxis and activate neutrophils besides reducing the release of leukotrienes and prostaglandins. Its administration provides fast relief from itching, and usually regression of cutaneous symptoms occurs in a week. It promotes improvement in skin lesions although it has no effect on intestinal disease.[3,6,79]

The commonly used dose is 100 mg per day, with an average maintenance dose of 1 mg / kg / day. In children it is necessary to use smaller doses.[79] The goal is to keep the patient under clinical control for 1-2 years until the benefit of diet is achieved. The lowest dose able to maintain the patient in remission should be sought and, when possible, the drug should be discontinued. Suspension of dapsone in the absence of diet will lead to recurrence of the lesions.[3,4,6]

The most common side effects with the use of dapsone are acute hemolytic anemia, and methemoglobinemia, which are dose-dependent. Elderly patients, especially those with comorbidities are at risk for instability of cardiac conditions, such as heart failure or coronary artery disease as a result of the decrease in hemoglobin levels. The initial reduction of hemoglobin (2-3g) is common, but it is usually compensated by reticulocytosis.[3,82]

Deficiency of glucose-6-phosphate dehydrogenase (G6PD), especially in African-Americans and Caucasians from southern Mediterranean origin, is an absolute contraindication for the use of dapsone, because of the high-risk of severe hemolysis; although patients without G6PD deficiency may also develop this complication.[83] Levels of hemoglobin, hematocrit and reticulocyte count should be monitored every two weeks during the first 3 months and after this period, every 3 months.[3,6] Daily administration of 800 units of vitamin A for 4 weeks could help prevent this side effect.[3,84]

Methemoglobinemia is more frequent and generally more insidious than hemolysis. The occurrence of headache and lethargy after the use of dapsone may evoke suspicion. Agranulocytosis is a rare side effect, of early occurrence, appearing usually during the first 3 months of therapy.[3]

Dapsone can still induce severe hypersensitivity reaction with fever, rash, lymphadenopathy, and systemic involvement of varying degrees. It occurs in up to 5% of patients after 2-6 weeks of introducing the drug.[3,4]

Sulfonamides can also be used to control the acute phase of the disease, and sulfapyridine and sulfamethoxypyridazine are the most prescribed ones. The recommended dose ranges from 500 mg to 4.5 g daily. Both drugs have similar side effects: hypersensitivity reactions, hemolytic anemia, proteinuria and crystalluria. Monitoring should be performed with CBC and urinalysis before the start of treatment, and monthly for the first 3 months of therapy, then twice a year after this period.[3,4,79]

Patients with rash that is hard to control even during drug therapy should limit their iodine intake because of its effect on disease exacerbation.[3]

FOLLOW-UP

Follow-up is required to confirm diagnosis through response to diet and also to detect and manage complications. Medical staff should evaluate these patients every 6 months to 1 year with clinical examination and consultation with the nutritionist. The following should always be monitored: diet adherence, development of related autoimmune diseases, metabolic disorders (dyslipidemia and diabetes, for example), and possible evolution to lymphoma. To monitor diet adherence, serological tests such as IgA antigliadin (especially in the deamidated form), antiendomysial and anti-transglutaminase should be ordered. However, small deviations from the diet may not be detectable.[4,7]

Some autoimmune cutaneous diseases such as bullous pemphigoid and pemphigus vulgaris may present clinical remission after a certain period, allowing drug therapy discontinuation. Nevertheless, long-term prognosis for DH remains uncertain.

Between 10 and 15% of the patients with clinical remission may interrupt the pharmacological treatment and diet.[85-87] So Yeon Pack *et al* noted clinical remission in 12% of patients and 6% remained without lesions, but they still needed to diet. In patients with early onset of symptoms there was a smaller likelihood of remission.[88]

Although patients with DH / CD have increased risk of developing lymphoma and autoimmune diseases, the mortality rate was not higher amongst them in studies. A slight increase in survival was evidenced in patients adhering to a gluten-free diet, especially due to reduction of atherosclerotic disorders such as coronary artery disease. This is the result of lower levels of cholesterol and triglycerides seen in these patients.[7,89,90]

FINAL CONSIDERATIONS

Researches on DH, especially about the elucidation of its pathogenesis, have shown that this is not simply a bullous cutaneous disease, but a cutaneous-intestinal disorder cause by gluten hypersensitivity. Its association with CD is well established, with both diseases being transmitted by HLA-DQ2 and HLA-DQ8 alleles.

Exposure to gluten remains as the starting point that triggers a not yet fully elucidated inflammatory

cascade. Alpha gliadins, especially their N-terminal portion, have high immunogenic potential in these individuals. And this inflammatory process starts the formation of autoantibodies, the key to understanding the cutaneous involvement.

IgA begins to recognize its own tissue transglutaminase and these autoantibodies, through cross-reaction, begin the attack on transglutaminase in the epidermis, where neutrophil collections will later be found. These in turn produce a number of extracellular matrix-degrading enzymes culminating in the appearance of vesicobullous lesions.

Lesions tend to be very pruriginous and are most often located on the elbows, knees and buttocks. A number of autoimmune diseases may be associated and the minimum required investigation must be performed. Progression to lymphoma can be seen in several studies, although with a widely varying frequency, it tends to occur mainly in the gastrointestinal tract of individuals who do not comply with the diet.

Direct immunofluorescence remains the gold standard test to confirm diagnosis, but various authors consider a compatible clinical presentation plus specific supporting serum testing as a confirmatory possibility. Some tests, in addition to helping diagnose the disease, can assist in the evaluation of dietary adherence.

A gluten-free diet is essential in the treatment of patients with CD / DH, since cutaneous and intestinal clinical manifestations are gluten-dependent, and improve with suspension of its intake. Benefits such as improvement of the intestinal mucosal atrophy, reduced risk of lymphoma and improved malabsorptive syndrome are usually noticed. The gluten-free diet diminishes lymphocyte infiltration in the dermal papilla, reduces IL-8 production and decreases IgA deposits. Dapsone remains the primary drug for treatment, but it requires monitoring of possible side effects, some with potential lethality.

The disease has a low rate of remission, around 10-15% even in the long term, but increase in mortality has not been detected in this group, despite the possibility of association with autoimmune diseases and lymphomas.❑

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QUESTIONS

1. We can find some peculiarities in Asian individuals with DH such as the lowest association with DC. Which of the following is another DH characteristic related to this race?
- **a)** It occurs more often in females.
- **b)** Dermatologic manifestations begin at older age.
- **c)** There is a greater association with autoimmune diseases.
- **d)** It causes IgA deposits with a fibrillar pattern.

2. About gluten, it is incorrect to state that:
- **a)** It is found in foods such as wheat, barley and rye.
- **b)** It is common that oat is contaminated with wheat due to milling processes.
- **c)** It has two peptides, gliadin and glutenin.
- **d)** Beta-gliadins are the most immunogenic ones.

3. About TTG, it is incorrect to state that:
- **a)** It has 64% structural homology when compared to ETG.
- **b)** It is considered the main serological marker in CD.
- **c)** It seems to be involved in the pathogenesis of other diseases such as Alzheimer's disease.
- **d)** It is the cutaneous target in DH.

4. About ETG, it is incorrect to state that:
- **a)** It is also known as TG3, and it is located especially in keratinocytes.
- **b)** One of its functions is the maintenance of the stratum corneum's integrity.
- **c)** Sera from patients with DH react preferentially against TTG.
- **d)** Its structure, similar to TTG allows the occurrence of cross-reactivity between them.

5. Regarding CD and DH pathogenesis, it is correct to state that:
- **a)** TTG can cause gluten peptide deamidation.
- **b)** IgA anti-TTG and IgA anti-ETG serum levels do not depend on intestinal inflammatory activity.
- **c)** IgA anti-ETG antibodies are formed in the epidermis.
- **d)** There are no reports of other IgA-mediated diseases in patients with DH.

6. Regarding interleukin-8, it is incorrect to state that:
- **a)** In DH it is produced particularly in the epidermis.
- **b)** It is one of the causes of the characteristic neutrophilic influx in this disease.
- **c)** Patients without cutaneous lesions, who do not follow the diet, maintain a higher production of IL-8.
- **d)** There may be an increase in the production of IL-8 after sun exposure and the occurrence of trauma.

7. Regarding vesicobullous lesion formation in DH, it is incorrect to state that:
- **a)** GM-CSF production appears to be important to attract neutrophils to areas with IgA deposits.
- **b)** IgA is usually deposited only in areas that are most affected by the disease, such as elbows, knees and buttocks.
- **c)** The formation process of these lesions usually occurs within 24 hours.
- **d)** Within 24 hours of evolution it is possible to identify the presence of collagenase and stromelysin-1 in regional keratinocytes.

8. Regarding DH clinical presentation, it is correct to affirm that:
- **a)** Pruritus is usually more intense in patients with more exuberant lesions.
- **b)** Areas that are more pruritic usually present more characteristic lesions.
- **c)** Petechial and purpuric lesions usually occur on the trunk region, especially in adults.
- **d)** Palmoplantar hyperkeratosis can be a cutaneous manifestation of DH.

9. Regarding oral cavity involvement in DH, it is correct to say that:
- **a)** DH often affects the oral cavity.
- **b)** IgA deposits rarely occur in this region, since salivary enzymes cause their degradation.
- **c)** This involvement, when present, usually spares areas that are subject to trauma.
- **d)** CD and DH can present similar involvements in oral cavity.

10. Regarding DH gastrointestinal involvement, it is correct to affirm that:
- **a)** Most patients have steatorrhea.
- **b)** Most patients have chronic diarrhea.
- **c)** Most patients show atrophy of intestinal villi.
- **d)** Intraepithelial neutrophil count increase is common, even in patients without intestinal atrophy.

11. Which of the following endocrinopathies is most associated with DH?
- **a)** Acromegaly
- **b)** Type I diabetes
- **c)** Type II diabetes
- **d)** Hashimoto's disease

12. Which of the following tests is less useful in the investigation of patients with DH?
- **a)** FAN
- **b)** Anti-gastric parietal cells antibodies
- **c)** HBSAg
- **d)** Anti-TPO (Anti-thyroperoxidase antibodies)

13. Regarding the association between DH and lymphomas, it is correct to state that:
- **a)** Hodgkin's lymphomas predominate in these patients.
- **b)** The occurrence of B-cell lymphoma associated with HD has not yet been reported.
- **c)** It usually affects extraintestinal lymph nodes.
- **d)** A gluten-free diet reduces the occurrence of this complication, especially after 5 years of adherence to it.

14. Mark the incorrect alternative regarding DH investigation:
- **a)** The skin fragment for histopathological analysis must be extracted from an erythematous or erythematopapulous area adjacent to the vesicles.
- **b)** Piérard microabscesses are neutrophilic collections that appear especially in the reticular dermis.
- **c)** Neutrophilic infiltration can reach the epidermis, in which case it must be differentiated from IgA pemphigus.
- **d)** Old or heavily excoriated lesions may not present the typical findings during histopathological examination.

15. Regarding DIF in the investigation of DH, it is incorrect to state that:
- **a)** DIF remains the gold standard for the diagnosis of DH.
- **b)** DIF should be performed preferentially in a vesicular lesion, since this region is rich in IgA deposits.

` **c)** IgA deposits with fibrillar patterns seem to occur preferentially in Asian patients.
d) Deposits of complement fraction 3 in dermal papillae may occur in about 50% of patients.

16. Which of the following exams has the lowest accuracy for DH diagnosis?
a) Anti TTG
b) Anti ETG
c) Deamidated anti-gliadin
d) Antireticulin

17. Which of the following benefits could not yet be verified in patients with DH on a gluten-free diet?
a) Better control of cutaneous symptoms.
b) Better control of intestinal symptoms.
c) Lower doses of dapsone required to control cutaneous symptoms.
d) Lower association with autoimmune diseases.

18. Regarding the use of dapsone in the treatment of DH, it is incorrect to state that:
a) It promotes rapid improvement in pruritus and cutaneous lesions.
b) Lower doses for clinical control may be needed if the patient is on a gluten-free diet.
c) Hemolytic anemia and methemoglobinemia, likely side effects, are dose-dependent.
e) Agranulocytosis is a possible late complication of this drug.

19. What percentage of patients with DH reaches clinical remission of the disease and may be without dieting and without pharmacological treatment?
a) 0-5%
b) 10-15%
c) 20-25%
d) 30-35%

20. Some studies demonstrate that patients with DH may have a higher survival rate than the normal population. Which of the following expresses the most likely cause of this finding?
a) Lower rates of atherosclerotic disease.
b) Lower BP values.
c) Lower glycemic index.
d) Lower risk of cancer.

Answer key
Complementary exams in the diagnosis of american tegumentary leishmaniasis. An Bras Dermatol. 2014;89(5):701-711.

1) B	6) D	11) A	16) C
2) B	7) A	12) D	17) B
3) D	8) C	13) C	18) A
4) A	9) B	14) B	19) C
5) B	10) C	15) C	20) D

Papers
Information for all members: The EMC-D questionnaire is now available at the homepage of the Brazilian Annals of Dermatology: www.anaisdedermatologia.org.br. The deadline for completing the questionnaire is 30 days from the date of online publication.