

Etiopathogenesis of dermatitis herpetiformis

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Abstract

Dermatitis herpetiformis is a rare chronic, autoimmune bullous disease linked to gluten sensitivity with intense pruritus and characteristic skin eruptions. Etiopathogenesis is complex and not fully understood. It is currently considered to be a specific cutaneous manifestation of celiac disease. Genetic, environmental and immunological factors influence both conditions. Exposure to gluten is the starting point of an inflammatory cascade leading to the formation of circulating IgA antibodies against tissue transglutaminase and skin immune IgA deposition followed by skin lesions. Binding of the immune complex deposits of IgA transglutaminases and epidermal antibodies with enzymes in the papillary dermis stimulates complement activation, neutrophil influx, proinflammatory cytokine release and overproduction of matrix metalloproteinases. We have collected current knowledge of the pathogenesis of dermatitis herpetiformis.

Key words: dermatitis herpetiformis, transglutaminases, vesicobullous, skin diseases.

Introduction

Dermatitis herpetiformis or Dühring's disease (DH) is a rare, chronic, subepidermal bullous disease, with autoimmunity to transglutaminases, characterized by a chronic relapsing course, pruritic polymorphic lesions and typical histopathological and immunopathological findings. DH etiopathogenesis is complex and only partly understood. Gluten exposure triggers an inflammatory cascade leading to the formation of circulating IgA antibodies to tissue transglutaminase. Genetic predisposition and environmental factors also influence the disease. Characteristic papulovesicular eruption on the skin is associated with severe itching and burning. Diagnosis of the disease is determined by a direct immunofluorescence of the presence of granular IgA deposits in the skin papillae and/or along the cutaneous-epidermal border. It is currently considered to be a specific cutaneous manifestation of celiac disease (CD). Both conditions share the same HLA haplotypes, are mediated by the IgA class of autoantibodies, react with the transglutaminases and improve on gluten-free diet [1, 2].

Genetic background

DH and CD are associated with specific human leucocyte antigen (HLA) class II: HLA-DQ2 and HLA-DR3 as

well as class I: HLA-A1 and HLA-B8. HLA-DR2 antigen is present only in DH [1, 2]. Among HLA-DQ2, DQB1*0201, DQA1*0501 alleles are relevant for both diseases, and for HLA-DR3, DRB1*0301 allele, which probably protects, similar as HLA-DR2, against the development of enteropathy in DH patients [3, 4]. Villous atrophy correlates with the presence of HLA-B8, which is more common in patients with enteropathy [5]. It is estimated that in DH or CD, antigens occur in almost all patients: HLA-B8 in 58–90%, HLA-DR3 in 88–95% and HLA-DQ2 in 95–100% compared to healthy people (21%, 23–31%, 40–41%, respectively) [6]. In DH, the frequency of HLA-DR2 is estimated to be 57% compared to the general population (31%) [4, 5, 7]. There are also differences depending on the population; there is no HLA-B8, -DR3 and -DQ2 haplotype in Japan but HLA-DR9 is present, which is associated with the fact that DH hardly ever occurs there and it is not accompanied by enteropathy, and CD is seen very rarely [8].

Determination of these HLA antigens in healthy people is characterized by very low specificity, responsible only for the predisposition to autoimmune response development [7]. The presence of HLA-DQ2/DQ8 alleles in DH is characterized by high, and HLA-DQ2 very high sensitivity. It can be used in the diagnosis and screening of first-degree relatives and siblings of patients with DH [6, 7, 9, 10]. The absence of HLA-DR3, -DQ2 and -B8 antigens

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has a high negative predictive value, which allows to rule out DH [7, 11].

Environmental factors

Environmental trigger factors are represented by the ingestion of gluten, a component of the complex protein mixture contained in wheat flour. Gliadin partially digested in the gut comprising digestion-resistant peptides can be modified by tissue transglutaminase (tTg) that increases their antigenicity. α -gliadin plays an important role because tTg reacts with it. It is likely that the tTg is a target for IgA class autoantibody deposition in the small bowel mucosa and anti-gliadin and anti-tTg antibodies are formed in the intestinal mucosa [12]. External or intradermal administration of gluten does not stimulate skin lesions and immunoreactive gluten does not find in the skin [1]. The rash responds to a strict gluten-free diet (GFD) and the symptoms return on gluten challenge. Currently, it is believed that a DH immunopathogenesis starts from latent CD in the intestine with a tTg and possibly an anti-epidermal transglutaminase (eTg) autoantibody response and results in immune complex deposits of high avidity IgA anti-eTg antibodies together with the eTg in the dermal papillae [13]. It is suspected that endocrine (hormonal) and immunologic (viral infections) factors play a role in modulating the inflammatory response in DH. Probably DH pathogenesis is much more complex than a simple interaction between HLA-DQ antigens and gluten [14].

Immunopathological phenomena in DH

The presence of granular IgA deposits at dermal papillae in direct immunofluorescence (DIF) is the basis for the diagnosis of DH. Circulating IgA antibodies against endomysium (EmA) and/or transglutaminases are also detected. Histopathological examination of skin lesions shows neutrophilic infiltration leading to the destruction of basement zone proteins, which, together with impaired type IV collagen and laminin, results in a damage to anchor fibres and blistering [9].

The role of tTg and eTg enzymes, the main autoantigens in DH pathogenesis, is not fully understood. Binding of the immune complex deposits of IgA anti-tTg antibodies with tTg in the papillary dermis stimulates complement activation, neutrophil influx, proinflammatory cytokine release and overproduction of matrix metalloproteinases (MMPs) [15–17]. tTg is released in small amounts by mononuclear cells, fibroblasts and intestinal mucosa cells. In DH, oxidative stress affects fibroblast DNA damage especially after exposure to gliadin peptides [18]. In the digestive tract, tTg reacts with gliadin in two ways. In the intestine, tTg binds to gliadin, and then catalyses the formation of gliadin – gliadin, protein and tTg complexes. Immunogenic complex stimulates

the production of IgA antibodies to tTg, which disrupts its physiological function. It is likely that the simultaneous deamidation of gliadin increases the affinity of tTg for antigen presenting cells and as a result, gliadin is recognized by intestinal T cells. Initiating an immune response stimulates Th1 and Th2 cells to increase cytokine secretion, which results in destruction of the intestinal mucosa. Increased Th17 cytokines are also reported in DH [19, 20]. Tumour necrosis factor α (TNF- α), produced by Th1, leads to the secretion of MMP1, MMP3 by fibroblasts, and B cell maturation stimulates the production of IgA autoantibodies against gliadin, tTg and cross gliadin-tTg complexes as a result of Th2 stimulation. It is believed that DH is stimulated mainly by Th2 and CD by Th1 [1, 19]. In untreated DH patients, a high number of T lymphocytes with the TCR γ/δ + receptor is observed in the jejunum mucosa, and this number is low in healthy people. High density of these lymphocytes in untreated patients after starting GFD decreases to the level found in healthy people. The assessment of the number of T lymphocytes with the TCR α/δ + receptor seems to be a marker of gluten-dependent diseases [21]. Immune gliadin and tTg complexes in the duodenal mucosa are present in healthy people, but their level is significantly lower [22]. Presence of IgA and tTg is also found in the small intestine of DH and CD patients [1].

It remains unclear why initially common immunological phenomena in the intestine differentiate into skin or intestinal pathology. EmAs are directed against tTg, which is its main autoantigen [23]. In DH, presence of circulating anti-tTg antibodies explain intestinal pathology, and anti-eTg antibodies can explain partly skin lesions [13]. Presence of tTg in the skin of DH patients and healthy people show no differences in the distribution of the enzyme [24]. Immune complexes in the papillary dermis of DH patients contain IgA – eTg and do not contain tTg [13, 25]. It is thought that in patients who develop DH in the future, tTg – gliadin complexes formed in the intestine may initiate production of IgA antibodies with low eTg affinity. After a long gluten provocation antibodies develop, with low affinity for tTg and high for eTg, and then the rash appears. DH should be treated as a sign of skin hypersensitivity to gluten in patients with mild CD who produce anti-eTg antibodies with high avidity and affinity [26]. DH late onset in comparison to CD, which often involves children, could be explained by the epitope spreading phenomenon as a result of an autoimmune response that is provoked by exogenous antigen. Probably this mechanism and/or cross-reactivity between tTg and eTg can lead to eTg autoimmunity and formation of circulating IgA-eTg complexes determines development of DH in some CD patients. The possible mechanism of a directly gluten-induced eTg autoimmunity could not be also excluded [27]. In the skin, IgA-eTg aggregates have been shown to activate fibrinogen, which can be found at the tips of the papillary dermis in a pattern similar

to that of IgA-eTg aggregates [14]. Constant presence of immunological deposits in the skin is probably associated with a defective tissue macrophages Fc receptor responsible for their poor removal from the circulation. eTg in the deposits may be of cutaneous origin, and under the influence of injuries (Koebner phenomenon), it is displaced to the papillae, which may explain different location of the active enzyme and that present in the deposits. It is also possible to store immune complexes displaced into the skin after the reaction of IgA anti-eTg antibodies with this antigen in other tissues. It is probably related to the enzymatic activity of eTg, which catalyses the formation of aggregates of these complexes with the skin structures, activation of complement, then the influx of specifically sensitized (possibly in the intestine) neutrophils and the release of proinflammatory cytokines, among others, MMP (stromelysin, gelatinase and matrylin), which leads to efflorescence in places typical for DH [13]. Activity and expression of eTg are also the reason for the formation of complexes in organs other than the intestine and skin, namely the kidneys (IgA nephropathy) in CD and DH patients [28].

The presence of granular or fibrillar IgA deposits at the dermal papillae characteristic for DH do not occur in people without DH. Accompanying IgM, IgG, C3 and fibrinogen deposits are found, as well as eTg in granular deposits [12]. IgA cutaneous deposits, the IgA1, rarely IgA2 class, are polyclonal, contain kappa and lambda chains, do not contain J fragment. Initially, IgA deposits were thought to bind strongly with microfibrils of the papillary dermis layer or cross-react with microfibrils by FAB fragment, however immunoelectron microscopy studies have not confirmed this theory [29]. The key receptor for IgA is probably CD89, which shows a great expression on neutrophils (as a modulator of their function). It may play a role in the immune response to gluten in DH [30].

In DH, there is an increased expression of vascular endothelial growth factor (VPF/VEGF) – a marker of vascular permeability [31]. DIF DH skin biopsy analysis, performed by Preisz *et al.* showed that typical IgA dermal papillae deposits are accompanied by deposits in the walls of vessels in 64% of cases. They occur most commonly in small skin papillae vessels (92%), and some are found in vessels located subpapillary and they are deposits of mainly IgA – C3 and IgA. IgG is not found at all. Deposits in vascular walls and peri-intravascular skin papillae structures also contain eTg, C3 – eTg or eTg occur partially and no eTg – IgM deposits are found [32].

Pathogenetic hypotheses of effector mechanisms in DH suggest that intestinal IgA skin deposits activate the complement via an alternative activation pathway, releasing chemotactic factors and the influx of inflammatory cells. This confirms the presence of the complement C3 component in the same location as IgA as well as the activity of properdin and B factor [33]. Histology shows characteristic micro-abscesses and granular IgA-deposits

in papillary dermis while C3-deposition can be found in up to 89%; no deposits of C1q were found in DH biopsies [34]. The C5 component is also detected, and its activation releases the C5a fraction, which chemotactically acts on neutrophils [33].

The effectiveness of sulfones is explained by inhibition of complement activation, since the presence of C3, accompanying IgA deposits, in the skin is found only in the active phase of the disease, and not in asymptomatic treated DPS patients [33]. There are also studies that deny the effect of DPS on the complement system. The C3 concentration in the serum of DH patients remains within normal limits and is not affected by DPS intake [35]. Co-occurrence of vitronectin and complement C9 is also found in the dermal papillae [36]. Immunological deposits are detected, in similar proportions, both in the skin surrounding the lesions as well as in non-affected skin. It proves that also in healthy skin, depending on the complement activation, an inflammatory process and probably other factors affect the appearance of skin lesions. Potassium iodide, applied orally or topical (as a patch test), causes a rash similar to DH, activating local mechanisms, probably of an immunological nature. The patch test is positive in patients with active disease and in patients on non-restricted GFD, while it is usually negative in patients treated with DPS and in remission. DIF examination of unchanged skin and the patch test site, both in symptomatic and in remission DH patients, showed no difference in the presence, amount and distribution of immunoglobulins, complement and fibrinogen [37]. The mere presence of IgA deposits in the skin is not a sufficient condition for skin lesions. Despite circulating antibodies and skin IgA deposits, no increase in IgA production is observed and total IgA serum levels are not elevated. It is probably associated with impaired IgA utilization due to spleen and reticuloendothelial system abnormalities [38].

Adhesion of neutrophils to the endothelial surface, migration through the vessel wall and accumulation at the site of inflammation are also mediated by selectins and B integrins. This is manifested by increased CD11b expression, decreased L selectin expression and increased ability to bind IgA [39]. This phenomenon begins in the intestine, as a result of a mucosal immune response, predisposing neutrophils to settle in the skin as a response to a trauma-dependent local stimulus. In DH, selectin E has strong expression in vascular walls and moderate on leukocytes, which may be associated with the intensity of neutrophilic infiltration in dermal papillae. Increased serum E-selectin levels indicate the activation of endothelial cells in the development of skin lesions [38].

The important role of IL-8, a granulocyte-macrophage colony-stimulating factor (GM-CSF) and a tumour necrosis factor α (TNF- α) in DH inflammation is also highlighted [40, 41]. Serum level of interleukin 8 (IL-8) is el-

evated, and its production in the intestine is provoked by gluten, because patients treated with DPS still have high levels, and GFD leads to its lowering [40]. In DH, factors such as trauma or UVB can also induce this cytokine production. Increased IL-8 expression in the basal epidermal layer has a chemotactic effect on neutrophils [42]. The production of GM-CSF, which is able to induce IgA receptor expression by neutrophils at sites of IgA deposits, begins mainly, through dermal-epidermal junction (DEJ). However, this does not explain why these deposits are also found in non-affected skin [9]. The serum of DH patients has higher levels of IL-17a, IL-36 and IL-17 than that of healthy people. IL-17 may also play a role in the activation and recruitment of neutrophils, contributing to tissue damage. IL-36 plays an important role in the recruitment of eosinophils and neutrophils, and stimulates tissue damage and its serum level can be helpful in diagnosing and monitoring disease activity [43–45].

A neutrophil infiltrate is considered to be crucial in the blister formation. Under the influence of collagenase and elastase produced by neutrophils, the basement membrane is damaged and vesicles are formed [17]. After gluten intake within asymptomatic skin, basal keratinocytes begin the production of urokinase-type plasminogen activator stimulating local keratinocytes and macrophages to form MMPs (collagenase and stromelysin-1), which then damage the intracellular matrix [46]. The activity of these enzymes, which take part in the physiological and pathological processes of rebuilding extracellular matrix components and in remodelling, is precisely regulated by their tissue inhibitors. The DH imbalance connected with an increased MMP expression and a decrease of their inhibitors, contributes to the formation of vesicles within 24 h of the stimulus. This is a result of the degradation of major parts of the basement membrane integrity, such as collagen type IV, VII and laminin-1. There is also laminin-5, responsible for the adhesion of keratinocytes to the basal lamina, which reflects local regeneration processes [47].

Mast cells, a source of many mediators, cytokines and enzymes, also play a role in the formation of lesions in DH. As a result of their degranulation, histamine, TNF- α and cytokines are released (IL-1, IL-6 and IL-8). Cell adhesion molecules, chemokines, leukotrienes, platelet activating factor and heparin derivatives also participate in the pathogenesis. Elevated levels of TNF- α and MMP9 are found in bulla fluid, skin lesions, and in perilesional skin [41, 48]. In the active DH phase, there are elevated levels of circulating antibodies to heat shock proteins (Hsp): Hsp60, Hsp70, Hsp90, which correlate with antibodies against tTg and eTg, and their titre decreases during remission and on GFD. Although their role in the DH pathogenesis is unknown, they may be a new marker of the disease [49]. There is a significantly higher level of IL-12 in serum and elevated level in perilesional and skin lesions, but the role is unclear. In DH, significantly

increased expression of corticoliberin and endothelin B receptor has been demonstrated, indicating their possible involvement in skin pruritus [48]. Studies on pruritus in DH also point to the role of IL-31, whose serum concentration is significantly lower than in the control group, which may be correlated with its role in the Janus-activated kinases/ signal transducers and activators of transcription (JAK/STAT) signalling pathway [50]. A recent study demonstrated that IL-31 is elevated in DH serum and significantly overexpressed in the skin, where it colocalized with IL31RA [51].

JAK3 is the only protein from the JAK group whose expression is higher in DH skin lesions than in healthy people. It probably mediates in response to IL-4 and Th17 differentiation. The expression of JAK/STAT proteins in DH and their suggested role in pathogenesis creates new potential therapeutic targets [52].

Immunohistochemical examination of skin biopsy of DH patients shows an elevated concentration of B granzyme within DEJ compared to the skin of healthy people. Its presence leads to the degradation of key parts of this combination ($\alpha 6/\beta 4$ integrin, collagen VII and collagen XVII) which are substrates for this protease, inducing proteolysis and DEJ separation. It is also found in micro-abscesses, mainly in the upper layer of papillary skin adjacent to DEJ, which suggests the involvement of neutrophils and lymphocytes in the secretion of this enzyme [53].

A protease inhibitor elafin plays an immunomodulatory and regulatory role in epithelium and, among others, inactivates neutrophil elastases and plays a protective role by slowing the gliadin deamidation process in the intestine. Keratinocytes, in normal conditions, show elafin overexpression, thus reducing the inflammatory response induced by neutrophils. In the active DH phase, in the skin, as well as in the intestine in CD, there is abnormal – reduced (in 30% of patients) or absent (in 70% of them) expression of elafin, which may be of significant importance in the pathogenesis of these diseases [54].

Dermatitis herpetiformis genetic predisposition, environmental factors and immunological phenomena are important in the development of disease symptoms. Epidermal transglutaminase and neutrophils play a key role in the pathogenesis of this disease. Binding IgA-eTg complex to the dermal papillae stimulates neutrophil influx, proinflammatory cytokine and chemokine release, and metalloproteinase overproduction. Gluten-free diet reduces the development of immune processes.

Conflict of interest

The authors declare no conflict of interest.

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