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Immunology Pathway of During Autoimmune Disease: A Review Article

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1. Abstract

1.1. Introduction: Dermatitis herpetiformis or also known as duhring disease is a rare autoimmune vesicobulosa disease, specific and recurrent chronic in nature and has a relationship with celiac disease and gluten-sensitive enteropathy. The diagnosis of dermatitis herpetiformis is based on a combination of physical examination, routine histopathological examination, immunofluorescence examination, and serological testing. The typical histopathological appearance of dermatitis herpetiformis when examined using a light microscope is a subepidermal cleft with neutrophils and several eosinophils in the papillary dermis. immunofluorescence examination is an examination that is also important for definitive diagnosis.

1.2. Discussion: The accumulation of ganular IgA at the papillary end of the dermis is a pathognomonic feature, whereas the serological test is an ELISA based test to detect anti-eTG IgA antibodies. Genetic testing to determine a patient's HLA halotype can be useful in cases where dermatitis herpetiformis cannot be excluded. The differential diagnosis of dermatitis herpetiformis is with pemphigoid vulgaris, pemphigoid bullosa, and linear IgA dermatosis. The immunological basis for the onset of dermatitis herpetiformis is closely related to the pathogenesis of gluten intolerance and celiac disease. Tissue transglutaminase (tTG) is the major autoantigen in celiac disease and epidermal transglutaminase (eTG) is an autoantigen that is closely related to dermatitis herpetiformis. Ig A anti eTG is the most sensitive serological marker for hermatitis herpetiformis.

1.3. Conclusion : From the latest research, dermatitis herpetiformis arises because of the interaction of various factors, both autoimmune, genetic, and environmental factors. Autoimmune factors that play a role include HLA-DQ2 and -DQ8, while environmental factors that play a major role are insensitivity to the gluten diet.

2. Introduction

Dermatitis herpetiformis or also known as Duhring's Disease or gluten rash is an autoimmune vesicobulose disease, this disease is not related to dermatitis, nor is it caused by the herpes virus, but a specific and recurrent chronic skin condition associated with celiac disease and gluten-sensitive enteropathy . The main predisposing factor is genetics, this is related to Human Leukocyte Antigens (HLAs) DQ2 and DQ8 [1-3].

This disease was first discovered by Dr. Louis Dühring in 1884 was marked by complaints of intense itching. The main lesions are erythematous papules, plaques, urticaria, or most commonly vesicles, of which large bullae rarely occur. The lesions seen in people with dermatitis herpetiformis may be crusted, and may not show the main lesion. On physical examination, excoriation and erosion are common. The distribution of lesions in dermatitis herpetiformis is symmetrical with a frequent predilection of the extensor surfaces of the forearms, elbows, shoulders, knees, buttocks and back [1,4,5].

Dermatitis herpetiformis can affect any age, but appears more often for the first time in young adults between the ages of 30 and 40, more often in men than in women, where the lesions in men are common in the mouth and genitalia [1,2,4,].

Antibodies in transglutaminase tissue and epidermal transglutaminase can be measured serologically. To make the diagnosis, a skin biopsy and direct

immunofluorescence examination is needed which shows granular IgA deposits in the papillary layer of the dermis. This disease can be distinguished from other vesicle eruption diseases by histologic, immunological and gastrointestinal criteria [3,6,7].

Gluten-free diet is the first-line therapy that can relieve the manifestations of the skin and intestinal conditions, while the results of therapy of dapsone and sulfones are only on skin eruptions. Combined therapy with a gluten and dapsone-free diet is the initial treatment option for controlling skin manifestations in dermatitis herpetiformis [1,3].

3. Discussion

3.1. Epidemiology

The only prevalence study conducted on dermatitis herpetiformis in Utah, the state of the United States, in 1987 found a prevalence of 11.2 per 100,000 population, with the predominant population being native descendants of Northern Europeans. The mean age of onset was 41.8 years, and the average symptom was 1.6 years before diagnosis. In Northern Europe, the reported prevalence is 1.2 to 39.2 per 100,000 population [2,8].

Two immunological studies suggest that 10-12% of dermatitis herpetiformis patients eventually recover. Patients with dermatitis herpetiformis who have associated gluten-sensitive enteropathy are usually asymptomatic. In a British study from 1971 to 1989, patients with dermatitis herpetiformis (a total of 152 patients) were followed from their first diagnosis until death. Death occurred in 38 patients less than 85 years of age, fewer than would be expected based on the national general population mean. The incidence of cancer with dermatitis herpetiformis is significantly increased. Cancer of the small intestine causes 1 death and lymphoma causes 1 death. Another British study comparing 846 dermatitis herpetiformis patients with 4225 healthy controls found that dermatitis herpetiformis did not increase the risk of lymphoproliferative cancer and did not increase fracture, malignancy or death [1,8].

3.2. Ethiology

Gluten is an amorphous protein containing gliadin and the amino acid glutenin found in cereal grains from the Grameneas family, such as wheat, barley, oats (oats), malt (water-soaked wheat) and rye (rye). Gluten is a grain that contains starch (starch), fat and protein (gliadin, glutenin, albumin and globumin). Wheat protein in particular contains 68% gliadin and 32% glutamine, which is why it is commonly referred to as wheat gluten. Examples of foods containing this protein are flour, chocolate milk containing malt, processed cheese, beer, whiskey, vodka, mustard, tomato sauce, mayonnaise and salami[9-11].

As in celiac disease, there is an increased intraepithelial density of small intestinal T cells with γ / δ T receptor cells in the jejunum in patients with dermatitis herpetiformis. The finding that the T-cell formation of dermatitis herpetiformis patients produced significantly more interleukin 4 (IL-4) than in patients with gluten-sensitive enteropathy and bowel biopsy of patients with gluten-sensitive enteropathy alone showed increased expression of interferon - γ which suggests that different cytokine patterns may contribute to the variation in clinical manifestations of the two diseases. Systemic events of intestinal mucosal immune response were also found in serum and skin in dermatitis herpetiformis [1,2,8,11].

3.3. Moleculer Pathway in Duhring's Disease

One gene that was found to be genetically associated with celiac disease and weakly with dermatitis herpetiformis in some populations is myosin IXB (MYO9B) on chromosome 9p13[20-23]. This association was not found in all studied populations but the possible role of myosin IXB (MYO9B) in the pathogenesis of celiac disease and dermatitis herpetiformis remains an interesting one.8 The function of MYO9B in cells is to provide cell signaling and regulation of dynamic cytoskeleton actin. thus has a role to maintain cell integrity and permeability of the intestinal barrier. There is an opinion that increased intestinal permeability may result in increased gluten penetration, and lead to the triggering of a continuing immunological event which results in the emergence of celiac disease or dermatitis herpetiformis [1,8,12,13].

Additional genetic and biochemical studies are needed to evaluate this hypothesis. Two well-known genomic bodies have recently released studies on celiac disease, namely the relationship between celiac disease and genomic variants in the interleukin-2 (IL-2) region to IL-21, the signal regulator protein G 1 (RGS1), IL-12A, IL-18 receptor protein (IL18RAP), cluster cemocin receptor 3 (CCR3), T cell activation GTP activating protein (TAGAP), and SH2B3 protein. The significant function of these genes in the development of celiac disease and their association with dermatitis herpetiformis is currently unclear. The predisposition for dermatitis herpetiformis has also been reported at the HLA locus [1,14].

A close association between dermatitis herpetiformis and HLA-DQ2 or HLA-DQ8 has been noted in several studies. In one study comparing 50 dermatitis herpetiformis patients with 280 healthy patients (controls), 86% of patients had the HLA-DQ2 allele (versus 25% in the control group), with the majority of the remaining cases being HLA-DQ8 related. A murine mouse model has shown an association with transgenic HLA-DQ81 mice suffering from gluten sensitivity similar to humans. Interestingly, mice that had been modified with the HLA-DQ81 transgene alone had fewer skin manifestations of gluten sensitivity. However, a murine mouse model that combined HLA-DQ8 expression against a diabetic nonobese mouse model background when given inflammatory stimuli would show a recapitulation of findings from dermatitis herpetiformis when gluten was given. Mice with a genetic predisposition, a tendency to autoimmunity, and an inflammatory trigger show clinical, histological, and immunofluorescence evidence of dermatitis herpetiformis, which once again confirms that the complex interactions of genes and the environment may play a role in the development of the disease. from the onset of dermatitis herpetiformis, it is found to be closely related to the pathogenesis of gluten intolerance and celiac disease. Tissue transglutaminase (tTG) is the major autoantigen in celiac disease and epidermal transglutaminase (eTG) is an autoantigen that is closely related to dermatitis herpetiformis. Ig A anti eTG is the most sensitive serological marker for dermatitis herpetiformis [1,3,5].

The tTg protein is mostly cytoplasm, a calcium dependent enzyme which catalyzes the protein residues of glutamine and lysine. Its biological functions vary widely, from stabilization of the cytoskeleton and extracellular matrix through protein polymeration, regulation of cell matrix adhesion and cell migration, and proliferation via integrin-dependent cell signaling effects. tTG is expressed on several networks. On the skin, tTG is found in basal keratinocytes and dermal capillaries. In the small intestine, tTG expression is localized to the accumulation of IgA seen in celiac disease

[1,3,5].

Transglutaminases play a central role in the pathogenesis of gluten intolerance. First of all, tTG modifies the alcohol-soluble fraction of a known gluten called gliadin into an efficient autoantigen with a stronger affinity for HLA-DQ2 on antigen-presenting cells, resulting in T-cell stimulation and resulting in an inflammatory response. In addition, protein cross-linking produces the tTG-gliadin complex which also produces a robust autoantibody response[3,8]. The ongoing inflammatory process results in intestinal injury and villous atrophy seen in celiac disease. Because the initial neutrophil infiltration in dermatitis herpetiformis occurs within the papillary dermis, most investigators consider vesicles to form beneath the lamina densa. This is supported by electron microscopy studies. However, immunomapping has revealed a subepidermal cleft, in fact, located within the lamina lucida. This may be associated with the development of dermal edema, which stimulates the formation of the sublamine densa cleft. In addition, electron microscopy studies are limited to the area examined at that minute, making it more likely that the gap in the lamina lucide will be missed [1].

Pathogenic autoantibodies in both celiac disease and dermatitis herpetiformis predominate in the IgA class, although the IgG class is also seen and becomes important in patients with gluten sensitivity and IgA deficiency. The typical finding in dermatitis herpetiformis is the accumulation of granular IgA within the tip of the papillary dermis and along the basement membrane as seen in direct immunofluorescence in the skin around the lesion. IgA build-up is thought to provide an inflammatory stimulant which in turn produces predominantly neutrophil infiltrates and skin vesiculation.[1,3,8] IgA and / or IgG anti-tTG and circulating antigliadin antibodies are found in patients with active celiac disease. However, in patients with dermatitis herpetiformis, eTG appears as the dominant and localized autoantigen along with IgA buildup in the skin. eTG is the homolog of tTG in the active domain of the enzyme. The main functions of eTG in the epidermis are cross-linking and maintenance of sheath integrity. The presence of eTG is less than tTG, and is mostly seen in the epidermis, small intestine, brain, and testes [1,3,8,14].

3.4. Complication

Leonard et al. reported that there is an increased frequency of occurrence of malignancy in patients with dermatitis herpetiformis, especially gastrointestinal lymphoma, and Collin et al. also reported a significant increase in the incidence of non-Hodgkin's lymphoma in patients with dermatitis herpetiformis. Hernoven et al. reported that 1% of 1104 patients with dermatitis herpetiformis developed lymphoma in the next 2 to 31 years since the diagnosis of dermatitis herpetiformis was established. In other literature the authors have also found that in studies of patients who were not strictly on a gluten-free diet, 1% of them would develop B-cell or T-cell lymphoma associated with enteropathy [1,10,15].

However Lewis et al. in the UK, found in a cohort study that of 846 dermatitis herpetiformis patients compared with 4.225 control patients, there was no increased risk of developing malignancy in patients with dermatitis herpetiformis. Lewis et al. stated that perhaps the difference between their study and other studies is that in studies before they occurred population bias in hospitalized patients resulted in differences in the degree of intestinal inflammation or unrelated diseases thereby increasing the likelihood of malignancy in patients with dermatitis herpetiformis [1,2,16].

Apart from celiac disease, atrophic gastritis, and pernicious anemia, patients with dermatitis herpetiformis have a higher incidence of other autoimmune diseases such as thyroid disease, type 2 diabetes, lupus erythematosus, Sjogren's syndrome, and vitiligo. The predilection of these associated autoimmune diseases is thought to be due to the high frequency of halotype 8.1 being genetically inherited in patients with dermatitis herpetiformis [1,10,16,17].

Neurological disorders that have been reported to occur in celiac disease, such as epilepsy, opsoclonus-myoclonus ataxics, and dementia, have also been reported by some authors in patients with dermatitis herpetiformis who consume a long-term gluten diet. However evaluation of a patient with dermatitis herpetiformis, found no evidence that immune-mediated neurological disease was present in a patient with dermatitis herpetiformis [1,16].

4. Conclusion

Duhring's disease or dermatitis herpetiformis arises because of the interaction of various factors, both autoimmune, genetic, and environmental factors. Autoimmune factors that play a role include HLA-DQ2 and -DQ8, while environmental factors that play a major role are insensitivity to the gluten diet.

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