Clinical and Developmental Immunology

Novel Advances in Dermatitis Herpetiformis

Guest Editors: Marzia Caproni, Alessio Fasano, and Takashi Hashimoto

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Editorial Board

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Editorial

Novel Advances in Dermatitis Herpetiformis

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Dermatitis herpetiformis (DH) is an inflammatory cutaneous disease with a chronic-relapsing course that presents with pruritic polymorphic lesions mainly distributed in typical areas such as the extensor aspects of the limbs, the sacral region, and the buttocks. There is growing evidence that DH should be considered the specific phenotypic cutaneous expression of a gluten-sensitive enteropathy indistinguishable from celiac disease (CD). Histologically, DH is characterized by subepidermal blister and accumulation of neutrophils and very few eosinophils at the dermal papillae, while the typical immunopathological finding consists in granular IgA deposits along the basement membrane zone, mainly localized at the papillary tips. Recent studies demonstrated that such IgA are directed against epidermal transglutaminase.

However, in the last years, several papers from the literature reported the presence of atypical findings in patients with DH, suggesting that the features described previously probably need a significant revision and leaving many critical points that should be investigated further in the near future. In the present issue, the recent advances of clinical, pathogenetic, and therapeutic aspects of DH will be addressed.

About the clinical presentation, an increasing number of papers have recently described uncommon features in patients with DH, as reviewed in the present issue by V. C. Bonciolini et al. Accordingly, Ohata et al. in their paper reported 91 Japanese DH cases showing atypical distribution of the lesions and, interestingly, showed that only two of the eight patients (25%) with DH were biopsied in their case series exhibited histopathological signs of CD. However, patients with DH may present the widest spectrum of histological findings of enteropathy, ranging from normal-appearing epithelium to a flat mucosa; moreover, patients with DH significantly increased the frequency of chronic atrophic gastritis than healthy controls, as demonstrated by A. Alakoski et al. in this issue.

From a pathogenetic point of view, the presence of a subepidermal cleft with neutrophilic infiltration at the tips of dermal papillae has been considered the histopathologic hallmark of DH, suggesting a major role for neutrophil granulocytes in the pathogenesis of the skin lesions, as described by D. Bonciani et al. and K. Nakajima in this issue. Besides neutrophils, another cell type has been suggested as a major actor in the pathogenesis of DH, namely, CD4+ T cells. The presence of such cells, with a cytokine expression pattern belonging to the Th2 phenotype, has been documented in recent DH skin lesions as well as in the perilesional skin, suggesting their role in the early phases of DH skin inflammation. Moreover, in this issue, Z. Agnieszka et al. focused the attention on apoptosis, a physiological process that has been shown to play a role in several autoimmune diseases.

Finally, in the present issue, A. Fasano reviewed novel therapeutic approaches for DH. Since DH is considered the specific cutaneous manifestation of CD, besides the symptomatic therapies often used in DH patients to control the skin flares at least in the first phases (i.e., dapsone),

gluten-free diet (GFD) is still regarded as the only curative approach to the disease. However, a GFD is very hard to comply with, and different approaches are still under investigations.

In conclusion, some of the more recent advances in DH are presented in this issue. DH is a complex disease, where the skin represents a clue for the identification of a gluten-sensitive enteropathy. The knowledge of the different clinical and immunopathological features of the disease as well as the understanding of its pathogenesis may lead to a better care of our patients.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Review Article

Novel Therapeutic/Integrative Approaches for Celiac Disease and Dermatitis Herpetiformis

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Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Gluten is a protein component in wheat and other cereals like rye and barley. At present, the only available treatment is a strict gluten-free diet. Recent advances have increased our understanding of the molecular basis for this disorder. Last decade has seen new scientific developments in this disease and led to the formulation of new concepts of pathophysiology that offer possible targets for new treatments or interventions integrative to the gluten-free diet.

1. Introduction

Celiac disease (CD) is an immune-mediated chronic enteropathy with a wide range of presenting manifestations of variable severity. It is triggered by the ingestion of gliadin fraction of wheat gluten and similar alcohol-soluble proteins (prolamins) of barley and rye in genetically susceptible subjects with subsequent immune reaction leading to small bowel inflammation and normalization of the villous architecture in response to a gluten-free diet (GFD). CD not only affects the gut, but it is a systemic disease that may cause injury to the skin (dermatitis herpetiformis, the topic of this special issue), liver, joints, brain, heart, and other organs. It is a complex genetic disorder, and human leukocyte antigen (HLA) status appears to be the strongest genetic determinant of risk for celiac autoimmunity. There is a propensity for individuals with CD to carry specific HLA class II alleles, which has been estimated to account for up to 40% of the genetic load [1]. In affected individuals, 95% have either DQ2 (*HLA-DQA1*05-DQB1*02*) or DQ8 (*HLADQA1*03-DQB1*0302*), in comparison with the general population in which 39.5% have either DQ2 or DQ8 [2]. It is the interplay between genes (both HLA and non-HLA associated) and environment (i.e., gluten) that leads to the intestinal damage typical of the disease [3]. Under physiological circumstances, this interplay is prevented by competent intercellular tight junctions (TJs), structures that limit the passage of macromolecules (including gluten) across the intestinal epithelial barrier. Recent evidence suggests that the gluten-induced upregulation of zonulin, a recently described intestinal peptide involved in TJ regulation, is responsible, at least in part, for the aberrant increase in gut permeability characteristic of the early phase of CD [4] and the subsequent abnormal passage of gluten into the lamina propria. Here, the protein is deamidated by tissue transglutaminase and is then recognized by HLA-DQ2/DQ8 bearing, antigen presenting cells, thereby triggering the onset of the CD autoimmune reaction [3] (Figure 1). Similar mechanisms are applied in the autoimmune response to gluten targeting the skin leading to dermatitis herpetiformis (DH). Given the undisputable role of gluten in causing inflammation and immune-mediated tissue damage, CD and DH represent unique models of autoimmunity in which, in contrast to most other autoimmune diseases, a close genetic association with HLA genes (DQ2 and/or DQ8), a highly specific humoral autoimmune response (autoantibodies to tissue transglutaminase), and, most importantly, the triggering environmental factor (gluten), are known. This information

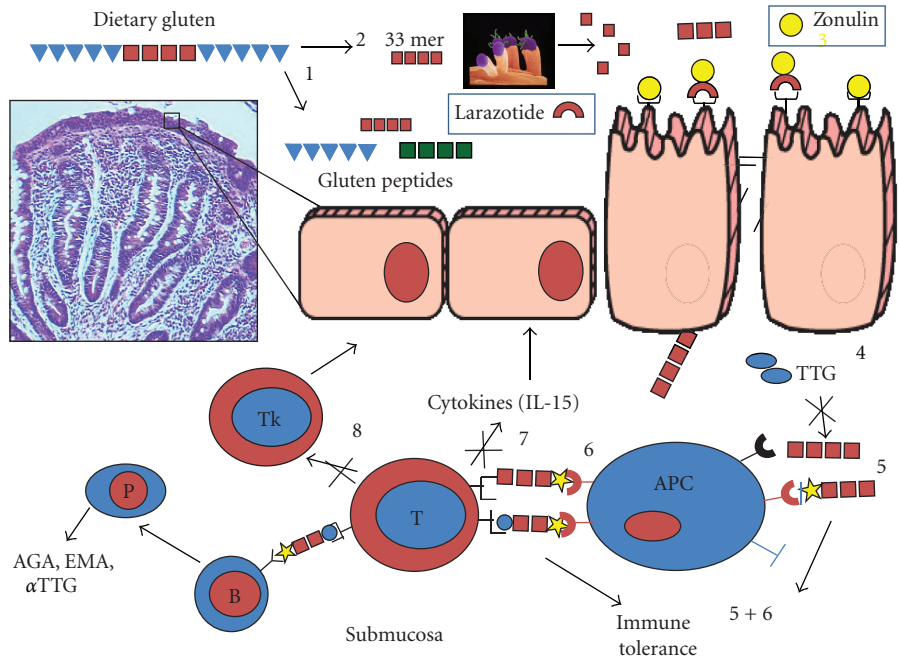

Figure 1: Schematic representation of intestinal mucosal events involved in celiac disease pathogenesis.

provides the rationale for the treatment of the disease based on complete avoidance of gluten-containing grains from the patients' diet, a task complicated by several factors, including poor compliance, inaccurate information, low level of awareness among health care providers, a food labeling policy still in progress, and the lack of consensus on proper safe gluten thresholds.

2. The Rationale for Alternative/Integrative Approaches to a Gluten-Free Diet

The cornerstone of treatment of CD and DH is a lifelong adherence to a strict GFD in which proteins from wheat, rye, barley, and related cereals are eliminated from the diet. Gluten is, however, a common (and in many countries unlabeled) ingredient in the human diet, presenting a big challenge for CD patients. Gluten-free products are not widely available and are more expensive than their gluten-containing counterparts. Dietary compliance is therefore suboptimal in a large proportion of patients. More than 50% of subjects that embrace a diet for medical reasons (hypertension, obesity, high cholesterol, diabetes, renal failure, etc.) fail to comply over time [5], making any diet therapy a high-risk proposition. Furthermore, even when compliance is not an issue, a high percentage of CD subjects on a GFD that are symptom free and test negative to CD serology show persistence of sever intestinal damage [6, 7]. Therefore, treatments alternative to the GFD or integrative to the diet in order to minimize cross-contamination accidents typically occurring outside patients' households would represent desirable interventions to minimize the risk of complications associated to prolonged gluten exposure in subjects affected by CD and DH.

3. Gluten Contamination: How Much Is Too Much?

A GFD completely devoid of gluten is unrealistic. CD and DH patients are exposed to products containing trace amounts of gluten, even when the products are sold as naturally gluten free. In order to estimate the safe threshold for daily gluten intake, the amount of residual gluten in gluten-free products and the total intake of these products must be considered. Provided that we can demonstrate that the use of a variety of gluten-free products results in both clinical and histological recovery, we can assume that the gluten level in these products is acceptable. Most wheat starch-based gluten-free products contain trace amounts of gluten [8]. These products were verified to be safe in clinical practice in a prospective controlled study where no differences in histology, serology, or quality of life were seen between wheat starch-based and naturally gluten-free products [9]. There is little information in the literature on minimal disease-eliciting doses of gluten for sensitive individuals [10]. Literature review suggests that an upper limit for gluten content in food, which would be safe for sufferers from CD, should lie between 10 and 100 mg daily intake [10]. A more evidence-based definition of this limit was identified recently by a recent study that evaluated the effects of exposure to either 10 or 50 mg of purified gluten per day for 3 months with a population of 49 celiac disease individuals in a double-blind, placebo-controlled trial [6]. The results suggest that minimal mucosal abnormalities occur even following a strict GFD, that both 10 mg and 50 mg daily gluten are clinically well tolerated, but that there is a trend for mucosal changes to occur at the 50 mg dose [6]. There is therefore an urgent need to develop safe and effective

therapeutic alternatives to the GFD, keeping in mind that any of these alternative approaches needs to match the high level of safety of the diet therapy.

4. Why Gluten Is Harmful to CD and DH Subjects

In order to identify possible targets for therapies alternative to a GFD, it would be helpful to review the significant progress made during the past decade on CD pathogenesis. CD is now considered to be a T-cell-mediated, chronic inflammatory disorder with an autoimmune component. Altered processing by intraluminal enzymes, changes in intestinal permeability, and activation of innate immunity mechanisms seem to precede the activation of the adaptive immune response [11]. In recent years, much has been discovered about the genetic and immunologic aspects of CD [4]. However, little is known about the possible interactions of gliadin (and/or its peptide derivatives) with intestinal epithelia and the mechanism(s) through which it crosses the epithelial barrier to reach the submucosa. Under physiological circumstances, intestinal epithelia are almost impermeable to macromolecules such as gliadin [12]. In CD, paracellular permeability is enhanced, and the integrity of TJ system is compromised [13–15]. The upregulation of zonulin, a recently described intestinal peptide involved in TJ regulation [16, 17], appears to be responsible, at least in part, for the increased gut permeability characteristic of CD [18]. Further, persistent presence of inflammatory mediators such as TNF-α and interferon (IFN)-γ has been shown to increase the permeability across the endothelial and epithelial layers [19, 20], suggesting that the initial breach of the intestinal barrier function caused by zonulin can be perpetuated by the inflammatory process after the access of gliadin to the submucosa [21]. Additionally, evidence exists suggesting also a transcellular passage of gliadin, particularly when the mucosal damage is already established and the transferrin receptor (CD71) that mediates this transport is expressed on the luminal side of enterocytes, so promoting retrotransport of secretory immunoglobulin (SIg) A-gliadin complexes [22, 23]. Direct evidence of the rapid activation of the innate immune system has been proven in organ culture studies. Interestingly, most of these events of innate immune activation were inhibited by antibodies neutralizing interleukin (IL)-15 [10], thus confirming the key role of this cytokine as a mediator of intestinal mucosal damage induced by ingestion of gliadin. The activation of lamina propria T cells by gliadin peptides in the context of HLA-DQ2 or DQ8 molecules has long been recognized as one of the key events in the pathogenesis of CD. A large number of T-cell-stimulating peptides have been characterized in gluten proteins [24–26]. Studies by Arentz-Hansen et al. [24] and Vader et al. [25, 26] have provided a model to explain the interplay between gliadin, DQ2 or DQ8 and tTG. In fact, these gliadin-specific T-cell responses have been found to be enhanced by the action of tTG. tTG converts glutamine residues into glutamic acid, which results in higher affinity of these gliadin peptides for HLA-DQ2 or HLADQ8. Recent studies have identified in the sequence motifs QXP, the glutamine residues that are preferentially substrate for tTG-mediated deamidation [26]. The repertoire of gluten peptides involved in the disease pathogenesis is greater than appreciated previously and may differ between children and adult patients [24]. Although there are at least 50 T-cell-stimulatory epitopes in gluten proteins, a unique 33 mer gliadin fragment is the most immunogenic peptide because it harbors six overlapping epitopes. Moreover, it is resistant to the enzymatic degradation by gastric acidity and pancreatic and brush border peptidases. This peptide might reach the immune districts of intestinal mucosa in an intact and stimulatory form [27]. Furthermore, the 33 mer peptide does not require further processing in antigen presenting cells for T-cell stimulation because it binds to DQ2 molecules with a pH profile that promotes extracellular binding [28]. The pattern of cytokines produced after gliadin activation is clearly dominated by IFN-γ (Th1 skewed) [29]. IFN-γ-dependent signaling pathways have been found to be enhanced in CD.

5. Potential New Therapies: Prevention versus Treatment

The aforementioned progress made in the understanding of the cellular and molecular basis of CD led to the identification of potential targets for preventive or therapeutic interventions [30, 31] (Figure 2).

5.1. Prevention. Several retrospective studies have suggested that the time of gluten introduction in the diet of infants at risk for CD may affect the incidence of the disease. However, the data supporting this hypothesis are circumstantial, limited by their retrospective design, and often criticized by alternative interpretations suggesting that the delay in gluten exposure merely postpones the onset of symptoms rather than preventing the disease. In order to clarify the role of infant nutrition on the risk of CD development in at-risk infants, two large prospective, intervention studies that are currently active have been recently initiated [30]. The results of these long-term studies will be available within the next few years. The PreventCD Family Study is currently ongoing in 10 European countries and a total of 1,000 children are involved. The participating children and mothers are to be followed for a period of 1–3 years. The general hypothesis of this study is that small amounts of gluten are administered gradually to induce oral immune tolerance to gluten. The second large study is a multicenter study from Italy aimed at evaluating the role of age at gluten introduction on CD-related autoimmune serological changes in a large cohort of at-risk infants (first-degree relatives of patients with CD). So far more than 700 infants have been enrolled and preliminary data suggest that postponing gluten introduction in the infant's diet at age 12 months decreases the prevalence of CD (Catassi C, personal communication). Both studies necessitate of much longer follow-up analysis to establish whether timing of gluten exposure can really prevent CD or merely delay its onset.

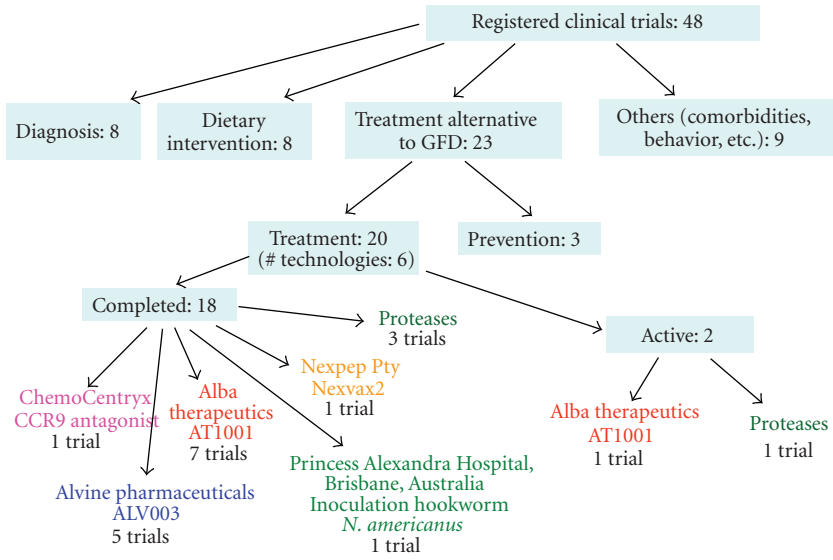

Figure 2: Current clinical trials in celiac disease involving preventive and therapeutic interventions. Data obtained from http://www.clinicaltrials.gov/ update to July 10th 2012.

5.2. Treatment with Enzyme Therapy. It has been shown that because of the high-proline content, gliadin peptides are highly resistant to digestive processing by pancreatic and brush border proteases [27]. Enzyme supplement therapy with the use of bacterial prolyl endopeptidases has been proposed to promote complete digestion of cereal proteins and thus destroy T-cell multipotent epitopes. One of these enzyme formulations, called ALV003, is currently in clinical trials and has shown promising safety and efficacy data. ALV003 has been administered both in the fasted state and with a gluten-containing meal. All ALV003 doses were well tolerated, and no serious adverse events or allergic reactions were observed. Gastric aspirates collected 30 min following a meal showed that 100 and 300 mg ALV003 degraded 75 ± 10% in the fasting phase and 88 ± 5% in the meal phase of one gram of wheat bread gluten [32]. It remains to be assessed whether the residual amount of undigested gluten can cause arm in the long term. An alternative approach to reduce gluten toxicity is based on a pretreatment of whole gluten or gluten-containing food with bacterial-derived peptidase [33]. Enzymatic detoxification of gluten has the potential to be an effective method for producing more palatable gluten-free products and possibly treating CD. Proteases of certain lactobacilli present in sourdough are able to proteolyze proline-rich gluten peptides [33]. CD patients subjected to an acute challenge tolerated breads produced with sourdough (lactobacillus digested) better than those with baker's yeast [33].

6. Engineered Grains and Inhibitory Gliadin Peptides

Breeding programs and/or transgenic technology may lead to production of wheat that is devoid of biologically active peptide sequences. Site-directed mutagenesis of wheat, which would not affect the baking properties, has also been proposed, although the number and the repetition of such sequences in wheat render this approach difficult. The identification of specific epitopes may also provide a target for immunomodulation of antigenic peptides. According to the nature of amino acid residue in the position interacting with the specific TCR, peptide recognition can turn out in a cellular activation (agonist), ignorance (null peptides), or unresponsiveness, known also as anergy (antagonist). Peptide analogues of gliadin epitope(s) can be engineered with antagonistic effects of native peptide(s). Of course, the chances of success of using analogue peptides to modulate specific immune responses could be hampered by the great heterogeneity of gliadin T-cell epitopes so far identified. Further studies aimed to elucidate the hierarchy of pathogenic gliadin epitopes, and their core region would be of crucial importance for engineering peptide-based therapy.

7. Immunomodulatory Strategies

The autoantigenic enzyme tissue transglutaminase (TTG) is mainly expressed in the lamina propria, and its expression is upregulated by various stimuli, such as mechanical stress or bacterial/viral infection, during active CD. The enzyme catalyzes transamidation between a glutamine residue of a glutamine-donor protein and a lysine residue of a glutamine-acceptor protein, linking these proteins with a stable intermolecular isopeptide bond and increasing their rate of phagocytosis by antigen-presenting cells [34]. Although the precise molecular details of this interaction in vivo remain unclear, selective inhibition of TTG in the small intestine might represent a therapeutically useful strategy for countering the immunotoxic response to dietary gluten in CD. The substitution of a glutamine residue with 6-diazo-5-oxo-norleucine (DON) transforms an immunodominant gluten peptide into a potent inhibitor of tissue transglutaminase

[35]. DON-modified peptides could be useful for the study and therapy of CD. The efficacy and side effects of TTG inhibitors as a treatment of CD are unknown. The crucial role of the HLA in CD development makes it an obvious target for therapeutic intervention. Blocking of peptide presentation by DQ2 is an attractive approach for a new treatment of CD because DQ2 (or DQ8) is a necessary but insufficient genetic component for disease development. Furthermore, other immunomodulatory targets, including IL-10, are possible alternative tools for promoting tolerance. However, evidence that gluten toxicity is not dependent only on T-cell recognition is growing. In this regard, the mechanism of toxicity of peptide remains unknown. Activation of innate immunity has been demonstrated, and antibodies to IL-15 have been proposed, particularly in the treatment of refractory sprue because of the IEL-activating role of IL-15 [10]. Nevertheless, one should realize that treated CD is a benign condition and dietary treatment is safe, although strenuous. Therefore, any immunomodulatory approach must have a safety profile equivalent to that of the GFD but with the advantage of increased compliance.

8. Correction of the Intestinal Barrier Defect

The primary functions of the gastrointestinal tract have traditionally been perceived to be limited to the digestion and absorption of nutrients and electrolytes and to water homeostasis. A more attentive analysis of the anatomic and functional arrangement of the gastrointestinal tract, however, suggests that its barrier function and ability to regulate the trafficking of macromolecules between the environment and the host are other extremely important functions of this organ. Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to non-self antigens. When the finely tuned trafficking of macromolecules is dysregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune disorders can occur [36]. This new paradigm subverts traditional theories underlying the development of autoimmunity, which are based on molecular mimicry and/or the bystander effect, and suggests that the autoimmune process can be arrested if the interplay between genes and environmental triggers is prevented by reestablishing the intestinal barrier function. A common denominator of autoimmune diseases is the presence of several preexisting conditions that lead to an autoimmune process. The first is the genetic susceptibility of the host immune system to recognize, and potentially misinterpret, an environmental antigen presented within the gastrointestinal tract. Second, the host must be exposed to the antigen. Finally, the antigen must be presented to the gastrointestinal mucosal immune system following its paracellular passage from the intestinal lumen to the gut submucosa, which is normally prevented by competent tight junctions [30]. In many cases, increased intestinal permeability seems to precede disease and causes an abnormality in antigen delivery that triggers the multiorgan process leading to the autoimmune response [36].

Taking the information above into consideration, it is conceivable to propose that the pathogenesis of autoimmune diseases, including CD, can now be described by the following three key points. First, autoimmune diseases involve a miscommunication between innate and adaptive immunity. Second, molecular mimicry or bystander effects alone might not explain entirely the complex events involved in the pathogenesis of autoimmune diseases. Rather, the continuous stimulation by non-self antigens (environmental triggers) seems to be necessary to perpetuate the process. Contrary to general belief, this concept implies that the autoimmune response can theoretically be stopped and perhaps reversed if the interplay between genes predisposing individuals to the development of autoimmunity and environmental triggers is prevented or eliminated. Third, in addition to genetic predisposition and exposure to triggering non-self antigens, the loss of the protective function of mucosal barriers that interface with the environment (mainly the gastrointestinal and lung mucosa) is necessary for autoimmunity to develop. Based on this theory, it is possible to conceptualize that the removal of any of the three elements necessary to develop autoimmunity (i.e., genetic predisposition, exposure to the environmental trigger(s), or defect of the intestinal barrier function) would be a valid therapeutic option. Given that elimination of the predisposing genes is not a valuable option and that the removal of the trigger antigen (an option available only for CD) has its own challenges (see above), the correction of the intestinal barrier defects may represent an innovative therapeutic alternative. Small intestinal permeability abnormalities are seen in untreated CD patients, which return to normal on a GFD [37]. The use of the zonulin inhibitor AT1001 to correct intestinal barrier defects has been already successfully explored in an animal model of autoimmunity [38]. More recently, AT1001 (now called larazotide acetate) has been tested in an inpatient, double-blind, randomized placebo-controlled human clinical trial to determine its safety, tolerability, and preliminary efficacy [39]. No increase in adverse events was recorded among patients exposed to larazotide acetate as compared to placebo. Following acute gluten exposure, a 70% increase in intestinal permeability was detected in the placebo group, while no changes were seen in the Larazotide acetate group [39]. After gluten exposure, IFN-γ levels increased in 4 out of 7 patients (57.1%) of the placebo-group, but only in 4 out of 14 patients (28.6%) of the larazotide group. Gastrointestinal symptoms were significantly more frequent among patients of the placebo group as compared to the larazotide acetate group [39]. Combined, these data suggest that larazotide is well tolerated and appears to reduce gluten-induced intestinal barrier dysfunction, proinflammatory cytokine production, and gastrointestinal symptoms in celiac patients. While the effect of larazotide on assembly and regulation of intercellular TJ and subsequent mucosal inflammation has been amply studied [40, 41], its possible impact on transcellular gluten trafficking remains to be established.

9. Summary

Although GFD is considered the only effective treatment for individuals with CD and DH, it has been recognized that its implementation is challenging and most of the time suboptimal. A better understanding of the complexity of the genetic/environmental interaction responsible for CD and DH development opens the way to explore alternative therapeutic strategies [42]. It is well possible that reducing the "strength" or the access of the environmental component will prevent disease recurrence, particularly in those patients with a lower genetic load of predisposing genes.

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Review Article

Recent Advances in Dermatitis Herpetiformis

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Dermatitis herpetiformis is an autoimmune bullous disease that is associated with gluten sensitivity which typically presents as celiac disease. As both conditions are multifactorial disorders, it is not clear how specific pathogenetic mechanisms may lead to the dysregulation of immune responses in the skin and small bowel, respectively. Recent studies have demonstrated that IgA and antibodies against epidermal transglutaminase 3 play an important role in the pathogenesis of dermatitis herpetiformis. Here, we review recent immunopathological progress in understanding the pathogenesis of dermatitis herpetiformis.

1. Introduction

Dermatitis herpetiformis (DH) is an autoimmune blistering, intensely pruritic papulovesicular rash typically located on the elbows, forearms, buttocks, knees, and scalp [1]. The disease can be clearly distinguished from other sub-epidermal blistering disorders by histological and immunological characteristics and presence of gastrointestinal disease. Histopathological findings of the lesional skin of patients with DH are characterized by subepidermal blisters with predominantly neutrophil infiltrates at the tip of the papillary dermis [2]. Direct immunofluorescence (DIF) reveals granular IgA deposition in the papillary dermis [2]. Gluten sensitivity typically presents as celiac disease (CD), a common chronic small intestinal disease. Although DH is highly associated with CD, the gastroenterological symptoms in DH are generally mild or are clinically completely absent [1]. However, inflammatory small bowel changes can often be found by histological examination even in the absence of clinical findings. Both disorders are associated with the IgA class of autoantibodies. A close association between DH and HLA-DQ2 and HLA-DQ8 has been established [2]. Several diseases, including thyroid abnormalities, systemic lupus erythematosus, dermatomyositis, Sjogren syndrome, and rheumatoid arthritis, are associated with DH [3]. As patients with DH have been reported to have an increased risk of intestinal lymphoma, recent reports showed that patients with DH who did not maintain a gluten-free diet had a greater risk for developing lymphoma [4]. On the other hand, several studies have failed to demonstrate an increased incidence of malignant neoplasms in patients with DH [4]. The standard therapy for DH is treatment with dapsone [2]. Here, we highlight the recent immunopathological advances in the pathogenesis of DH.

2. *InVivo* IgA-Associated Pathogenesis in DH

The deposition of IgA in the papillary dermis is the immunopathological hallmark of DH. Firstly, it was found that both the perilesional and the uninvolved skin of patients with DH have granular IgA deposition in the papillary dermis [5]. These IgA deposits decreased in intensity or disappeared after the patient maintained a gluten-free diet [3]. Although early studies showed that IgA was associated with bundles of microfibrils and anchoring fibrils below the basal lamina, later studies demonstrated that almost all IgA deposits were related to nonfibrillar components of the skin and other connective tissues [6, 7]. IgA is thought to play an important part in the infiltration of neutrophils into the papillary dermis and in the formation of basement membrane zone vesicles in the lamina lucida. The cutaneous IgA deposits in DH have been shown to function *in vitro* as a ligand for neutrophil migration and attachment [8]. However, the specific IgA antibody responsible for granular deposition in the papillary dermis has not yet been identified definitively.

Dieterich et al. identified tissue transglutaminase (tTG) as the autoantigen involved in CD [9]. They also showed that circulating autoantibodies to tTG could differentiate patients with DH from those with linear IgA bullous dermatosis [9]. Linear IgA bullous dermatosis often closely mimics the clinical pattern seen in patients with DH [2]. However, the findings of linear IgA deposits at the basement membrane by DIF can distinguish linear IgA bullous dermatosis from DH. Circulating IgA and/or IgG anti-tTG and anti-gliadin antibodies are found in patients with active CD [2]. tTG is a member of the TG family, which in humans consists of nine distinct proteins expressed in a wide variety of cell types [10]. TG family members show conservation, especially of certain enzymatically relevant domains. Strikingly, Sárdy et al. demonstrated that sera from patients with gluten-sensitive disease (GSD) reacted both with tTG and epidermal transglutaminase 3 (TG3) and that sera from patients with DH showed a higher affinity for TG3 [10]. They also demonstrated the colocalization of TG3 with IgA deposition in the papillary dermis of DH patients. In addition, they also revealed that TG3 and IgA complexes at the papillary dermis did not contain tTG. Therefore, they proposed that TG3, rather than tTG, may be the dominant autoantigen in DH. TG3 is homologous to tTG regarding their enzymatically active domains [10]. The function of TG3 in the epidermis involves cross-linking and maintenance of cornified envelop integrity. While TG3 is localized in upper layer keratinocytes, tTG is seen in basal layer keratinocytes in normal skin [10]. On the other hand, TG3 in DH skin is found in the papillary dermis and overlaps with the same sites of IgA deposition. It has been suggested that TG3 might be released from keratinocytes and bound by circulating IgA antibodies in the papillary dermis [10]. Another hypothesis is that preformed circulating complexes of IgA and TG3 might be deposited in the papillary dermis [10]. In fact, these circulating complexes were found in the vessel walls of patients with DH [11]. However, the exact mechanism whereby IgA anti-TG3 deposits are localized in DH skin is not known.

Donaldson et al. also reported that patients with DH have TG3 in the papillary dermis overlapping with the deposits of IgA [12]. Additionally, they found TG3 deposits in uninvolved skin at least 5 cm away from the lesions. Moreover, IgA deposits were seen in all skin specimens where TG3 was found, suggesting that TG3 is bound by autoantibodies as the mechanism of deposition. TG3 was not found in the dermis in the absence of IgA. The intensity of IgA by DIF roughly correlated with the intensity of staining for TG3. These findings suggest that factors beyond these complexes are necessary for the formation of DH skin lesions.

3. Granular or Fibrillar IgA Deposits in the Skin of DH Patients

Although DH is most common in Europe and the United States, it is very rare among African Americans and Asians including Japan, perhaps because of differences in the frequency of HLA antigens associated with DH [1]. The incidence of fibrillar patterns of IgA deposits in the papillary dermis of patients with DH has been reported, although it is common that granular deposits of IgA in the papillary dermis are pathogenic for DH [3]. Interestingly, those patients seem to have a decreased frequency of a GSD [3]. In Chinese patients with DH, granular IgA deposits in the papillary dermis were seen in 95.5% (21/22) of patients and fibrillar IgA deposits in the papillary dermis were seen in 1 patient (4.5%) [13]. A recent study also described 3 DH patients with fibrillar patterns of IgA deposition in the papillary dermis and 2 of 3 patients did not have anti-TG antibodies and antiendomysial antibodies [14]. Although patients showing a fibrillar pattern of IgA deposits typically have other clinical findings consistent with DH, it has been suggested that those patients may have a higher incidence of atypical features, such as urticarial or psoriasiform skin lesions, the absence of GSD, or an HLA-B8/DR3/DQ2 haplotype [3]. It is not clear whether this difference in IgA deposits may be associated with the decreased frequency of GSD in patients with DH.

4. Immunological Diagnostic Markers of DH

Firstly, Chorzelski et al. reported that IgA antibodies bind to an intermyofibril substance (the endomysium of smooth muscle) in the skin of patients with DH [15]. Amazingly, Sárdy et al. showed that these IgA antibodies have a specificity for TG, particularly epidermal-specific TGs, which were also found in the sera of DH patients as well as CD patients [10]. It is well known now that patients with DH have IgA antibodies that are specific for TG3 and IgA antibodies that react with both TG3 and tTG. A recent study demonstrated that IgA anti-TG3 is more sensitive in detecting DH than any other marker associated with GSD in a large cohort of DH patients [16]. Serum IgA endomysial antibodies (EMAs), which can be detected by indirect immunofluorescence, are serologic markers for both DH and CD. The endomysium is the fine connective tissue sheath surrounding each muscle fiber. Moreover, IgA anti-tTG, which is a major endomysial antigen detectable by enzyme-linked immunosorbent assay (ELISA), has a high range of specificity and sensitivity in DH patients [2]. Levels of anti-tTG and anti-TG3 IgA correlate with the extent of small bowel pathology in CD [2]. Moreover, levels of anti-endomysial, anti-tTG and anti-TG3 antibodies are low in patients with DH and CD that follow a strict gluten-free diet [2]. In addition, serum IgA antibodies directed at gliadin are positive in about 70% of CD and DH patients. However, a potential role for tTG and gliadin IgA antibodies in the pathogenesis of DH has not been proposed. As selective IgA deficiency is about 10 to 15 times more prevalent in patients with CD, no case of selective IgA deficiency in DH has been reported. However, partial IgA deficiency has been reported in DH, indicating that pathogenically directed IgA antibodies were likely sufficient for cutaneous IgA depositions in DH [17]. A recent report indicated that intestinal damage may be associated with the production of IgA anti-tTG and IgA anti-TG3 antibodies in DH patients [18]. Dahlbom et al.

demonstrated that high levels of IgA anti-tTG and IgG anti-tTG antibodies are associated with the grade of mucosal villous atrophy and a more severe clinical presentation of CD [19]. However, there are no data available at this time about a possible correlation between serological marker(s) and the clinical severity of DH.

5. Neutrophils in the Pathogenesis of DH

The skin lesions in patients with DH are characterized by the infiltration of neutrophils and IgA deposits in the papillary dermis [2]. When the activity of DH is high, circulating neutrophils in patients with DH show a high level of CD11b [3]. Moreover, neutrophils in skin lesions of DH patients showed increased expression of CD11b, a slightly deceased expression of L-selectin, and increased function of the FcIgA receptor, all of which suggest the partial priming of the neutrophils [3]. IL-8 (CXCL-8) is a chemokine that plays an important role in neutrophil inflammatory responses, including the upregulation of neutrophil expression of CD11b and the shedding of L-selectin, steps that are necessary for firm adhesion to endothelial cells and movement into tissue. It has been previously shown that patients with DH show increased levels of serum IL-8, and IL-8 is also increased in patients who are on gluten-containing diets [3]. A recent study suggested that IL-8 in the sera of patients with DH originates from the small bowel as a mucosal immune response to gluten ingestion [20].

6. Animal Models of DH

Animal models of gluten sensitivity have been used to better understand the pathogenesis of the disease. Marietta et al. developed a mouse model for DH [21]. They reported an HLA-DQ8 transgenic nonobese diabetic mouse that, when immunized with gluten, develops neutrophilic skin lesions along with cutaneous deposits of IgA. Additionally, the subsequent withdrawal of dietary gluten results in the resolution of the skin lesions. Recently, another excellent model of DH was reported [22]. Zone et al. injected a goat anti-human TG3 antibody (IgG) into recipient immunodeficient (SCID) mice grafted with human skin. Those mice showed papillary dermal immune deposits, and those deposits reacted with both rabbit anti-TG3 and DH sera. Deposition of the transferred IgG appeared in a granular pattern in the papillary dermis of the human skin graft. However, there was minimal neutrophil infiltration. Additionally, the transfer of sera from DH patients resulted in deposits in the papillary dermis, if the sera has a high level of anti-TG3 IgA. Sera with the highest levels of anti-TG3 IgA also had minimal neutrophil infiltration at the basement membrane. In this way, they demonstrated that the passive transfer of an anti-TG3 antibody, both goat IgG and sera from patients with DH, produced granular deposits in the papillary dermis.

7. Conclusion

Advances in genetics and immunology have demonstrated the relevance of the immune pathway to the pathogenesis of DH. Many clinical and experimental studies have established IgA and TG3 as the key players and have provided exciting advances in our understanding of the pathogenesis of DH. Future investigations will further clarify the role of IgA and TG3 and their interplay with other relevant cellular and molecular pathways of the immune systems in DH.

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Clinical Study

The Expression of Selected Proapoptotic Molecules in Dermatitis Herpetiformis

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The role of the process of apoptosis is investigated in the pathogenesis of many autoimmune diseases; however at present, there is not much information about its role in dermatitis herpetiformis. Skin biopsies were taken from 18 DH patients and from 10 healthy subjects. The localization and expression of Bax, Fas, FasL, TRAIL, TRAIL-R in skin lesions, and perilesional skin were studied by immunohistochemistry. Expression of Bax, Fas, and Fas ligand was detected in the keratinocytes in skin biopsies from DH patients. Expression of TRAIL and TRAIL receptor was confirmed in epidermis, infiltration cells, and some fibroblasts. The expression of examined molecules in biopsies from healthy people was observed only in single cells. There were statistically significant differences between lesional, perilesional, and healthy skin of control group in Bax expression analysis and between lesional skin and control group in Fas, FasL, and TRAIL expression. There were statistically significant differences between control group and perilesional skin in Bax and FasL expression. Our results show that selected proapoptotic molecules may take part in pathogenesis of dermatitis herpetiformis, but the role of apoptosis in this process is not clear.

1. Introduction

Dermatitis herpetiformis (DH) is a chronic subepidermal autoimmune bullous diseases characterized by skin and intestinal lesions. Skin lesions include polymorphic eruption (papules, vesicles), mainly distributed over the shoulders, elbows, backs, buttocks, and knees. They are usually symmetric and accompanied by severe pruritus. These symptoms are usually associated with asymptomatic and gluten-sensitive enteropathy. Diagnosis of DH is established on the results of direct immunofluorescence test (DIF) revealing granular deposits of IgA in the top of the papillae and the presence of circulating IgA antibodies directed against endomysium and/or tissue, and epidermal transglutaminase (tTG, eTG). Skin lesions in DH are histologically characterized by neutrophilic infiltrate leading to destruction of basement membrane zone (BMZ) proteins. Impairment of type IV collagen, laminin, and entactin results in degradation of anchoring fibres and blister formation. [1, 2] To date, the exact mechanisms that lead to lesions formation, are only partially known.

The role of the process of apoptosis is investigated in the pathogenesis of many autoimmune diseases; however at present, there is not much information about its role in subepidermal blistering diseases.

Apoptosis, also known as programmed death of a cell, is an outcome of the intracellular cell "suicide," which is regulated by cellular pathways of passing the signal. It prevents many pathological processes, for example, autoimmunization and neoplasm [3, 4].

Up to this day, two pathways of apoptosis have been described, that is, intrinsic and extrinsic and the basis for its distinction is a way of activation of the procaspases which initiate them [5, 6].

The intrinsic one, called mitochondrial, is connected with the activation of cytochrome c by the proapoptotic

genes belonging to Bcl-2 family (*B-cell leukemia/lymphoma-2*) as a result of, for example, medicine administered or the destruction of DNA structure [7]. The features triggering the mitochondrial pathway of death can be for example: the increase in concentration of the reactive forms of oxygen, nitrogen oxide, ions Ca^{2+}, thermal shock, active toxins, the disturbance of the electron transport, or DNA damage [6].

The extrinsic pathway is associated with attaching the ligands to the receptor belonging to the superfamily of TNF receptors, which possess the so-called *death domain* (DD), by means of which the activation of the procaspases inside the cell occurs [3].

The intrinsic and extrinsic pathways stimulating apoptosis are linked to each other by, for example, Bid protein, belonging to Bcl-2 family [6].

The proteins composing the superfamily of TNF receptor also take an active part in the process of apoptosis. These are Fas, TRAIL-R1 (DR4), TRAIL-R2 (DR5, Apo2), TNF-R1, TNF-R2, TRAMP (*TNF-related apoptosis-mediating protein*), and DR-6 [8]. The pathway of operation of the Fas ligand on the receptor Fas has been most thoroughly described. At present, it is believed that the constitutive coexpression of the receptor and the ligand Fas takes place in the cells of the rapid apoptotic turnover [9].

As TNF-R, Fas, and TRAIL receptors appear on the keratinocytes, they can take part in the pathogenesis of some skin diseases such as: toxic epidermal necrolysis, Graft-versus-host disease, skin neoplasms, and contact oversensitivity [8].

In the tissue material *ex vivo*, the apoptosis is difficult to determine quantitatively because of the dynamics of the process; therefore, the number of the registered apoptotic cells often constitute only a small percentage of the total number of cells which entered the state of apoptosis [10]. In general, the majority of cells of the hematopoietic line atrophies in the process of apoptosis and manifests the typical features of apoptosis, while the death of the epithelial cells is more complicated and very often hard to classify [11].

2. Material and Methods

The study of selected proapoptotic proteins (Bax, TRAIL, TRAIL-R-DR4, Fas, Fas ligand) was performed on 18 patients (age: 44.8 years; range: 18–58 years) with dermatitis herpetiformis, who were treated in Department of Dermatology and Venereology of Medical University of Lodz. The patients were before treatment, at an active stage of the disease, that is, with skin lesions (erythemas, papules, vesicles) developed. The lesions were accompanied by itch of different intensification. DH was diagnosed based on clinical picture, histological, and immunological findings.

10 healthy volunteers, selected according to their sex and age, made up the control group.

All the participants of the experiment gave an explicit consent in writing before entering the study and the study protocol was approved by The Local Ethical Committee of Medical University of Lodz (no. RNN/132/07/KE, 20.02.2007).

The biopsies from all patients were taken from lesional and from uninvolved skin (trunk) before administration of any treatment (topical or systemic). In control group, biopsy specimens were taken from buttock or abdominal skin of healthy volunteers.

Paraffin-embedded sections (3-4 μm) were used for routine H + E staining and for immunohistochemistry in DAKO EnVision detection system using immunoperoxidase method. The following primary monoclonal antibodies were used: Bax (Dako, Denmark) (1 : 650), TRAIL (Abcam, the United States) (1 : 200), TRAIL-R (R&D, the United Kingdom) (1 : 200), Fas, Fas ligand (Novocastra, the United Kingdom) (1 : 200).

For immunohistochemistry, the paraffin-embedded sections were placed on adhesive plates and dried at 56°C for 24 hours. Later, they were deparaffinated in a series of xylenes and alcohols with decreasing concentrations (96%, 80%, 70%, and 60%). In order to retrieve the antigenicity of tissues and allow them to react with antibodies, sections were prepared in bath (98°C-1 h) or microwave oven. Then the sections were washed with TRIS buffer (pH 7.6) for 5 min. Activity of endogenous peroxidase was inhibited with 0.3% hydrogen peroxide solution in methanol for 30 minutes. Primary antibody solution directed against human antigens was put on these sections. After incubation with diluted antibodies for 60 minutes at room temperature or for 12 hours at 4°C, they were washed with TRIS buffer twice. DAKO EnVision double-step visualization system was then used in order to visualize the antigen-antibody reaction. In cases of positive immunohistochemical reaction, cellular nuclei were stained with Meyer haematoxylin for 2 minutes. After dehydratation and processing through series of acetones and xylenes, the sections were fixed in DPX. For every antibody a negative control was performed using TRIS buffer instead of antibody.

2.1. Semiquantitative Analysis. In each specimen staining intensity of TRAIL and TRAIL receptor, Fas as well as Fas ligand in the epithelium and inflammatory infiltrates were recorded by two independent observers in 4–7 adjacent high power fields and graded from 0 (staining not detectable), 1 (minimal immunostaining in some cells), 2 (weak immunostaining intensity in most cells), and 3 (strong staining in most cells). The mean grade was calculated by averaging grades assigned by the two authors and approximating the arithmetical mean to the nearest unity.

Morphometric analysis was used for Bax (MultiScan 8.08 software, Computer Scanning System, Polska). The percentage of Bax immunopositive cells was estimated by counting in each slide 500 cells in 4–7 adjacent high power fields (semiautomatic function).

All data are shown as mean ± SD. Student's t-test was applied where appropriate after evaluation of distribution. Mann-Whitney test was used where necessary. The difference was considered statistically significant when $P < 0.05$.

3. Results

Bax protein expression was discovered in the cytoplasm of keratinocytes in samples of lesional skin (mean

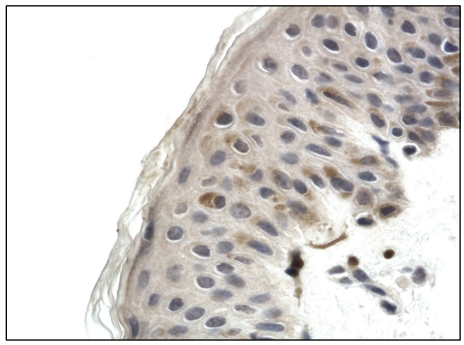

Figure 1: Cytoplasmic Bax immunoexpression in skin lesions, (score 2), 400x.

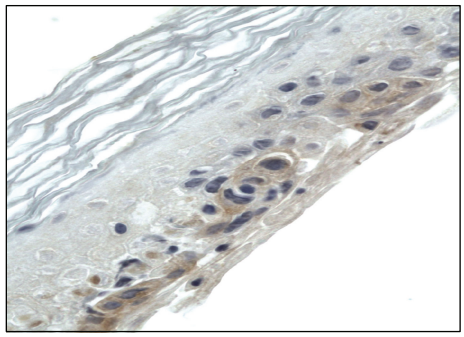

Figure 2: Fas immunoexpression in the cytoplasm of keratinocytes, (score 2), 400x.

immunoexpression 39.742 ± 7.295) (Figure 1). The expression was weaker in uninvolved skin (22.347 ± 3.814) and the weakest Bax expression was revealed in samples taken from healthy volunteers (16.60 ± 3.6).

Fas expression in lesional skin was detected in the cytoplasm of keratinocytes (0.75 ± 0.347) (Figure 2). In uninvolved skin, the expression was less intense 0.306 ± 0.290. None of the samples taken from healthy patients revealed Fas expression.

Fas ligand expression was revealed in the basal layer of the epidermis and inflammatory infiltrates in lesional skin (0.923 ± 0.427) (Figure 3). In uninvolved skin, the expression was weaker in the basal layer of the epidermis and in few cells infiltrating the skin (0.66 ± 0.292). Immunostaining for Fas ligand was negative in control group.

Immunostaining of TRAIL was detected in the cytoplasm of keratinocytes as well as in inflammatory cells, and some fibroblasts in lesional skin (1.555 ± 0.783) (Figure 4). In uninvolved skin, the expression was detected in keratinocyte, mainly of the basal layer, and in some fibroblasts was less intense (0.468 ± 0.304). As for healthy skin, the expression was discovered in keratinocytes and in some fibroblasts (0.25 ± 0.191).

Immunostaining of TRAIL receptor was revealed in inflammatory infiltration, in the cytoplasm of keratinocytes as well as in some fibroblasts in lesional skin (0.735 ± 0.634) (Figure 5), in uninvolved skin (1.005 ± 0.639), and in healthy skin (0.5 ± 0.258).

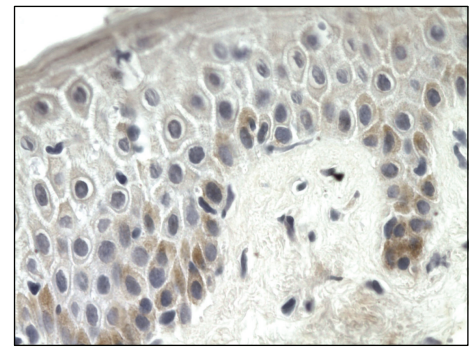

Figure 3: Fas ligand immunoexpression in the basal layer of the epidermis, (score 1), 400x.

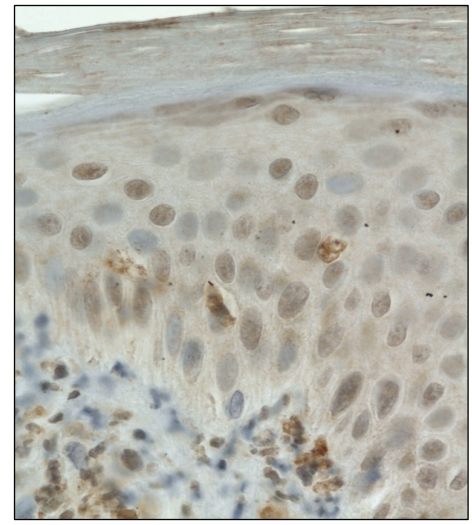

Figure 4: TRAIL immunoexpression in the cytoplasm of keratinocytes and inflammatory cells, (score 1), 400x.

There were statistically significant differences between lesional, perilesional, and healthy skin of control group in Bax expression analysis. The expression of Fas and TRAIL was higher in lesional skin than in perilesional, and in healthy group. FasL expression was significantly higher in skin lesions and perilesional skin than in control group. In TRAIL-R analysis, there was no statistically significant difference, although the expression of TRAIL-R was more intense in uninvolved than in lesional skin.

Statistical analysis was presented in Table 1.

4. Discussion

Apoptosis is claimed to be involved in a number of chronic inflammatory and neoplastic skin diseases such as contact dermatitis, toxic epidermal necrolysis, acantholytic dermatoses, and systemic lupus erythematosus [3, 4, 12, 13], also may play role in pathogenesis of bullous diseases, although there are only a few works considering apoptosis in DH. Mikalowski [14] showed cytolysis and desmosomal

Table 1: Expression of proteins in examined tissues. Statistical results. Data expressed as means ± SD; $^*P < 0.05$.

Groups	Protein				
	BAX means ± SD	Fas means ± SD	FasL means ± SD	TRAIL means ± SD	TRAIL-R means ± SD
DH skin lesions	39.742±7.295	0.75 ± 0.347	0.923 ± 0.427	1.555 ± 0.783	0.735 ± 0.634
DH perilesional skin	22.347±3.814	0.3060 ± 0.29	0.66 ± 0.292	0.468 ± 0.304	1.005 ± 0.639
Control group	16.60 ± 3.6	0.0	0.0	0.25 ± 0.191	0.5 ± 0.258
Control versus DH skin lesions	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.004$	$P = 0.4$ (NS)
Control versus DH perilesional skin	$P < 0.02$	$P = 0.06$ (NS)	$P < 0.001$	$P = 0.18$ (NS)	$P = 0.15$ (NS)
DH skin lesions versus DH perilesional skin	$P < 0.001$	$P < 0.001$	$P = 0.06$ (NS)	$P < 0.001$	$P = 0.19$ (NS)

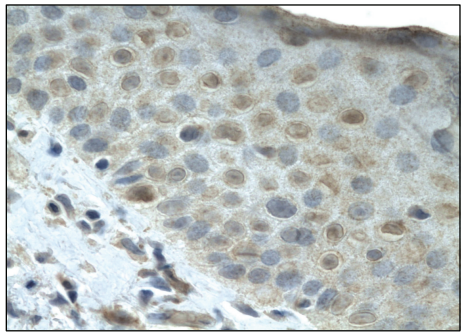

Figure 5: TRAIL receptor immunoexpression in skin lesions, (score 2), 400x.

alterations in basal keratinocytes in DH skin lesions, that is a sign of cellular damage.

Caproni et al. [15] examined apoptosis in 13 DH patients by TUNEL method (terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labelling technique). Apoptosis was seen in the basal and suprabasal layers of epidermis. In dermis, in the area of blood vessels, there were only a few apoptotic cells. In skin biopsies taken from the healthy control group there were no apoptotic cells.

Proapoptotic Bcl-2 family consists of many proteins for example, Bax, that takes part in intracellular pathway of apoptosis. In nonapoptotic cells, Bax and Bcl-2 form heterodimers keeping the homeostasis [6]. In our study, Bax expression was detected in keratinocytes of suprabasal layers, which was observed in earlier studies [16].

Caproni et al. [15] also examined the expression of proapoptotic protein Bax and antiapoptotic Bcl-2 in lesional skin. In our study similar to Caproni et al., Bax expression was seen in basal layer of epidermis and in papillary dermis and was more intense in lesional than perilesional skin. Bcl-2 expression was present in epidermis and in dermis near superficial vessels.

The results of our study showed significant difference of Bax expression between lesional, perilesional, and healthy skin; that is why the overexpression of Bax protein seems to take part in DH pathogenesis, but explanation of the precise mechanism of starting the intrinsic pathway of apoptosis needs more studies.

Extrinsic pathway of apoptosis starts for example, after activation of Fas receptor (also known as APO-1 or CD95) by its ligand FasL [4]. In physiological condition, Fas expression is weak and is present in cell membrane, or in intracellular compartment, which prevents spontaneous apoptosis [17–19]. Although in physiological condition FasL is present on keratinocytes in granular layer, spinous layer and external hair shaft however, neither we, nor Caproni et al., [15] detected Fas and FasL expression in healthy skin from control group.

Also in other bullous diseases, Fas was examined, Morawej et al. [20] described the elevation of soluble Fas (sFas) in pemphigus vulgaris patients' sera and suggest that particularly in the initial phases of autoimmune disorders, sFas may take part in the resistance of autoreactive lymphocytes to death.

Also our earlier research [21], considering pemphigoid, showed overexpression of Fas and FasL in lesional skin. In this DH study, we observed expression of Fas and FasL in epidermal cells, and FasL was seen also in inflammatory infiltration. Studies of other authors showed FasL on activated T cells, neutrophils, natural killer cells, and macrophage lineage other cell types. [4, 22, 23] In DH neutrophils and T cells are main cells of inflammatory infiltration, therefore, we suggest that infiltrating cells with FasL on the surface act on keratinocytes with Fas receptor. The connection of ligand to Fas receptor triggers intracellular cascade leading to apoptosis. Expression of both Fas on keratinocytes and FasL cells in the same topographic place implies that after the ligand and receptor have joined apoptosis gets started.

Similar data showed Caproni et al. [15] described Fas expression on basal keratinocytes in lesional and perilesional skin in DH and same in perilesional skin within perivascular superficial dermis. Higher expression of epidermal Fas than FasL and inversely in dermis, in the authors' opinion, indicates importance of extrinsic pathway of apoptosis in skin lesion formations [15].

Fas has not only proapoptotic activity, but also proinflammatory one [24, 25]. Inflammatory activity of Fas showed Farley et al. [24], who described the influence of FasL on Fas receptor which leads to its oligomerization without caspase activation. The effect of that process is not apoptosis, but expression of genes of proinflammatory factors, for example, IL-6, IL-8, MCP-1. This way of activation cannot be excluded in DH, because overexpression of many

proinflammatory cytokines (e.g., GM-CSF, IL-4, IL-5, IL-8 [26, 27] was observed in this disease. Although, in our earlier studies MCP-1 was absent in DH lesional and perilesional skin, but we reported receptors for IL-8 [28].

Many factors, such as UV radiation, cytokines (e.g., IL-1β, TNF-α, IFN-γ, and IL-15), viral infections (hepatitis B or C, HIV infection) can induce expression of Fas in epidermis [4, 29]. More precise studies are needed to establish which of these factors can take part in DH.

Other proapoptotic protein of extracellular way of apoptosis activation is TRAIL, also known as Apo-2L. TRAIL-R1 (DR4) and TRAIL-R2 (DR5), which transduces the death signal and induces apoptotic cell death [30, 31]. Although both of them coexist on keratinocytes, DR4 seems to be more effective [32]. These receptors do not take part in terminal differentiation of keratinocytes [33]. There are also TRAIL receptors on keratinocytes which do not promote apoptosis, because recombinant TRAIL does not induce apoptosis on healthy keratinocytes. By decoy receptors, TRAIL activates NF-κB, which leads to transcription of genes that are antagonists of caspase 8 and promote inflammatory process. In endothelial cells line which avoids TRAIL-induced apoptosis, expression of E-selectin, ICAM-1, IL-8, and IL-1Ra is observed. That leads to lymphocyte adhesion [5, 32, 34]. In our earlier study [28, 35] thus, we observed overexpression of E-selectin and receptors for IL-8 in dermatitis herpetiformis.

The role of TRAIL in physiological condition is not completely known. *In vitro* TRAIL is a stronger proapoptotic factor than TNF. In spite of that, it seems that most of cells are resistant to TRAIL-induced apoptosis. TRAIL protein is constitutively present on many cells, but in T and NK cells and dendritic blood cells, it is synthesized after their stimulation [13]. Interferon stimulation on neutrophils makes the expression of TRAIL is detected. mRNA for DR2 and DR4-TRAIL receptors constitutively is found in neutrophils [36].

The role of TRAIL in autoimmune diseases is discussed. Some researchers suggest that high level of TRAIL can increase disease activity, whereas some others present opposite opinion. TRAIL can induce the process of apoptosis of dendritic cells and neutrophils and its high expression was seen in T cells infiltrating skin in atopic dermatitis [13]. In our study, TRAIL and its receptor DR4 expression was present on keratinocytes and infiltarting cells. The TRAIL expression was significantly higher in lesional than perilesional and control group skin, which may suggest its role in DH pathogenesis. The influence of TRAIL on human eosinophils did not induce chemotactic effect, but led to apoptosis [36], therefore, the presence of TRAIL and its receptor in infiltrating cells seems to be related to apoptosis.

The recent study of Wu et al. [37] reported that TRAIL can induce the expression of the keratinocyte differentiation markers involucrin and type 1 transglutaminase in normal human epidermal keratinocytes. Activation of caspases 3 and 8 critically mediates these processes, but apoptosis can also be triggered.

Higher expression of TRAIL receptor in perilesional rather than lesional skin seems interesting, but these results were not statistically significant. The more intense in uninvolved than in lesional skin expression of TRAIL receptor DR4 on keratinocytes and cells of inflammatory infiltration may suggest its role in maintaining inflammatory process and damage to dermoepidermal junction.

The proteins from intrinsic (Bax) and extrinsic (Fas and TRAIL) pathway of apoptosis activation were assessed in our study. However, some authors hold the opinion that the recognition of autonomy of these two apoptotic ways is a simplification, as there are proteins which connect these two ways, for example, Bid protein [6]. Also Suliman et al. [38] showed that TRAIL besides activation of extrinsic way, decreases transmembrane potential in mitochondria and induces intrinsic way of apoptosis.

Caproni et al. [15] state that apoptosis in DH seems to be induced by extrinsic pathway, but other factors can also be influential: hypoxia due to mechanical tension of blister fluid or loss of link between the skin and epidermis may enhance the apoptotic process.

Our earlier study [21] considered the same molecules in bullous pemphigoid (BP). The Bax, Fas, FasL, TRAIL, and TRAIL-R were overexpressed in lesional skin in comparison to healthy control. Although the semiquantitative visual scale and morphometric analysis showed that immunostaining of examined proteins was more intense in DH comparing to BP. However, in Caproni et al. [15] study, the epidermal expression of Bax in BP was significantly higher than in DH. The difference may be the result of number of examined biopsies (BP: 5 [15] versus 22 [21], DH: 13 [15] versus 18 [21]). Next, also *in vitro* research seems to be needed to clarify the role of apoptosis in DH.

Our results as well as studies conducted by other authors showed that the role of apoptosis in DH pathogenesis is not clear. The exact stimulus triggering apoptosis in DH skin lesion still remains unknown, but the present study provides strong evidence that there is a difference between expression proapoptotic proteins in skin lesions, perilesional skin, and healthy skin. Cell death by apoptosis is a physiological process that enables the elimination of cells without causing an inflammatory response, but inflammation can provoke apoptosis so this mechanism in DH should be more explained.

Acknowledgment

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Research Article

Distinct Characteristics in Japanese Dermatitis Herpetiformis: A Review of All 91 Japanese Patients over the Last 35 Years

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We reviewed all 91 Japanese dermatitis herpetiformis (DH) patients reported over the last 35 years. The male-to-female ratio was 2 : 1. The mean age at onset was 43.8, and 13 years earlier for female patients. More than half of these Japanese DH patients showed granular IgA deposition in the papillary dermis, and another one-third showed fibrillar IgA deposition. The male patients with granular IgA deposition were 10 years older than those with fibrillar deposition. Whereas patients with granular IgA deposition showed typical distribution of the skin lesions, the predilection sites of DH tended to be spared in patients with fibrillar IgA deposition. Only 3 patients had definite gluten-sensitive enteropathy. There was a statistical difference in the frequency of human leukocyte antigen (HLA)-DR9 between the granular group and controls among Japanese. No patients had HLA-DQ2 or -DQ8, which is frequently found in Caucasian DH patients. The absence of HLA-DQ2/DQ8, the inability to identify celiac disease in most cases, the predominance of fibrillar IgA, and the unusual distribution of clinical lesions in Japanese patients suggest that Japanese DH may be a subset of DH patients and have a pathogenesis which is different from that currently proposed in Caucasian DH patients.

1. Introduction

Dermatitis herpetiformis (DH) is a rare, intensely pruritic, chronic and recurrent papulovesicular disease, in which the lesions usually develop symmetrically on the extensor surfaces. This disease can be clearly distinguished from other subepidermal blistering diseases by histopathological and immunological criteria. Biopsy of an early lesion shows collections of neutrophils at the papillary tips, and direct immunofluorescence (DIF) reveals nonlinear (mostly granular, or fibrillar) IgA deposition in the papillary dermis.

DH is most prevalent among the Caucasian population, and several population-based studies have been conducted, which disclosed a close association with gluten-sensitive enteropathy (GSE) and the human leukocyte antigen (HLA)-DQ2 or HLA-DQ8 [1–5]. In contrast, only case reports and one review article have been published in Japan, reflecting rare occurrence of DH in Japan [6–85]. The previous review of Japanese DH cases revealed differences from Caucasian DH, such as a high frequency of fibrillar IgA deposition in the papillary dermis, a rarity of GSE, and the absence of HLA-B8/DR3/DQ2 haplotype [59].

The fibrillar immunofluorescence pattern of IgA deposition in DH was hypothesized to be related to longitudinal sectioning of affected dermal microfibril bundles, while the granular pattern represents transverse sectioning. However, confocal laser-scanning microscopy revealed numerous fibrils stained with anti-IgA antiserum, extending from the dermoepidermal junction to 50 to 110 μm deep in the dermis. They crossed each other at various angles to form a three-dimensional network. Moreover, immune electron microscopy demonstrated the diffuse dispersion of immune deposits on the surface of microfibrils of dermal microfibril bundles [86]. These findings signify that fibrillar IgA deposition is a distinct pattern. Although fibrillar IgA deposition

in DH is ignored in some review articles of DH [87–89], it cannot be dismissed if DH is to be understood sufficiently.

To disclose the unique features of Japanese DH, we have reviewed all reports of Japanese DH patients from 1976 to 2011, most of which were written in Japanese [6–85]. We also compare the characteristics of patients with granular IgA deposition to those with fibrillar IgA deposition.

2. Materials and Methods

First we selected Japanese DH cases by searching Ichushi Web (ver. 5), a Japanese medical literature database provided by NPO Japan Medical Abstracts Society, using the term, "dermatitis herpetiformis Duhring" in Japanese, and PubMed using the term, "dermatitis herpetiformis AND Japanese." Then, we also collected all articles for Japanese DH cited by these articles. Eventually, more than 200 articles were collected. Since earlier Japanese reports of DH included linear IgA bullous dermatosis cases, we omitted these cases. Thus, we selected only cases, which showed subepidermal blisters, neutrophilic microabscesses, and nonlinear IgA deposition in the papillary dermis. Finally, 91 Japanese DH cases reported from 1976 to 2011 were accumulated [6–85].

Because one of the characteristics of Japanese DH is a high frequency of fibrillar IgA deposition, we compared the cases with granular IgA deposition (granular group) and those with fibrillar IgA deposition (fibrillar group). We performed Student's t-test for comparison of age distribution, and the χ^2 test for the HLA study using the SPSS software (ver. 19). A P value of less than 0.05 was considered to indicate statistical significance. P values for the HLA study were corrected by multiplying the P value by the number of antigens tested (HLA-DR = 10).

3. Results

3.1. Overview of Japanese DH (Table 1). Ninety-one Japanese DH patients consisted of 61 males aged between 1 and 87 years (mean 51.5 years, SD 20.5) and 30 females aged between 18 and 72 years (mean 36.8 years, SD 14.1). The data on the age at onset of DH were available for 48 males (1–87 years, mean 48.5 years, SD 19.6) and 27 females (14–72 years, mean 35.3 years, SD 13.0). The female patients started suffering from DH 13 years earlier than the male patients. No patients had any family history of DH or celiac disease (CD).

Clinical manifestation was polymorphic, consisting of erythemas, urticarial plaques, papules, and herpetiform vesicles and blisters. Superficial erosions and excoriation due to scratching were also frequently noted. Most patients presented intense pruritus, being mild in other patients. More than half Japanese DH patients had lesions on the predilection sites as in Caucasian DH, that is, the elbow, buttock, knee, face, ear, neck, scalp, and groin. In particular, 44% of Japanese DH patients had lesions on the elbow, buttock, and/or knee. The face, ear, neck, scalp, and groin were affected in only a few patients. Interestingly, 41 and 55 Japanese DH patients presented skin lesions on nonpredilection sites such as the extremities and trunk, respectively, with or without concurrent lesions on predilection sites. Six patients had lesions on the whole body. No mucosal involvement was reported.

Most biopsy specimens showed subepidermal blisters and an accumulation of neutrophils with or without a few eosinophils at the papillary tips. In DIF, 50 (54.9%) cases showed granular IgA deposition (referred as granular group), and 33 (36.3%) cases showed fibrillar IgA deposition in the papillary dermis (referred as fibrillar group). Seven cases showed both granular and fibrillar IgA depositions, and only one case showed cluster IgA deposition [80]. Twenty (22.0%) cases showed C3 deposition, and 9 (9.9%) cases showed IgG deposition in the papillary dermis. No circulating antibodies to the basement membrane zone were shown in the cases for whom indirect immunofluorescence (IIF) results were available.

Gluten-sensitive enteropathy (GSE) was associated with only 3 cases, who responded to gluten-free diet (GFD) with dapsone [24, 47, 59]. However, GFD for one case was not strict, and no information about long-term strict GFD was obtained for another 2 cases. While jejunum biopsy revealed villous atrophy in 3 patients including 1 patient with GSE [14, 39, 59], other 3 patients with no clinical symptoms of gluten sensitivity did not show any change [24, 33, 52].

Eight cases had diabetes mellitus (DM). One of those had noninsulin-dependent type DM, and four also seemed to have noninsulin-dependent type DM according to their therapy. The type of DM of three cases was unknown. Three cases had lymphoma. One case each had mycosis fungoides and anaplastic large cell lymphoma although the type of lymphoma was unknown in one case [47, 52]. Thyroid disease and Sjögren syndrome were also found in one each case of Japanese DH [9, 59].

The most common HLA antigen found in Japanese DH was Cw3, followed by A2, DR9, A24, and DR4 in the descending order. Compared with the controls Japanese population [90], there was no increase in the frequencies of HLA class I antigens (A, B, and C antigens), whereas there was a slightly increased frequency of HLA-DR9 in all the DH patients examined for HLA. No patient had either HLA DQ2 or DQ8.

Antireticulin, antigliadin and antiendomysial antibodies were investigated in small number of Japanese DH cases, and none had these antibodies. IgA antitransglutaminase antibodies have been reported in only 2 Japanese DH patients. In both cases, antiepidermal transglutaminase (eTG) antibodies were detected, while antitissue transglutaminase (tTG) antibodies were not [84].

Dapsone was effective for most patients. Although most patients treated with dapsone required reduced dosage of dapsone for maintenance therapy, the lesions of 5 patients were completely cleared, and no therapy was required after several-month administration of dapsone without any other treatment [41, 44, 46, 64, 78]. The efficacy of GFD was difficult to evaluate, particularly, in patients without clinical symptoms of GSE because they had dapsone administration concurrently, and GFD was not strict at all [13, 19, 20]. In contrast, GFD seemed to relieve abdominal symptoms in the patients with GSE although GFD for one patient was not strict [24, 47, 59]. Topical steroid was sufficient to cure the lesions completely in some patients. In one case

Table 1: Clinical characteristics of 91 patients.

	N or age/*N* of data available	
Gender		
Male	61/91	
Female	30/91	
Age at the initial visit, mean ± SD (range), years	46.6 ± 19.9/91	(1–87)
Male	51.5 ± 20.5/61	(1–87)
Female	36.8 ± 14.1/30	(18–72)
Age at onset, mean ± SD (range), years	43.8 ± 18.6/75	(1–87)
Male	48.5 ± 19.6/48	(1–87)
Female	35.3 ± 13.0/27	(14–72)
Site of lesion		
Elbow	33/84	(39.3%)
Knee	29/84	(34.5%)
Buttock	30/84	(35.7%)
Elbow and/or knee and/or buttock	37/84	(44.0%)
Face	11/84	(13.1%)
Ear	9/84	(10.7%)
Neck	8/84	(9.5%)
Scalp	6/84	(7.1%)
Groin	4/84	(4.8%)
At least one predilection site	49/84	(58.3%)
Extremities*	41/84	(48.8%)
Trunk**	55/84	(65.5%)
Whole body***	6/84	(7.1%)
IgA deposition in the papillary dermis		
Granular	50/91	(54.9%)
Fibrillar	33/91	(36.3%)
Granular and fibrillar	7/91	(7.7%)
Cluster	1/91	(1.1%)
Other deposition in the papillary dermis		
C3	20/91	(22.0%)
IgG	9/91	(9.9%)
IgM	4/91	(4.4%)
Fibrinogen	2/91	(2.2%)
GSE	3/91	(3.3%)
Jejunum mucosa biopsy		
Villous atrophy****	3/6	(50.0%)
No change*****	3/6	(50.0%)
Associated diseases		
Diabetes mellitus	8/91	(8.8%)
Lymphoma	3/91	(3.3%)
Thyroid disease	1/91	(1.1%)
Sjögren syndrome	1/91	(1.1%)
HLA antigen§		
DR4	13/31	(41.9%)#
DR9	15/31	(48.4%)##

Table 1: Continued.

	N or age/N of data available	
Other antibodies		
Antireticulin antibodies	0/9	(0.0%)
Antigliadin antibodies	0/3	(0.0%)
Antiendomysial antibodies	0/3	(0.0%)
Anti-tTG IgA antibodies	0/2	(0.0%)
Anti-eTG IgA antibodies	2/2	(100.0%)
Therapy		
Dapsone	62/82	(75.6%)
Dapsone + gluten-free diet	7/82	(8.5%)
Gluten-free diet + topical steroid	1/82	(1.2%)
Topical steroid	9/82	(11.0%)
Others[†]	3/82	(3.7%)

*Not including cases limited only to elbow or knee; **not including cases limited only to buttock, neck, or groin; ***not including cases limited to combination of predilection sites; ****including 1 patient with GSE; *****no patients had GSE; GSE: gluten-sensitive enteropathy; tTG: tissue transglutaminase, eTG: epidermal transglutaminase; [†]including minocycline and topical steroid, salazosulfapyridine, and zinc oxide ointment; [§]frequency in HLA antigens of control was depicted from [90]. [#]$P = 0.9$, [##]$P = 0.007$, corrected $P = 0.07$.

the lesions disappeared 4 months after tonsillectomy [51]. Except for the 3 patients with GSE, no patients developed clinical symptoms of gluten sensitivity throughout the course although they were taking a normal diet.

3.2. Comparison of Granular and Fibrillar Groups (Table 2). The number of cases in the granular group was approximately 1.5 times higher than that in the fibrillar group. In both groups, the male patients were twice the number of the female patients. The mean age at onset of male patients in the granular group was almost 10 years older than that in the fibrillar group although no statistical significance was obtained. The mean ages at onset of female patients in both groups were relatively close. The mean ages at onset of the male and female patients were relatively close in the fibrillar group, while the mean age at onset of the male patients was 15 years older than that of the female patients in the granular group.

Patients in the granular group had lesions on the elbow, knee, buttock, face, ear, neck, scalp, and/or groin, which were common sites in the Caucasian DH patients, more frequently than those in the fibrillar group. Particularly, patients in the granular group had lesions on the elbow, knee, and/or buttock almost three times as frequently as those in the fibrillar group. C3 deposition was more frequently seen in the granular group than the fibrillar group. Comparison for small bowel disease and associated diseases was difficult because of a small number of cases involving these diseases in both groups. Although there were no statistical differences in the frequency of the HLA type between the granular and the fibrillar groups, a statistical difference in the frequency of HLA-DR9 between the granular group and the controls was found (corrected $P = 0.02$).

4. Discussion

The mean age of Japanese DH patients at the initial visit was 46.6, with a male predominance of 2 : 1. The age range and the male-to-female ratio in Japanese DH study are very similar to those in the Caucasian study [5, 91, 92]. Caucasian female patients with DH also tend to develop skin lesions at a younger age than male patients [5, 92]. Although a high incidence of familial DH has been reported in Caucasian patients [93, 94], no family history was found in Japanese patients. The clinical manifestation and distribution, as well as histopathological features, were also similar to those found in Caucasians [95, 96].

The distinct results of DIF in Japanese DH were noteworthy. More than one-third (36.3%) of Japanese DH patients showed fibrillar IgA deposition in the papillary dermis. In contrast to the result in a previous review of Japanese DH, which pointed out a higher frequency of fibrillar IgA deposition than that of granular IgA deposition [59], our study revealed that most common IgA deposition in Japanese DH was the granular pattern. However, the frequency of fibrillar IgA deposition is still high, when compared to that in Caucasian DH [97].

When compared between the granular and fibrillar groups, male patients in the granular group were older than those in fibrillar group although apparent statistical significance was not obtained. The lesions in the fibrillar group seemed to spare the predilection sites of DH, such as elbow, knee, and buttock, while the lesions in the granular group frequently involve these sites.

Recently cases with combined granular and fibrillar IgA deposition were reported although it is not clear whether this combined deposition is just extraordinary or incidental findings or not [17, 19, 41, 49, 71, 79, 81]. Only one case showed cluster IgA deposition although detailed data were not available [80]. The results of IIF studies showed no specific IgA antibodies. This was different from Caucasian results, which showed 63.5% positivity against the endomysium of smooth muscle [92].

In Caucasian patients, DH has a clear relationship to CD and is considered to be the cutaneous expression of

Table 2: Comparison of granular and fibrillar deposition groups.

	Granular ($N = 50$)		Fibrillar ($N = 33$)		t-test
	N or age/N of data available		N or age/N of data available		
Gender					
Male	33/50	(66.0%)	22/33	(66.7%)	
Female	17/50	(34.0%)	11/33	(33.3%)	
Age at the initial visit, mean ± SD (range), years	47.2 ± 20.1/50	(1–86)	43.8 ± 18.0/33	(16–78)	$P = 0.436$
Male	53.1 ± 19.5/33	(1–86)	45.9 ± 20.2/22	(16–78)	$P = 0.071$
Female	35.9 ± 15.9/17	(18–72)	39.6 ± 11.4/11	(22–68)	$P = 0.780$
Age at onset, mean ± SD (range), years	44.4 ± 18.2/42	(1–73)	39.7 ± 16.0/25	(12–74)	$P = 0.295$
Male	50.3 ± 17.0/26	(1–73)	40.9 ± 19.4/16	(12–74)	$P = 0.114$
Female	34.9 ± 15.9/16	(14–72)	37.7 ± 5.7/9	(29–50)	$P = 0.630$
Site of lesion					
Elbow	23/46	(50.0%)	5/30	(16.7%)	
Knee	20/46	(43.5%)	5/30	(16.7%)	
Buttock	25/46	(54.3%)	4/30	(13.3%)	
Elbow and/or knee and/or buttock	30/46	(65.2%)	7/30	(23.3%)	
Face	8/46	(17.4%)	3/30	(10.0%)	
Ear	7/46	(15.2%)	2/30	(6.7%)	
Neck	3/46	(6.5%)	5/30	(16.7%)	
Scalp	5/46	(10.9%)	1/30	(3.3%)	
Groin	4/46	(8.7%)	0/30	(0.0%)	
At least one predilection site	36/46	(78.3%)	12/30	(40.0%)	
Extremities*	20/46	(43.5%)	17/30	(56.7%)	
Trunk**	27/46	(58.7%)	22/30	(73.3%)	
Whole body***	3/46	(6.5%)	3/30	(10.0%)	
Other deposition in the papillary dermis					
C3	13/50	(26.0%)	4/33	(12.1%)	
IgG	5/50	(10.0%)	4/33	(12.1%)	
IgM	3/50	(6.0%)	1/33	(3.0%)	
Fibrinogen	2/50	(4.0%)	0/33	(0.0%)	
Small bowel disease	3/50	(6.0%)	1/33	(3.0%)	
Associated diseases					
Diabetes mellitus	5/50	(10.0%)	2/33	(6.1%)	
Lymphoma	3/50	(6.0%)	0/33	(0.0%)	
Thyroid disease	0/50	(0.0%)	1/33	(3.0%)	
Sjögren syndrome	1/50	(2.0%)	0/33	(0.0%)	
HLA antigen§					
DR4	4/14	(28.6%)#	8/13	(61.5%)##	
DR9	9/14	(64.3%)¶	3/13	(23.1%)¶¶	

*Not including cases limited only to elbow or knee; **not including cases limited only to buttock, neck, or groin; ***not including cases limited to combination of predilection sites; §frequency in HLA antigens of control was depicted from [90]. #$P = 0.3$ (versus controls), $P = 0.09$ (versus Fibrillar); ##$P = 0.2$ (versus controls), ¶$P = 0.002$ (versus controls, corrected $P = 0.02$), $P = 0.03$ (versus Fibrillar), ¶¶$P = 0.8$ (versus controls).

GSE [87, 89]. Although most of Caucasian DH patients have clinically no or mild gastrointestinal symptoms, they are treated with strict GFD [89]. The maintenance of GFD is important because gluten challenge leads to a flare of the cutaneous symptoms in Caucasian DH [88]. However, this is not the case in Japanese DH. Only 2 Japanese DH patients were treated with strict GFD [47, 59], while most patients continued to take a normal diet and were successfully controlled by dapsone or topical steroid. In addition, the lesions of some Japanese DH patients were completely cleared by short-term administration of dapsone or topical steroid while taking a normal diet. Moreover, except for the 3 patients with GSE, no patients developed clinical symptoms of gluten sensitivity throughout the course on a normal diet. Taken together, Japanese DH may not be closely associated with gluten sensitivity, in contrast to Caucasian DH.

The final diagnosis of CD is made by the results of jejunum biopsy, but not by clinical symptoms. In fact, the jejunum biopsy in 2 Japanese DH patients with no clinical symptoms of gluten sensitivity revealed villous atrophy [14, 39]. However, the fact that the jejunum biopsy of 3 patients with no clinical symptoms of gluten sensitivity revealed no pathological changes may raise the possibility that some Japanese DH patients did not have GSE. To confirm the exact association of GSE in Japanese DH, jejunum biopsies are necessary. However, most Japanese DH patients refused jejunum biopsy and GFD because of no clinical symptoms [84]. Accordingly, it may be difficult to clarify the exact association of GSE in Japanese DH based on the histopathological changes of the jejunum. Nevertheless, GSE in Japanese DH seems rare, considering the good response to the dapsone or topical steroid therapy during taking a normal diet. The rarity of GSE in Japanese DH patients is considered to be well correlated with the extreme rarity of CD in Japan [98].

Regarding genetic testing for Caucasian DH, the absence of HLA-DQ2 or DQ8 has a high negative predictive value because patients lacking these alleles are very unlikely to have DH [87, 99]. However, because the prevalence of these alleles among the Caucasian population is rather high, positive results in the HLA test are not sufficient to diagnose DH. In contrast, our study disclosed that Japanese DH patients never had HLA-DQ2 or -DQ8. Although no frequencies of HLA class I antigens in Japanese DH patients were increased in comparison with the controls among Japanese [90], there was a slightly increased frequency of HLA-DR9 in all the Japanese DH patients examined for HLA. Moreover, patients in the granular group showed a statistically significant frequency of HLA-DR9 when compared to Japanese normal controls. Since the number of data available was small, further analyses are needed to conclude whether Japanese DH is associated with specific HLA alleles.

Serologic tests of IgA antigliadin and antireticulin antibodies are no longer considered to be sensitive and specific markers of DH [87]. Instead, tests for IgA antibodies to eTG, tTG, and endomysium are considered to be useful diagnostic tools for Caucasian DH [87, 88]. Intestinal damage caused by exposure to gluten was suggested to produce IgA anti-tTG and anti-eTG antibodies [100]. Among them, eTG, rather than tTG is considered as the domain autoantigen in DH [101]. Recent studies reported a high sensitivity and specificity of eTG ELISA for DH [102, 103]. In a few Japanese DH patients who were tested for DH-related autoantibodies, no autoantibodies except for IgA anti-eTG antibodies were detected. A recent report suggested that the absence of GSE in Japanese DH may be due to an absence of anti-tTG antibodies, and that anti-eTG antibodies may be a diagnostic marker for Japanese DH [84]. These serologic tests, particularly for IgA anti-eTG antibodies should be performed in the future studies of Japanese DH.

Caucasian DH is known to be associated with a number of autoimmune conditions, including thyroid disease, type I DM, and autoimmune connective tissue diseases such as Sjögren syndrome, rheumatoid arthritis, and lupus erythematosus [89]. However, in Japanese DH, these diseases were relatively rare. Most Japanese DH patients with DM had type II DM. A higher risk of non-Hodgkin lymphoma was also reported in Caucasian DH [89], but this relation was not found in Japanese DH.

In summary, the absence of HLA-DQ2/DQ8, the inability to identify CD in most cases, the predominance of fibrillar IgA, and the unusual distribution of clinical lesions in Japanese patients suggest that Japanese DH may be a subset of DH patients and have a pathogenesis which is different from that currently proposed in Caucasian DH patients.

5. Conclusions

In conclusion, we reported the differences between Caucasian DH and Japanese DH. The characteristics of Japanese DH are (1) a high frequency of fibrillar IgA deposition in the papillary dermis, (2) a rare occurrence of GSE, (3) the absence of HLA-DQ2 or -DQ8, and (4) a rare association with autoimmune diseases or lymphomas. Although a previous Japanese DH review reported the prevalence of fibrillar IgA deposition, our study revealed that Japanese DH patients showed granular IgA deposition more frequently than fibrillar IgA deposition. In addition, we found that HLA-DR9 was frequently detected in Japanese DH, particularly in the granular group. These data suggest distinct characteristics of Japanese DH and raise the possibility that Japanese DH has a different pathogenesis from Caucasian DH. Serological tests for IgA anti-eTG antibodies and HLA genotyping should be performed in the future because Japanese DH may frequently have anti-eTG antibodies and HLA-DR9.

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Review Article

Dermatitis Herpetiformis: From the Genetics to the Development of Skin Lesions

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Dermatitis herpetiformis (DH) is a rare autoimmune disease linked to gluten sensitivity with a chronic-relapsing course. It is currently considered to be the specific cutaneous manifestation of celiac disease (CD). Both conditions are mediated by the IgA class of autoantibodies, and the diagnosis of DH is dependent on the detection of granular deposits of IgA in the skin. There is an underlying genetic predisposition to the development of DH, but environmental factors are also important. This paper describes these different factors and discusses the known mechanism that lead to the development of skin lesions.

1. Introduction

Dermatitis herpetiformis (DH) is an autoimmune disease linked to gluten sensitivity with a chronic-relapsing course, characterized by pruritic polymorphic lesions and typical histopathological, immunopathological, and serological findings. It is currently considered to be the specific cutaneous manifestation of celiac disease (CD) [1].

Patients with DH and CD share many common features such as gluten sensitivity, the same strong human leukocyte antigen (HLA) association, the presence of circulating IgA antitissue (tTG), and epidermal transglutaminase (eTG) antibodies [2]. Moreover, both DH and CD show the same typical histologic features of villous atrophy of the small bowel. In DH, the spectrum of enteropathy varies, and 20% of patients show apparently normal small-bowel mucosal architecture, but there are virtually always inflammatory changes consistent with latent CD [3, 4].

Both the rash and the enteropathy improve after a gluten-free diet (GFD) [5].

DH presents with diffuse, symmetrical, grouped polymorphic lesions consisting of erythema, urticarial plaques, papules, herpetiform vesiculae, and blisters followed by erosions, excoriations, and hyperpigmentation [6–9]. The most commonly involved sites are the elbows (90%), knees (30%), shoulders, buttocks, sacral region, and face. Itching of variable intensity, scratching, and burning sensation immediately preceding the development of lesions are common [6–9].

The presence of granular deposits of IgA at the tips of the papillary dermis is considered highly suggestive of the disease [10], even if DH may have a fibrillar rather than granular pattern of IgA deposition on direct immunofluorescence (DIF) microscopy, and patients with this pattern may lack circulating autoantibodies [11].

Although DH is a rare disease, it is more common in Caucasians, while it is rarer in Asian populations, including the Japanese. Several differences between Caucasian and Japanese DH are reported, such as a higher frequency of the fibrillar pattern, a rarer gluten-senstiive enteropathy (GSE), and different HLA haplotype in Japanese [12].

The pathophysiology of DH is complex and involves genetic factors, such as HLA predisposition, environment trigger (gluten), and disregulation of the immune system [13].

2. Genetic Factors

As in CD, virtually all patients with DH carry either HLA DQ2 or HLA DQ8 haplotypes [14]. This association has been demonstrated both in human and animals models.

In a study by Spurkland, comparing 50 patients with DH to 289 healthy controls, 86% of affected patients carried the HLA DQ2 allele and 12% carried the HLA DQ8 allele. The presence of either of both alleles provides a sensitivity of close to 100% for CD and DH. In individual lacking these alleles, CD and DH are virtually excluded [15].

NOD DQ8+ murine models reproduced by Marietta et al. have confirmed these associations. Fifteen NOD DQ8+ mice out of 90 that were sensitized to gluten developed blistering pathology similar to that seen in DH. Accordingly, neutrophil infiltration of the dermis, deposition of IgA at the dermal-epidermal junction (DEJ), and a complete reversal of the blistering phenomenon with the administration of a GFD with or without dapsone were observed [16]. Although it was a gliadin immunocomplex disease model rather than an experimental DH, such a model emphasized the role of HLA-DQ8 haplotype. In fact, according to the authors, the addition of DQ8 contributes sensitivity to gliadin, while the addition of the NOD background contributed to the autoimmune diathesis.

Previous genetic studies conducted in the 1970s and 1980s showed an increased expression of the HLA-A1 [17], HLA-B8 [18, 19], and HLA-DR3 [20] haplotypes in patients with DH and CD. For HLA-B8, the association with DH was 58–87% versus 20–30% for control patients [18, 19]. For HLA-DR3, the association with DH was 90–95% versus 23% for control patients [21]. However, these associations have not been subsequently confirmed by further studies, and they do not seem statistically significant in relation to the HLADQ2 and HLA DQ8 haplotypes.

Several studies showed differences in HLA haplotype between Caucasian and Asian patients. In particular in Japan, the HLA-B8/DR3/DQ2 frequency is very low in the general population (1% or less), and no HLA-B8/DR3/DQ2 haplotypes were found in DH patients [22].

Many studies emphasized that genetic factors, other than HLA, play an important role in the pathogenesis of DH [23–28]. A high concordance was demonstrated in monozygotic twins [23] (concordance ratio 0.91), and the incidence of both CD and DH is higher among first-degree relatives than that in general population [24].

Recently, a novel candidate gene, myosin IXB (*MYO9B*) on chromosome 19p13, was shown to be associated with CD in the Dutch and Spanish populations [25, 26]. Myosin IXB functions in cell signalling and regulation of actin cytoskeleton dynamics, thereby regulating cell integrity and permeability of the gut barrier. In patients with myosin IXB mutations, there could be an increased permeability of the intestine with more gluten penetration and a subsequent immunologic triggering results in clinically overt CD or DH [27].

Koskinen et al. [28] studied linkage and association of four *MYO9B* single-nucleotide polymorphisms (SNPs) on chromosome 19p13 with CD in a total of 1259 patients with CD; 161 (13%) of them suffered from DH.

The results showed significant linkage to 19p13 which supports the presence of a genuine risk factor for CD in this locus, while weak evidence of association with DH was found. In fact, when the family material of patients with the disease was divided into two groups according to the occurrence of DH, the *MYO9B* risk SNP alleles were found to be significantly overtransmitted to the offspring in only the families with DH [28].

3. Environmental Factors

Environmental trigger factors for DH are essentially represented by the ingestion of gluten (a glycosylated storage protein of cereals like wheat, rye, and barley), the same component whose addition or removal can turn the disease process on and off in CD [29, 30]. DH and CD are significant examples where an environmental factor plays a central role in the pathogenesis of the disease [31].

Gliadins are the alcohol soluble part of gluten with particularly high content of glutamine and proline [32]. Gliadins are only partially digested in the gut comprising peptides which are resistant to digestion [33]. Such digestion-resistant peptides can thus be modified by tTG in two alternative ways that include deamidation and transamidation [34, 35]. *In vitro* studies have demonstrated that transamidation is the major reaction thus increasing the antigenicity of gliadin peptides [36]. Neoantigens are created by these enzymatic modifications of dietary gluten. Cross-linking also outside the active site of tTG results in permanently and covalently linked deaminated gliadin/peptide/tTG complexes [37, 38] which are found in small intestine biopsies of patients with CD [39].

Gliadins are separated according to their electrophoretic mobility into four groups (α, β, γ, and δ), each one is further subdivided into other fractions [40]. It has been shown that the fraction most involved in bowel mucosa lesions is gliadin A, the main constituent of α-gliadins [41, 42]. The primary amino acid structure of this subfraction is known, and it is believed that its immunoreactive activity is related to the N-terminal region of the molecule [43].

The most convincing demonstration that gluten, as in CD, represents the etiological factor in DH is the finding that a strict GFD, even if after many months, can resolve cutaneous manifestations, in addition to the intestinal disorder [44, 45]. Several lines of evidences support the interpretation that the gastrointestinal alterations induced by α-gliadin are also able to trigger the mucosal immunoresponse, which is not limited to this antigen but is extended to tTG and moreover to eTG, with a title related to the entity of intestinal damage [46].

4. Antitransglutaminase IgA Antibodies

Until the 90s, circulating IgA EMAs were considered the most important serologic marker both in DH and in CD [47]. In 1997, Dieterich et al. identified tTG as the unknown endomysial autoantigen in CD [48]. tTG is a primarily

cytoplasmatic, calcium-dependent enzyme that catalyzed cross-linking between glutamine and lysine protein residues [49]. tTG is ubiquitously expressed in many tissues; in the skin, it is found in the basal keratinocytes and dermal capillaries [50].

The presence of circulating anti-tTG IgA is the most sensitive marker for CD, and it is commonly used as a screening tool [51]. Anti-tTG IgA antibodies are also diagnostic markers for enteropathy in DH patients [52]; their levels, in fact, correlate with the degree of intestinal damage and decrease under a GFD [53]. Therefore, levels of tTG-specific antibodies serve as a useful indicator of patient adherence to a GFD [54, 55].

In 2002, another autoantigen, namely eTG, was identified for DH [56]. eTG is homologous of tTG within enzymatically active domains [50, 57], and its main function in the epidermis involves cross-linking and the maintenance of cornified envelope integrity [57, 58]. eTG is not ubiquitary expressed, but it is primarily seen in the epidermis, small intestine, brain, and testis [58].

In 2002, Sardy et al. [56] demonstrated that the IgA deposits in the perilesional skin of DH patients colocalize with eTG deposits. Recently, Donaldson et al. [59] and Marietta et al. [60] independently confirmed these results in two different studies.

Patients with DH produce two IgA antibody populations against eTG. The first population binds exclusively eTG, whereas the second one cross-reacts with both eTG and tTG [53]. The cross-reactive eTG-specific antibodies are found in CD without DH yet, but they demonstrate a lower avidity for eTG than in patients with DH. In contrast, eTG-specific antibodies non-cross-reactive with tTG are found only in patients with DH [56]. Furthermore, eTG but not tTG colocalizes with granular IgA deposits in the skin of patients with DH [56, 59], and levels of antibodies against eTG correlate with the extent of enteropathy in DH but not in CD without DH [60]. Taken together, these data suggest that eTG rather than tTG seems to be the autoantigenic target in patients with DH, while tTG is the dominant antigen for CD. A study by Rose et al. [53] demonstrated that antibodies to eTG are the most sensitive serologic marker for the diagnosis of DH. In particular, a sensitivity of 95% was reported, confirming the study by Sardy et al. [56], in which the sensitivity was 92%, although Heil et al. [61] and Hull et al. [62] found anti-eTG antibodies in only 45% and 52% of patients with untreated DH, respectively.

Basing on these data, DH could be seen as a cutaneous IgA-eTG immunocomplex disease, developing only in a few patients with gluten-sensitive enteropathy. In agreement with this view, a histopathological pathogenetic model has been recently suggested by Zone and coworkers [63], trying to explain the onset of DH. They proposed that, during childhood, patients with CD initially have elevated levels of IgA anti-tTG antibodies but normal levels of IgA anti-eTG antibodies. As time goes on and patients with CD become adults, some of them, probably due to "intermoleculary epitope spreading," develop elevated levels of IgA anti-eTG antibodies compared with their childhood counterparts. It has been hypothesized that these patients who develop elevated level of IgA anti-eTG antibodies in adulthood are at high risk of developing DH.

However, though interesting, such a model should be confirmed by further studies. In fact, DH is not uncommon in children, but according to the theory by Zone, they would not have had time to undergo epitope spreading and develop anti-eTG antibodies [64].

Confirming the role of anti-eTG in the pathogenesis of DH, Zone et al. demonstrated that passive transfer of both goat IgG anti-eTG and human IgA anti eTG antibodies in SCID mice bearing human skin grafts induces granular IgA deposition in dermal papillae of human skin in a pattern similar to that of DH. However, mice did not develop inflammatory lesions with either IgG or IgA anti-eTG antibodies transfer, suggesting that additional proinflammatory events could be required for the eventual development of inflammatory skin lesions [65].

The exact mechanism of antibody production as well as the cascade by which gastrointestinal inflammation translates into cutaneous disease is not known. A recent study [66] revealed that the cutaneous IgA deposits present in DH skin were IgA1. Furthermore, whereas normal gut secretions contained more IgA2, gut secretions from patients with DH were predominantly IgA1. These studies suggested that IgA1 antibodies could be of gut origin, linking closely the IgA immune response in the gut to the IgA deposits in DH skin. Moreover, circulating autoantibodies against tTG and eTG appear both related to the degree of enteropathy, suggesting that the gut is the site where autoimmune response occurs.

Definitively, the mucosal immune response to gluten could lead to IgA antibodies of mucosal origin, which persist in circulation, and a specific group of these antibodies, namely IgA anti-eTG, are able to deposit into the skin. However, the mechanism of that binding remains unknown [66].

It has been hypothesized that eTG is released from keratinocytes and drops to basement membrane in response to trauma; another hypothesis is that preformed circulating complex of IgA and eTG deposit in the papillary dermis [67]. Evidence of the presence of these circulating complexes is shown by the precipitation of these complexes in vessel walls of some patients with DH; however, other studies failed to demonstrate an increase of circulating immunocomplexes in DH sera [68].

5. Immune Response

In the recent literature, many studies have attempted to clarify the exact mechanism through which gastrointestinal sensitivity results into the development of the specific lesions of DH, but such mechanism is not already completely understood [66].

The skin lesions of DH are characterized by the presence of an inflammatory infiltrate mainly composed by neutrophils, localized at the dermal papillary tips, the region where the cutaneous IgA deposits are found [69]. A recent histopathological study of patients with DH showed that in nearly 40% of the biopsies, only a lymphocytic infiltrate with fibrosis and ectatic capillaries were seen [70]. The initial inflammatory event is variable edema in the papillary dermis

with discrete subepidermal vacuolar alteration and neutrophils along the DEJ. As the lesion develops, neutrophils, to a lesser extent eosinophils, and fibrin accumulate within the dermal papillae and form microabscesses. These become confluent, resulting in a subepidermal blister. It has been demonstrated that split formation occurs within the lamina lucida of the basement membrane zone (BMZ) [71].

The predominant neutrophilic nature of the disease is confirmed by the improvement of the skin lesions after the somministration of dapsone, which inhibits neutrophil function. It has been demonstrated that neutrophils from DH patients with ongoing skin lesions showed increased expression of CD11b, a slight decreased expression of L-selectin, and increased function of the FcIgA receptor, all suggesting partial priming of the neutrophils [72]. IL-8 (CXCL8) is a potent chemoattractant and activator of neutrophils; it also causes changes in surface adhesion protein expression in neutrophils by inducing the shedding of L-selectin and upregulation of CD11b/CD18 binding activity [73]. It has previously demonstrated that patients with DH have increased levels of serum IL-8 [74], but the source of this increase is not known yet. Although elevated levels of serum IL-8 are seen in patients with active skin disease, IL-8 is also elevated in patients who are on gluten-containing diets but have no active skin lesions owing to therapy with dapsone. These observations suggest that the gastrointestinal mucosa, and not inflamed epidermis, may be the source of IL-8 [75].

However, small bowel biopsy from patients with isolated CD or in CD associated with DH shows that neutrophils are not the predominant cells; it is possible that neutrophils represent the earliest inflammatory cell, but the continued stimulation with gluten results in a transition to the more typical mononuclear cell infiltrate. Confirming this hypothesis, it has been demonstrated a pronounced neutrophilic activation in CD after rectal gluten challenge in the first 4–6 hours [76, 77].

Skin lesions are predominantly associated with characteristic areas (extensor surfaces, elbows, knee, and buttocks) that are the site of constant minor trauma.

Even if sun exposure can improve skin lesions in DH patients, it has been postulated that minor trauma and UVB irradiation to the skin may lead to the expression of critical adhesion molecules on epidermal endothelial cells (E-selectin) and proinflammatory cytokines such as IL-8, which would predispose these areas to the development of skin lesions [78, 79]. These events are required to lead the chemotaxis of the partially primed neutrophils (with an activated Fc IgA receptor to move into the skin) from the microvessels and their progressive accumulation at the top of the dermal papillae [80]. In microtraumatic areas, the neutrophils, through Fc fragment of IgA receptor, bind to this immunoglobulin and then can release lysosomial enzymes such as proteases and increase their phagocytic activity. Proteases, together with collagenases and stromelysin 1 released by keratinocytes, are essential to the development of the blister. Moreover, apoptosis, that has been shown to be increased in DH basal keratinocytes, could contribute to the development of DH skin lesions. Using TUNEL technique, we demonstrated an early activation of programmed cell death in perilesional DH skin with respect to healthy specimens, while Bax/Bcl-2 ratio was almost the same in the epidermis of perilesional/lesional DH and healthy skin specimens. In DH, both Bax and Bcl-2 proteins were increased in the dermal perivascular compartment. Fas showed a prevalently epidermal staining, while FasL was distributed in perivascular and subjunctional dermis; some FasL+ cells infiltrated the DEJ and the basal layer of epidermis [81].

Together with the neutrophils and, to a lesser extent, the eosinophils, other immune cell populations have been implicated in the skin damage. In particular, T cells are always detected both in perilesional and lesional skin of DH patients, suggesting their role in triggering the inflammatory response. Accordingly, T cells found in DH skin, that mainly belong to the Th2 pattern, are able to express IL-4 and IL-5, inflammatory cytokines that can activate mast cells and endothelial cells, and can enhance neutrophil and eosinophil recruitment, amplifying the skin inflammatory process [82]. We previously demonstrated a strong extracellular staining with anti-IL-4 monoclonal antibody in the upper dermis with a prevalent perivascular pattern in perilesional areas, whereas in the dermal-epidermal separation sites, there was an intense, scattered distribution. IL-5 was intensely expressed, mainly at the intracellular level, by eosinophils and lymphocytes, the staining intensity of this cytokine correlating with the number of infiltrating cells. Moreover, an intense expression of HLA-DR was detected not only on basal keratinocytes but also on dermal papillary and subpapillary infiltrate and endothelium.

To summarize, the development of skin lesions in DH could depend upon an ongoing mucosal immune response in the gut associated with elevated IL-8 levels and the production of a sufficient local concentration gradient of IL-8 and other chemokines (perhaps as a result of local trauma) that would attract "partially primed neutrophils" to the skin. The presence of IgA in the skin of patients with DH and the presence of IgA receptors on the surface of neutrophils suggest that IgA may function as an additional proinflammatory stimulus.

6. Conclusions

The pathogenic mechanism underlying DH is multifactorial, involving genetic, environmental, and autoimmune factors. A potential explanation is that in susceptible individuals (HLA association) the development of skin lesions is related to an active chronic gastrointestinal mucosal inflammation as a result of a persistent gluten challenge, with a local immune response and the production of mucosal IgA. A part of circulating IgA (anti-eTG) binds to the skin. Consequently, the gastrointestinal mucosal immune response results in increased levels of circulating cytokines which may partially prime neutrophils as well as active Th2 and endothelial cells. UVB and minor microtrauma to the skin increase local cytokines production, leading to the egress of neutrophils, deposition of IgA at the DEJ, and thus to the development of DH skin lesions.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Review Article

Newly Described Clinical and Immunopathological Feature of Dermatitis Herpetiformis

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Dermatitis herpetiformis (DH) is an inflammatory cutaneous disease with typical histopathological and immunopathological findings clinically characterized by intensely pruritic polymorphic lesions with a chronic-relapsing course. In addition to classic clinical manifestations of DH, atypical variants are more and more frequently reported and histological and immunological are added to them, whereas the impact on quality of life of patients with DH is increasingly important to a certain diagnosis. The aim of this paper is to describe all the possible clinical, histological, and immunological variants of DH in order to facilitate the diagnosis of a rare disease and, therefore, little known.

1. Introduction

Dermatitis herpetiformis (DH) is an inflammatory cutaneous disease with typical histopathological and immunopathological findings clinically characterized by intensely pruritic polymorphic lesions with a chronic-relapsing course, first described by Duhring in 1884 [1]. In 1966, Marks et al. [2]. reported small-bowel changes in patients with DH and later gastrointestinal abnormalities described in patients affected by DH were found to be the same as in those with celiac disease (CD) [3]. Currently, DH is considered as the cutaneous manifestation of gluten-dependent enteropathy, corresponding to CD.

DH is an autoimmune disease, a finding that is strongly supported by landmark studies revealing the granular deposition of immunoglobulin A (IgA) in the skin [4–6]. The same type of immunoglobulin was detected in the small intestinal mucosa of patient affected by CD, even before the development of the gluten-induced flat jejunal lesions. This observation on one hand emphasized the pivotal pathogenetic role of these immune deposits and from the other side represented a link between the two diseases [7, 8].

2. Clinical Features

The clinical morphology, in particular a polymorphous presentation and distribution of the lesions, are the hallmarks of the DH. Primary lesions of DH consist of grouped erythematous papules, urticarial plaques surmounted by vesicles or also blisters, which may be often replaced by erosions and excoriations, because of the intense itching characteristically associated with this condition. Chronic pruritus and excoriations might lead to lichenification, furthermore a transient postinflammatory hyperpigmentation may occur when the lesion resolve [9–13]. The symmetrical distribution of the herpetiform lesions on the extensor surfaces of the elbows (90%), knees (30%), shoulders, middle line of the back, buttocks, and sacral region is also a typical feature of the disease. In particular, Cottini [14]. In 1955 first described a clinical variant with exclusive localization of the lesions on the knees and elbows symmetrically. Anyway, scalp, nuchal area, face, and groin may be also involved. No clinical differences were described between darker- and white-skinned individuals, although DH remains primarily a prerogative of Caucasian population [15]. Most of the patients suffer

not only itching but also tickle or burning sensation even before the onset of the skin lesions.

An uncommon skin manifestation of DH is represented by purpuric lesions occasionally described on palmo-plantar surfaces of children, but rarely reported in adults. First descriptions of DH presenting as purpuric, erythematous, or hemorrhagic palmar or plantar lesions date from 1971 [16, 17]. Fraser et al. reported such lesions in four of 14 patients with DH [17]. In 1979, Katz and Marks noted that vesicles may be hemorrhagic, particularly if they are located on the hands [18]. Moulin et al. [19] eventually described reported four DH patients with palmar "pseudopurpuric lesions" which showed typical histologic changes of DH in three out of four cases. Pierce et al. [20] described a 27-year-old man with typical DH and additional purpuric lesions on the palms. In 1986, 47 pediatric series of 47 DH cases by Karpati et al. [21], 30 (64%) showed red-brown palmar purpuric lesions, which, however, were not biopsied. Sometimes, petechial lesions on the fingertips may be the only symptom of DH, as reported by Moulin et al. [19], Rutten and Goos [22], Hofmann et al. [23], and recently Flann et al. [24]. Finally, the last case was described in 2011 by Heinlin et al. [25]. In a 15-year-old female with a 6-month history of recurrent painful petechiae on the fingers and feet, that was diagnosed as DH after histopathology, direct- and indirect- immunofluorescence (DIF, IIF).

However, atypical clinical presentation of DH reported in the literature includes also palmoplantar keratosis, wheals of chronic urticaria and lesions mimicking prurigo pigmentosa [26–28]. In particular, Ohshima et al. [26] in 2003 described a 63-year-old Japanese man which presented palmoplantar keratosis, in addition to itchy areas of erythema on the buttocks and knees with small blisters on the border that were clinically, histologically, and immunologically compatible with DH. The histologic evaluation of palmoplantar keratotic lesions showed hyperkeratosis, acanthosis, and cellular infiltration, mainly of lymphocytes, in the dermal papillae, aspects that were more compatible with psoriasis, but DIF showed granular IgA deposits in the dermal papillae confirming the diagnosis of DH. An unusual clinical presentation of DH in children described instead by Powell et al. [27] in 2004 consisted of chronic urticaria-like skin lesions. Histologic evaluation showed neutrophilic microabscesses in the dermal papilla with subepidermal blister formation, suggestive of DH, that was confirmed by fibrillar IgA deposition along the basement membrane zone (BMZ) with papillary accentuation revealed by DIF. Finally, Saito et al. [28] in 2005 described another atypical clinical presentation of DH, that was also in a Japanese subject, with features of prurigo pigmentosa but characterized by both histological and immunological aspect of DH.

3. Histopathology

The classic histopathologic features of DH seen on light microscopy include a subepidermal cleft with neutrophils, that are considered the most likely responsible for the dermal-epidermal separation [29], and a few eosinophils at the tips of dermal papillae, that are often accompanied by a perivascular mixed inflammatory infiltrate [12, 26]. While these findings are characteristic, there are a number of patients who present with pruritic, excoriated skin lesions with clinical and immunological features of DH in whom the histologic findings are nonspecific and do not confirm the diagnosis as showed by Warren and Cockerell [30], which found that 37.5% of DH patients had hematoxylin and eosin findings of a lymphocytic infiltrate only with fibrosis in the dermal papillae and ectatic capillaries. The authors hypothesized that the nonspecific histologic findings could represent both a sampling error on the part of the clinician taking the biopsy, in particular, choosing excoriated lesions that correspond to a later stage of the disease, or the pathology laboratory in sampling the lesion for histology, considering appropriate a progressive cutting of the tissue block, or distinct subgroup of dermatitis herpetiformis, possibly with a separate antigenic target [30].

4. DIF

Actually DIF of uninvolved skin collected in the perilesional site is considered as the diagnostic gold standard for DH [12]. The choice of normal appearing perilesional skin as site of biopsy specimen for DIF is not random, because in this site DH patients showed greater IgA deposition than in nonlesional or lesional skin as demonstrated by Zone et al. [4].

Two different patterns are possible: (a) granular deposits in the dermal papillae and (b) granular deposits along the basement membrane. In both cases, deposits are thought to be polyclonal but are mainly composed of IgA1 [31]. The two patterns may also be present as a combination resulting in granular IgA deposition along the basement membrane with accentuation at the tips of the dermal papillae [9–11, 32]. A third different pattern, presents in 50% of Japanese populations, first described in 1993 by Kawana and Segawa [33] as "fibrillar pattern," was subsequently reconsidered by Ko et al. [34] in 2010. The fundamental difference between this last and previous is that the IgA deposition presents as linear streaks rather than fine granules in the papillary dermis. As suggested by Ko et al., the fibrillar pattern of IgA deposition may correlate with a clinical variant of DH or another as yet undefined disorder, and some case reports of atypical clinical presentations, that may be urticarial or psoriasiform, support this hypothesis [35, 36]. The correlation between the fibrillar DIF pattern and DH is, however, still debated. Although often the granular and the fibrillar patterns are associated in patients with DH, the last one alone more often correlates with atypical features, including atypical clinical presentations, absence of HLA-B8/DR3DQ2 haplotype, and lack of gluten-sensitive enteropathy or detectable circulating autoantibodies [37]. However, not all authors agree that, considering that the two different pattern may be the expression of a different method of sectioning [33].

5. Serologic Findings

Serologic testing is a useful adjunct to tissue-based studies. Contrary to the other bullous disorders, DH patients have no circulating autoantibodies binding to the cutaneous

basement membrane components or to other adherent structures of the skin, but they have gluten-induced IgA autoantibodies against transglutaminase (TG) 2 and TG3 also called tissue-TG (t-TG) and epidermal-TG (e-TG), respectively [13].

TG represents an evolutionary conserved family of Ca^{+2}-dependent enzymes that covalently cross-link or modify proteins by formation of an isopeptide bond between a peptide-bound glutamine residue and a primary amine, most commonly a lysine residue either within the same or a neighboring polypeptide chain [38]. Nine human types of TG were identified and some of them are expressed in the epidermis. TG2, among them, is the best characterized and also the most abundant and widely distributed [39]. Over time, different authors demonstrated that the enzymatic activity of TG2 is implicated in several diseases as Huntington disease, Alzheimer disease, and CD [40–42]. In particular, CD TG2 catalyzes highly specific deamidation of gluten peptides improving the binding of the peptides to the disease-associated HLA DQ2 and DQ8 molecules and becoming essential for the T-cell-mediated immune response against gluten. TG2 is also the primary autoantigen of CD recognized by autoantibodies of IgA1 class. These autoantibodies are considered the main serological marker of CD as disease-specific and more generally of gluten-sensitivity diseases and therefore of DH [12, 38, 43]. Levels of anti-TG2 correlate with bowel damage and gluten-free diet adherence in DH/CD patients and are measured using an enzyme-linked immunosorbent assay (ELISA) [44]. In DH, some authors have demonstrated an IgA anti-tTG specificity higher than 90%, and a sensitivity ranging from 47% to 95% [45–49]. However, as demonstrated by Sárdy et al. [50] the target autoantigen of DH is represented by TG3, that shares a 64% of homology with TG2 and overlapping sensitivity and specificity. As recently demonstrated by Stamnaes et al. [39] is also able to accommodate gluten peptides as substrates and form either thioester or isopeptide-linked complexes with these peptides stimulating the immune system's response, even if it is still unclear how it gets to the skin lesions. Although promising, the anti-eTG assay has not yet been approved in the United States for *in vitro* use to diagnose DH [51].

In addition to anti-TG2 antibodies, also those anti-EMA have become relatively sensitive and specific tools for initial detection of gluten-sensitive disease and, therefore, of DH. In particular, anti-EMA antibodies belong to the IgA1 subclass and are directed against primate smooth muscle reticular connective tissue. The detection of EMA is based on an indirect immunofluorescence assay on monkey oesophagus and it is more time-consuming and operator-dependent than the one of anti-TG2 ELISA testing [52], showing a specificity close to 100%, and a sensitivity ranging from 52% to 100% for the diagnosis of DH [44–47, 53].

Other autoantibodies are shared between DH and CD such as antigliadin antibodies and antireticulin antibodies, without, however, the same diagnostic value of anti-TG2 and anti-EMA.

In 2006, Sugai et al. first showed that the most reliable diagnostic test to identify gluten sensitivity in DH patients was the detection of antibodies against deamidated synthetic gliadin-derived peptides, both IgA and IgG isotypes [54]. Recently, a new CD serum marker based on TG2 covalently cross-linked to deamidated gliadin peptides, coined "neo-epitope," was carefully studied by Matthias et al. and data supporting the use of this new assay (AESKULISA CeliCheck New Generation) in CD diagnosis were obtained in a longitudinal study of 2684 eligible subjects demonstrating a sensitivity of 92,31% and a specificity of 82,89%, that were highest when compared to TG2 ELISA test or anti-EMA tests [55]. The diagnostic value of these antibodies was also confirmed by Jaskowski et al. [56], which demonstrated the superior sensitivity of anti-tTG/DGP EIA screen (IgA + IgG) compared to IgA anti-tTG both in pediatric CD (92,6% versus 90,7%) and adult DH (65% versus 48,8% and 62% versus 44% in retrospective and prospective sera, resp.). Furthermore, very recently, Kasperkiewicz et al. [57] showed the higher sensitivity of the anti-GAF3X ELISA, a novel CD serologic assay using deamidated gliadin-analogous fusion peptides, to detect CD-associated autoantibodies in patients with DH compared with tests using native gliadin, tTG or endomysium as substrates.

6. Conclusion

From the data reported above, it seems evident that the diagnosis of DH can be difficult and, therefore, requires a complex approach, that should be clinical, histological and immunological, having regards to the atypical variants more and more frequently described in the literature. This becomes crucial since, as it is known, patients with DH present a significant reduction in their quality of life, mainly due to the need of a lifelong gluten-free diet and, consequently, to a significant change in lifestyle and eating habits.

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Clinical Study

Chronic Gastritis in Dermatitis Herpetiformis: A Controlled Study

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Background and Objective. Previous small studies suggest that chronic atrophic gastritis is common in dermatitis herpetiformis (DH). We here examined the frequency and topography of chronic gastritis in 93 untreated DH subjects and in 186 controls with dyspepsia. *Methods*. Specimens were drawn from the gastric corpus and antrum and examined for atrophy, intestinal metaplasia, and *Helicobacter pylori*. Duodenal biopsies were taken. *Results*. Atrophic corpus gastritis was more frequent in DH than in controls (16.0% and 2.7%, resp., $P < 0.001$); atrophy in the antrum was rare in both groups (3.2% and 1.1%, $P = 0.34$). Intestinal metaplasia was present in 13 (14.0%) DH and 12 (6.5%) control patients ($P = 0.038$) and *H. pylori* in 17 (18.3%) and 17 (9.3%) ($P = 0.028$), respectively. Small-bowel villous atrophy was seen in 76% of the DH patients, equally in patients with and without chronic gastritis. One DH patient with atrophic gastritis developed gastric cancer. *Conclusion*. In DH, chronic atrophic gastritis was common in the corpus, but not in the antrum. *H. pylori* will partly explain this, but corpus atrophy is suggestive of an autoimmune etiology. Atrophic gastritis may increase the risk of gastric cancer. We advocate performing upper endoscopy with sufficient histologic samples in DH.

1. Introduction

The majority of patients with dermatitis herpetiformis (DH) evince small-bowel mucosal damage or inflammation similar to that in classic or early-stage celiac disease [1, 2]. Patients rarely suffer from abdominal symptoms, and irrespective of small-bowel mucosal morphology, the rash in DH responds to a gluten-free diet, the treatment of choice for the condition [3, 4]. Coeliac disease and DH share a similar genetic background and occur frequently in the same families; even identical twins may have different phenotypes [5, 6]. Tissue-type transglutaminase is the major autoantigen in coeliac disease, but an immune response to epidermal transglutaminase is probably essential for the development of DH, although this is not fully proven [7, 8]. Altogether, DH is indisputably an extraintestinal manifestation of coeliac disease.

Again similarly to coeliac disease, autoimmune conditions occur together with DH [9]. Earlier studies indicate that chronic atrophic gastritis (CAG) is common in DH and may be of autoimmune origin, but the data are based on a limited number of patients only [10–12]. *Helicobacter pylori* infection is the main agent causing chronic gastritis [13, 14], but autoimmune gastritis may also occur. *H. pylori* gastritis is often patchy and affects the antral mucosa, whereas autoimmune gastritis occurs typically in the corpus of the stomach.

The Sydney System is a systematic approach to determine the topography, morphology, etiology, and severity of gastritis [15]. It has not previously been applied in DH. Small-intestinal biopsy helps to estimate the severity of villous atrophy but is not necessary for the ultimate diagnosis of DH. Provided that CAG is common in patients with DH, this

Table 1: Gastric findings in the 93 patients with dermatitis herpetiformis (female 40, median age 48 years; range 7–76) and 186 control patients with dyspepsia (female 80, median age 56 years; range 18–86).

	Dermatitis herpetiformis $n = 93$	Control patients $n = 186$	Odds ratio	P-value
Corpus atrophy	15 (16.0%)	5 (2.7%)	6.96 (CI 2.29–25.16)	<0.001
Antrum atrophy	3 (3.2%)	2 (1.1%)	3.07 (CI 0.34–37.16)	0.34
Intestinal metaplasia[1]	13 (14.0%)[2]	12 (6.5%)[3]	2.36 (CI 1.05–5.30)	0.038
Helicobacter pylori[1]	17 (18.3%)	17 (9.1%)	2.22 (CI 1.09–4.54)	0.028

[1]in corpus or antrum.
[2]antrum 8, corpus 8.
[3]antrum 8, corpus 5.

would constitute a further indication for endoscopy. In the present study we examined the occurrence of CAG and *H. pylori*, as classified by the Sydney System, in a large series of DH patients sampled over the past 20 years. The histologic data were compared to those from patients of similar sex and age who were suffering from dyspepsia.

2. Material and Methods

The study was carried out over the period 1990–2009 at the Department of Dermatology, Tampere University Hospital. The cohort comprised 93 patients with DH, from whom biopsy samples had been taken from duodenum and from stomach for the classification of gastritis according to the Sydney System. The diagnosis of DH was based on the typical clinical picture and direct immunofluorescence showing granular IgA deposits in the papillary dermis in the uninvolved skin [16]. Patients' medical records were examined. Duodenal biopsy specimens were graded as subtotal villous atrophy, partial villous atrophy, and normal mucosa. Gastric mucosal atrophy was graded from 0 to 3, grade 0 indicating normal morphology and 3 the most severe involvement, in line with the Sydney System [15]. *H. pylori* was not graded, since a positive finding anywhere in the stomach was considered diagnostic for the infection. The patients with DH were regularly followed up in the special outpatient clinic for 1-2 years [17]. A questionnaire was sent to all DH patients who were alive in 2011, and it included questions on adherence to the gluten-free diet, the use of dapsone, and the occurrence of associated diseases and malignancies.

The control group comprised patients suffering from dyspepsia and undergoing upper gastrointestinal endoscopy at the Regional Hospital of our catchment area in 2009–2011. Two control patients of similar sex and age (±5 years) and no small-bowel mucosal villous atrophy were chosen for each DH case, the final series thus consisting of 186 control subjects.

The statistical differences between DH and control patients and DH patients with and without CAG were calculated by chi-square test or Fisher's exact test when appropriate. Odds ratios were given with 95% confidence intervals.

The study was based on the case records, and permission to read these was obtained. A statement of the Ethical Committee was not considered obligatory.

3. Results

Atrophy of the corpus and intestinal metaplasia were significantly more common in DH than in the control subjects (Table 1). By contrast, there was no significant difference between the groups in the occurrence of antral atrophy, which was altogether a relatively uncommon finding. The mean score for atrophy in the corpus was 1.6 in DH patients and 2.3 in control subjects.

Seven (44%) DH patients with CAG had associated intestinal metaplasia in the body of the stomach and additional two patients in the antrum (Table 2). *H. pylori* infection was significantly more frequent in DH than in controls (18% and 9%, resp., Table 1). One patient (no. 3, Table 2) with pangastritis and intestinal metaplasia in the initial biopsy developed gastric cancer one year later. Forty-four percent of DH patients with CAG showed *H. pylori* in the gastric mucosa, compared to 14% without CAG (Table 3).

Table 3 shows the 16 DH patients with CAG to be older (mean 63 years) than the 78 without (mean 44 years). Small-intestinal villous atrophy was found in 76.6% of patients with DH and was equally common in patients with and without CAG. Thirty percent of patients with DH reported abdominal complaints; again, there was no significant difference between patients with or without CAG (Table 3).

All 16 DH patients with CAG started a gluten-free diet after the diagnosis of DH, nine in addition using daily 25 mg to 50 mg of dapsone to control the rash. All maintained a strict diet and no longer needed dapsone at the end of the followup.

Associated autoimmune diseases were found in three DH patients with CAG; one had hypothyroidism, one pernicious anaemia and Graves' disease, and one vitiligo (Table 2). One DH patient with CAG developed prostate cancer, and two patients had had breast cancer before the diagnosis of DH.

4. Discussion

The frequency of CAG in the corpus was significantly more common in the DH patients than in the control subjects suffering from dyspepsia. No such a difference was seen in the antrum of the stomach. Previously, Primignani et al. [12] conducted a study in 57 Italian patients with DH and found a prevalence of CAG of 30%, compared to 15% in non-DH

Table 2: Gastric and duodenal findings, dapsone, and gluten-free diet (GFD) treatment, and associated diseases and malignancies in 16 dermatitis herpetiformis (DH) patients with chronic atrophic gastritis.

Patient no.	Sex/age (years)	Year of DH diagnosis	Gastric findings			Duodenal histology at diagnosis/on GFD	Associated autoimmune diseases and malignancies
			Corpus atrophy/metaplasia[1]	Antrum atrophy/metaplasia[1]	*Helicobacter pylori*		
1	F/53	1996	1/1	0/0	−	PVA	Breast cancer 1992
2	F/69	1999	1/0	0/0	−	PVA	—
3	M/68	2000	1/2	2/2	−	PVA/N	Gastric cancer 2001
4	M/64	2001	3/2	0/0	−	PVA/N	Hypothyreosis >10 yrs before DH diagnosis Prostate cancer 2010
5	M/61	2001	1/0	0/1	−	N/N	—
6	F/58	2001	1/0	0/0	+	PVA/N	—
7	F/62	2001	2/0	0/0	−	PVA	Breast cancer 1992
8	M/57	2001	1/0	0/0	+	PVA	—
9	M/48	2002	1/0	0/0	+	N	—
10	M/71	2003	2/1	0/0	−	N	Vitiligo 2003
11	F/56	2003	3/1	0/0	−	PVA/N	Pernicious anemia 2004 Graves' disease 2005
12	M/71	2004	2/1	0/2	+	N	—
13	M/76	2006	3/2	0/1	−	N	—
14	F/74	2007	1/0	1/0	+	PVA	—
15	F/63	2007	1/0	0/0	+	SVA	—
16	M/69	2008	0/0	2/2	+	SVA	—

SVA: subtotal villous atrophy, PVA: partial villous atrophy, N: normal mucosa at diagnosis and on a gluten-free diet (GFD).
[1]score 0–3 according to the Sydney System.

Table 3: Data on 94 patients with dermatitis herpetiformis. Comparison between cases with and without chronic atrophic gastritis (CAG).

	DH patients with CAG $n = 16$	DH patients without CAG $n = 78$	P-value
Mean age at diagnosis years (range)	63.0 (47–76)	43.9 (7–76)	
Men	9 (56.3%)	45 (57.7%)	
Duodenal histology			
(i) partial or subtotal villous atrophy	11 (68.8%)	61 (78.2%)	0.52
(ii) normal mucosa	5 (31.2%)[1]	17 (21.8%)	
Helicobacter pylori	7 (44.0%)	11 (14.1%)	0.012
Abdominal complaints	5 (31.2%)	23 (40.4%)[1]	0.36

DH: dermatitis herpetiformis.
[1]Data available on 57 patients.

control subjects with dyspepsia ($P < 0.05$). Patients with DH do not usually suffer from dyspepsia, and therefore the control group was not analogous to the study group. Storskrubb et al. [18] carried out esophago-gastroduodenoscopy at random for 1000 Swedish adults. The overall frequency of corpus atrophy was 5% and antrum atrophy 2%. Our data thus indicate that atrophic corpus gastritis is more common in patients with DH than in the population in general.

H. pylori infection is common in CAG [13, 14, 19]. In line with this, the present DH patients with CAG had *H. pylori* significantly more often than those without CAG. This may be partly explained by the age difference; *H. pylori* is more common in older people, and our patients with GAG were older that those without (Table 3). However, the presence of *H. pylori* in all DH patients (18.3%) was significantly higher than among dyspeptic control subjects with a similar age distribution (9.1%, Table 1). By comparison, Crabtree et al. [20] examined 58 DH patients in Britain and by serological methods found *H. pylori* IgG antibodies in 63% of patients, this frequency being however only slightly higher than in other dermatological patients.

There are some limitations to the present study. It was based on the case records, and it was not possible to re-read the biopsy samples. Nevertheless, we considered that the activity of gastritis, as defined by the Sydney System, [15] would have been unreliable to analyze here. Circulating parietal cell and intrinsic factor antibodies could not be determined. Our DH patients were recruited during the years 1990–2009, whereas the controls were enrolled later, in 2009–2011. This may have affected the results in that during the last decades, the prevalence of *H. pylori* has decreased in Finland and elsewhere [21]. However, all but two DH patients with CAG and also patients with *H. pylori* were diagnosed in 2000–2009.

Previous studies have shown that patients with DH similar to those with celiac disease frequently have associated autoimmune conditions such as thyroid diseases and insulin-dependent diabetes mellitus [9, 22, 23]. In the present study two DH patients with CAG had thyroid disease, one of them also pernicious anemia and one patient vitiligo. Due to the limitations of the study, we cannot be sure whether the CAG in the present DH patients was of autoimmune origin. However, this is quite possible judging from the topography of CAG, that is antrum-sparing gastritis [15], and the overall autoimmune nature of DH [23].

CAG is known to be associated with an increased risk of gastric cancers, which seems to decrease after eradication of *H. pylori* [24, 25]. One of our DH patients with CAG developed gastric cancer one year after the diagnosis of DH. Prior to this, he had shown pangastric atrophy and moderate intestinal metaplasia without *H. pylori* infection. The patient had adhered strictly to a gluten-free diet since the diagnosis; the small-bowel mucosa showed no atrophy, and the rash was controlled without dapsone. Similarly, the small-bowel mucosa and the rash in the other DH patients with CAG responded well to GFD treatment. In contrast, CAG persisted in all 4 patients subjected to control biopsies, indicating that CAG in DH does not respond to gluten withdrawal, as also previously documented [26, 27]. Patients with DH run an increased risk of lymphoma [28, 29], but previous large DH studies have not shown any increased risk of gastric or other cancers [28, 30]. Whether persisting CAG in DH involves a risk of gastric cancer is a possibility which should be examined in further studies.

5. Conclusion

The present controlled study showed that patients with DH have at the time of the diagnosis a significantly increased frequency of CAG in the corpus but not in the antrum. In addition to *H. pylori* infection, autoimmune mechanisms may be implicated in the development of gastritis. The DH patients here did not present with any specific gastrointestinal symptoms. One DH patient with CAG developed gastric cancer. In untreated DH we recommend upper gastrointestinal endoscopy, upon which biopsy specimens should be taken not only from the duodenum but also from the gastric corpus and antrum.

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