Dermatitis Herpetiformis

Subjects: Dermatology

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Dermatitis herpetiformis (DH) is a blistering dermatosis, which shares common immunologic features with celiac disease (CD).

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1. Introduction

Dermatitis herpetiformis (DH), also known as Duhring-Brocq disease, is a rare subepidermal blistering dermatosis, currently regarded as the specific extraintestinal manifestation of celiac disease (CD) [1][2]. It most commonly affects the skin, while associated gluten sensitive enteropathy (GSE) can be clinically variable to absent. Histologically, DH is characterized by subepidermal blisters with predominant neutrophilic infiltration in the papillary dermis. A pathognomonic finding in DH, detected by direct immunofluorescence (DIF) microscopy on perilesional uninvolved skin, is the presence of granular deposits of immunoglobulin A (IgA) along the dermo-epidermal junction (DEJ) and at the tips of the dermal papillae. Recently, it has been documented that the autoantigen for deposited cutaneous IgA is epidermal transglutaminase (eTG, TG3)—an enzyme closely related, but not identical to the tissue transglutaminase (tTG, TG2) autoantigen-specific for CD [3]. IgA deposits in skin represent antibodies against gut tTG that cross-react with the highly homologous eTG by forming insoluble aggregates in the papillary dermis [4].

The pathophysiology of DH is closely related to that of CD and involves a complex interplay among genetic, environmental, and immune factors. Both diseases occur in gluten-sensitive individuals, heal with a gluten-free diet (GFD), and relapse on gluten challenge [5]. DH and CD share the same genetic background with a high frequency of human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 haplotypes [6][7]. The majority of patients with DH exhibit morphologic small-bowel changes characteristics of CD, ranging from slight villous atrophy to increased density of intraepithelial lymphocytes [8]. However, overt enteropathy is reported in less than 10% of patients, and the gastrointestinal symptoms are usually absent or so mild that the DH patients are unaware of them [9]. Last but not least, patients with DH and CD often have the same associated autoimmune diseases, such as juvenile diabetes, hypothyroidism, pernicious anemia, and connective tissue disorders [10].

A hallmark of CD is the loss of tolerance to wheat gluten with enhanced production of various gluten-dependent autoantibodies, as a result from the gluten-induced small-bowel mucosal T-cell activation, which is the cornerstone in the pathogenesis of the celiac pathology [10]. These circulating CD-specific antibodies are widely used to diagnose GSE serologically before proceeding to small-bowel mucosal biopsies. Historically, among the first serum-based antibody tests introduced in CD diagnostics are the antigliadin antibody (AGA) [11][12], the gluten-dependent IgA-class R1-type reticulin (ARA) [13], and endomysial autoantibody (EMA) assays [14]. In 1997, Dieterich and co-workers identified TG2 as the autoantigen of CD [15]. As various TG2-based enzyme-linked immunosorbent assays (ELISA) became available, a new era in celiac disease case finding by serology began [16]. Later research has shown that TG2 was also the specific protein antigen in the ARA and EMA tests [17]. As a result of the constant development of serologic tests for CD, a new generation of assays detecting the presence of antibodies against deamidated gliadin peptides (DGPs) as antigens appeared [18][19]. The accurate diagnosis of DH is essential, similar to CD, as the disease requires a lifelong commitment to a GFD. It relies on few but essential specific criteria, including clinical, histologic, immunopathologic, and serologic celiac-related markers, the latter being detected in DH patients as well [2][20]. Perilesional biopsy with a specific DIF microscopy finding has remained the gold standard along with the presence of suggestive clinical picture and supportive serological results [21].

Furthermore, the predictive accuracy of serological tests depends on the disease prevalence in the population [22]. In this regard, it is of interest to analyze the performance of celiac-related tests in patients from different countries and origin. In a previous report of a series of 78 DH patients from Bulgaria, the prevalence of DH among other autoimmune blistering diseases was 7.45% with a minimum estimated incidence of 0.88 cases per million annually [23].

An early event in blister formation in DH is the accumulation of neutrophils in the papillary dermis, the upregulation of the adhesion molecules, and release of enzymes and inflammatory mediators causing basement membrane damage and subsequent clefting, which could also explain the typical distribution of skin lesions at sites of trauma [24]. Interleukin (IL)-17A is involved in the production of other pro-inflammatory cytokines and matrix metalloproteinases, as well as in the attraction of neutrophils implicated in the pathogenesis of DH [25]. However, the suggested hypothesis for the role of IL-17A in DH pathogenesis needs further investigation.

2. Celiac-Related Autoantibodies and IL-17A in Bulgarian Patients with Dermatitis Herpetiformis

Growing evidence shows that patients with DH may possess most of the specific autoantibodies that can be found in patients with CD, including circulating autoantibodies against gliadin, tTG, and DGP [1]. On the other hand, conflicting results were obtained by the use of the anti-DGP ELISA for detecting gluten enteropathy in DH patients. Previously reported sensitivities for IgA anti-DGP antibodies vary from 46% to 78% [20][26]. In this study, the relative sensitivities and specificities of a panel of CD-related autoantibodies in Bulgarian patients with DH were compared with the reactivities of control healthy subjects. We included conventional celiac-related antibodies—anti-tTG, anti-DGP, and AGA, as well as AAA, the latter being used for non-invasive evaluation of villous atrophy. ASCA were tested along with other antibodies due to the presence of coated Mannan on the Line blot. Moreover, we were interested in assessing the serum levels of IL-17A in DH patients. We chose not to compare EMA with the other autoantibodies in our celiac-related panel due to the subjective semiquantitative nature of EMA testing that is not easy to standardize.

All investigated celiac-related antibodies—anti-tTG, anti-DGP, and AGA, independent of the used method (ELISA or Line blot), were significantly higher in the DH group compared to the healthy controls. Nevertheless, the sensitivity and specificity of the applied tests were acceptable. We found that 42.3% of our DH patients were positive for anti-tTG (IgA + IgG) assessed by ELISA. When we tested the serum samples for IgG anti-tTG by line blot, we found a higher sensitivity of 46%. Half of the DH patients had IgG AGA (Line blot) in their serum samples, and 46.4% had anti-DGP (ELISA) antibodies. We also defined the specificity of 100% for anti-tTG (ELISA and line blot), AAA, and AGA in discriminating DH from healthy persons, as well as a specificity of 95% for anti-DGP antibodies. These results are in accordance with other studies, demonstrating sensitivity ranges between 47% and 100% and specificity ranging 90% to 100% for celiac-related antibodies in patients with DH [9,27,28,29,30,31,32]. PPVs for all tests were 100%, except for anti-DGP, which was 90.9% due to one positive healthy individual. Unfortunately, the NPVs of the tests remained slightly above 50%, and the highest NPV was observed for AGA (60%) and anti-tTG (59%) assessed by line blot. However, during the last decade, only a few studies updated this information. Thus, our results contribute to previously published literature data.

Comparing tests by the ROC curve analyses, the best performance was revealed for anti-DGP antibodies, followed by anti-tTG (ELISA) testing and anti-tTG (Line blot) antibodies. Although the specificity of AGA was 50%, the AUC of 0.600 was non-significant and therefore, unreliable.

Among all celiac-related serological tests, IgA anti-tTG antibodies have been considered the most sensitive and specific ones that should be tested in patients with DH symptoms [1]. Since some patients with DH or CD may have selective IgA deficiency, we chose the dual IgG/IgA test system to exclude false-negative results. [27][28]. In our study, the performance of anti-DGP in diagnosing DH was shown to be superior to the anti-tTG antibodies. In previous comparative studies among DH patients, the sensitivity and specificity of anti-DGP were either lower than those of anti-tTG and EMA, similar, or superior to them [29], as it is in the present study. The possible explanations for such discrepancies lie in the fact that anti-DGP and AGA, which are directed against deamidated gliadin peptides and whole gliadin peptide, respectively, are related to the presence of intestinal damage, whereas antibodies against the converting enzyme tTG are linked not only to mucosal but also to skin lesions as well [29]. However, current knowledge has shown that the available serologic armamentarium lacks sensitivity when used in patients with mild or minor enteropathy [30][31]. The similarity of DH and CD related to the enteropathy makes DH a fascinating model of skin CD, where papulovesicular and pruritic rash can be concomitant with a broad spectrum of intestinal damage varying from normal structure to villous atrophy [32]. However, DH is the second gluten-sensitive disorder exhibiting varied histological damage where one can assess the performance of the celiac serology [29]. In the present study, we chose to assess by ELISA anti-tTG and anti-DGP antibodies of both IgA and IgG subclasses. The results obtained allowed us to conclude that the combination of both isotypes of anti-DGP assays has higher specificity than IgA anti-tTG.

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