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BRIEF REPORT

Evaluation of serum cytokine and chemokine levels in dermatitis herpetiformis: a systematic review and meta-analysis

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Introduction

Characterized as an autoimmune bullous skin disease, dermatitis herpetiformis (DH) is preceded by burning pruritus and subsequent papulovesicular eruptions over the extensor surfaces of the knees, elbows, and buttocks. It is the most common extraintestinal manifestation of celiac disease and exhibits a therapeutic response to a gluten-free diet. While not all patients exhibit gastrointestinal symptom characteristic of celiac, all exhibit a celiac-type enteropathy in the small bowel (SB) mucosa. DH is thought to occur due to an immune response to transglutaminase (TG) 2 in the SB with cross reactivity and deposition of IgA-TG3 complexes in the papillary dermis [1]. How the immune complex deposition induces a cascade of proinflammatory cytokines and granulocytic infiltration resulting in subepidermal blistering remains unclear. To better understand and summarize the immune cascade, we performed a systematic review and meta-analysis of cytokine and chemokine changes involved in DH.

Methods

In September 2018, we queried the PubMed/Medline database for DH and an exhaustive list of chemokines and cytokines. Only studies of humans reporting quantitative measures (ELISA, qPCR, and densitometry) with mean values with standard deviation or standard error were included for analysis. The expected outcome from each study was the difference in mean levels of serum marker between DH patients and control subjects. Given differences in the measurement methods and units, standardized mean difference (SMD) with 95% confidence intervals (CI) was calculated using Cohen's *d* in random-effects or fixed-effects models as appropriate depending on a test for heterogeneity. Significant heterogeneity of results was detected across studies as judged by a Cochrane Q statistic *P* value less than 0.05, I^2 statistic greater than 50%, or both. A 2-sided *P* value of 0.05 was taken as significant. For the calculation of SMD, cytokine levels were considered as zero when their concentration was reported to be under the detection threshold.

Due to dearth of eligible studies, subgroup analyses and meta-regression aiming to explore potential sources of heterogeneity were not performed. Statistical analyses were conducted by using Comprehensive Meta-Analysis software (version 3.3, 2014), Englewood, NJ, USA.

Results

Out of 56 pertinent articles, 9 met inclusion criteria. Serum levels of five cytokines (interleukin (IL)-4, IL-5, IL-17, IL-31, and eotaxin) were evaluated in the meta-analysis. Mean serum levels of IL-17 were significantly higher in DH patients than in matched controls (SMD = 5.240, 95% CI 0.932 to 9.548, $I^2 = 94.07$, $P < 0.001$), but comparable with bullous pemphigoid (BP) patients (SMD = 0.842, 95% CI − 1.396 to 3.081, $I^2 = 92.46$, $P < 0.001$).

IL-4 levels were greater in the sera of DH patients relative to control participants, albeit with marginal statistical significance (SMD = 1.132, 95% CI − 0.01 to 2.27, $I^2 = 80.24$, $P = 0.006$). Serum levels of IL-5, IL-31, and eotaxin did not show a significant difference between DH patients and control subjects (IL-5: SMD = 4.372, 95% CI − 1.879 to 10.623, $I^2 = 91.31$, $P = 0.001$; IL-31: SMD = − 0.121, 95% CI − 10.353 to 10.111, $I^2 = 99.21$, $P < 0.001$; eotaxin: SMD = 1.126, 95% CI − 1.29 to 3.54, $I^2 = 87.23$, $P = 0.005$). Additionally, levels

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of IL-31 among DH patients were not elevated when compared with BP patients (SMD = − 0.318, 95% CI − 3.547 to 2.911, $I^2 = 97.52$, $P < 0.001$).

Discussion

Our systematic review and meta-analysis found IL-17 levels in DH to be significantly increased in comparison with healthy controls. IL-17 is involved in acute and chronic inflammation and is overproduced in several autoimmune diseases [2]. Release of IL-1β from keratinocytes is known to stimulate production of IL-17 from Th17 cells [2, 3]. Elevated systemic levels of IL-17 in DH patients may reflect its direct role in the production of neutrophil-specific chemokines, metalloproteinases, and its synergistic effect with TNF-α in inducing gene expression of proinflammatory mediators and tissue degradation [2–4].

The dermal and perivascular infiltrates in DH are activated through a Th2 cytokine profile, including IL-4 and IL-5. IL-4 and IL-5 localize to a perivascular pattern in the upper dermis of DH lesions [5]. However, we found serum IL-4 levels in DH patients only marginally higher than in controls. This may be due to differences between the local immune response and serum levels which are seen in other autoimmune blistering diseases [6].

Although staining for IL-5 has been shown in the dermis of DH lesions, no significant elevations of IL-5 or eotaxin were found in DH patients [5]. IL-5 functions in the activation and degranulation of eosinophils while eotaxin is a potent eosinophilic chemokine [5, 7]. Although it has been shown that eosinophils contribute to blister formation in DH, the cytokines involved in their infiltration and activation (IL-4, IL-5, and eotaxin) are not adequate systemic markers of their activity in autoimmune bullous skin diseases [5]. It is plausible that these cytokines exert a predominantly local effect on eosinophilic infiltration and are thus not representative of disease activity when measured in serum [5]. One study found significant elevations of serum eosinophilic cationic protein and myeloperoxidase as systemic markers for activated granulocytes to support the theory of a locally acting Th2 cytokine profile in DH lesion development [5].

While previous studies on BP have noted IL-31 to be primarily locally produced by eosinophils, with minimally elevated serum levels, our analysis failed to identify an increase in this pruritogenic cytokine in DH [8].

This review was limited by a lack of eligible studies. Additionally, because several cytokines are hypothesized to act locally and were not found to be elevated in the serum, studies including quantifiable vesicular levels of these cytokines would prove useful in a meta-analysis to establish a potential lesional serum gradient. Still, the significant elevation of IL-17 in DH raises several questions about a putative role in the pathogenesis of the disease and may offer a promising therapeutic target in the future. Further experimental studies are highly required to substantiate these results and to elucidate the role of IL-17 in DH.

Learning points

A significant association between DH and IL-17 was found which may point to future areas of immunotherapeutic intervention through targeting of Th17 cell differentiation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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