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Review

Autoimmune comorbidity in chronic spontaneous urticaria: A systematic review

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ABSTRACT

Background and objective: Numerous autoimmune diseases (AIDs) have been linked to chronic spontaneous urticaria (CSU). Here, we provide the first extensive and comprehensive evaluation of the prevalence of AIDs in patients with CSU and *vice versa*.
Methods: A Pubmed and Google Scholar search was performed to identify studies reporting the prevalence of various AIDs in CSU and *vice versa* published before April 2017.
Results: The prevalence of individual AIDs in CSU is increased (≥1% in most studies vs ≤1% in the general population). AIDs with relatively high prevalence in the general population are also quite common in CSU patients, whereas those with low prevalence remain a rare finding in CSU. The rates of comorbidity in most studies were ≥1% for insulin-dependent diabetes mellitus, rheumatoid arthritis (RA), psoriasis and celiac disease (CD), ≥2% for Graves' disease, ≥3% for vitiligo, and ≥5% for pernicious anemia and Hashimoto's thyroiditis. Organ-specific AIDs are more prevalent in CSU than systemic (multiorgan or non organ-specific) AIDs. >2% of CSU patients have autoimmune polyglandular syndromes encompassing autoimmune thyroid disease (ATD) and vitiligo or pernicious anemia. Antithyroid and antinuclear antibodies are the most prevalent AID-associated autoantibodies in CSU. >15% of CSU patients have a positive family history for AIDs. The prevalence of urticarial rash in AID patients is >1% in most studies. This rash is more prevalent in eosinophilic granulomatosis with polyangiitis, ATD, systemic lupus erythematosus, RA and CD.
Conclusions: CSU patients have an increased risk of AIDs, especially adult female patients and those with a positive family history and a genetic predisposition for AIDs, who should be screened for signs and symptoms of AIDs.

Contents

Abbreviations: AID, autoimmune disease; ATD, autoimmune thyroid disease; ANA, antinuclear antibodies; Anti-dsDNA, antibodies against double-stranded DNA; Anti-Sm, anti-Smith antibodies; Anti-SSA, antibodies against the Ro/SSA antigens; Anti-SSB, antibodies against the La/SSB antigens; APS, autoimmune polyglandular (polyendocrine) syndrome; EGPA, eosinophilic granulomatosis with polyangiitis; CSU, chronic spontaneous urticaria; FH, family history; GD, Graves' disease; HT, Hashimoto's thyroiditis; IDDM, insulin-dependent diabetes mellitus (diabetes mellitus type 1); MAS, multiple autoimmune syndromes; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus.

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1. Introduction

Chronic spontaneous urticaria (CSU) is a mast cell-driven disease characterized by the development of wheals, angioedema (AE), or both for >6 weeks [1]. The etiopathogenesis of CSU is thought to be associated with autoimmune mechanisms [2]. Numerous autoimmune diseases (AIDs) have been linked to CSU [3], most of which are complex chronic inflammatory disorders that involve a plethora of cells and mediators, affect many tissues and organs, and cause substantial morbidity and mortality, mostly in women aged 40 to 50 years [4,5].

AIDs can be classified as systemic (multiorgan or non organ-specific) and organ-specific [6,7]. Some systemic AIDs are primary, i.e. they occur alone, while secondary AIDs develop during the course of other AIDs, e.g. Sjögren's syndrome in patients with rheumatoid arthritis or systemic lupus erythemasosus. The etiopathogenesis of AIDs involves many factors that include, but are not limited to, predisposing genes, epigenetic alterations, hormonal effects, and environmental triggers, leading from premorbid B and T cell dysregulation to the development of clinically evident disease [8].

Recently, we systematically reviewed the association of CSU and autoimmune thyroiditis [9] and of CSU and systemic lupus erythematosus [10], and we found that CSU is strongly linked to both of these AIDs. Here, we provide the first extensive and comprehensive evaluation of the prevalence of AIDs in patients with CSU and *vice versa*.

2. Methods

A Pubmed search was performed to identify studies published before April 2017 with the keywords “urticaria” and “chronic urticaria” in combination with the terms that are listed in Table 1. No language filter was applied. We also examined the reference lists of the retrieved articles and we searched Google Scholar with the same keywords to identify additional studies. In total, 64 studies were included in this systematic review. Most of these studies looked at whether or not the patients included had AID at the time they were assessed (point prevalence). A few studies reported whether patients had a history of AID or not. In some studies, it was not specified if the patients still had the AID at the time they had their urticaria. Some studies evaluated the prevalence of more than one AID. The selection process of relevant studies is summarized in Table 1. In studies identified, we did a search for the prevalence of autoantibodies (antinuclear, rheumatoid factor, anti-dsDNA, anti-parietal cell, anti-transglutaminase, anti-smooth muscle, anti-mitochondrial, anti-SSA, anti-SSB, anti-Sm, anti-cardiolipin) and a family history of AIDs. The term “urticarial rash” was used for studies where CSU was not clearly differentiated from acute urticaria, chronic inducible urticaria and/or urticarial vasculitis.

3. Results

3.1. All investigated autoimmune diseases occur in >1% of CSU patients in most studies

In CSU patients, the prevalence of the 21 investigated individual AIDs ranged from 0% to 27.5% (Tables 2, 5). Almost all studies (95%) found each investigated AID in one or more CSU patient. AIDs with relatively high prevalence in the general population [11] proved to be also quite common in CSU patients, whereas those with low prevalence remained a rare finding in CSU group (Tables 2, 5). For example, the prevalence of comorbidity in most studies were ≥1% for insulin-dependent diabetes mellitus (IDDM), rheumatoid arthritis (RA), psoriasis and celiac disease, ≥2% for Graves' disease (GD), ≥3% for vitiligo, and ≥5% for pernicious anemia and Hashimoto's thyroiditis (HT) (Fig. 1).

3.2. Organ-specific AIDs are more prevalent in CSU than systemic AIDs

Prevalence of individual organ-specific AIDs and systemic AIDs in CSU ranged from 0 to 27.5% in 60 studies (including 24 studies on ATD previously analyzed [9]) and 0–4.7% in 40 studies, respectively (Tables 2, 5). In 48 of 60 studies (80%), the investigated organ-specific AIDs occurred in ≥1% of CSU patients. In contrast, this was the case in only one third of the studies that assessed comorbidity rates of systemic AIDs. The most common organ-specific autoimmune comorbidities in CSU were endocrine (most prevalent: HT), hematological (most prevalent: pernicious anemia) and skin AIDs (most prevalent: vitiligo). Among the systemic AIDs, the most common CSU comorbidites were connective tissue diseases, the most prevalent being RA. In CSU patients, comorbid systemic autoimmune connective tissue diseases were found by 35 studies as compared to only one study describing comorbid autoimmune vasculitis in CSU [12].

3.3. >2% of CSU patients have autoimmune polyglandular syndrome encompassing ATD and vitiligo or pernicious anemia

The rates of comorbidity of two AIDs, ATD and another autoimmune disorder, in CSU patients ranged from 0.9–6.1% (Table 6). Autoimmune polyglandular syndromes (APS) type 3 with ATD and vitiligo (APS type 3C) or ATD and pernicious anemia (APS type 3B) were found in 1.2–5.5% and 5.5–6.1% of CSU patients, respectively (>2% in most studies). The prevalence of overlap syndromes and mixed connective tissue diseases appears to be low and was 0.4–0.5% according to two studies (Table 2).

3.4. Antithyroid and antinuclear antibodies are the most prevalent autoantibodies (AAbs) in CSU

We previously reported that ≥10% of CSU patients exhibit antithyroid AAbs (3.7–37.1% in 24 studies; anti-thyroid peroxidase > anti-thyroglobulin) [9]. In the present analysis, we found that the prevalence of