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Chronic spontaneous urticaria and internal parasites – a systematic review

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Abstract

Chronic spontaneous urticaria (CSU) is defined as persistent wheals, angioedema, or both lasting for >6 weeks due to known or unknown causes. Some epidemiological studies and case reports suggest that internal parasite infections (PI) can cause CSU. Here, we provide a systematic overview of published findings on the prevalence and relevance of PI in CSU and we discuss possible pathomechanisms. The prevalence of PI in CSU was investigated by 39 independent studies and comorbidity reportedly ranged from 0-75.4% (two thirds of these studies reported infection rates of 10% or less). The prevalence of PI in adult and pediatric CSU patients ranged from 0 to 75.4%, and from 0 to 37.8%, respectively. CSU patients were more often diagnosed with protozoa, had a significantly higher risk of toxocariasis seropositivity and *Anisakis simplex* sensitization when compared to healthy controls. Patients with chronic urticaria more frequently had seropositivity of fasciolosis, *Anisakis simplex* sensitization and presence of *Blastocystis hominis* allele 34 (ST3) as compared with control subjects. In 21 studies, efficacy of treatment with anti-parasitic drugs ranged from 0 to 100% (35.7% of 269 CSU patients benefitted). In 9 (42.8%) of 21 studies more than 50% of efficacy was observed. The reported rate of urticaria comorbidity in PI patients in 18 independent studies is 1-66.7%. Urticaria including CSU might be a quite common symptom of strongyloidiasis and blastocytosis. Pathogenic mechanisms in CSU due to PI may include specific IgE, Th2 cytokine skewing, eosinophils, activation of the complement and the coagulation systems.

Keywords: chronic spontaneous urticaria, parasites, review, prevalence, pathogenesis, helminth, protozoa, treatment

Abbreviations

AE: angioedema

CIC: circulating immune complexes

CSU: chronic spontaneous urticaria

GI: gastrointestinal

MC: mast cells

PAR: protease-activated receptors

PI: parasitic infections

TF: tissue factor

TSLP: thymic stromal lymphopoietin

Introduction

Chronic spontaneous urticaria (CSU) is defined as the recurrent development of transient wheals (hives), angioedema (AE), or both for >6 weeks due to known or unknown causes (1). The prevalence of CSU in the general population has been estimated to range from 0.5% to 5% (1, 2). In up to 90% of CSU cases the search for underlying causes is not successful, in routine clinical practice (1-3). Autoimmunity, food intolerance, and infections, including internal parasitic infections (PI), have been described as underlying causes of CSU (1, 4). A possible role for PI in urticaria was suggested as early as in 1949 (5): in a 16-year old boy with *Giardia lamblia* and CSU. His CSU resolved completely after specific and effective treatment of the infection. Since then, infections with endoparasites, such as helminths (worms, which consist of many cells and have internal organs) and protozoa (consist of only one cell), have been discussed to cause chronic urticaria, and several clinical studies and reviews on the prevalence and relevance of PI in patients with CSU were performed and published (4, 6-10).

Parasites are more prevalent in equatorial regions and countries with a tropical climate, high humidity, poor sanitation, dirty water, substandard and crowded housing, and in populations with low socio-economic status (sub-Saharan Africa, Asia, Latin America and Caribbean) (11, 12). According to a recent WHO report, more than 1.5 billion people, or 24% of the world's population, are infected with soil-transmitted helminths such as *Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus*, *Ancylostoma duodenale*, *Strongyloides stercoralis* (13). Other common helminthiasis include infections with tapeworms (Cestodes, e.g. *Taenia solium*), flukes (trematodes, e.g. *Schistosoma* spp., *Opisthorchis viverrini*, *Fasciola hepatica*), and roundworms (nematodes, e.g. *Onchocerca volvulus*, *Wuchereria bancrofti*), with a global prevalence of more than 120, 207, and

400 thousand affected people, respectively (14). The worldwide prevalence of major intestinal protozoa parasites such as flagellates (e.g. *Giardia spp.*, *Dientamoeba fragilis*), amebas (e.g. *Entamoeba histolytica*), spore-forming protozoa (e.g. *Cyclospora cayetanensis*, *Cryptosporidium spp.*), and *Blastocystis hominis* based on WAO report and results of different studies is 2-30% (15-17), 12% (17, 18), 1-30% (19), and 2-54%, respectively (20).

Many studies have linked CSU with PI (6, 8, 9, 21, 22), but the true rate of comorbidity, the role of parasites in CSU etiology and the pathomechanisms in CSU due to PI are still unclear. Here, we review and evaluate the prevalence of PI in CSU and vice versa, we assess the role of PI as a cause of CSU and the effect of anti-parasitic treatment on CSU, and we discuss possible pathomechanisms in CSU due to PI.

Materials and methods

A PubMed and Google Scholar search with the keywords “chronic urticaria” and “parasite”, “infection”, “infestation”, “helminth” or “protozoa” for the period from 1940 to 2015 identified 611 studies, of which 483 were excluded from further analysis after review of titles and/or abstracts because of non-relevant data (e.g. studies on other forms of infections). 62 of the remaining 128 studies were excluded through review of the abstracts and/or full texts: case reports (n=31), reviews (n=15), in vitro studies (n=6), articles without abstract and/or full text in English (n=2), and duplicate studies from the same authors including the same patient groups (n=8). The remaining 66 reports were used for analyses and included in Table 1 (n=39, prevalence of PI in CSU), Table 3 (n=10, comparison of PI prevalence between urticaria including CSU and control groups), Table 4 (n=18, prevalence of urticaria including CSU in PI), and Table 5 (n=6, comparison of urticaria prevalence between patients with PI and control groups). The data of 4 studies were used in both Tables 1 and 3 and the data of 3 studies were used in both Tables 4 and 5. Studies included adult patients (>15 years in two studies (23, 24) and >18 years in other studies), pediatric patients (<18 years) or both. Subsequent analyses were done for evaluation of PI prevalence in CSU (Table 1), i.e. we excluded cases of acute and inducible urticaria. Not in all studies a clear differentiation between acute and chronic urticaria (the term “urticaria” was used) as well as between chronic spontaneous urticaria and chronic inducible urticaria (the term “chronic urticaria” was used) has been made. In Tables 3-5 we used all definitions (“urticaria”, “chronic urticaria” and “CSU”) depending on available data provided from the studies.

The heterogeneity of the data in different studies regarding the frequency of PI and response to treatment is most likely to be due to the differences in diagnostic tools used for PI diagnosis and in the evaluation of treatment efficacy. Other drivers of heterogeneity may include differences in study design and in patient populations, as well as in the duration of the follow-up period. For example, stool examination was used alone for the diagnosis of PI in 24 of 39 studies and in combination with serology in 4 of 39 studies (Table 1). PI were found in 0-50% and 1-38.8% of patients with CSU, respectively. The prevalence of PI in adult CSU patients (11 studies), pediatric (13 studies) and in studies including both age groups (15 studies) ranged from 0-75.4%, 0-37.8% and 0-66.7%, respectively (Table 1). The prevalence of PI in CSU in retrospective (n=12), prospective (n=26) and cross-sectional (n=1) studies was 0-37.8%, 0-75.4% and 6.5%, respectively.

Results

Prevalence and relevance of parasitic infections in CSU

Rates of parasite infections in CSU patients investigated for them

In 39 independent studies, the prevalence of PI in CSU patients ranged from 0% to 75.4% (Table 1). Two thirds of these 39 studies reported infection rates of 10% or less. For the detection of parasites, stool examinations alone or in combination with other investigations were performed in 37 studies. Other tests included serology (including measurements of total and/or specific anti-parasitic IgE/IgG levels, n=6), blood eosinophil counts (n=6), skin prick tests (n=2), PCR (n=1), basophil activation test (n=1) and duodenal fluid aspiration (n=1). In some studies several investigations were performed.

Helminth-infected patients were seen in 15 studies and protozoa-infected patients in 20 studies (Table 2). Six studies identified PI but did not specify the parasite. Eight of 39 studies did not find any PI in CSU patients.

Most studies evaluating the rate of PI in CSU came from Turkey (9), India (4) and Thailand (3). The prevalence of PI in CSU ranges from 0-38.8% (Turkey), 3.3-37.8% (India) and 0.7-10.5% (Thailand). The most frequent and relevant PI were *Blastocystis hominis* (n=121 in 3 studies from Turkey), *Giardia spp.* (n=13 in 4 studies from Turkey), *Giardia lamblia* (n=33 in 2 studies from India), *Entamoeba histolytica* (n=13 in 1 study from India), and helminths (n=34 in 4 studies from India). In many studies the type of parasites was not defined. The general prevalence of *Blastocystis hominis* in Turkey was found to be from 0.54-15.24% (25, 26). In a retrospective study, the prevalence of intestinal parasites in general population in Turkey was reported to be 5% (5,486 of 111,889 patients

had positive stool samples). The most common parasites were *Giardia intestinalis* (62%), *Enterobius vermicularis* (16%), *Ascaris lumbricoides* (7%), and *Blastocystis hominis* (6%)(27). In other study, intestinal parasites were found in 1114 (4%) out of 27664 stool samples examined (28). *Blastocystis hominis* (2.1%) and *Giardia intestinalis* (1.4%) were the most frequently detected parasites. The prevalence of internal parasites in India was found to be 75.8% (194 of 256 stool samples were positive). The most common parasites were *Entamoeba coli* (23%), *Cyclospora sp.* (22.2%), *Entamoeba histolytica* (21.8%), *Giardia intestinalis* (14.4%) and *Ascaris lumbricoides* (6.2%)(29). Other studies conducted in India have reported the prevalence of intestinal PI ranging from 60-91% (30). The prevalence of PI in general population of Thailand was reported to be 8.9% (557/6,231)(31). The most commonly identified parasites were *Strongyloides stercoralis* (33.4%) and *Giardia spp.* (14.4%). In rural communities of Thailand helminths were found in 6.2% (13/209) of stool samples. Hookworms (4.3%) and *Strongyloides stercoralis* (1.4%) were the most common parasites (32). In other study *Blastocystis sp.* was the most common PI with general prevalence of 13.6% (33).

Rates of parasite infection in adults vs children with CSU

The prevalence of PI in adult (11 studies) and pediatric (13 studies) CSU patients ranged from 0 to 75.4%, and from 0 to 37.8%, respectively. Helminths were found in 3 and 4 studies in adult and pediatric CSU patients, respectively, and protozoa in 8 and 2 studies, respectively. The most common parasites seen in children were *Ascaris lumbricoides* (15 patients in 3 studies) and *Giardia spp.* (32 patients in 2 studies). Adult CSU patients most frequently were infected by *Giardia spp.* (>22 patients in 5 studies), *Entamoeba spp.* (>16 patients in 3 studies), *Ascaris lumbricoides* (10 patients in 2 studies), *Blastocystis hominis* (>7 patients in 2 studies), and *Anisakis simplex* (43 patients in 1 study).

Rates of parasite infection in CSU patients from countries with high vs low infection rates

We divided the countries into those with high and low PI rates based on literature data and climate and socioeconomic characteristics, e.g. high prevalence of PI is correlated with tropical climate, high humidity, poor hygiene, water and food supply, low sanitation and health services and/or rural environments (12, 17).

22 studies included patients from countries with high rates of parasite infections (range: 0-66.7%, Thailand, India, Egypt, Turkey, South Africa, Mexico, Pakistan, Brazil), and 17 studies included patients from countries with low rates of infections (range: 0-75.4%, Netherlands, Greece, France,

USA, Finland, Italy, Hungary, Spain, Switzerland, Canada, Germany). Helminths were found in 8 and 7 studies in countries with high and low rates of PI, respectively, and protozoa in 13 and 7 studies, respectively. The most common parasites detected in patients from countries with high rates of PI were *Giardia spp.* (>63 patients in 9 studies), *Blastocystis hominis* (>148 patients in 5 studies), *Entamoeba spp.* (>35 patients in 4 studies), *Ascaris lumbricoides* (17 patients in 4 studies), and *Ancylostoma duodenale* (3 patients in 2 studies). In countries with low rates of PI CSU patients most frequently were infected by *Giardia spp.* (19 patients in 5 studies), *Ascaris lumbricoides* (10 patients in 3 studies), *Anisakis simplex* (51 patients in 2 studies), and *Enterobius vermicularis* (2 patients in 2 studies).

Rates of parasite infection in CSU patients vs non CSU patients

In 10 studies, patients with urticaria including CSU were compared to control subjects without urticaria for their prevalence of PI (Table 3). All 10 studies report significantly higher rates of PI in patients with urticaria including CSU. CSU patients were more often diagnosed with protozoa (*Entamoeba coli*, *Blastocystis hominis* or *Giardia spp.*), had a significantly higher risk of *Toxocara canis* seropositivity when compared to healthy controls and with *Anisakis simplex* sensitization when compared to healthy and atopic controls. Patients with chronic urticaria had a significantly higher risk of positive result for IgG antibodies against *Toxocara canis*, more frequently had seropositivity of fasciolosis, *Anisakis simplex* sensitization and presence of *Blastocystis hominis* allele 34 (ST3) as compared with control subjects. Patients with undifferentiated urticaria more frequently had *Blastocystis hominis*, *Microsporidia* infections as well as a significantly higher risk of toxocariasis seropositivity than healthy controls. Giacometti et al. found protozoa and helminths in stools of 48 (22%) of 218 adults and children with chronic urticaria, atopic dermatitis, or pruritus of unknown origin and only 24 (11.5%) of 208 controls ($p=0.004$). 18 of them exhibited GI symptoms and there was a statistically significant difference in comparison to control group ($p=0.023$). The presence of *Giardia lamblia* and ≥ 5 *Blastocystis hominis* organisms per field was significantly associated with cutaneous manifestations ($p=0.030$ and $p=0.046$, respectively), including CSU (22).

Effects of PI treatment on CSU

In 22 of the 39 studies analysed (56.4%), CSU patients were treated for PI infections, in 21 studies with anti-parasite drugs and in 1 study with a fish-free diet (in *Anisakis simplex* sensitized patients). The total number of CSU patients treated with anti-parasitic drugs was 269 of which 35.7% benefitted (173 non responders, 64.3%). 16 (76.2%) of 21 studies report improvement of CSU

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symptoms in one or more patients after treatment with anti-parasitic drugs, whereas 5 (23.8%) of 21 studies report no improvement of CSU in any of the patients who received anti-parasitic medication. In 21 studies, efficacy of treatment with anti-parasitic drugs ranged from 0 to 100%. In 9 (42.8%) of 21 studies more than 50% of efficacy was observed.

Patients with chronic urticaria and *Anisakis simplex* sensitization more frequently experienced clinical improvement of urticaria after administration of fish-free diet when compared to non-sensitized chronic urticaria patients ($p=0.001$) (34) and to patients who did not change their dietary habits ($p<0.001$) (35). A significant improvement of urticarial symptoms was observed more often in the patients with detectable specific IgG4 against *Anisakis simplex* than in those without IgG4 (34).

Prevalence of urticaria including CSU in parasitic infection

Rates of urticaria in patients with parasite infections

Cases of CSU in patients with PI were described as early as in the 1970ies (36) and are often observed in clinical practice (37-39). As of yet, only few studies have assessed the prevalence of CSU in patients with different PI. We only found 18 independent studies, and in most of them the duration of urticaria was not defined (Table 4). The reported rate of urticaria comorbidity in PI patients in these studies is 1-66.7%. 5, 3, 3, 2, 1, 1, 1 studies included patients with *Strongyloides stercoralis*, *Blastocystis hominis*, *Toxocara canis*, *Giardia lamblia*, *Anisakis simplex*, *Gnathostoma spinigerum*, and *Echinococcus granulosus*, respectively. Two studies included patients with different PI: *Giardia lamblia* or *Ascaris lumbricoides* and *Endolimax nana*, *Blastocystis hominis*, *Entamoeba coli*, *Entamoeba histolytica* or *Giardia lamblia*, respectively.

Patients with Strongyloides stercoralis or Blastocystis hominis infection show increased rates of urticaria as compared to controls

In 6 studies comparisons with control groups were described (Table 5). Patients with strongyloidiasis were more often diagnosed with urticaria and had a significantly higher risk of developing urticaria when compared to healthy controls and subjects without strongyloidiasis (40-43). *Blastocystis hominis* was also described to be a risk factor for urticaria (44). In a retrospective study urticaria was more frequently detected in children ≥ 5 years of age with *Giardia lamblia* infection than <5 years of age [35].

Effects of PI treatment on CSU

9 (50%) of 18 studies indicate whether patients were treated (Table 4). In 8 (88.8%) of 9 studies patients were treated with known results and in 1 (11.1%) of 9 studies the outcome of treatment was not defined. In 7 (87.5%) of 8 studies anti-parasite drugs were administered and in 1 (12.5%) of 8 studies fish-free diet was used for the treatment of *Anisakis simplex* sensitization. The total number of urticaria patients treated with anti-parasitic drugs was 88. 7 (100%) of 7 studies report improvement of urticaria symptoms in one or more patients after treatment with anti-parasitic drugs, with 85 (96.6%) of 88 urticaria patients showing benefit. 0 of 7 studies reports no improvement of urticaria in any of the patients who received anti-parasitic medication, with 3 (3.4%) non responders of 88 treated patients. In 7 studies, efficacy of treatment with anti-parasitic drugs ranged from 78.6 to 100%, in 6 studies, it was equal to 100%.

In another study urticaria symptoms statistically significant reduced in 11 of 14 patients with strongyloidiasis after a course of ivermectin treatment ($p < 0.05$) (45).

Thus, the findings of above mentioned studies indicate that urticaria including CSU might be a quite common symptom of strongyloidiasis and blastocytosis, but its more accurate prevalence in other parasite-infected patients has yet to be established in further studies.

Common pathomechanisms in CSU and parasitic infection

The pathogenic links between CSU and PI are ill-defined and remain unclear (8, 46). Here, we describe several mechanisms that could explain how PI lead to CSU (Figure 1).

Role of specific IgE

It is well established that the key events in the pathogenesis of urticaria are activation and degranulation of mast cells (MCs) and basophils with the subsequent release of vasoactive substances such as histamine. The latter acts on H1 receptors of skin blood vessels, which leads to vasodilation and extravasation of fluid into the dermis with formation of edema and urticarial lesions. MCs and basophils can be activated by different stimuli, e.g. via antigen-specific IgE and its interaction with high-affinity IgE receptors (FcεRI) (47). In PI, interaction and crosslinking of a specific parasite antigen (antigenic products of parasite metabolism or the parasite itself) with parasite-specific IgE bound to FcεRI on MCs may induce the degranulation of MCs, release of mediators such as histamine, and development of CSU (46, 48, 49).

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Helminths, such as *Toxocara canis* or *Fasciola hepatica* (46), and protozoa, such as *Blastocystis hominis* (50) or *Giardia lamblia* (51), can stimulate the production of high serum levels of specific IgE antibodies against their own antigens leading to sensitization and degranulation of host MCs (52, 53). As early as in 1960, it was suggested that these mechanisms play a role in protection against intestinal nematodes (54) and may contribute to parasite expulsion as was shown in *Trichinella spiralis* infection (48).

High levels of total and specific IgE antibodies against *Anisakis simplex* were detected in patients with CSU and anaphylaxis (34, 55). Oteifa et al found that *Toxocara* seropositive children with chronic urticaria had significantly increased specific IgE and eosinophil levels when compared to healthy controls (56). Among patients with toxocariasis, high levels of specific anti-*Toxocara* IgE were significantly associated with itchy rashes (57). Vaccination with a single dose of Na-ASP-2 hookworm vaccine caused generalized urticaria in several volunteers with pre-existing Na-ASP-2-specific IgE due to previous *Necator americanus* infection (58). A significant association was found between IgE specific to *Echinococcus granulosus* antigen EgEF-1 β/δ and urticaria related to cystic echinococcosis in comparison to atopic and healthy controls ($p < 0.0001$) (59). Mahmoud and coworkers found significantly increased serum levels of specific anti-*Giardia* IgE, and IL-6 in patients with *Giardia*-related urticaria in comparison to 30 symptomatic giardiasis patients without urticaria and healthy controls ($p < 0.001$) (60). These findings indicate that specific anti-parasitic IgE may importantly contribute to the development of urticaria in patients with PI. However, exact mechanism why skin MCs get activated still remains unknown. There may be host antigens in the skin similar to parasite antigens that lead to IgE cross-reactivity and skin MCs degranulation. For example, Chandrashekar et al. showed that OV1CF protein of *Onchocerca volvulus* in sera from onchocerciasis patients is immunologically cross-reactive with human keratin (61).

Role of Th2 cytokine skewing

Another hypothesis of CSU development suggests that Th2 cytokines produced during PI may lead to MC activation. Excretory/secretory products released by helminths as well as tissue damage during invasion of parasite can trigger the release of Th2-initiating cytokines also called alarmins such as IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) from necrotic epithelial or/and endothelial cells (62, 63). It was shown that IL-33 binds to ST2L, a member of the interleukin 1 receptor family, present on MCs (64) and can induce the degranulation of IgE-sensitized skin MCs even in the absence of antigen (65, 66). TSLP was also shown to activate skin MCs by IgE-independent innate immune mechanisms (67). IL-25 not only enhances Th2 cytokine production, but has the potential to

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promote angiogenesis that may play a role in capillary leakage in CSU (68, 69). Kay et al. found an increased expression of Th2-initiating cytokines (IL-33, IL-25, TSLP) in lesional skin in CSU in comparison to nonlesional skin and controls as well as more pronounced increase in IL-4 (+) and IL-5(+) cells in lesional skin of CSU patients vs. controls (70). Increased IL-4 levels (71) and IL-4 and IL-5 levels (72) in serum were shown in CSU patients in comparison with healthy controls. Bischoff et al. found that IL-4 enhances mediator release in MCs (73). TSLP was strongly expressed in the epidermis of CSU lesional skin and non-lesional tissue, but not in normal and psoriasis skin (74). In a mouse model, MC degranulation was required for enhanced IL-33, IL-25 and TSLP expression which could drive helminth expulsion (75).

Role of eosinophils and coagulation system

Eosinophils are involved in protection against parasitic infections (76) and have been shown to contribute to the skin infiltrate in lesions of CSU. Eosinophils may cause MC and basophil degranulation in CSU by releasing different proteins such as major basic protein (77, 78), which is toxic for helminths (79).

PI induce peripheral blood and tissue eosinophilia (80-83) that may lead to easier recruitment and persistence of eosinophils in the skin and facilitate CSU development. Tissue (84) and blood (85) eosinophilia was observed in patients with CSU and in those who had both CSU and PI (43, 56, 80, 86). Elevation in vascular markers, eosinophils and MCs were found in CSU wheals and uninvolved skin compared with the control subjects (84).

Eosinophil recruitment in skin may be mediated by synthesis of chemoattractants and activation of complement system. It was shown in a mice model that eosinophils were recruited in the skin in large numbers during the early phase of infection with gastrointestinal parasite *Nippostrongylus brasiliensis* and it was mediated by IL-5 and eotaxin-1 (87). *Strongyloides stercoralis* and *Anisakis* larvae were also described to express eosinophil chemoattractants (88, 89). IL-4 and eotaxin-mediated recruitment of eosinophils in skin was observed in both helminth infections and allergic skin diseases (90). Inhibition of the C5a receptor with the antagonist PMX53 during the early phase of infection with *Nippostrongylus brasiliensis* led to impaired eosinophil and neutrophil recruitment to the skin (91).

Eosinophil-mediated activation of the coagulation system may be another mechanism of MC degranulation in patients, who have both CSU and PI (92). In CSU patients, the activation of eosinophils by autoantibodies to low-affinity receptors (FcεRII)(77), circulating immune complexes (CIC)(93) and cytokines such as IL-5, IL-6 and tumor necrosis factor alpha (TNF-α) (94, 95) was shown

to lead to the expression of tissue factor (TF), the main activator of blood coagulation (96), the activation of the coagulation cascade and the production of thrombin (92). Thrombin interacts with protease-activated receptors (PAR) 1 and 2 on mast cells that results in the subsequent degranulation of these cells and urticaria development (92). TF was observed in the infiltrate of CSU skin lesions (97), and this may be due to eosinophil activation.

Activation of the coagulation system was also noted in some PI. Eosinophils were shown to be activated in helminth infection by Th2 cytokines such as IL-5 (98). Vasquez et al. described an increase in the levels of fibrin degradation products, fibrinogen, platelet number and β -thromboglobulin in 31 patients with hypereosinophilia, 9 of those had PI (99). Patients with PI had significantly higher levels of fibrinogen compared with healthy controls. A significantly higher expression of TF mRNA of immunologically isolated eosinophils was confirmed in 9 patients with hypereosinophilia than in normal subjects. Two of these patients had an active phase of nematode infestation (strongyloidiasis and ascariasis) with blood eosinophilia level more than 3000 n/ μ l (100). 15 case reports were included in the review of Ames et al. and showed peripheral blood eosinophilia and thrombosis in the course of a parasitic disease (101) that implies the activation of the coagulation system. Opisthorchiasis and *Schistosoma* infections were accompanied by marked elevation of D-dimer level and high thrombin generating potentials (102, 103), but these phenomena were not observed in other PI (104, 105). It could explain, at least in part, the differences in frequency of urticaria development in different PI.

Role of circulating immune complexes and complement system

Through formation of CIC, parasites can activate the complement system with subsequent generation of C5a, a strong trigger of skin MC degranulation, via the complement receptor C5aR (46, 47, 51, 106).

Antigens of *Toxocariasis* and *Fasciolosis* were found in the peripheral circulation (107, 108) to form CIC by interaction with IgG (46). CIC were detected in sera of patients with malaria, leishmaniasis, schistosomiasis and onchocerciasis (109-111). In animal models, IgG was shown to activate complement that results in death of *Angiostrongylus cantonensis* larva (112). Asymptomatic cases of human lymphatic filariasis and onchocerciasis were characterized by high plasma concentrations of the complement-fixing antibodies IgG1, IgG2 and IgG3 (113). In a subpopulation of CSU patients, IgG1 and IgG3 autoantibodies to the high-affinity IgE receptor on MC can fix complement and induce MC degranulation by a direct mechanism and by the generation of anaphylatoxin C5a and its action via the complement receptor C5aR (114, 115).

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Production of C5a was shown in different PI. For example, mice infected with *Hymenolepis diminuta* showed significant increase in serum levels of C5a that led to MC activation and degranulation in knee joints in an experimental K/BxN model of polyarthritis (murine synovial mast cells as well as human skin mast cells are unique in the expression of the C5a receptor) (116). *Entamoeba histolytica* released cysteine proteinases that provoke complement activation and production of C3a and C5a (117). C5a levels were significantly elevated in women with placental malaria (118). Activation of the complement system and formation of anaphylatoxins induced by hydatid cyst fluid of *Echinococcus granulosus* were shown *in vitro* in rat serum, and vascular permeability changes were produced *in vitro* in humans after intradermal inoculation of complement interacting fractions of hydatid fluid (119). In a rat model, it was shown that cercarial extracts of *Schistosoma mansoni* generates anaphylatoxin in plasma similar to C5a. Anaphylatoxin induced MC degranulation in guinea pig mesentery as well as enhancement of vascular permeability in guinea pig skin (120). Formation of anaphylatoxin can explain CSU occurring during penetration and migration of parasites such as *Schistosoma mansoni* cercaria through the skin.

Summary

PI is relatively common in CSU (range: 0-75.4%) and urticaria is often detected in PI patients (range: 1-66.7%). CSU patients were more often diagnosed with protozoa, had a significantly higher risk of *Toxocara canis* seropositivity when compared to healthy controls and with *Anisakis simplex* sensitization when compared to healthy and atopic controls. Patients with chronic urticaria more frequently had seropositivity of fasciolosis, *Anisakis simplex* sensitization and presence of *Blastocystis hominis* allele 34 (ST3) as compared with control subjects. Patients with undifferentiated urticaria more frequently had *Blastocystis hominis* and Microsporidia infections than healthy controls. Urticaria including CSU might be a quite common symptom of strongyloidiasis and blastocytosis, but its more accurate prevalence in other parasite-infected patients has yet to be established in further studies. The efficacy of treatment with anti-parasitic drugs on CSU and undifferentiated urticaria symptoms ranged from 0 to 100% (PI in CSU) and 78.6-100% (urticaria in PI), respectively.

Analyzing the available data, we can conclude that PI is an uncommon underlying cause of CSU. PI should only be regarded as the underlying cause of CSU when the treatment of parasitosis led to the eradication of the parasite and the remission of CSU. Concurrent GI symptoms, a history of previous parasite infections, travel abroad, and unexplained eosinophilia may point to PI in CSU patients. Based on the literature we suggest that CSU may be closely pathogenically related to PI. Possible hypotheses of skin MC activation in PI include a role of specific IgE, Th2 cytokine skewing, eosinophil

recruitment to the skin and activation of the coagulation and complement systems. Further studies are needed to determine the prevalence of CSU in PI and vice versa, and better characterize underlying pathomechanisms in both diseases.

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Table 1. Prevalence of PI in CSU patients according to published studies

Authors	Age	n	n (%) of patients with PI	PI	Diagnosis	Treatment with anti-PI drugs, n	Improvement of CSU after treatment		Year	Country	Design	Ref
							Yes, n (%)	No				
Colgecen et al	A, C	369	117 (31.7)	H, PR	SE	72	4 (5.6)	68	2015	Turkey	R	(121)
Misirlioglu et al	C	31	0	—	SE	—	—	—	2013	Turkey	R	(122)
Isik et al	C	61	1 (1.6)	—	SE	—	—	—	2013	Turkey	R	(123)
Dilek et al	A	49	19 (38.8)	PR	SE, S	19	8 (42.1)	11	2012	Turkey	CC, P	(124)
Hameed et al	A, C	36	24 (66.7)	PR	SE, PCR	24	24 (100)	0	2011	Egypt	CC, P	(125)
Gupta et al	C	45	17 (37.8)	H	SE	5	5 (100)	0	2011	India	R	(126)
Sahiner et al	C	75	2 (2.7)	—	SE	2	0	2	2011	Turkey	R	(127)
Jirapongsananuruk et al	C	94	5 (5.4)	PR	SE, BEC	5	2 (40)	3	2010	Thailand	P	(128)
Kilic et al	C	27	0	—	SE	—	—	—	2010	Turkey	R	(129)
Krupa Shankar et al	A	150	5 (3.3)	PR	SE	—	—	—	2010	India	P	(130)
Frezzolini et al	A	57	43 (75.4)	H	SPT, S, BAT	10 ¹	10 (100)	0	2010	Italy	CC, P	(131)
Gregoriou et al	A	2092	5 (0.2)	H, PR	SE	—	—	—	2009	Greece	P	(132)
Doğruman et al	A, C	55	16 (29.1)	PR	SE, S	13	7 (53.8)	6	2009	Turkey	P	(133)
Ferrer	A, C	200	13 (6.5)	H, PR	SE	—	—	—	2009	Spain	CS	(21)
Kulthanan et al	A	407	3 (0.7)	PR	SE	3	1 (33.3)	2	2007	Thailand	R	(23)
Silvares et al	A, C	116	6 (5)	H, PR	SE	—	—	—	2007	Brazil	P	(134)
Godse	A, C	50	5 (10)	H, PR	SE, BEC	5	0	5	2006	India	P	(135)
Buss et al	A, C	215	0	—	SE	—	—	—	2006	Germany	R	(136)
Du Toit et al	C	39	1 (2.5)	H	SE, S, BEC	1	0	1	2006	South Africa	P	(137)
Salgado et al	A	32	16 (50)	H, PR	SE	16	5 (31.2)	11	2005	México	P	(138)
Sackesen et al	C	8	0	—	SE	—	—	—	2004	Turkey	P	(139)
Nettis et al	A, C	394	4 (1)	H, PR	SE, S	4	4 (100)	0	2003	Italy	P	(140)
Bakos et al	A, C	48	0	—	—	—	—	—	2003	Hungary	P	(141)
Kozel et al	A	102	6 (5.9)	—	SE, BEC	6	0	6	2001	Netherlands	P	(24)
Pigatto and Valsecchi	A	348	22 (6.3)	H, PR	SE	—	—	—	2000	Italy	P	(142)
Erel et al	A	38	1 (2.6)	PR	DFA	—	—	—	2000	Turkey	P	(143)
Trachsel et al	A, C	46	16 (35)	PR	SE	—	—	—	1999	Switzerland	R	(144)
Khan and Murtaza	A, C	57	13 (22.8)	PR	SE	13	8 (61.5)	5	1998	Pakistan	P	(145)
Wolfrom et al	A, C	51	33 (64.7)	H	S	14	8 (57.1)	6	1996	France	CC, P	(146)
Uthman et al	A, C	136	0	—	SE	—	—	—	1995	Saudi Arabia	R	(147)
Zuberbier et al	A	64	3 (1.9)	H, PR	SE	3	0	3	1995	Germany	P	(148)
Ghosh et al	C	300	59 (19.7)	H, PR	SE	48	9 (18.7)	39	1993	India	P	(149)

Volonakis et al	C	189	7 (3.7)	—	SE	7	7 (100)	0	1992	Greece	P	(150)
Sibbald et al	A	175	6 (3.4)	PR	SE, BEC	6	1 (16.7)	5	1991	Canada	P	(151)
Tuchinda et al	C	19	2 (10.5)	H	SE	2	2 (100)	0	1986	Thailand	P	(152)
Kauppinen et al	C	41	1 (2.4)	—	SE	1	1 (100)	0	1984	Finland	R	(153)
Harris et al	C	86	0	—	—	—	—	—	1983	USA	R	(154)
Jacobson et al	A, C	125	0	—	SE, BEC	—	—	—	1980	USA	P	(155)
Miller et al	A, C	13	1 (7.7)	—	SE	—	—	—	1968	USA	P	(156)

H – helminths; PR – protozoa; P – prospective study; R – retrospective study; CS – cross-sectional study; CC – case-control study; SE – stool examination; BEC – blood eosinophil count; SPT – skin prick tests; S – serology; BAT – basophil activation test; — not found; no data or not relevant; ¹patients with *Anisakis simplex* infection who were treated by fish-free diet administration; A – adults; C – children; DFA – duodenal fluid aspiration.

Table 2. Prevalence of different parasites in CSU patients

Type of parasite	N of studies	N of patients
<i>Giardia spp.</i>	16	>82
<i>Blastocystis hominis</i>	7	>160
<i>Ascaris lumbricoides</i>	7	27
<i>Entamoeba spp.</i>	5	>37
<i>Anisakis simplex</i> *	2	104
<i>Enterobius vermicularis</i>	3	4
<i>Ancylostoma duodenale</i>	2	3
<i>Taenia spp.</i>	2	3
<i>Toxocara canis</i>	1	33
<i>Trichuris trichiura</i>	1	3
<i>Dientamoeba fragilis</i>	1	1
<i>Necator americanus</i>	1	1

*Unlike other helminths *Anisakis simplex* is thought to cause CSU due to IgE-mediated sensitization to chemicals left by the worms in fish flesh

Table 3. Comparison of PI prevalence between urticaria including CSU and control groups

Studies	Form of urticaria	Age	Parasite	n of urticaria patients	n (%) patients with PI	n of healthy controls	n (%) of healthy controls with PI	p	Year	Country	Design	Ref
Casero et al	CU	A, C	BH	21	18 (85.7)	21	1 (4.8)	<0.0001 ³	2015	Argentina	CC	(157)
Ventura et al	CU	A	AS	213	106 (49.7)	187	30 (16)	<0.001	2013	Italy	CC, P	(35)
Dilek et al	CSU	A	PR ²	49	19 (38.8)	36	4 (11.1)	<0.05	2012	Turkey	CC, P	(124)
Hameed et al	Urticaria	A, C	BH	54	33 (61.1)	50	4 (8)	0.001	2011	Egypt	CC, P	(125)
Karaman et al	Urticaria	A	M	132	26 (19.7)	36	1 (2.8)	0.028	2011	Turkey	CC	(158)
Bellanger et al	CU	A	TC	84	36 (42.9)	84	20 (23.8)	0.009, OR 2.4	2010	France	P	(159)
Frezzolini et al	CSU	A	AS	57	43 (75.4)	22/20 ¹	4 (18)/2 (10)	< 0.0001	2010	Italy	CC, P	(131)
Demirci et al	CU	A	FH	62	9 (14.5)	62	1 (1.6)	<0.05	2003	Turkey	CC, P	(46)
Humbert et al	Urticaria	A, C	TC	128	25 (19.5)	249	30 (12.7)	0.02, OR 2.23	2000	France	CC	(160)
Wolf from et al	CSU	A, C	TC	51	33 (64.7)	81	17 (21)	0.0001, OR 6.9	1996	France	CC, P	(146)

¹Healthy/atopic controls; ²Entamoeba coli, Blastocystis hominis or Giardia spp.; ³detection of allele 34 (ST3); A – adults; C – children; CU – chronic urticaria, OR – odd ratio; BH – Blastocystis hominis; AS – Anisakis simplex; PR – protozoa; M – Microsporidia; TC – Toxocara canis; FH – Fasciola hepatica; P – prospective study; CC – case-control study.

Table 4. Prevalence of urticaria including CSU in parasitic infections according to published studies

Authors	Parasite	Age	n	n (%) of patients with urticaria	n of parasite-infected urticaria patients treated with anti-parasite drugs			Year	Country	Design	Ref
					Total	Urticaria improvement					
						Yes, n (%)	No				
Bálint et al	BH	A, C	80	5 (6.25)	5	5 (100)	0	2014	Hungary	R	(161)
Khieu et al	SS	A, C	21	14 (66.7)	14	11 (78.6)	3	2013	Cambodia	CC, P	(45)
Sanchez et al	Protozoa ³	A, C	549	44 (8) ¹	—	—	—	2012	RD	R	(162)
Qualizza et al	TC	A, C	240	36 (15)	—	—	—	2011	Italy	R	(37)
Escobedo et al	GL	C	170	5 (2.9)	—	—	—	2011	Cuba	R	(163)
Trabelsi et al	BH	A, C	237	15 (6.5)	—	—	—	2010	Tunis	R	(38)
Pattison et al	SS	A	13	4 (30.8)	4	4 (100)	0	2008	Solomon Islands	R	(164)
Almannoni et al	GL	—	114	36 (31.6)	36	36 (100)	0	2008	Cuba	P	(165)
Paludo et al.	TC	C	130	8 (6.1)	—	—	—	2007	Brazil	CS	(166)
Massoud et al	SS	A	24	1 (4.2)	1	—	—	2006	Egypt	P	(167)
Herrera et al	SS	A, C	50	16 (32)	—	—	—	2006	Peru	CC, D	(42)
Figueiredo et al	TC	A	208	2 (1) ¹	2	2 (100)	0	2005	Brazilia	CC, CS	(168)
Chai et al	GS	A, C	38	12 (31.6)	12	12 (100)	0	2003	Korea	P	(169)
Barahona Rondón et al	BH	A, C	74	12 (16.2)	—	—	—	2003	Peru	CC, P	(44)
Varga et al	GL, AL	A	55	15 (27.2) ¹	15	15 (100)	0	2001	Romania	P	(39)
Ortona et al	EG	A	98	31 (31.6)	—	—	—	2001	Italy	CC	(59)
Gracia-Bara et al	AS	A	17	11 (64.7) ¹	9 ²	9 (100)	0	2001	Spain	P	(55)
Grove	SS	A	44	29 (66)	—	—	—	1980	Australia	CC, CS	(43)

D – descriptive study; CS – cross-sectional study; CC – case-control study; P – prospective study; R – retrospective study; ¹patients had chronic urticaria with acute urticaria excluded; — not defined in the paper or in the abstract; ²patients were treated by diet administration; ³Endolimax nana, Blastocystis hominis, Entamoeba coli, Entamoeba histolytica or Giardia lamblia; A – adults; C – children; BH – Blastocystis hominis; AS – Anisakis simplex; TC – Toxocara canis; SS – Strongyloides stercoralis; GL – Giardia lamblia; AL – Ascaris lumbricoides; GS – Gnathostoma spinigerum; EG – Echinococcus granulosus; RD – Republica Dominicana.

Table 5. Comparison of urticaria prevalence between patients with PI and control groups

Studies	Form of urticaria	Age	Parasite	n of PI patients	n (%) of patients with urticaria	n of controls	n (%) of controls with urticaria	p	Year	Country	Design	Ref
Vonghachack et al	Urticaria	A, C	SS	299	—	430 ¹	—	0.001, OR 2.40	2015	Southern Laos	CS	(40)
Khieu et al	CU	A, C	SS	601	138 (23.0)	2260 ¹	397 (17.6) ¹	0.001, OR 1.4	2014	Cambodia	CS	(41)
Almirall et al	Urticaria	C	GL	122 ²	1 (0.8) ²	48 ²	4 (8.3) ²	0.023, OR 11.0	2013	Cuba	R	(170)
Herrera et al	Urticaria	A, C	SS	50	16 (32)	50	4 (8)	0.03	2006	Peru	CC, D	(42)
Barahona Rondón et al	Urticaria	A, C	BH	74	12 (16.2)	70	—	<0.05, OR 3.19	2003	Peru	CC, P	(44)
Grove	Urticaria	A	SS	44	29 (66)	114/43 ³	3 (3)/0 ³	<0.005	1980	Australia	CC, CS	(43)

¹participants without *Strongyloides stercoralis* infection; ²children <5 years vs ≥5 years; ³men without strongiloidosis/ex-prisoners in Europe; — no data was found in abstract and/or paper; BH – Blastocystis hominis; SS – *Strongyloides stercoralis*; GL – *Giardia lamblia*; CU – chronic urticaria; P – prospective study; R – retrospective study; CS – cross-sectional study; CC – case-control study; D – descriptive study.

FIGURE LEGENDS

Figure 1. Possible pathogenetic relationship between chronic spontaneous urticaria and helminth parasitic infections

CSU in helminth infections may develop by multiple mechanisms. All these may not be equally crucial for CSU to appear but illustrate the diversity of pathways for possible mast cell and basophil activation. The helminth parasite damages endothelial or/and epithelial barriers during the invasion into the host. It provokes anti-parasitic Th2 immune response and processes of tissue repair. Damaged tissue can trigger the release of alarmins such as thymic stromal lymphopoietin (TSLP), IL-25 and IL-33. The action of alarmins leads to the activation of innate lymphoid cells (ILC) and other cells populations that take part in the development of Th2 immune response. Moreover, these cytokines can induce IgE-independent activation and degranulation of MC resulting in the release of inflammatory mediators. Furthermore, helminths themselves release excretory/secretory products which also enhance the Th2 response through their effects on dendritic cells. It results in inhibition of Th1 cell differentiation mediated by dendritic cells and promotes Th2 cell development in lymph nodes. Mast cells and basophils may be activated through the engagement of the high-affinity Fc receptors (FcεRI) by parasite-specific IgE produced by B cells. B cells also participate in Th1 response producing complement-fixing IgG1-3, which form CIC with parasite antigens. This cascade leads to activation of complement system with consequent generation of anaphylotoxins C5a and C3a, their action on C5aR and C3a receptors on mast cells and urticaria development. Activated by CIC or cytokines such as IL-5, eosinophils can induce MC activation and urticaria development by release of tissue factor (TF). TF activates coagulation cascade that leads to thrombin formation. Thrombin in its turn acts on PAR 1 and 2 receptors on MC causing their degranulation. Th2 response also participates in tissue repair where M2 macrophages, eosinophils and Th2 cells were shown to have an important role by suppressing the pro-inflammatory action of M1 macrophages and Th1 cells (62, 63).

PAR: protease-activated receptors; IL: interleukin; TF: tissue factor; CIC: circulating immune complexes; TGFβ: transforming growth factor-β; VEGF: vascular endothelial growth factor; ARG1: arginase 1; IGF1: insulin-like growth factor 1; MMPs: matrix metalloproteinases.

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