Parasitic Infections in Children with Chronic Spontaneous Urticaria

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Key Words
Abdominal pain · Children · Chronic spontaneous urticaria · Gastrointestinal symptoms · Parasite · Urticaria

Abstract
Background: Parasites have been proposed to be an underlying cause of chronic spontaneous urticaria (CSU) in childhood, but a clear causal relationship between them has not been established. This study aimed to investigate the prevalence of parasitic infection-related CSU (PIRCSU) in children and to determine the factors associated with PIRCSU. Method: Data from 211 children with CSU were analyzed. Information on stool examination, antiparasitic medications received, and response to treatment was recorded. The disappearance of urticaria for more than 6 months is defined as remission, and remission of urticaria after antiparasitic treatment is defined as PIRCSU. Results: Parasites were detected in 21 (10%) patients. Blastocystis hominis was the most common parasite. After antiparasitic medication, all samples became normal; urticaria continued in 5, was reduced in 6, and disappeared in 10 patients. The latter 10 patients were considered as cases of PIRCSU (4.7%). The erythrocyte sedimentation rate was significantly higher in patients with PIRCSU than in those without. The occurrence of abdominal pain was a significant risk factor that increased the probability of PIRCSU [OR = 6.60, 95% CI = 1.35–32.23, p = 0.020]. Conclusion: Parasites may cause CSU even in nontropical countries, and remission may only be possible with the treatment of the parasitic infection. The occurrence of abdominal pain points to parasitic infection in patients with CSU. Therefore, we suggest that parasites should be investigated routinely, especially if the patient has gastrointestinal symptoms of CSU in childhood.

Introduction
Chronic spontaneous urticaria (CSU), which is defined as the spontaneous and transient appearance of urticaria, angioedema, or both for more than 6 weeks, is a rare but often distressing allergic skin disorder in childhood [1]. Its estimated prevalence in children is 0.1–3% [2]. Data on the etiology of CSU in the pediatric age group are limited. The underlying etiology has been described...
in a small number of patients in a few studies [3]. To date, foods, infections, thyroid diseases, and autoimmune
have been shown to be etiologic factors [4–10]. Parasites
have also been proposed to be an underlying factor of
CSU, but a causal relationship between them has not been
described in the literature. In fact, complete remission is
required by elimination of the suspected factor to be the
underlying cause of CSU. Although information on the
prevalence of parasitic infections in CSU is available, data
on the effect of its eradication in the natural course of ur-
ticaria are limited.

In a recent systematic review [11], the prevalence of
parasitic infection in children with CSU and the efficacy
of antiparasitic medication in CSU symptoms were found
to have a wide range of 0–37.8 and 0–100%, respectively.
Studies mentioned that parasitic infections in patients
with CSU showed important differences in study design,
inclusion criteria, and definition of disease or remission
criteria. The relationship between parasitic infections and
CSU remains unclear.

In the present study, we aimed to determine the effect
of parasitic infection treatment on urticaria symptoms in
patients with parasites in the stool and to investigate the
prevalence of parasite-associated CSU in children in a
large cohort. We also examined the factors related to par-
asitic infection-related CSU (PIRCSU).

Method

Study Population

This study has both prospective and retrospective aspects. A
total of 248 children who had been diagnosed with CSU at the
Department of Pediatric Allergy, Hacettepe University School of
Medicine, Ankara, Turkey, between 1992 and 2015 were enrolled.
Among these patients, those who had been diagnosed between
2010 and 2015 were followed up and analyzed prospectively (n = 158),
and those who had been diagnosed between 1992 and 2009
were analyzed retrospectively (n = 90). In total, 211 patients had
stool examinations.

CSU was defined as the transient appearance of urticaria without
a specific physical trigger for more than 6 weeks [1]. The daily or al-
most daily (>4 days/week) occurrence of urticaria symptoms was
considered chronic persistent urticaria, and the occurrence of urti-
caria for 2–4 days a week was considered chronic recurrent urticaria
[12]. Patients with inducible urticaria were excluded. The urticaria
activity score 7 (UAS7) was calculated by the sum of the daily UASs
for 7 consecutive days in patients according to the guideline [1].

The following demographic features were recorded: gender,
age, duration of urticaria, UAS7 at admission, concomitant sys-
temic symptoms other than urticaria or angioedema such as gas-
trointestinal complaints, accompanying allergic diseases including
atopic dermatitis, allergic rhinitis, and asthma, chronic diseases
other than allergic diseases and family history of allergic diseases.

Laboratory investigations included complete blood count, C-
reactive protein, erythrocyte sedimentation rate (ESR), total IgE,
C3 and C4 levels, free thyroxine and thyroid-stimulating hormone,
thyroid autoantibodies (antithyroid peroxidase antibody, anti-
thyroglobulin antibody and anti-thyroid-stimulating hormone
antibody), antinuclear antibody, anti-double-stranded DNA anti-
body and urine analysis.

Stool samples were obtained at admission. Samples were col-
lected in clean plastic containers and then assessed within 30 min.
Sampling was also performed by the sellotape method when sus-
picion of Enterobius vermicularis infection was present. Fresh stool
samples were examined by a light microscope at ×100 and ×400
magnifications. Samples were also processed with a semiautomat-
ed system, FE-2 Intestinal Parasite Analysis Workstation, and then
stained with iodine before assessment. Both methods were applied
to the samples at the same time, and the detection of parasites in
one of them was considered a positive result.

All patients were asked to answer a questionnaire about para-
sic infection. This questionnaire included gastrointestinal symp-
toms (e.g. abdominal pain/cramp, diarrhea, mucus or blood in
stool, anal pruritus and emesis), general symptoms (e.g. loss of ap-
petite, fatigue, teeth grinding and fever) and previous detection of
any parasite.

Patients who were found to have a parasite in the stool exami-
nation received parasite-directed treatments as indicated. Stool ex-
amination was repeated after treatment. If a parasite was again
detected in the control stool examination, treatment was given un-
til stool was cleared from the parasite. Response to the treatment
was recorded.

A telephone interview was conducted to obtain information on
the current status of symptoms in the participants. The disappear-
ance of urticaria for more than 6 months was defined as remission,
and remission of urticaria with negative stool examination after antiparasite treatment is considered PIRCSU. Patients with PIR-
SU and non-PIRCSU were compared with each other according to
the above-mentioned demographic, clinical, and laboratory char-
acteristics.

A skin prick test was performed with common allergens
and common food allergens as indicated by history. Histamine (10
mg/ml of histamine phosphate) was used as the positive control,
and 0.9% sterile saline was used as the negative control. The mean
wheat diameter of the skin prick test ≥3 mm compared with the
negative control was considered a positive result. Diagnosis of food
allergy was made by oral food challenge tests with positivity of the
skin prick test and/or specific IgE with the culprit food. Diagnosis
of food additives was made with the disappearance of urticaria af-
ter 3 weeks of elimination diet and recurrence of urticaria with the
addition of food additives in the diet.

An autologous serum skin test was performed as an intrader-
mal skin test with 0.05 ml of sterile, fresh autologous serum and
0.9% sterile saline as the negative control. A skin prick test with
histamine (10 mg/ml of histamine phosphate) was used as the posi-
tive control. The test was evaluated 30 min after injection, and it
was considered a positive result if a wheal diameter of ≥1.5 mm
was obtained compared with that of the saline solution [13].

Statistical Analyses

Data were analyzed using SPSS statistical software version 18.0
(SPSS Inc., Chicago, Ill., USA). The proportions in different groups
were compared with the Pearson χ2 or Fisher’s exact test where ap-

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Parasites in Children with CSU
propriate. All numeric variables were compared with Mann-Whitney U or Kruskal-Wallis tests where appropriate, and the results were given as median and interquartile ranges. The risk factors related to PIRCSU were determined by univariate and multivariate logistic regression analyses, and the results were given as odds ratio (OR) with a relevant 95% confidence interval (CI). A p value of less than 0.05 was considered statistically significant.

Results

A total of 211 patients (187 chronic persistent urticaria and 24 chronic recurrent urticaria) were analyzed, and a parasite was detected in 21 (10%; 2 patients were in the retrospective arm and 19 in the prospective arm). The most common parasite was Blastocystis hominis in 12 samples, followed by Giardia intestinalis (n = 5), Dientamoeba fragilis (n = 3), Enterobius vermicularis (n = 3), and Entamoeba spp. (n = 1). All these patients had received antiparasitic medication as indicated. After the antiparasitic treatment for 10 days, stool examination became normal in all patients. Among the patients who had been given antiparasitic treatment, urticaria continued in 5, reduced in 6, and disappeared in 10 patients. In the follow-up, urticaria did not recur in these 10 patients, and they were considered cases of PIRCSU (4.7%). All patients with PIRCSU were in the prospective arm. The causative parasites were detected as B. hominis (n = 5), G. intestinalis (n = 4), and D. fragilis (n = 1).

Among the patients with non-PIRCSU, the etiology was identified in 8 patients (4%) as food allergy (n = 2), hypersensitivity to food additives (n = 3), pollen sensitization (n = 2), and Hashimoto thyroiditis (n = 1).

Comparison of the clinical and laboratory characteristics of patients with PIRCSU and those without is shown in table 1. Age at admission was slightly lower in patients with PIRCSU than in those without [7.4 years (3.9–12.7) vs. 10.4 (6.9–13.2), p = 0.118]. Duration of urticaria was shorter in patients with PIRCSU than in those without [0.5 years (0.2–1) vs. 1 (0.3–2.5) p = 0.112]. No differences were found among UAS7, angioedema or concomitant allergic diseases between the two groups. However, the prevalence of gastrointestinal symptoms was significantly higher in patients with PIRCSU than in those without (40 vs. 11.2%; p = 0.010). The most frequent gastrointestinal complaint was abdominal pain and nausea/vomiting (40 vs. 8%, p = 0.001, and 20 vs. 4%, p = 0.028).

Table 1. Comparison of clinical and laboratory characteristics between patients with PIRCSU and non-PIRCSU

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PIRCSU (n = 10)</th>
<th>Non-PIRCSU (n = 201)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls</td>
<td>4 (40)</td>
<td>96 (47.8)</td>
<td>0.631</td>
</tr>
<tr>
<td>Age at admission, years</td>
<td>7.4 [3.9–12.7]</td>
<td>10.4 [6.9–13.2]</td>
<td>0.188</td>
</tr>
<tr>
<td>Age at symptom onset, years</td>
<td>6.9 [3.4–11]</td>
<td>9.2 [5–11.9]</td>
<td>0.226</td>
</tr>
<tr>
<td>Symptom duration, years</td>
<td>0.5 [0.2–1]</td>
<td>1 [0.3–2.5]</td>
<td>0.112</td>
</tr>
<tr>
<td>UAS7 at admission</td>
<td>31.5 [22.8–42]</td>
<td>28 [21–42]</td>
<td>0.480</td>
</tr>
<tr>
<td>Angioedema, %</td>
<td>30</td>
<td>52.5</td>
<td>0.165</td>
</tr>
<tr>
<td>Concomitant allergic disease, %</td>
<td>20</td>
<td>16.9</td>
<td>0.800</td>
</tr>
<tr>
<td>Concomitant symptoms, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>20</td>
<td>4</td>
<td>0.028</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>40</td>
<td>8</td>
<td>0.001</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>40</td>
<td>11.2</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Laboratory findings

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PIRCSU (n = 10)</th>
<th>Non-PIRCSU (n = 201)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count, n/mm³</td>
<td>5,325 [7,905–9,525]</td>
<td>7,840 [6,530–9,500]</td>
<td>0.560</td>
</tr>
<tr>
<td>Thrombocyte count, n/mm³</td>
<td>253,000 [276,000–326,000]</td>
<td>289,000 [250,250–352,750]</td>
<td>0.708</td>
</tr>
<tr>
<td>Peripheral eosinophil percentage</td>
<td>2.3 [1.3–3.5]</td>
<td>1.5 [0.8–2.6]</td>
<td>0.180</td>
</tr>
<tr>
<td>Total IgE, kU/l</td>
<td>26.1 [12–169]</td>
<td>66.8 [30.6–171]</td>
<td>0.120</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>8.5 [3.5–14.5]</td>
<td>2 [0–7]</td>
<td>0.011</td>
</tr>
<tr>
<td>Autoantibody positivity, n</td>
<td>4/7 (57.1)</td>
<td>57/192 (29.7)</td>
<td>0.122</td>
</tr>
<tr>
<td>Autologous serum skin testing positivity, n</td>
<td>1/3 (33.3)</td>
<td>42/123 (34.1)</td>
<td>0.977</td>
</tr>
<tr>
<td>Skin prick test positivity, n</td>
<td>1/6 (16.7)</td>
<td>50/178 (28.1)</td>
<td>0.539</td>
</tr>
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</table>

Results are expressed as n (%) or median [interquartile range]. UAS7 = The sum of the daily urticaria activity score of 7 consecutive days.
respectively]. In laboratory investigations, although ESRs were within the normal limit in most patients, they significantly increased in patients with PIRCSU compared to those without [8.5 mm/h (3.5–14.5) vs. 2 (0–7), p = 0.011].

According to the multivariate logistic regression analysis (table 2), abdominal pain was found to be a significant risk factor that increased the probability of PIRCSU (OR = 6.600, 95% CI = 1.352–32.226, p = 0.020).

**Discussion**

In this study, we found a 4.7% prevalence of PIRCSU in childhood in a large cohort. A high prevalence of gastrointestinal symptoms was observed in these patients. Moreover, the inclusion of abdominal pain in the clinical history was found to be a significant risk factor for PIRCSU.

Several studies proposed parasites as etiologic factors of CSU in the pediatric age group. The prevalence of parasites in the stool examination, regardless of the treatment response, was reported as 2.4% by Kauppinen et al. [5], 2.5% by Du Toit [14], 2.7% by Sahiner et al. [9], 3.7% by Volonakis et al. [6], and 5.3% by Jirapongsananuruk et al. [8]. Similarly, in a systematic review of the underlying causes of chronic urticaria in childhood, 6 studies were assessed, and the prevalence of parasites was found to be 3.5% [15]. However, the type of parasites or the effects of parasitic infection treatment on CSU were established only in a few small studies with an improvement rate of urticaria of 0–2% after antiparasitic medication [8, 9]. In our study, the prevalence of parasites detected in stool in children with CSU was 10% and relevance with CSU was 4.7%. This ratio appears to be slightly higher than those in other studies. The prevalence of parasites may vary according to the geographic area and socioeconomic status or environmental sanitation conditions of a country. In 2 retrospective studies from our country, the prevalence of intestinal parasites in the general population was reported as 4 [16] and 5% [17], which are lower than that of our cohort. Previous studies showed that the prevalence of intestinal parasites in patients with allergic skin disorders including chronic urticaria was significantly higher than in healthy controls [18, 19]. This reason may explain the slightly higher prevalence of parasites in our cohort.

In the present study, most of the causative parasites were protozoa, and the most common were *B. hominis* and *G. intestinalis*. In a study comparing the prevalence of intestinal parasites among patients with allergic skin disorders such as chronic urticaria and healthy controls, the prevalence of *Giardia* spp. and *B. hominis* was significantly higher in patients than in the controls [18]. Similarly, these parasites were considered the most com-

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
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<tbody>
<tr>
<td>OR</td>
<td>95% CI</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.729</td>
<td>0.200–2.662</td>
<td>0.633</td>
</tr>
<tr>
<td>Age at admission</td>
<td>0.893</td>
<td>0.770–1.035</td>
<td>0.133</td>
</tr>
<tr>
<td>Age at symptom onset</td>
<td>0.910</td>
<td>0.785–1.056</td>
<td>0.215</td>
</tr>
<tr>
<td>Symptom duration</td>
<td>0.706</td>
<td>0.404–1.233</td>
<td>0.221</td>
</tr>
<tr>
<td>UAS7</td>
<td>1.026</td>
<td>0.957–1.099</td>
<td>0.475</td>
</tr>
<tr>
<td>Angioedema</td>
<td>0.388</td>
<td>0.097–1.542</td>
<td>0.179</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>6.000</td>
<td>1.003–35.908</td>
<td>0.050</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7.667</td>
<td>1.852–31.738</td>
<td>0.005</td>
</tr>
<tr>
<td>Allergic disease</td>
<td>1.228</td>
<td>0.350–6.038</td>
<td>0.801</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>1.095</td>
<td>0.807–1.486</td>
<td>0.559</td>
</tr>
<tr>
<td>Total IgE</td>
<td>0.999</td>
<td>0.994–1.005</td>
<td>0.787</td>
</tr>
<tr>
<td>ESR</td>
<td>1.062</td>
<td>0.988–1.140</td>
<td>0.101</td>
</tr>
<tr>
<td>CRP</td>
<td>2.468</td>
<td>0.916–6.645</td>
<td>0.074</td>
</tr>
<tr>
<td>ASST</td>
<td>0.964</td>
<td>0.085–10.945</td>
<td>0.977</td>
</tr>
<tr>
<td>Skin prick test positivity</td>
<td>0.512</td>
<td>0.058–4.492</td>
<td>0.546</td>
</tr>
</tbody>
</table>

UAS7 = The sum of the daily urticaria activity score of 7 consecutive days; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ASST = autologous serum skin testing positivity.
mon parasites in CSU according to the results of the systematic review [11]. In our country, *B. hominis*, *G. intestinalis*, and *E. vermicularis* are prevalent during childhood [20].

The exact pathogenesis of parasites related to urticaria is still unclear. The proposed mechanism is the activation of skin mast cells leading to the release of histamine and other vasoactive mediators. This mechanism can be triggered by an interaction between a parasite-specific IgE and its high-affinity IgE receptors. It can also be triggered by the production of Th2 cytokines during parasitic infection, increased skin eosinophils, or activation of coagulation and the complement system [11]. Distinct mechanisms may be responsible for the diverse parasites. For example, the production of specific IgE against parasites has been shown for *Toxocara* [21] or *Anisakis simplex* [22]. Although some studies or case reports indicated high total IgE and/or parasite-specific IgE values in chronic urticaria patients infected with *Giardia* [23] or *B. hominis* [24], other studies reported no difference in total IgE levels between patients who had the same parasites and healthy controls [18]. In our cohort, total IgE levels did not differ from those of patients with PIRCSU or non-PIRCU.

Several pathophysiologic mechanisms of the induction of CSU by *B. hominis* have been proposed. For example, IgE-mediated allergic responses to parasite antigens were suggested in a few studies [25]. The significant oxidative stress caused by this protozoon was suggested as a predisposing factor of CSU [26]. Moreover, different subtypes were proposed to have distinct pathogenicity [27]. For example, the ameboid form was suggested to adhere strongly to gut epithelia and cause urticaria by an immune response to the antigens of the parasite surface [28]. Different factors, such as the parasite itself or the host, may play a role.

In this study, ESRs were within the normal limit in most of our participants, but patients with PIRCSU had significantly higher levels of ESR than those without. The ESR is a nonspecific measure of both acute and chronic inflammation. Chronic bacterial, viral or parasitic infections may induce an inflammatory response and increase ESR. Some studies showed high levels of ESR in a small proportion of patients with CSU. CSU itself is a chronic inflammatory condition of the skin that causes a slightly increased ESR.

Gastrointestinal symptoms, including nausea, vomiting, and abdominal pain, were frequent in the parasite-related group, but some patients with PIRCSU did not have any gastrointestinal symptoms. Intestinal parasites usually cause poorly localized abdominal pain and, although less frequently, diarrhea, nausea, vomiting, cramps, abdominal distention, flatulence, mucus or blood in stool, fatigue, and weight loss in patients while being sometimes asymptomatic [29]. Our results suggest that urticaria may be the only symptom of intestinal parasites.

Although some possible factors, such as concurrent gastrointestinal symptoms, previous parasitic infection, traveling abroad and unexplained peripheral eosinophilia may increase the risk of parasitic infection in a patient with CSU [11], specific risk factors associated with a parasite triggering CSU have not been established in publications to date. In the present study, we found for the first time that having abdominal pain increased the risk of PIRCSU. Recent guidelines recommend inquiring about gastric or intestinal complaints in patients with CSU [1] as supported by our data.

In conclusion, parasites may cause CSU, and remission may only be possible with the treatment of parasitic infection. The presence of abdominal pain may point to parasitic infection in patients with CSU. Therefore, we suggest that parasites should be investigated routinely as a causative factor of childhood CSU not only in tropical countries, but also in nontropical countries, especially if the patient has gastrointestinal symptoms.

### Statement of Ethics

The local ethics committee gave approval of this study.

### Disclosure Statement

All authors declare that there is no conflict of interest and no funding involved.

### References


Arik Yilmaz et al.


