

REVIEW ARTICLE

Aetiological Factors Associated with Chronic Urticaria in Children: A Systematic Review

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Chronic urticaria is a distressing condition with high costs. The aim of this literature review was to assess the relative frequency of causes of chronic urticaria in childhood and to provide guidance on which laboratory tests should be performed. Using PubMed, EMBASE and Cochrane databases, the literature from 1966 to 2010 (week 25) was systematically reviewed. Data from studies conducted on children who had had urticaria for at least 6 weeks, and assessing at least 3 different causes of urticaria, were analysed by reviewers using independent extraction. Six studies, all of low quality, met the inclusion criteria. Idiopathic and physical urticaria were common. Infections, autoimmunity and allergy were also reported. We conclude that children with chronic urticaria not caused by physical stimuli should undergo tests for allergy or infections only when there is a history of cause–effect correlation. High-quality trials are warranted to evaluate the causes of chronic urticaria in childhood. Key words: chronic urticaria; childhood; systematic review; physical urticaria; infections; idiopathic urticaria; autoimmune urticaria; allergy; food allergy; additive.

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Chronic urticaria (CU) has been defined as daily or nearly daily occurrence of wheals and/or angioedema, occurring over a period of ≥ 6 weeks (1–3). CU has a long mean duration in Western countries (4). The condition affects 0.1–0.3% of children (5). The direct cost of CU, in terms of healthcare visits, investigations and treatments, is high (6). Many aetiological factors have been associated with the onset of CU, but most cases are idiopathic (7). In order for health systems to cope with growing demands and to maximize benefits from restricted funding, it is important to identify the relevant diagnostic investigations (1, 2, 7) that should be performed in children with CU.

The aim of this systematic review of the literature was to examine studies addressing the relative frequency of different aetiologies of CU in children, in order to provide guidance as to which tests should be performed.

MATERIALS AND METHODS

A literature search of electronic databases was undertaken for relevant English-language studies published during the period 1966 to 2010 that assessed the relative frequency of aetiological factors associated with CU. The databases searched were: EMBASE, PubMed and Cochrane Library. Inclusion criteria for the studies were: children aged 0–18 years with urticaria lasting for ≥ 6 weeks, and assessment of at least 3 different causes of urticaria. The choice of selecting studies with at least 3 causes of urticaria is arbitrary in order to have enough factors whose frequency may be compared. The structure of the electronic search was as follows: “urticaria AND sensitive [Title/abstract] OR sensitivity and specificity [MeSH] OR diagnosis [Title/abstract] or diagnosis [MeSH] or diagnostic [MeSH] OR diagnosis differential [MeSH] OR diagnosis [Subheading]”, chronic urticaria AND risk [Title/abstract] OR risk [MeSH] OR cohort studies [MeSH] OR group [Text Word]”, “chronic urticaria AND relative [Title/abstract] AND risk [Title/abstract] OR relative risk [Text Word] OR risks [Text Word] OR cohort studies [MeSH] OR cohort [Title/abstract] AND studies [Title/abstract]”, “chronic AND urticaria”, “chronic urticaria AND diagnosis OR diagnostic test OR test”. The search was limited to include clinical trials, cohort and cross-sectional studies. Case reports and conference abstracts were excluded.

The database search was conducted independently by 2 reviewers for each database. The titles and abstracts of the articles retrieved by the search strategy were reviewed independently by 2 of the authors. If the study was considered potentially to meet the inclusion criteria and further details were needed to assess the study, the full text of the publication was obtained. Selected studies were assessed independently as included or excluded by 2 reviewers. The reference lists from these articles were analysed for other potentially relevant studies not identified in the database search.

Articles that met the inclusion criteria were separately subjected to full review by 2 reviewers, including quality of evidence according to GRADE (8, 9) Any disagreement between the 2 reviewers was resolved by consensus.

RESULTS

Overall results of the literature search

The search strategy yielded 3,362 papers, 141 of which were considered relevant for more detailed analysis. Of these, 6 were found to meet the inclusion criteria. There

was no disagreement between the 2 reviewers about quality scoring. For details of each included study see Table I. The number of children in each case series varied from 17 to 226 (median 89.5) for a total of 565 children ((271 males, 239 females, 55 unknown) (Table I). Overall, CU was by far most commonly classified as idiopathic, followed by autoimmune and physical (Table II).

A variety of causes was associated with CU in these studies; a summary of the investigations is shown in Table III (available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1511>).

Kauppinen et al. (10) carried out a retrospective study from 1976 to 1980. Basic laboratory tests included examination of blood values, urine and stool samples to search for intestinal parasites to determine the aetiology of urticaria (Table SI). Moreover, in an undetermined number of children, skin prick test (SPT), radioallergosorbent test (RAST) for aero-allergens, prick by prick to fruits and vegetables, and oral challenge tests for additives were carried out. In case of angioedema, serum complement was studied. On the basis of clinical findings, other diagnostic tests were carried out, as depicted in Table SI. The aetiology was established in 65% of the patients (Table III). Physical causes (29%) were the most common, followed by additives (21%), food allergy (9%) and infections (7%). The type of physical causes, additives, foods and infection eliciting symptoms was unclear. Urticaria disappeared after healing of infection. For the remaining causes, data were not shown. After a follow-up period of 3–8 years, 29 (50%) out of 46 patients had become symptom-free. The frequency of symptom-free patients was the same in children with urticaria with or without associated aetiological factors.

Volonakis et al. (11) prospectively surveyed a group of infants and children with CU, from 1985 to 1989.

Table II. *Diagnosis in children with chronic urticaria*

Diagnosis	n (%)
Idiopathic	316/565 (55.9)
Autoimmune (positive autologous serum skin test)	76/267 (28.4)
Physical triggers	59/391 (15)
Allergy/intolerance	52/565 (9)
Additives	18/95 (18.9)
Food allergy	22/565 (3.8)
Drugs	7/298 (2.3)
Inhalant allergy	5/268 (1.8)
Parasites	14/394 (3.5)
Infections	33/307 (1)
Thyroid disease	0/220
Collagen vascular disease	0/485

All children underwent medical history, physical examination, erythrocyte sedimentation rate (ESR), haemoglobin, white cell count, urinary glucose, proteinuria and urine microscopic examination (Table SI). The remaining investigations were performed on the basis of clinical findings (Table SI). No child was omitted. Positive test results were found in 61/196 children to SPT, 56/226 to dermatographism test, 4/36 to ice cube test, 1/32 to pressure test, 6/54 to exercise test, and 3/22 to cold agglutinins. ESR was elevated in 17/226 children. Parasites in stool were found in 7/189 children, both throat swab culture to streptococci and sinus X-ray in 2/22, Antistreptolysin O antibodies (ASO) in 12/56, C-reactive protein (CRP) in 3/56. Total serum immunoglobulin (Ig)E antibodies were positive in 52/196 children, specific circulant IgE antibodies in 12/134, food challenge in 6/21, and additives challenge in 6/23. Overall, physical factors were the most common triggering factors (Table III). However, the aetiology of CU remained unknown in most cases (76%). Remission of urticaria after resolution of associated aetiological

Table I. *Features of included studies on the aetiology of chronic urticaria*

Authors	Study design and duration	Population	Setting	Inclusion criteria	Quality of evidence (GRADE)
Kauppinen et al., 1984 (10)	Retrospective, case-study, 4 years	n=55 Age range: 6 months–16 years	Hospitalized at Hospital for Allergic Diseases, University Central Hospital, Helsinki, Finland	Urticaria >2 months	Low
Volonaki et al., 1992 (11)	Prospective, case-study, 4 years	n=226 M/F: 122/104 Age range: 1–14 years	In- and out-patients, St Sophia Children's Hospital, Athens, Greece	Urticaria >6 weeks	Low
Brunetti et al., 2004 (12)	Prospective, case-study, 2 years	n=93 M/F: 52/41 Age range: 9 months–16 years	Pediatric Immuno-Allergology Clinic, University of Bari, Bari, Italy	Urticaria >2 times/week and >2 months	Low
Sackesen et al., 2004 (13)	Prospective, case-study, 10 months	n=17 M/F: 12/5 Age range: 1–19 years	Pediatric Allergy and Asthma Unit, Hacettepe University, Dogramaci Children's Hospital, Ankara, Turkey	Urticaria >6 weeks	Low
Du Toit et al., 2006 (14)	Prospective, case-control study open, 5 years	n=80 M/F: 43/37 Age range: 1.25–19 years.	Allergy and Dermatology Clinic of the Red Cross Children's Hospital, Cape Town, South Africa	Urticaria >6 weeks	Low
Jirapongsananuruk et al., 2009 (15)	Prospective, case-study, 3 years	n=94 M/F: 42/52 Age range: 4–15 years	Pediatric Allergy Clinic, Siriraj Hospital Mahidol University, Bangkok, Thailand	Urticaria ≥6 weeks	Low

Table III. Percentages of causes or associations in the reviewed studies of childhood urticaria

Causes	Kaappinen et al. (10)	Volonakis et al. (11)	Brunetti et al. (12)	Sackesen et al. (13)	Du Toit et al. (14)	Jirapongsananuruk et al. (15)
Idiopathic	19/55 (34%)	171/226(75%)	27/93 (29%)	8/17 (47%)	42/80(52%)	49/94 (52%)
Physical triggers	16/55 (29%)	14/226(6%)	25/93 (26%)	9/17 (52%)	Not done	Excluded from the study
Infections	4/55(7%)	(6 cholinergic, 4 cold, 3 dermatophytosis, 1 pressure) 3/226 (13%) streptococcal infections	20/93 (21%) (7 EBV, 6 S. aureus, 4 S beta-hemolyticus, 2 HP)	6/17(35%) (3 H. pylori 1 urinary tract infection, 1 C. pneumoniae, 1 EBV)	Not done	Not done
Parasites	1/55(1%)	7/189 (3%)	Not done	0/17	1/39 (2%)	5/94 (5.3%)
Food allergy	5/55(9%)	6/21 (28%) (5 to milk, 2 to egg, 1 to fish, nuts)	5/93 (4%)	2/17(11%)	0/80	4/94 (4.2%)
Inhalant allergy	0/55	5/196 (2.5%) (2 to cat, 3 to pollens)	Not done	0/17	Not done	Not done
Additives	12/55(21%)	6/23 (26%) (3 tartrazine, 3 salicylates)	Not done	0/17	Not done	Not done
Drugs	0/55	4/226 (17%) (3 penicillin, 1 phenobarbital)	Not done	3/17(17%)	Not done	Not done
Anti-thyroid Ab	Not done	Not done	0/93	0/17	Not done	0/94
T3, T4, TSH	Not done	0/16	0/93	Not done	Not done	0/94
ASST	Not done	Not done	22/49(44%)	Not done	18/44 (40%)	36/94 (38.3%)
Other tests	Not done	Not done	HR-test. 21/52 (40%)	Not done	FceR1α Ab. 37/78 (47%)	Not done
RA	Not done	0/56	Not done	Not done	Not done	Not done
ANA	Not done	0/56	0/93	0/17	Not done	2/94 (2.1%)
Anti-DNA Ab	Not done	Not done	0/93	0/17	Not done	Not done
Serum complement	0/55	0/112	Not done	Not done	Not done	0/94

EBV: Epstein-Barr virus; Ab: antibody; ANA: anti-nuclear antibody; TSH: thyroid-stimulating hormone; ASST: autologous serum skin test; RA: rheumatoid factor test; HR-test: basophil histamine release test; T3: triiodothyronine; T4: thyroxine.

factors was reported in children with infectious diseases and in those with allergy to inhalants. For the remaining causes, data was lacking.

Some extra comments on the most recent studies (12–15)

Brunetti et al. (12) assessed the aetiology of CU by medical history, physical examination and multiple laboratory investigations. Among investigations in order to evaluate an autoimmune aetiology, the autologous serum skin test (ASST) was performed in a proportion of the initial population who had negative laboratory tests and serum-induced basophil histamine-release test (HR test) in 52 subjects. The results of ASST and HR tests reduced idiopathic urticaria from 53% to approximately 25% of cases. The ASST had sensitivity, specificity and positive and negative predictive values of 78%, 85%, 74% and 88%, respectively. The concordance between the ASST and HR test was 83%. Autoimmune tests were positive, both in children with idiopathic urticaria and in those with a known cause of urticaria (physical, infective, allergic).

Sackesen et al. (13) carried out a prospective study in children (aged 1–19 years). Despite inclusion criteria, this study has been selected since a low number of subjects was 19 years old, an age that is close to childhood. All the children underwent medical history and laboratory investigations. Idiopathic urticaria was the most frequent cause (47%), followed by physical causes and infections. The percentages of documented infections in patients with and without infectious symptoms were similar. After antibiotic treatment, remission of urticaria was reported only in 2 children who received antibiotics because of *Helicobacter pylori* and urinary tract infection.

In contrast to the two previous studies, Du Toit et al. (14) included 2 control groups in the study: 50 healthy children and 38 children with atopic dermatitis (AD) who served as controls for specific IgE and autoimmune assays. Allergic, physical and infective causes were investigated. Moreover, ASST and functional anti-Fcε receptor assays (FceR1α) were performed in order to assess an autoimmune aetiology. The methodology of execution of the test was reported. However, the value of the study was limited, since more than 20% of participants were lost from testing for IgE specific to *Ascaris lumbricoides* and from the ASST test. The CAP-RAST results were positive in 20 out of 77 children with CU and in 31 out of 38 with AD ($p < 0.001$). The elimination diet in children with suspected food allergy, with or without positive specific IgE did not result in an improvement in symptoms or in a reduction in the children's requirement for antihistamine medication. Results of stool microscopic examinations were positive for *A. lumbricoides* in one of 39 children with CU and in none of 36 eczematous children ($p < 0.005$). Specific IgE for *A. lumbricoides* were found in 21/72 (29%) children with CU and in 25/38 (66%) with AD; eosinophil count was similar in the 2 groups. The FceR1α auto-antibodies tests were positive in 37 out of 78 (47%) children with CU and in none with AD. There was no association between positive ASST results and disease remission. At variance with the findings of Brunetti et al. (8), FceR1α autoantibodies did not correlate positively with ASST. The lack of correlation between the ASST results and the presence of FceR1α in this study could be related to the fact that the ASST was performed in only 44 children. There was no difference between males and females regarding positive FceR1α autoantibodies and

ASST. This result differs from other paediatric data, which showed a male bias (12).

Jirapongsananuruk et al. (15) prospectively assessed 94 children (age range 4–15 years) by medical history, physical examination and laboratory investigations. Children with CU induced by physical causes were excluded from the study. Allergic, autoimmune and parasitic causes were investigated. Idiopathic urticaria was the most common diagnosis. CU was frequently associated with positive ASST testing. Clinical hypersensitivity reaction to food, ascertained by oral food challenge, was rarely a triggering factor when the child had a history of suspected food allergy. The prevalence of parasitic infestation was low. Moreover, the number of patients treated with metronidazole who had remission of urticaria did not differ from that observed in children who did not have parasitic infestation.

DISCUSSION

An extensive search of the literature obtained only 6 studies addressing the relative proportion of at least 3 causes of CU in children. The low quality of available trials according to the GRADE method and their poor consistency limit the possibility of drawing general conclusions and of meta-analysis of the data.

Differences in inclusion criteria for participants, definition of disease, choice and methods of laboratory investigations may explain the inconsistent findings in selected studies. Furthermore, a major caveat is that the population selection varied among studies; inpatients or outpatients, patients referred to dermatologists, allergologists or paediatricians were differently included in the trials (Table I). All the studies were open and not controlled, with the exception of one (14). One study was retrospective (10).

The reviewed studies have several limitations. A considerable loss of data, because of either incomplete ascertainment or loss at follow-up was commonly reported. Kauppinen et al. (10) lost 19% of enrolled children at follow-up, Brunetti et al. (12) 44% in execution of HR-urticaria test, Du Toit et al. (14) 51% in performance of specific IgE and 45% in execution of ASST, Sackesen et al. (13) 51% in performance of prick test and tests for the diagnosis of physical urticaria. In most cases, the investigations were not performed in the whole study population. For example, Du Toit et al. (14) and Jirapongsananuruk et al. (15) excluded from the study children with physical urticaria, and Brunetti et al. (12) Du Toit et al. (14) and Jirapongsananuruk et al. (15) did not investigate urticaria due to additives. Another possible selection bias of the reviewed surveys was that included children were a selected population of patients because they were recruited at specialized clinics. Another weakness of the selected studies was that the aetiological diagnosis was not confirmed by the remission of symptoms if the cause was dismissed, with the exception of Kauppinen et al. (10) and Volonakis et al. (11) for parasites and infections, Volonakis et al. (11) for aero-allergens and food allergens, and Jirapongsananuruk et al. (15) for food allergy and parasite infestation.

Finally, some investigations into factors associated with CU, such as serological tests for coeliac disease (16), were not considered in the reviewed studies. This makes the interpretation of the studies less clear.

Among different causes of CU in children, idiopathic urticaria was the most common diagnosis when all studies were combined. However, Sackesen et al. (13) found that physical urticaria was the most common, and Brunetti et al. (12) showed that autoimmune urticaria was the more frequent. These results bring into question the suggestion that CU in children is mainly idiopathic (7).

IgG autoantibodies towards IgE or its receptor were also frequently associated with CU in children (in 40–47% of cases) (12, 14). Du Toit et al. (14) found a significant difference in FcεR1α autoantibodies between study group and control group. The correlation between *in vivo* and *in vitro* methods used to determine IgG autoantibodies is however unclear. Du Toit et al. did not observe a correlation between a positive FcεR1α and ASST. However, their results suffered from high loss (45%) of subjects in the performance of the ASST. Conversely, Brunetti et al. (12) found a good correlation between HR-test and ASST. The advantage of ASST is that it is less expensive and easier to perform than *in vitro* assay. However, there is no evidence that a positive ASST result indicates that a specific treatment is of benefit (17). Thus, the clinical usefulness of ASST is unclear.

Regarding physical urticaria, the studies showed that this was either the most frequent cause (47%) (13), the second most frequent cause (34%) (10) or the third most frequent cause (26%) (12). On the other hand, Volonakis et al. (11) found only 6% of cases to be due to physical triggers. Among physical causes, cholinergic urticaria was the most frequent (11, 13). However, confirmation of the diagnosis by healing of urticaria after avoidance of physical stimuli is lacking in the reviewed studies (10–14). It is therefore unclear to what percentage physical urticaria is the only cause of CU.

With reference to CU and allergy, the reviewed studies showed that food allergy may be a rare cause, as confirmed by oral challenge (11, 15). Sackesen et al. (13) and Kauppinen et al. (10) stated that approximately 10% of children had food allergy. However, these rates may not be reliable, because diagnosis was made on the basis of history and positive IgE and not after food challenge, which is the gold standard for diagnosis of food allergy. Overall, the reviewed studies showed no indication for routinely testing for IgE to foods, or for children who are sensitized to foods going on an elimination diet (11).

The rate of association of CU with intolerance to additives confirmed by oral challenge ranged from 21% (10) to 2.6% (11). The relevance of such data is under debate, since it is unclear whether avoidance of additives results in remission of urticaria.

Aero-allergens should be taken into consideration as a rare cause of CU. Only Volonakis et al. (11) described

the resolution of urticaria in children with allergy to aero-allergens when the main pollen season ended. In the examined studies (10–14) a diagnosis of drug allergy was not clearly established because it was made only on the basis of medical history and not on a challenge test, which is the definite means of ascertaining the role of drugs in eliciting urticaria. Only Volonakis et al. (11) described the sort of drugs, penicillin and phenobarbital, which provoked urticaria.

The selected studies suggest that the rate of bacterial and viral infectious diseases as a possible contributing factor in CU varied greatly, from 7% (10) to 35% (13), and that of intestinal parasite infestation from 1% (10) to 3% (11). A causal association with urinary tract infection, *H. pylori*, *Streptococcus*, Epstein-Barr virus (EBV) and *Chlamydia pneumoniae* was occasionally claimed.

The role of infection in CU is sustained by the fact that healing of urticaria after resolution of infections and parasite infestation was reported by Kauppinen et al. (10) and Volonakis et al. (11). Sackesen et al. (13) anecdotally reported disappearance of wheals in 2 patients treated with antibiotic therapy, whereas in the studies of Brunetti et al. (12) and Du Toit et al. (14) the diagnosis was not confirmed by remission of urticaria after healing of infection.

Our findings show that limited investigations should be performed routinely in children with CU. Diagnostic tests should be guided by medical history and physical examination and are rarely necessary. This is in accordance with the findings of Thomas et al. (18), who showed on the basis of medical history that additional analysis of SPT and specific IgE gave positive results in only 5.2% of children with CU.

Our study suggests that physical urticaria may be the most common avoidable factor associated with CU. Among physical triggers, physicians should highlight cholinergic stimuli, cold, dermatographism, sun exposure and pressure.

We found that allergy to foods, additives, pollens and drugs or infections, including intestinal parasites, have a relatively low incidence. We therefore suggest that tests for allergy and infections are performed only when there is a history of cause–effect correlation.

Among autoimmune related causes, our survey shows that investigations for thyroid diseases or connective vascular diseases are useless (11–13). High rates of children with CU have positive IgG autoantibodies to IgE or its receptor. Their detection may enter into the clinical routine only when there is clear evidence in such patients that different and more effective treatments can be used than those already used for patients with idiopathic urticaria.

The current review highlights that judgement on the relative frequency of causes of CU in children should wait until controlled studies in the general population are available. These studies should investigate all the possible causes and verify the amelioration of urticaria after their removal when possible.

There is a need for these reports to formulate guidelines concerning diagnostic test strategies.

The authors declare no conflicts of interest.

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