Acute Urticaria in Infancy and Early Childhood

A Prospective Study

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Objectives: To establish the clinical, etiological, and prognostic features of acute urticaria in infancy and early childhood and to define its optimal management.

Design: Prospective study. The inception cohort was collected from April 1, 1992, through March 31, 1994. After initial evaluation, the course of the disease was assessed at 2 months and after 1 to 2 years.

Setting: Emergency department of a regional teaching pediatric hospital (referral center), which is also the only pediatric hospital for the general community in the city (population, 600,000 inhabitants).

Patients: Fifty-seven consecutive infants, aged 1 to 36 months, hospitalized with a final diagnosis of acute urticaria. Follow-up at 1 to 2 years was available in 40 of 57 patients.

Intervention: Oral antihistamines (dexchlorpheniramine maleate, terfenadine, or hydroxyzine hydrochloride) for 2 weeks.

Main Outcome Measures: Recurrence and chronicity.

RESULTS

CLINICAL FINDINGS

Urticaria is a common disease in childhood; however, few reports concern urticaria in infants and young children. Most studies include pediatric and adult patients or children of different age groups, although clinical and causative features may be different in the young child. In a previous retrospective study, we emphasized the presence of angioedema and hemorrhagic lesions and identified or suspected an underlying cause in 65% of cases.

The aim of this study was to define more precisely the clinical features, cause, and prognosis of acute urticaria in infants and young children, and to define the management of this frequent, alarming disorder.

Fifty-seven consecutive children with acute urticaria were included in this study (31 boys and 26 girls). The mean age was 20 months (range, 1-36 months), with only 2 patients younger than 6 months. During the same period, 14,542 patients in the same age group were hospitalized in the medical wards in our hospital. Of the 57 children, 33 (58%) had criteria for atopy.

Urticaria was generalized in 39 patients (68%) and featured annular or geographic papules and plaques in 40 patients (70%). Hemorrhagic lesions were present in 28 patients (49% of cases) and were statistically more frequent when infection and/or drug intake were associ-
PATIENTS AND METHODS

This prospective study included all children aged 1 to 36 months hospitalized for acute urticaria at Bordeaux University Pediatric Hospital, Bordeaux, France, from April 1, 1992, through March 31, 1994. This hospital is the only medical facility for children in the city and its surroundings (600,000 inhabitants). The diagnosis of urticaria was made on clinical grounds. Urticaria was defined by the appearance of circumscribed, slightly elevated, erythematosus, edematous papules or plaques. Lesions varied from moment to moment and disappeared within minutes or hours. Urticaria was considered acute if symptoms had been present for less than 6 weeks, and in many cases, hospitalization was justified by the dramatic clinical features in the first hours of eruption. The study included an initial evaluation and a follow-up.

The initial evaluation included a careful history taking based on a standardized questionnaire with emphasis on precipitating events (eg, food intake, drugs, infections, and physical factors) and complete physical examination, with detailed study of clinical features of urticaria (ie, number, size and form of lesions, pruritus, angioedema, hemorrhagic pattern, and dermatographism). The laboratory tests performed were a complete blood cell count and levels of serum aminotransferases, alkaline phosphatase, C-reactive protein, serum antibodies to Epstein-Barr virus, cytomegalovirus, and hepatitis B virus; total IgE antibodies (radioimmunological assay); and specific IgE antibodies (Dome Hollister Stier chemoluminescent assay [CLA], Epernon, France for 36 food allergens). In infants younger than 6 months, specific IgE to bovine milk proteins (b-lactalbumin, b-lactoglobulin, and casein) was determined by radioallergosorbent assay (RAST) (Pharmacia, Uppsala, Sweden). When penicillin allergy was suspected, IgE to penicillin was determined by RAST.

Microbiological studies included sampling of urine for bacterial culture, stool (bacterial and viral cultures), direct examination, and adhesive tape examination for parasites, and upper respiratory tract (nasal and throat) secretions for bacterial and viral cultures.

All children were given oral antihistamines for 2 weeks: dexchlorpheniramine maleate (0.5 to 1 mg/d), terfenadine (2 mg/kg per day), or hydroxyzine hydrochloride (1 mg/kg per day). A follow-up visit at 2 months investigated the duration of urticaria. Skin tests were performed during this visit by the prick method with the following undiluted commercial allergens (Stallergenes SA, Antony, France): cow’s milk, whole eggs, egg white, egg yolks, orange, fish, pork, corn, chocolate, strawberry, peanut, shrimp, celery, tomato, green peas, apple, artemisia, ambrosia, and other possible foods oriented by clinical history. Before 6 months, only the first 8 foods were tested. Physical tests were performed only if history was suggestive of physical urticaria. After 1 to 2 years, a questionnaire was sent to the family to assess follow-up.

Patients were arbitrarily considered atopic if they had a personal or first-degree family history of atopy (asthma, allergic rhinitis, or atopic dermatitis). A cause was considered probable when strongly suspected by history and confirmed by laboratory investigations with identification of infectious agents in association or not with drug intake, food, or a physical agent. A possible cause was an agent or a factor suspected by history and physical examination, sometimes with indirect evidence such as serological findings, but without identification of the causative agent. This category always concerned suspected viral infections, often associated with drug intake.

Statistical analysis was performed with the x² test and Fisher exact test.

LABORATORY INVESTIGATIONS

Laboratory data are summarized in the Table. Leukocytosis was found in 36 children. Among them, 34 had a probable or possible viral infection. Monocytosis was found in 4 children with Epstein-Barr virus infection—2 with identified viral infection and 1 with a suspected one. Eosinophilia was found in only 2 patients. In one, it was associated with peanut allergy and in the other, with adenovirus infection.

C-reactive protein level did not discriminate infectious from other causes (the level was normal in 30 patients with infection). Serum aminotransferase levels were increased in 7 children who had viral infection, associated in 6 cases with drug intake.

Total IgE level was elevated in 30 cases (mean, 117 kU/L; range, 2-1248 kU/L). Elevation of IgE level was not more frequent in atopic children (found in 50% of atopic children and 60% of nonatopic children), but 6 of 8 children with total IgE levels higher than 200 kU/L had personal history or clinical signs of atopy.

CAUSE

A presumptive cause was identified (25 cases) or suspected (27 cases) in 92% of cases. The probable causes were viral infections in 18 cases—associated with drug intake in 12 cases. The following viruses were found: adenovirus (5 patients), Epstein-Barr virus (5 patients), enterovirus (3 patients), respiratory syncytial virus (3 patients), rotavirus (1 patient), and varicella-zoster virus (1 patient). Probable causes in the other 7 cases in which a presumptive cause was identified were Escherichia coli.
infection in 1 case and food intake in 6 cases. The 27 cases in which a cause was suspected (possible cause) were all possible viral infections, associated with drug intake in 21 cases.

The diagnosis was established when suggestive clinical symptoms were associated with isolation of virus in stool sample (7 cases), nasal secretions (4 cases), and throat secretions (2 cases). Epstein-Barr infection was diagnosed when suggestive clinical symptoms were found in association with positive IgM antibodies (5 cases). Results of other viral serologic tests were always negative. Monocytosis (7 cases) and elevation of serum aminotransferase levels (7 cases) were considered indirect evidence of viral infection.

Bacterial infection was identified in 1 patient with gastroenteritis, in whom E coli was isolated in stool sample and throat culture.

Parasitic infestations were encountered in 5 children—3 had Giardia lamblia in the stool and in 2 oxyuriasis was diagnosed by adhesive tape method. Those infestations were not considered causative factors for urticaria for the following reasons: (1) they were asymptomatic, (2) clinical symptoms and other investigations favored another cause (especially acute viral infection of the upper respiratory tract sometimes associated with drug therapy), and (3) evolution of urticaria did not parallel the treatment of the parasitic infestation.

Twenty-seven patients had various symptoms suggestive of acute viral infection, particularly general and respiratory tract symptoms, but the infectious agent could not be identified. In 21 of these patients, an associated drug intake was found. Overall, infectious diseases (probable and possible) accounted for 81% of cases (46 patients).

A drug intake was found in 33 patients, especially antibiotics (29 cases): amoxicillin (13 cases), the oral cephalosporins cefaclor and cefatrizine (10 cases), macrolides (4 cases), and the erythromycin-sulfoxazole combination (2 cases). In most cases, urticaria occurred between the 6th and 10th days of therapy, and with a drug not always given for the first time. Others drugs, particularly antipyretics (aspirin and acetaminophen) were frequently associated (14 cases).

Foods were considered responsible for urticaria in 6 cases (11%). Angioedema of the lips was associated with food intolerance in 5 of 6 cases. The diagnosis of food intolerance was established by the association of history (recent introduction of the suspected food and appearance of urticaria in the first hours after food intake), positive specific RAST, and positive prick test (performed in only 4 cases, but always positive). The results of a challenge test were positive in 2 patients tested. The foods responsible were eggs (2 cases), cow’s milk (1 case), peanuts (1 case), mustard (1 case), and exotic fruits (1 case). The last was found in a young girl with a history of polycystic kidneys operated on in the neonatal period and who also had latex allergy. All 6 children with urticaria caused by food intolerance (except the 1-month-old infant with cow’s milk allergy) had atopic dermatitis. Atopic dermatitis was found in only 12% of children with urticaria from other causes. The cause remained unknown in 5 cases (8%).

### Results of Laboratory Investigations in Patients With Acute Urticaria

<table>
<thead>
<tr>
<th>Test</th>
<th>No. of Cases With Abnormal Results†</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBCs</td>
<td></td>
</tr>
<tr>
<td>Leukocytosis (&gt;12.0 x 10^9/L)</td>
<td>36</td>
</tr>
<tr>
<td>Monocytosis (&gt;0.10)</td>
<td>7</td>
</tr>
<tr>
<td>Eosinophilia (&gt;0.5 x 10^9/L)</td>
<td>2</td>
</tr>
<tr>
<td>CRP (&gt;12 mg/mL)</td>
<td>16</td>
</tr>
<tr>
<td>Aminotransferase (&gt;40 U/L)</td>
<td>7</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>0</td>
</tr>
<tr>
<td>Viral serologic tests</td>
<td>5 (EBV, with positive IgM anti-VCA)</td>
</tr>
<tr>
<td>Urine culture</td>
<td>0</td>
</tr>
<tr>
<td>Throat culture</td>
<td>1 (Escherichia coli)</td>
</tr>
<tr>
<td>Stool culture</td>
<td>1 (E coli)</td>
</tr>
<tr>
<td>Stool viral culture</td>
<td>7</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>1</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>3</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>3</td>
</tr>
<tr>
<td>Throat viral culture</td>
<td>2 (RSV)</td>
</tr>
<tr>
<td>Nasal viral culture</td>
<td>4</td>
</tr>
<tr>
<td>RSV</td>
<td>2</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>2</td>
</tr>
<tr>
<td>Stool for ova and parasites</td>
<td>5</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>3</td>
</tr>
<tr>
<td>Oxyuriasis</td>
<td>2</td>
</tr>
<tr>
<td>Total IgE (&gt;100 kU/L)</td>
<td>30</td>
</tr>
<tr>
<td>Penicillin RAST</td>
<td>0 (9 cases studied)</td>
</tr>
<tr>
<td>Food RAST</td>
<td>14 (7 relevant)</td>
</tr>
<tr>
<td>Prick tests</td>
<td>14/40‡</td>
</tr>
</tbody>
</table>

†Denominator is 57 unless otherwise specified.
‡Relevant in 5 and dermatographism in 3.

### COURSE AND PROGNOSIS

Forty-nine patients attended the visit at 2 months, and after 1 to 2 years, 40 patients responded to the follow-up questionnaire. Of the children, 92% were symptom free at 2 months, but only 70% after 1 to 2 years. Twelve children had chronic (3 cases) or recurrent (9 cases) urticaria irrespective of whether a cause was found at the initial episode (8 had possible viral infection [associated in 4 cases with drug intake], 2 had probable viral infection [associated in 1 case with drug intake], and in 2 the cause was unknown). Fifty percent of children with recurrent or chronic urticaria were atopic. In the 5 children with possible drug reaction to antibiotics, only 3 had recurrent urticaria when they received the same (3 cases) or another (2 cases) antibiotic. One of these 2 patients who had a relapse when given another class of antibiotics also had a recurrence of urticaria during an episode of rhinopharyngitis without antibiotic intake. On the other hand, 1 child with acute urticaria of unknown cause had a recurrence when treated with amoxicillin for an upper respiratory tract infection. None of the children with recurrent urticaria had repeated food allergen exposure leading to recurrent urticaria.
The characteristics of acute urticaria in young children are not well established. Despite its lesser frequency, most reports have concerned chronic urticaria, or have included both acute and chronic urticaria.

Our study included only hospitalized patients and therefore does not reflect the total group of patients with acute urticaria in childhood. It probably reflects a bias for more severe cases, which would lead to hospital admission. On the basis of our experience, around 4 medical admissions per 1000 within the 1- to 36-month age group are caused by acute urticaria.

Our findings show that some clinical features appear more specific to urticaria in the young child, such as frequent hemorrhagic pattern and angioedema, found in 50% and 60% of cases, respectively. Awareness of these characteristics is important because urticaria is frequently misdiagnosed as erythema multiforme or anaphylactoid purpura and is sufficiently alarming to justify hospital admission.

On the other hand, our study suggests that hemorrhagic lesions and arthralgia are statistically more frequent in urticaria caused by infections, associated or not with drug intake. Angioedema of the lips, reported in 8 children, often seems to be associated with a food cause (5 of 6 cases), as already reported. Fever was present in 50% of cases and was not always related to underlying infection. Leukocytosis was more consistently associated with possible or probable infection (noted in 34 of 36 patients within these 2 categories).

The association of acute urticaria with atopy is common, being found in more than 50% of cases in this study. This figure is difficult to compare with those in the literature, since no universally accepted criterion is applicable, and we noted a discordance between clinical criteria and IgE serum levels. The increase in total IgE level in acute urticaria may represent a nonspecific marker of the immune mechanisms involved in urticaria rather than a sign of underlying atopy.

In the present study, with the conjunction of clinical and laboratory criteria, a cause was identified or suspected in 92% of cases. An association with underlying or precipitating factors is often difficult to establish, however, especially for infectious causes, since there is no possibility to challenge the patient with the suspected agent. Success in identifying a cause in childhood urticaria is extremely variable in the literature, from 21% to 83%.

This high variability is mostly caused by the various criteria used for establishing cause and the type of recruitment, often including both patients with acute and those with chronic urticaria. Various acute benign infections, most frequently associated with drug therapy, are the main triggers of acute urticaria. We have considered infection and drug intake together because, in practice, it is impossible to dissociate between the 2 distinct causal factors. On the basis of our findings at follow-up concerning drug challenges, it is possible that the virus-drug association triggers urticaria, as is the case for rashes in Epstein-Barr virus infection treated with ampicillin. The drugs used were mainly antibiotics, especially amoxicillin and the oral cephalosporins cefaclor and cefazolin, which caused a classic serum sickness reaction between the 6th and 10th days of therapy. The RASTs to penicillin were always negative when determined in patients given β-lactam family antibiotics. Further skin testing was not done. When drug-induced urticaria is suspected, avoiding the suspect drug seems reasonable, as challenge tests are not often possible. This contraindication is probably unjustified in most cases, however, as noted when accidental challenge occurred. Only 3 of 5 children with drug-related urticaria experienced a recurrence of urticaria when given the same antibiotic. Some children who had urticaria associated with viral disease and antibiotic therapy had a relapse when another infectious illness occurred, without being given antibiotics.

Infections responsible for urticaria are the most common benign viral upper respiratory tract or digestive infections found in the young child. The major role of viral infection as trigger of acute urticaria has recently been demonstrated in a study including both pediatric and adult patients. The classic streptococcal cause of urticaria has been already debated. In our study, this cause was never found. In the young child, classic causes such as sinusitis or dental infection have not been investigated. In our study, parasitic infection was not considered a cause of urticaria as classically described. Usually, only helminths, particularly *Toxocara canis*, not investigated in our study, can induce urticaria, and only exceptionally protozoal infections are reported to do so. After completion of this study, our group found a possible association of chronic urticaria with *T. canis* infection in a mixed population of adults and children. The role of parasites is often overestimated in childhood urticaria, because if infestation is frequent in the young child, most surveys do not demonstrate a relation between the two, and most of the time, eradication of parasitic infection does not improve urticaria.

Only 11% of our cases of urticaria were caused by food, which has been considered a major classic cause of childhood urticaria, occurring in 15% to 62% of cases. The reasons for the discrepancy are multiple but relate mostly to the type of recruitment. Our study concerns only hospitalized patients with an alarming presentation, and this bias probably underestimates the number of cases caused by foods, which are easily recognized, especially for seasonal foods such as berries. Among foods, eggs are the most frequently found cause, even before 1 year of age. Cow’s milk allergy, always suspected before 6 months of age, is not the only cause, since we could find a viral infection in 1 of our 2 patients within this age group. Our study demonstrates that food-related acute urticaria is strongly associated with atopic dermatitis.

Long-term (2 years) follow-up shows that 30% of patients experience recurrent or chronic urticaria. There was no clear relationship between course and duration of initial antihistamine intake. The magnitude of the percentage of cases with a chronic/relapsing course in childhood was not suspected before our study. This percentage is most likely artificially increased because follow-up was not complete and because only 40 of 57 families responded to the written questionnaire. This might have favored a response by the parents of the children who...
were still affected. However, if we assume that those who did not respond were free of disease, a figure of around 20% remains high.

To summarize, urticaria is a frequent benign disease in the young child, but it is sometimes alarming enough to cause hospital admission. Some clinical characteristics are important to consider so that urticaria will not be misdiagnosed as a more rare and serious illness, such as erythema multiforme or Kawasaki disease. In most cases, investigations are not necessary because benign viral illnesses often associated with antibiotic therapy trigger most cases. Reassurance and antihistamine therapy are sufficient. Avoidance of the drug involved is recommended when needed. In patients with atopic dermatitis, food allergy should be investigated. Our main finding is that between 20% and 30% of young patients with acute urticaria are at risk of chronic or recurrent urticaria.

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