

Exposures and Outcomes of Children With Urticaria Seen in a Pediatric Practice-Based Research Network

A Case-Control Study

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Objectives: (1) To determine the duration, outcome, and associated findings of urticaria in children seen by general pediatricians; (2) to compare the exposure to foods, medications, insect stings or bites, and the presence of other symptoms in children with urticaria with controls; (3) to determine general pediatricians' management of urticaria.

Design: Case-control.

Participants: Children with urticaria seen by Utah Pediatric Practice Based Research Network members between August 1, 1999, and August 31, 2000. Control patients were matched for age and sex.

Main Outcome Measures: Duration of urticaria; associated symptoms; personal and family history of atopy; medications; ingestion of peanuts, nuts, shellfish, tomatoes, strawberries, or eggs; being stung by an insect; suspected cause, diagnostic studies; treatment.

Results: Fifty-two cases and 47 controls were enrolled. The mean duration of urticaria was 8.9 days (range, 1-50 days). Seventeen patients (33%) and 1 control patient were taking antibiotics (odds ratio [OR], 22.3; 95% confidence interval [CI], 2.8-176; χ^2 , $P < .001$). Fourteen patients and 5 controls had gastrointestinal symptoms (OR, 3.1; 95% CI, 1.02-9.4; χ^2 , $P = .04$). There were no differences between cases and controls for other symptoms, personal or family history of atopy, ingestion of the foods listed, insect sting, or other medications. A cause was suspected in 28 patients (54%): a "viral illness" (19%), antibiotics (15%), or a combination (35%).

Conclusions: Patients were more likely than controls to be taking an antibiotic and were more likely to have a personal or family history of atopy or to report ingesting foods commonly associated with urticaria. A viral illness was the most common cause suspected by pediatricians.

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URTICARIA or hives is a common skin condition in children that, because of its dramatic appearance and occasional association with life-threatening anaphylactic reactions, frequently results in a visit to a physician. Although most children with urticaria are probably seen by primary care physicians, the literature regarding diagnosis and treatment is primarily based on studies of adults seen by dermatologists,^{1,2} children seen in dermatology clinics,³ hospitalized children,^{4,5} or studies carried out in emergency departments.⁶ Of these studies, all but one, which reported on the use of prednisone in adult patients, were conducted outside of North America. The findings in these studies may not be generalizable to pediatric patients with urticaria in the United States. Margolis and Nisi⁷ described urticaria in an

Ohio family practice. Their retrospective medical record review series from a primary care setting of 72 patients included 16 who were younger than 17 years.

Most studies attempt to ascribe etiologies to urticaria based on histories of atopy or of reported exposures to foods, medicines, infections, or other agents. However, no study has compared the frequencies of such exposures with those of similar children who did not have urticaria. Opinions expressed in review articles by specialists in pediatric dermatology^{8,9} or pediatric allergy^{10,11} seem to be based on the authors' experiences supplemented by their reviews of the limited primary literature. Thus, these too may offer advice regarding management that may not be applicable to the typical patient seen in a pediatric practice.

To overcome the limitations of previous studies and to provide data that

METHODS

The study was conducted from August 1, 1999, to August 31, 2000, in the offices of pediatricians and physician assistants who are members of the Utah Pediatric Practice Based Research Network (UPPBRN). Participating members of the UPPBRN were asked to enroll every child with urticaria whom they saw. There were no exclusion criteria. Children who were seen more than once for the same episode of urticaria were enrolled only once. Parents of children with urticaria were invited by the physician to participate. The purpose and procedures of the study were explained and informed consent to permit telephone follow-up by the investigators was obtained. Using a checklist (**Figure**), physicians recorded the date of onset, presence or absence of other symptoms, personal and family history of atopy, medications taken in the past 14 days, ingestion of peanuts, nuts, shellfish, tomatoes, strawberries, or eggs in the 48 hours prior to onset, and whether the child had been stung or bitten by an insect during the same interval. The arbitrary times chosen to assess exposures to foods, insects, and medications, and for the presence of other symptoms were developed by consensus of the members of the research network as representing their usual practice. Physicians were asked to identify as a control the next child whom they saw of the same sex and age. For children younger than 5 years the age of the control was to be within 6 months of the age of the index patient and, for index patients older than 5 years, the age of the control was to be within 1 year of the index patient. Parents of this child completed a checklist that contained the same items indicated above.

On a checklist for each patient, physicians indicated the suspected cause, their degree of certainty about the cause, the diagnostic study results obtained, and the treatment recommended. Parents were contacted by telephone by one of the investigators (J.P.) at 2 to 3, 14, and 30 days after their visit to determine the duration of the urticaria, whether additional symptoms had developed, whether medications were used, and whether they caused any adverse effects. The study was approved by the institutional review boards of both the University of Utah Health Science Center and Primary Children's Medical Center (Salt Lake City). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to compare patients with controls with respect to exposures to possible etiologic agents. Odds ratios whose 95% CIs did not include 1.0 were judged to be significant. Descriptive statistics were used to characterize various aspects of the patients and χ^2 or t tests were used to test for differences between patients and controls. An α of .05 was considered to be significant. Analyses were performed using StatView (Abacus Concepts, Berkeley, Calif).

might better assist in decision making by primary care physicians, we designed a study of children with urticaria who were being seen in primary care pediatric offices. The study had 3 principal objectives: (1) to

URTICARIA IN PEDIATRIC PRACTICE PATIENT ENCOUNTER FORM

1. Date of Visit _____
2. Date of Onset of Urticaria _____
3. Has this child had a previous episode of urticaria?
☐ No
☐ Yes: If yes about how many times? _____ Approximately when was the most recent episode? _____
4. Has this child ever had: ☐ Asthma ☐ Hay fever ☐ Eczema
5. Has this child's brothers, sisters, mothers or father ever had: ☐ Asthma ☐ Hay fever ☐ Eczema
6. Has this child had any of the following symptoms in the 2 weeks prior to onset of urticaria? Check all that apply

a. ☐ no symptoms	f. ☐ diarrhea
b. ☐ fever	g. ☐ any other symptoms; please list _____
c. ☐ cough or runny nose	
d. ☐ sore throat	
e. ☐ vomiting	
7. Has this child been on any medications, prescription or non prescription, in the 2 weeks prior to the onset of urticaria?
☐ No ☐ Yes (please list) _____
8. Please indicate if the child had eaten foods containing any of the following in the 48 hours prior to the onset of urticaria?

☐ nuts	☐ strawberries
☐ peanut (including peanut butter)	☐ tomatoes
☐ eggs	☐ none of the above
☐ shellfish	
9. Had this child been stung or bitten by an insect in the 48 hours prior to the onset of urticaria?
☐ No ☐ Yes
10. Did you perform any laboratory studies on this patient?
☐ No ☐ Yes (please list) _____
11. Did you prescribe or recommend medications for this episode of urticaria?
☐ No ☐ Yes (what?) _____
12. How certain are you that you know the cause this episode of urticaria?

a. ☐ 100% certain that it was caused by _____
b. ☐ Most likely (75%-90% certain) it was caused by _____
c. ☐ May have been (50%-74% certain) caused by _____
d. ☐ Could have been (25%-49% certain) caused by _____
e. ☐ Don't know (<25% certain) what caused it

Sample physician checklist.

determine the duration, outcome, and associated findings of children with urticaria seen in pediatric practice; (2) to compare children with urticaria with controls matched for age and sex with respect to ingestion of foods commonly believed to be associated with urticaria, medication exposure, presence of symptoms of other illnesses, and being stung or bitten by an insect; and (3) to determine the management of children with urticaria by primary care physicians.

RESULTS

During the study period, 52 patients with urticaria were enrolled by 14 pediatricians and 1 physician's assistant, with 1 to 10 patients per physician. None of the parents who were asked to participate refused. For 5 of the patients no control was identified. Patients ranged in age from 6 months to 18 years (mean age, 69 months) and 29 (56%) were female. Successful telephone contacts were made with 46 of the parents.

Odds Ratios of Exposures: Cases and Controls*

Characteristic	Patients, No. (%) (n = 52)	Controls, No. (%) (n = 47)	Odds Ratio (95% CI)
Atopic	17 (33)	20 (43)	0.66 (0.29-1.48)
Family history of atopy	29 (58)	31 (66)	0.71 (0.31-1.62)
Fever	15 (29)	16 (34)	0.78 (0.34-1.84)
URTI	31 (59)	30 (63)	0.84 (0.37-1.89)
Sore throat	9 (17)	11 (23)	0.68 (0.26-1.84)
GI symptoms†	14 (27)	5 (11)	3.10 (1.02-9.4)
All medications	32 (62)	23 (49)	1.67 (0.75-3.71)
Antibiotics‡	17 (33)	1 (2)	22.3 (2.84-176)
Nuts	6 (12)	8 (17)	0.63 (0.20-2.0)
Peanuts	21 (40)	18 (38)	1.09 (0.49-2.45)
Eggs	18 (35)	17 (36)	0.93 (0.41-2.13)
Shellfish	1 (1.9)	0	... (...)
Strawberries	2 (4)	7 (15)	0.23 (0.05-1.16)
Tomato	25 (48)	26 (55)	0.75 (0.34-1.65)
Stung/bitten	6 (12)	3 (6)	1.90 (0.45-8.12)

*CI indicates confidence interval; URTI, upper respiratory tract infection; GI, gastrointestinal; and ellipses, not applicable.

† $P = .04$ (χ^2 ; patients vs controls).

‡ $P < .001$ (χ^2 ; patients vs controls).

The 46 parents who were successfully contacted reported a mean duration of 8.9 days (range, 1-50 days). The median duration was 5 days and 33 (72%) reported that the urticaria had cleared within 10 days of onset.

The **Table** shows the ORs with 95% CIs for exposures to potential etiologic agents or the presence of other symptoms reported by parents of patients and controls. Significant differences were found in reported antibiotic use and the presence of gastrointestinal symptoms. Parents of 17 patients (33%) reported antibiotic use in the previous 2 weeks compared with parents of one of the controls (OR, 22.3; 95% CI, 2.8-176) (χ^2 , $P < .001$). Fourteen patients (27%) were noted to have gastrointestinal symptoms compared with 5 controls (11%) (OR, 3.1; 95% CI, 1.02-9.4; χ^2 , $P = .04$). Confidence intervals of the ORs included 1.0 for all other factors studied. This suggests that there were no significant differences between patients and controls with respect to the presence of fever, sore throat, upper respiratory tract symptoms, a personal or family history of atopy, ingestion of the 6 foods, medications other than antibiotics, or of being stung or bitten by an insect.

Physicians reported performing laboratory tests on 7 of the 52 patients: 4 were tested for group A streptococcal pharyngitis (all negative), 2 had complete blood cell counts performed, and 1 had a urinalysis. A cause was suspected by physicians in 28 of the patients (54%): "viral illness" (19%), antibiotics (15%), or a combination (35%). Physicians reported that they were "less than 50% certain" of the cause for 60% of the patients. No physician reported "100% certainty" for any of the patients, but in 15 (30%) certainty was reported as being between 75% and 90%. Antihistamines were recommended for 41 (79%) of the patients and prednisone for 3. Of the children for whom medications were recommended or prescribed, all but 3 reportedly took them as directed. Drowsiness or irritability believed to be secondary to the medications was reported by 30% of the

parents and 2 discontinued the medications because of these adverse effects.

COMMENT

Our study is the first that we are aware of to describe children with urticaria who were seen in primary care pediatric offices in the United States and to use a case-control design to compare them with similar children without urticaria. While the mean duration of urticaria was about 9 days, it had resolved within 5 days in half of the children in our study. We found that a specific cause was not identified in most of the patients and that when pediatricians did suspect a particular cause, their confidence that there was a true cause and effect relationship was relatively low. Laboratory tests were done infrequently, and most children were treated with antihistamines, which were well tolerated.

Although viral or group A streptococcal infections, the ingestion of certain foods, or being stung by an insect have been suggested in the literature to be causally associated with urticaria,⁷⁻¹¹ we found that a positive history was no more likely to be reported in children with urticaria than in matched children who were being seen in the office on the same day for some other reason. Similarly, children with hives were no more likely to be atopic or to have first-degree relatives with asthma, hay fever, or atopic dermatitis compared with control children. However, children with hives were significantly more likely to be taking or to have recently taken antibiotics. We suspect that the barely significant difference between patients and controls with respect to the presence of gastrointestinal symptoms is probably a chance finding given the many variables (14) and the fact that the lower limit of the 95% CI was 1.02. In contrast, the difference in use of antibiotics seems statistically robust and is likely to be clinically valid.

This study has several important limitations. First, it is likely that some children with urticaria who

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were seen by Utah PPBRN physicians were not enrolled in the study because of time pressures or other reasons. Thus, some selection biases, possibly toward including children with more severe manifestations, could have been present. Additionally, children with hives who were not brought to the pediatrician were not included in the study. Second, we were unable to estimate the prevalence of urticaria because we were unable to accurately determine how many patients were seen by reporting physicians during the study period. Third, the physicians are all from Utah and their patients, mostly white and middle class, may not be representative of children seen by pediatricians in the general population of the United States. The pediatrician's diagnostic and management choices may also not be representative of pediatricians in general. The wide CIs for some of the items being compared between the patients and controls reflects the infrequent occurrence of some of the exposures. For example, only 1 child with urticaria reported ingestion of shellfish in the previous 48 hours compared with no children from the control group.

Even though we found an association between antibiotic use and hives, a case-control study cannot prove causality. One should not conclude that the items with no association could not be causal; it is also possible that the items with no association could be causal. However, one should be very cautious in attributing a cause and effect relationship if the conclusion is based only on a history of exposure since we found that a history of exposure was just as likely to be obtained from parents of children who did not have urticaria as it was from parents of children who did.

Our study calls into question many of the associations reported in previous reports and repeated in review articles. For example, Legrain et al³ reported that based on "a careful history and physical examination . . . drug intake and infection accounted for 37.5% of all cases of urticaria," in their series of 40 infants hospitalized for urticaria at a children's hospital in Bordeaux, France. Similarly, physicians in our study suspected this combination in 44% of their patients but when we compared children with and without urticaria we found that the 2 groups were equally likely to report a history of such exposures. The role of foods as a cause

What This Study Adds

Descriptions of urticaria in children and recommendations for management are based primarily on reports and reviews of hospitalized children or those seen by dermatologists. Understanding the condition as it is commonly seen in general pediatric practice may provide information that is more helpful to primary care practitioners. A case-control design allows comparison of children with and without urticaria with respect to associated exposures or other possible causal factors.

Exposures to foods often cited as potential causes of urticaria, symptoms of other illnesses, and insect stings or bites are as common in controls as in children with urticaria. Children with hives are more likely to be taking antibiotics than are controls. Children with hives who are seen by general pediatricians differ little from matched controls. Thus, attributing a relationship between exposure to a particular substance or an associated illness based only on a history of exposure may be unwarranted.

for urticaria remains uncertain. Legrain et al³ reported that 25% of their cases were caused by foods while Morureux et al⁴ and associates indicated that 11% of their cases were food related. Kauppinen et al⁵ from Finland found a similar number in children (13%) but a greater number in adults (25%), and other figures as high as 62% have been quoted.⁹ We found no differences in histories of recent ingestion of 6 foods reportedly associated with urticaria^{8,9} between patients and controls. Other foods sometimes associated with allergic reactions such as chocolate, cows' milk, or soy were not included in our history checklist. Without further evaluation, such as skin testing or blinded challenge, attributing a child's hives to ingestion of a particular food should be a tentative conclusion. We were unable to find reports of the etiology of hives being verified by an experimental technique such as blinded food challenge. Of course, immediate reactions of an anaphylactic nature following ingestion of a food should be carefully evaluated and treated with great caution. Because of different definitions of atopy, it is not surprising that its potential association with urticaria varies, with studies reporting 20%,³ 26%,¹ 29%,⁷ and 50% rates of occurrence.⁴ Our findings showed that 33% of the children with hives were atopic, which was defined as having a history of asthma, seasonal rhinitis, or atopic dermatitis. This percentage is in line with these studies but it should be considered in light of the fact that 43% of controls also had a history of atopy. As expected, we found greater percentages when a first-degree relative of patients (58%) and controls (66%) had one of the atopic conditions. This was not significantly different.

Similar to many conditions seen in primary care practice, uncertainty regarding the etiology of urticaria is common. In a family practice setting, no cause was identified for 54% of the patients.⁷ The pediatricians in our study suspected a cause in 52% of the patients but they gen-

erally expressed low degrees of certainty about the particular cause.

All but one of our patients had acute urticaria, the exception being a child whose urticaria finally resolved on day 50, about 1 week longer than the arbitrary separation between acute and chronic (6 weeks' duration). Chronic urticaria seems to be much less common even in specialty clinics¹⁻⁴ so it is not surprising that it is rare in primary care settings. A carefully performed case-control study of children with chronic urticaria might produce different results from ours.

Studies of diseases and conditions conducted in practice-based research networks may provide different results from those conducted in specialty clinics or academic centers. Using a case-control design in pediatric practice-based research networks, we found that recent antibiotic use was significantly more common in children with urticaria but that other agents, such as foods, insect bites and stings, or symptoms suggesting infection, were no more common in children with urticaria than in age- and sex-matched children who were being seen in a primary care pediatrician's office for reasons other than urticaria. Physicians seeing children in settings similar to ours should inquire about antibiotic use as well as the other factors but should be cautious in attributing a cause and effect relationship based only on a history of exposure.

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REFERENCES

1. Humphreys F, Hunter JAA. The characteristics of urticaria in 390 patients. *Br J Dermatol*. 1998;138:635-638.
2. Zuberbier T, Ifflander J, Semmler C, Henz BM. Acute urticaria: clinical aspects and therapeutic responsiveness. *Acta Derm Venerol (Stockh)*. 1996;76:295-297.
3. Legrain V, Taieb A, Sage T, Maleville J. Urticaria in infants: a study of forty patients. *Pediatr Dermatol*. 1990;7:101-107.
4. Mortureux P, Leaute-Labreze C, Legrain-Liferman V, Lamireau T, Sarlangue J, Taieb A. Acute urticaria in infancy and early childhood. *Arch Dermatol*. 1998;134:319-323.
5. Kauppinen K, Juntunen K, Lanki H. Urticaria in children. *Allergy*. 1984;39:469-472.
6. Pollack CV Jr, Romano TJ. Outpatient management of acute urticaria: the role of prednisone. *Ann Emerg Med*. 1995;26:547-551.
7. Margolis CF, Nisi R. Urticaria in family practice. *J Fam Pract*. 1985;20:57-64.
8. Weston WL, Badgett JT. Urticaria. *Pediatr Rev*. 1998;19:240-244.
9. Mahmood T, Janniger CK. Childhood urticaria: cutis. 1993;52:78-80.
10. Zacharisen MC. Pediatric urticaria and angioedema. *Immunol Allergy Clin N Am*. 1999;19:364-385.
11. Kwong KY, Maalouf N, Jones CA. Urticaria and angioedema: pathophysiology, diagnosis and treatment. *Pediatr Ann*. 1998;27:719-724.