Acute Urticaria Associated with Streptococcal Infection

Diane E. Schuller, MD, and Sharon M. Elvey, MD

From the Division of Pediatrics, Department of Pediatric Cardiopulmonary and Allergic Diseases, Geisinger Medical Center, Danville, Pennsylvania

ABSTRACT. Eighty-one cases of acute urticaria were treated in our institution over a two-year period. In 13 of 32 cases screened for streptococcal pharyngitis, either positive throat culture, significant streptococcal exoenzyme antibodies (Streptozyme test), or both were found. Other causative factors for the acute urticaria had been excluded. It is our feeling that β-hemolytic streptococcal infection may be a causative agent in many cases of acute urticaria, and that the infection may not always be clinically apparent. We therefore recommend a throat culture and determination of streptococcal enzyme level as routine procedures in evaluating acute urticaria. We also suggest, based on the findings in one case, that discontinuing antibiotic therapy for a streptococcal infection when urticaria develops, even though necessary, might be inappropriate. *Pediatrics* 65:592–596, 1980; *urticaria, streptococcal infections, antibiotic therapy.*

Acute urticaria is a frequent problem seen by the pediatrician. Most physicians immediately assume that an allergy is involved and pursue this belief when questioning the child or parent. Inquiries are made regarding the ingestion of medications, new or different foods, soaps or detergents, etc. Commonly, when the answers given fail to reveal the etiology, we dismiss the condition as "idiopathic." In any event, the acute condition is usually felt to be benign. It is easily suppressed by treatment with antihistamines and often resolves spontaneously.

In the past, urticaria has been reported to be associated with viral infections.[1,2] Recently, we have noted a significant incidence of β-hemolytic streptococcal infection as a cause of acute urticaria in children. This correlation has not been well documented in the literature. Obviously, we feel that such an observation is significant, in view of the importance of discovering these infections. It may further have implications regarding the development of urticaria in children with streptococcal infection who are treated with antibiotics, since the physician usually assumes that such reactions result from the use of the drug.

A review of 81 cases of acute urticaria treated in our hospital over the past two years revealed that streptococcal infection was implicated in 16%. Unfortunately, a search for this type of infection was not done in more than 60% of the cases. Thirteen (40%) of the 33 cases examined for streptococcal infection were found to have it. Hence, one may assume that the actual incidence could be higher than 16%.

METHODS

Documentation of streptococcal infection was made by obtaining either a positive streptococcal throat culture or a significant streptococcal exoenzyme antibodies titer (Streptozyme test).

A streptococcal screening throat culture is performed routinely at our hospital. We are interested only in finding β-hemoltyic *Streptococcus*, and no other pathogen is sought, making the test less expensive. An appropriately collected throat swab specimen is plated on blood agar medium, incubated at 37 C for 24 hours, and then examined. The presence of hemolysis alerts the observer to the possible presence of β-hemolytic *Streptococcus*, and the colonies are then further examined for identification.

The streptococcal exoenzyme antibodies test is a simple, two-minute slide hemagglutination procedure that quantitatively measures multiple antibodies to the streptococcal extracellular products, including antistreptolysin O, deoxyribonuclease B, hyaluronidase, streptokinase, and nicotinamide adenine dinucleotide glycohydrolase. Because it mea-

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Reprint requests to (D.E.S.), Department of Pediatric Cardiopulmonary and Allergic Diseases, Geisinger Medical Center, Danville, PA 17821.

sures multiple antistreptococcal antibodies, it is a reliable indicator of streptococcal infection.[3,4]

RESULTS

All cases diagnosed by positive throat cultures are reviewed in Table 1.

In cases 1 through 3 the children had urticaria without angioedema noted on physical examination, complained of a sore throat, and had pharyngitis on physical examination.

In case 4, the child was initially afebrile when he developed urticaria and an exudative tonsillitis, but the next day he became further symptomatic with fever and generalized angioedema of his hands and feet. Interestingly, this was the only case of typical exudative streptococcal tonsillitis noted. A test for heterophile titer was negative. The ESR was elevated (55 mm/hr) and the WBC count showed a leukocytosis (16,000/cu mm) with an increased number (17%) of band forms.

Case 5 deserves special mention. This case involved a 9-year-old girl with pruritic urticarial lesions over the sides of her abdomen that progressed over a 24-hour period to involve the forearms with swelling of her fingers and toes. She had no other physical complaints. Her history was negative for food allergy, drug ingestion, and new contactants. Physical examination, aside from the above findings, showed only a mildly injected pharynx. Laboratory studies showed a normal complete blood cell (CBC) count, ESR, C_3 level, SGOT level, and negative heterophile, antinuclear antibody, and streptococcal exoenzyme antibodies titers. A throat culture was positive for β-hemolytic *Streptococcus*. She was initially treated with epinephrine (Sus-Phrine), intramuscular diphenhydramine hydrochloride (Benadryl), oral hydroxyzine hydrochloride (Atarax), and prednisone. Oral penicillin therapy was started the next day. At a follow-up appointment two weeks later, she reported continued occasional episodes of urticaria. A repeat throat culture was again positive for β-hemolytic *Streptococcus*. The streptococcal exoenzyme antibodies level was not positive at a 1:100 dilution, indicating an antibody response to infection. She was subsequently treated with 1.2 million units of penicillin G benzathine and penicillin G procaine suspension (Bicillin C-R). She returned again for a follow-up visit ten days later and had no further recurrence of hives. A throat culture taken then was negative for *Streptococcus* and the streptococcal exoenzyme antibodies titer was also negative.

Case 6 is an example of a suspected drug reaction that was subsequently rejected. This 4-year-old girl was treated for ten days with penicillin for a documented β-hemolytic streptococcal throat infection. Medication had been discontinued for only five days when she became ill with intermittent fever and irritability. A β-hemolytic streptococcal throat infection was again documented. On the third day of this second course of penicillin therapy, urticaria developed. She was given diphenhydramine and the antibiotic was changed to erythromycin. She was taking no other medication, including aspirin. Her condition subsequently improved and repeat cultures were negative. Six months later, she was again treated with penicillin for a pharyngitis and had no reaction. It would seem more reasonable to assume that her urticaria was secondary to infection rather than a drug reaction.

In cases 7 through 13, an elevated streptococcal exoenzyme antibodies titer indicated a recent streptococcal infection. These cases are reviewed in Table 2. Only in case 7 was a positive pharyngitis noted on physical examination. Only two other children (patients 8 and 10) had complaints of a sore throat. One child, patient 9, had abdominal discomfort, which is known to be associated with streptococcal pharyngitis. Two children, patients 12 and 13, were asymptomatic and had normal results of physical examinations.

No children were taking aspirin when the hives developed. Only patient 7 was taking medication—theophylline. He subsequently took this medication after recovery with no difficulty. This is also the only child who had a history of inhalant allergies. Interestingly, he had no history of urticaria and has not experienced a subsequent episode.

The highest titers were obtained between four days and one month after the onset of hives. One month before her visit, patient 11 had experienced urticaria lasting for several days associated with fever and vomiting. She was subsequently treated on that occasion with erythromycin estolate (Ilosone) although no throat culture was obtained. The parents sought evaluation retrospectively. A CBC count, results of urinalysis, and complement titer were normal. The streptococcal exoenzyme antibodies titer was positive at a 1:400 dilution, indicating recent infection. As noted, no other factor could be implicated as the possible cause of her urticaria.

Patient 8 had a positive streptococcal exoenzyme antibodies titer at a dilution of 1:100. However, this was three weeks after the onset of continuing urticaria, hence a higher titer may have been missed. Because of his associated symptoms and persisting urticaria, this titer was considered significant enough to warrant treatment despite a negative culture. His condition subsequently improved with no return of the urticaria.

In case 12, unfortunately a throat culture was not done. The patient in this case is the only with a past history of urticaria. The previous episode,

TABLE 1. Diagnosis of Streptococcal Infection by Positive Throat Culture

Case	Age (yr)/ Sex	Temperature	Sore Throat	Cervical Adenitis	Inflamed Throat	Other Complaints	Associated Foods/Medicines	Medical Treatment	Previous/Subsequent Culture Negative	Streptococcal Exoenzyme Antibodies Titer	Onset of Hives Before Diagnosis	History of Hives	Known Allergy
1	12/F	Afebrile	+	+	+	None	None/none	Erythromycin, hydroxyzine hydrochloride	Yes/yes	NR*	4 days	...	NR
2	11/F	Afebrile	+	–	+	None	None/none	Diphenhydramine hydrochloride, penicillin	Yes/yes	NR	4 days	...	...
3	7/F	NR	+	–	+	None	None/none	Hydroxyzine, penicillin	NR/NR	NR	1 wk	...	...
4	9/M	Afebrile	–	–	+	Headache	None/none	Erythromycin, prednisone, diphenhydramine	NR/yes	1:200	1 day	NR	...
5	9/F	Afebrile	–	–	+	None	None/none	Prednisone, hydroxyzine, oral & intramuscular penicillin	NR/yes	1:100	1 day	NR	...
6	4/F	Afebrile	–	–	+	None	None/penicillin	Erythromycin, diphenhydramine	Yes/yes	NR	1 day	...	...

* NR, not recorded.

TABLE 2. Diagnosis of Streptococcal Infection by Positive Streptococcal Exoenzyme Antibodies Titer

Case	Age (yr)/ Sex	Temperature	Sore Throat	Cervical Adenitis	Throat Appearance	Other Physical Findings	Other Symptoms	Throat Culture	Streptococcal Exoenzyme Antibodies Titer	Associated Medications/ Foods	Onset of Hives Before Diagnosis	Known Allergy	History of Hives	Medical Treatment
7	6/M	Afebrile	–	+	Inflamed	None	Cough, wheeze	–	1:800	Theophylline/ none	9 days	+	–	Cephalexin, hydroxyzine hydrochloride
8	11/M	Afebrile	+	+	Normal	None	None	ND*	1:100	None/none	3 wk	–	–	Penicillin, diphenhydramine hydrochloride
9	7/M	Afebrile	–	–	Normal	Abdominal tenderness	Abdominal pain	ND	1:600	None/none	4 days	–	–	Penicillin, hydroxyzine, epinephrine
10	10/F	Afebrile	+	–	Normal	None	Headache, abdominal pain	–	1:800	None/none	4 days	–	–	Penicillin, diphenhydramine
11	7/F	Febrile 1 mo before visit	–	–	Normal	None	Vomiting 1 mo before visit	ND	1:400	None/none	1 mo before visit	–	–	Erythromycin estolate 1 mo before visit, diphenhydramine
12	14/F	Afebrile	–	–	Normal	None	None	ND	1:200	None/none	1 day	–	+	Epinephrine, erythromycin, diphenhydramine
13	8/F	Afebrile	–	–	Tonsillar hypertrophy	None	Swollen lips	ND	1:800	None/none	1 mo (4 episodes)	–	–	Diphenhydramine

* ND, not done.

which had occurred one year earlier, was also associated with an infection, an episode of *Mycoplasma* pneumonia. Laboratory studies done during the current episode showed no evidence of *Mycoplasma* pneumonia. CBC count and results of urinalysis were normal, and heterophile and streptococcal MG antibody titers were negative. The latter are agglutinins for the MG strain of nonhemolytic streptococci which are often nonspecifically elevated when there is an infection with *Mycoplasma pneumoniae*. These had been elevated during her prior episode and she also had documented pneumonia on chest x-ray at that time. Cold agglutinin titers were unchanged from the previous year. However, the ESR was elevated (20 mm/hr) and the streptococcal exoenzyme antibodies titer was positive at 1:200. No medications, including aspirin, could be implicated as a causative factor and she had no fever. Because we did not want to risk withholding treatment for streptococcal disease, she was given a ten-day course of erythromycin therapy. She had no recurrence of hives.

In case 13, the child was not treated initially with antibiotics because the elevated titer of 1:800 was obtained but not observed until two months after her initial visit when she returned for follow-up. No throat culture was obtained on her initial visit. Intermittent urticaria continued, and a repeat titer obtained at the second visit had fallen but was still elevated at 1:400. A throat culture taken at that time was negative; however, one taken a month later was positive. Because intermittent urticaria continued to occur, she was finally treated with penicillin and the hives resolved.

DISCUSSION

Previously, streptococcal infections have been associated with rashes such as erythema marginatum, erythema annulare, erythema circinatum, or erythema nodosum.[5] In an extensive search of the medical literature, we could find no cases reported with the association of typical urticaria. From our observations, we conclude that this occurrence is fairly frequent.

Reviewing our observations, cases 1 through 5 clearly comprise acute urticarial episodes associated with positive streptococcal throat cultures. The children were properly treated and the hives resolved. One could argue that resolution of the hives may have been spontaneous and would have occurred even without penicillin treatment. However, in case 5, the urticaria did not resolve while *Streptococcus* persisted in the pharynx. It did finally clear after eradication of the *Streptococcus* with intramuscular penicillin therapy. One might try to argue that these patients were carriers of *Streptococcus* and that the positive throat culture was coincidental. However, in cases 1, 2, 4, and 5, previous and/or subsequent cultures were negative. Likewise, fever cannot be the precipitating or exacerbating factor, as it was known to be absent in cases 1, 2, and 5. In case 3, no mention is noted of a fever but unfortunately the temperature was not recorded. In case 4, the child was initially afebrile when the rash appeared and then he developed fever 24 hours later. In none of these cases were the patients taking medicines, including aspirin, at the time of onset of these hives. In no instance could food, contactants, or any other precipitating factor be implicated. Lastly, they had no history of urticaria and no known allergies.

The asymptomatic nature of a streptococcal throat infection is seen in case 5. This patient did not complain of a sore throat, nor did she have any symptoms of an upper respiratory tract infection. The only sign of illness was the urticaria. Subclinical infections are well known. Ayoub et al[6] studied institutionalized children and demonstrated asymptomatic streptococcal infection occurring in 40 children during an epidemic. This realization is extremely important because throat cultures are rarely done when there is no subjective or objective sign of throat involvement. In case 5, if a throat culture had not been done despite the negative history of sore throat and no physical signs indicative of streptococcal pharyngitis, the cause for urticaria would have never been documented.

Unfortunately, by the time a physician sees a child with hives the lesions have usually been present for varying lengths of time. We must then attempt to look retrospectively for what may have been the inciting cause. One manner of further determining if a child has had a recent streptococcal infection is to perform the streptococcal exoenzyme antibodies test.[3,4] It has a reported sensitivity of 73% and a specificity of 90%,[7] making it as sensitive and no less specific than any one test. It also demonstrates an increase in antibody level earlier than other tests: from 6 to 9 days in 50% of the patients in one study[7] and from 8 to 12 days in 87% of the patients in another study.[4] While peak titers occur early, falling titers do persist in the blood for as long as four months.[4] As with any titer, a single reading may be difficult to interpret, so it is preferable to examine sequential pairs of serum samples. This necessitates obtaining blood samples at the onset of illness, but unfortunately, as we have mentioned, the patient is frequently not seen at that time. In any event, a positive streptococcal exoenzyme antibodies titer (especially a titer of 300 or greater) seems to indicate a recent infection.[8] We therefore used this test in a further attempt to discover if *Streptococcus* was involved in producing urticaria.

In reviewing our observations, we see that there

were seven urticarial cases in which the streptococcal exoenzyme antibodies titer was positive. In five of these cases, the titers were greater than 1:300, indicating a recent infection. In case 8, where the titer was present at a 1:100 dilution, the child had had a sore throat three weeks earlier at the time of onset of urticaria. As the titers peak between the 6th and 12th days after onset of infection, it is likely that this level was obtained during the period of decline. In this particular case, because the child had persistent urticaria despite the use of antihistamines during this three-week period, we felt that antibiotic treatment was appropriate. The hives did indeed clear after antibiotic therapy.

In case 12, failure to demonstrate a rise in titer (the patient failed to return for follow-up at the scheduled interval) might preclude a conclusion of a causal relationship between the urticaria and streptococcal infection. However, the patient did have an elevated ESR and a streptococcal exoenzyme antibodies titer positive at 1:200 only one day after onset of the urticaria and angioedema. In patient 4, who had a documented streptococcal throat infection, the titer was likewise 1:200 one day after onset of symptoms. Thus the titer may have subsequently risen higher, since the peak level is not attained before five days. Her only symptom was a severe urticaria and angioedema which initially warranted the use of sustained release epinephrine and diphenhydramine for control. No cause for the urticaria could be found other than the implication of streptococcal disease.

Case 13 represents persisting intermittent urticaria of three month's duration associated with continuing significant elevation of the streptococcal exoenzyme antibodies titer. Resolution of the urticaria did not occur until the patient was treated with penicillin after a positive throat culture was obtained.

In the seven urticarial cases in which streptococcal exoenzyme antibodies titers were positive, throat cultures were not done in five and they were negative in two. It has been noted that throat cultures taken on only one occasion may miss a documented streptococcal throat infection in 9% of the cases.[9] We also cannot be certain that a streptococcal infection was not present elsewhere in the body. In all seven of these cases, other causes of urticaria were excluded. Most important, in each case when the child was given appropriate treatment for a streptococcal infection, the urticaria ceased. While one may argue that resolution of the urticaria might have been due to natural processes rather than treatment with penicillin, it must be remembered that in cases 5, 8, and 13 the urticaria persisted and did not finally resolve until the streptococcal infection was noted and appropriately treated.

There are important implications for the realization that streptococcal infection is associated with urticaria. This is illustrated in case 6. This patient had a streptococcal throat infection and developed urticaria on the third day of penicillin therapy. In this case, we were aware of the association of urticaria with streptococcal infection. While another physician appropriately substituted a different antibiotic, when the opportunity arose six months later, she was orally challenged with penicillin and subsequently completed a full ten-day course of therapy with no adverse reaction. It is therefore conceivable that some urticarial reactions that occur in children during antibiotic therapy for streptococcal throat infections are secondary to the infection itself and not the drug. However, one obviously has to use extreme caution in making this decision. Safety precautions generally necessitate discontinuing the drugs' use.

Obviously, our review has limitations. It is not prospective, and our conclusions are diminished by the absence of a control group of well children with throat cultures and streptococcal exoenzyme antibodies titers. However, we feel our observations are important and should alert every physician to the fact that streptococcal infection, even a subclinical one, may result in acute urticaria. A throat culture and streptococcal exoenzyme antibodies titer should be obtained in every patient at the initial visit and repeat titers obtained two weeks later. This should be done not only because we are obligated to make an accurate diagnosis, but also because streptococcal infection, if undetected, could have serious further sequelae.

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