
Association of acute urticaria with *Mycoplasma pneumoniae* infection in hospitalized children

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Background: Acute urticaria is a common and disturbing disorder in children and has a versatile etiology.

Objective: To investigate the association of acute urticaria with *Mycoplasma pneumoniae* infection in hospitalized children.

Methods: Hospitalized children with acute urticaria from Taiwan who did not respond to antihistamine treatment and avoidance of food allergens were studied from February 1, 2006, to July 31, 2007. These patients with urticaria were compared with those who had other respiratory tract diseases and were classified into 2 groups: urticaria patients with and without *M pneumoniae* infection. The presence of *M pneumoniae* infection was determined by positive serologic findings.

Results: Sixty-five patients with acute urticaria and 49 patients with other respiratory tract diseases were enrolled in this study. Patients with urticaria had significantly less febrile duration but significantly higher platelet and lymphocyte counts than those with other respiratory tract diseases. Of the 65 patients with urticaria, 21 (32%) showed serologic evidence of *M pneumoniae* infection. Patients with *M pneumoniae*-associated urticaria received azithromycin treatment and needed a shorter time for improvement ($P = .01$) and complete resolution ($P = .04$). The total IgE levels and the results of specific IgE tests were not significantly different between urticaria patients with and without *M pneumoniae* infection.

Conclusion: This study found that in Taiwan one-third of acute childhood urticaria leading to patient hospitalization was related to *M pneumoniae* infection. Therefore, children with urticaria who are not responding to antihistamine treatment and abstinence from food allergens should be encouraged to undergo serologic examinations for *M pneumoniae* to diagnose this antibiotic-responsive disorder.

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INTRODUCTION

Acute urticaria is a common and disturbing disorder in children, with a lifetime prevalence of 12% to 15%.¹ It is characterized by the rapid appearance of skin wheals, sometimes associated with angioedema. A rash consisting of wheals is characterized by central swelling of varying sizes, associated with itching or sometimes burning for a fleeting duration of several hours. Angioedema is the sudden and pronounced swelling of the lower dermis and the subcutaneous regions. The resolution of angioedema is slower than that of wheals (up to 72 hours).² With regard to pathophysiology, urticaria can be divided into 2 types: immunologic and nonimmunologic urticaria. Immunologic urticaria is a hypersensitivity reaction mediated by IgE (type 1 hypersensitivity), IgG autoantibodies (type 2 hypersensitivity), circulating immune complexes to mast cell-expressing Fc receptors for IgG and IgM (type 3 hypersensitivity), and T-cell activation (type 4 hypersensitivity). Nonimmunologic urticaria usually results from mast cell activation through membrane receptors involved in innate immunity (eg, complement, toll-like, cyto-

kine/chemokine, opioid) or from direct toxicity of xenobiotics (haptens and drugs).³

In a previous study, acute urticaria in pediatric patients was usually triggered by viruses, allergic reactions to foods and drugs, chemical irritants, or physical stimuli.⁴ Urticaria is frequently considered to be caused by drug or food allergy and is treated with antihistamine or corticosteroid medication. However, increasing recent evidence suggests that various kinds of infections, mostly viral infections, play a more important role in the occurrence of acute urticaria than either drugs or food allergies, especially in children.^{4–6} In addition, a few case studies have revealed that *M pneumoniae* infection might cause acute urticaria in children.^{7,8} Considering that *M pneumoniae* infection in children may cause urticaria, this study investigates the association of *M pneumoniae* infection with acute urticaria to better define this antibiotic-responsive disorder and to explore whether the mechanism of *M pneumoniae* urticaria is different from that of other urticaria.

MATERIALS AND METHODS

This is an age-matched case-control study. Most children with acute urticaria are treated with antihistamines and are often advised for a trial of elimination of suspected food allergens, such as seafood, peanuts, and egg white. This study enrolled Taiwanese patients with acute urticaria, particularly those with fever. They were unresponsive to antihistamine treatment and/or corticosteroids and were admitted to Chang-Gung Memorial Hospital-Kaohsiung Medical Center between

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Table 1. Demographic Data and Clinical Manifestation Between Patients With Urticaria and Those With Other Respiratory Diseases^a

Variable	Urticaria (n = 65)	Control group (n = 49)	P value
M/F, No.	35/30	25/24	.76
Age, mean (SE), y	4.76 (0.34)	4.8 (0.37)	.95
Period of hospitalization, mean (SE), d	4.82 (0.24)	5.22 (0.27)	.27
Duration of fever, mean (SE), d	1.95 (0.30)	3.39 (0.30)	.001
Presence of fever, No. (%)	39/65 (60)	42/49 (85)	.003
URI symptoms, No. (%)	46/65 (70)	49/49 (100)	<.001
Abdominal pain, No. (%)	18/65 (27)	6/49 (12)	.04
Vomiting, No. (%)	5/65 (7)	15/49 (30)	.001
Diarrhea, No. (%)	3/65 (3)	9/49 (18)	.02

Abbreviation: URI, upper respiratory tract infection.

^a Control group includes febrile patients who had pharyngotonsillitis or bronchopneumonia. Fever is defined as a body temperature in excess of 38°C. P values were tested by the χ^2 test, except for age, period of hospitalization, and fever duration, which were tested by the *t* test.

Table 2. Complete Blood Cell and Laboratory Data Between Patients With and Without Urticaria^a

Variable	Urticaria (n = 65)	Control group (n = 49)	P value
WBC count, / μ L	11123 (572)	8792 (586)	.006
Platelet count, $\times 10^3$ / μ L	328 (13)	249 (13)	<.001
Segment count, / μ L	6939 (542)	5625 (524)	.09
Lymphocyte count, / μ L	3457 (259)	2432 (207)	.004
Monocyte count, / μ L	515.82 (35.94)	598.51 (47.13)	.16
Eosinophil count, / μ L	118.33 (17.57)	117.42 (25.71)	.98
Basophil count, / μ L	17.44 (3.84)	19.50 (3.29)	.70
AST, U/L	34.49 (1.85)	35.79 (1.54)	.60
ALT, U/L	21.94 (4.93)	15.91 (.91)	.25
CRP, mg/L	23.93 (5.91)	21.56 (3.70)	.75

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; WBC, white blood cell.

^a Data are expressed as mean (SE). P values are derived from the *t* test.

February 1, 2006, and July 31, 2007. Among these patients, the first episode of urticaria accounted for approximately 88% of cases (56 of 63). The second episode accounted for 3 and the third for 4 patients. However, none of these cases progressed to chronic urticaria. These patients were compared with other patients of the same age who were hospitalized because of other respiratory diseases, such as pharyngotonsillitis or tracheobronchitis, during the same period. This study was reviewed and approved by the institutional review board of the hospital. The urticaria patients were then classified into 2 distinct groups, namely, *M pneumoniae* urticaria and non-*M pneumoniae* urticaria, based on the serologic findings of *M pneumoniae*, including *M pneumoniae* IgM and cold agglutination tests. In this study, patients with positive results for *Mycoplasma* IgM (>20 U/L) or *Mycoplasma* IgM equivalent (10–20 U/L) and with a positive cold agglutination test result constitute the *M pneumoniae* urticaria group; the remaining patients constitute the non-*M pneumoniae* urticaria group. The equivocal reaction of *M pneumoniae* IgM and positive cold agglutination test results were also taken into consideration while forming the *M pneumoniae* group because the cold agglutination tests can detect the presence of *M pneumoniae* infection, which can have an

insidious onset with subacute characteristics, thereby causing the acute phase of IgM to decline and the other isotype immunoglobulins to become increasingly detectable. Demographic and laboratory data, including complete blood cell and differential cell counts and C-reactive protein, aspartate aminotransferase, alanine aminotransferase, and total IgE levels of the urticaria patients were obtained and analyzed, in addition to performing specific IgE tests.

The laboratory data were analyzed with the *t* test. Demographic data, including sex distribution, age, specific IgE tests, and presentation of clinical symptoms, were analyzed with the χ^2 test. *P* < .05 was considered statistically significant. All statistical tests were performed using SPSS statistical software, version 13.0 for Windows XP (SPSS Inc, Chicago, Illinois).

RESULTS

Comparison of Clinical Characteristics Between Patients With and Without Urticaria but With Other Respiratory Tract Diseases

Sixty-five patients with acute urticaria (duration, 1–14 days; mean, 3.05 days) were age matched to 49 patients with other

Table 3. Comparison of Demographic and Laboratory Data Between Patients With Febrile and Afebrile Urticaria^a

Variable	Febrile (n = 39)	Afebrile (n = 26)	P value
M/F, No.	21/18	14/12	>.99
Age, mean (SE), y	4.74 (0.43)	4.79 (0.58)	.95
Period of hospitalization, mean (SE), d	5.23 (0.27)	4.19 (0.43)	.04
Urticaria duration before hospitalization, mean (SE), d	2.53 (0.26)	3.84 (1.14)	.27
URI symptoms, No.	33/39	13/26	.003
Abdominal pain, No.	13/39	5/26	.21
Vomiting, No.	5/39	0/26	.06
Diarrhea, No.	3/39	0/26	.15
<i>Mycoplasma pneumoniae</i> infection, No.	13/39	8/26	.83
CRP, mean (SE), mg/L	34 (8)	4 (1)	.002

Abbreviations: CRP, C-reactive protein; URI, upper respiratory tract infection.

^a P values shown are derived from the *t* test, except for sex, URI symptoms, abdominal pain, vomiting, diarrhea, and *M pneumoniae* infection, which were tested by the χ^2 test.

Table 4. Comparison of Clinical Features and Laboratory Results Between Urticaria Patients With and Without URI^a

Variable	With URI (n = 46)	Without URI (n = 19)	P value
M/F, No.	23/23	12/7	.3
Age, mean (SE), y	4.83 (0.40)	4.61 (0.66)	.77
Period of hospitalization, mean (SE), d	4.96 (0.26)	4.47 (0.57)	.38
Urticaria duration before hospitalization, mean (SE), d	2.37 (0.22)	4.72 (1.55)	.15
Febrile symptoms, No.	33/46	6/19	.003
Abdominal pain, No.	16/46	2/19	.05
Vomiting, No.	5/46	0/19	.14
Diarrhea, No.	3/46	0/19	.25
<i>Mycoplasma pneumoniae</i> infection	15/46	6/19	.94
CRP, mean (SE), mg/L	25 (7)	18 (10)	.56

Abbreviations: CRP, C-reactive protein; URI, upper respiratory tract.

^a P values were derived from the *t* test, except for sex, febrile symptoms, abdominal pain, vomiting, diarrhea, and *M pneumoniae* infection, which were derived from the χ^2 test.

respiratory tract diseases for this study. We found that 60% of the patients admitted with acute urticaria had febrile episodes, 70% had upper respiratory tract infection symptoms, 27% complained of abdominal pain, and 7% complained of vomiting. Although the patients with acute urticaria showed a statistically significantly shorter mean (SD) febrile duration (1.95 [0.30] days vs 3.39 [0.30] days; $P < .001$) and fewer respiratory and gastrointestinal symptoms than those without urticaria (Table 1), the former had significantly higher leukocyte counts and higher lymphocyte and platelet counts than the latter (Table 2); this might imply a proinflammatory pathophysiologic cause for acute urticaria.

Comparison of clinical features between patients with febrile and afebrile urticaria showed that the former had higher C-reactive protein levels, more respiratory tract symptoms, and a longer hospitalization period than the latter. The positive results of the serologic tests for *M pneumoniae* infection (13/39 vs 8/26, $P = .83$) and the mean (SD) duration of urticaria before hospitalization (2.53 [0.26] vs 3.84 [1.14] days, $P = .27$) were not statistically significantly different between the 2 groups (Table 3). We also compared the

demographic and clinical features between urticaria patients with and without upper respiratory tract symptoms. Patients with upper respiratory tract symptoms tended to have a higher febrile rate and more incidence of abdominal pain than patients without upper respiratory tract symptoms. The serologic tests for *M pneumoniae* infection (15/46 vs 6/19, $P = .94$) revealed no statistically significant differences between the 2 groups (Table 4).

Comparison of the Clinical Characteristics Between Urticaria Patients With and Without *M pneumoniae* Infection

Twenty-one (32%) of the 65 patients with urticaria had *M pneumoniae* infection (13 patients with positive *Mycoplasma* IgM test results and 8 patients with an equivocal reaction of *Mycoplasma* IgM coupled with positive cold agglutination test results). Forty-four patients with urticaria had no *M pneumoniae* infection according to the results of the serologic tests.

The comparison of the initial conditions between urticaria patients with and without *M pneumoniae* infection showed no

Table 5. Clinical Manifestations Between Urticaria Patients With and Without *Mycoplasma pneumoniae* Infection^a

Variable	<i>M pneumoniae</i> urticaria (n = 21)	Non- <i>M pneumoniae</i> urticaria (n = 44)	P value
Age, mean (SE), y	5.29 (0.58)	4.51 (0.42)	.30
M/F, No.	9/12	26/18	.22
Urticaria duration before hospitalization, mean (SE), d	2.60 (0.45)	2.67 (0.34)	.91
Period of hospitalization, mean (SE), d	4.95 (0.52)	4.75 (0.27)	.71
Duration of fever, mean (SE), d	1.86 (0.42)	2.00 (0.40)	.83
Total IgE, mean (SE), kU/L	183 (49)	220 (61)	.68
URI symptoms, No. (%)	15/21 (71)	31/44 (70)	.94
Abdominal pain, No. (%)	5/21 (23)	13/44 (15)	.63
Vomiting, No. (%)	1/21 (4)	4/44 (7)	.54

Abbreviation: URI, upper respiratory tract infection.

^a P values were derived from the χ^2 test, except for age and duration of admission and fever, which were derived from the *t* test.

Table 6. Comparison of Complete Blood Cell and Laboratory Data Between Urticaria Patients With and Without *Mycoplasma pneumoniae* Infection^a

Variable	<i>M pneumoniae</i> urticaria (N = 21)	None- <i>M pneumoniae</i> urticaria (N = 44)	P value
WBC count, / μ L	10,310 (991)	11,501 (700)	.34
Platelet count, $\times 10^3$ / μ L	299 (16)	343 (17)	.12
Segment count, / μ L	6,514 (958)	7,137 (663)	.60
Lymphocyte count, / μ L	3,103 (470)	3,621 (310)	.36
Monocyte count, / μ L	470 (54)	536 (46)	.39
Eosinophil count, / μ L	140 (36)	108 (19)	.40
Basophil count, / μ L	20 (8)	16 (4)	.59
CRP, mg/L	30 (14)	20 (5)	.42
AST (U/L)	30 (1)	36 (2)	.11
ALT (U/L)	18 (4)	24 (7)	.55

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; WBC, white blood cell.

^a Data are expressed as mean (SE). P values are derived from the *t* test.

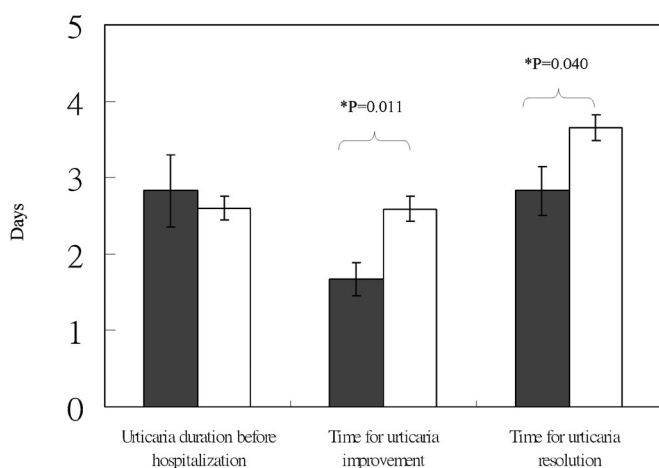


Figure 1. Effect of azithromycin treatment on the duration of urticaria. The black bars and the white bars represent urticaria patients who did and did not receive azithromycin treatment, respectively. Urticaria duration before hospitalization was not statistically significantly different between the 2 groups of patients represented by the black and white bars. Azithromycin treatment statistically significantly shortened the time for improvement ($P = .01$) and the time for complete resolution ($P = .04$).

statistically significant differences in urticaria duration before hospitalization, age, sex, fever duration, hospitalization period, total IgE levels, and the presence of upper respiratory tract infections and gastroenterologic symptoms (Table 5). Even the complete blood cell count, differential cell count, C-reactive protein level, aspartate aminotransferase level, and alanine aminotransferase level were not statistically significantly different (Table 6).

Patients with *M pneumoniae* infection were treated with azithromycin (10 mg/kg daily) for 3 days. Azithromycin-treated urticaria patients had a statistically significantly shorter mean (SD) period of convalescence (1.67 [0.22] vs 2.59 [0.16] days, $P = .01$) and shorter duration for complete resolution (2.83 [0.32] vs 3.65 [0.17] days, $P = .04$) than untreated urticaria patients (Fig 1).

Comparison of Total IgE Levels and Allergen Specific IgE Tests Between Urticaria Patients With and Without *M pneumoniae* Infection

The mean (SD) total IgE levels in urticaria patients with and without *M pneumoniae* infections were 183 (49) kU/L and 220 (61) kU/L ($P = .68$), respectively (Table 5). Forty urticaria patients underwent specific IgE tests to compare their reactions to common allergens: cockroach, dog dander,

Table 7. Food Allergen and Aeroallergen Specific IgE Tests Between Urticaria Patients With and Without *Mycoplasma pneumoniae* Infection^a

Variable	<i>M pneumoniae</i> urticaria (n = 14)	Non- <i>M pneumoniae</i> urticaria (n = 26)	P value
Food mixture	3/13 (23)	7/24 (29)	.69
Cockroach, <i>Blattella germanica</i>	1/14 (7)	2/26 (7)	.95
Dog dander	0/14 (0)	1/26 (3)	.46
<i>Blomia tropicalis</i>	1/13 (7)	3/19 (15)	.50
<i>Dermatophagoides pteronyssinus</i>	2/14 (14)	8/26 (30)	.25

^a Data are presented as number (percentage) of patients. Food mixture includes egg white, milk, wheat, peanut, soya bean, and fish (cod). P values are derived from the χ^2 test.

Dermatophagoides pteronyssinus, and food mix (including egg white, milk, wheat, peanut, soya bean, and cod fish). No statistically significant differences were found between urticaria patients with *M pneumoniae* (n = 14) and without *M pneumoniae* (n = 26) (Table 7). This finding suggests that most cases of childhood urticaria may not be related to IgE-mediated allergic reaction but may be more related to infection.

DISCUSSION

Acute urticaria in children is often regarded as a food or drug allergy, leading to the unnecessary elimination of diet or drugs and administration of corticosteroids rather than antibiotics. Zuberbier et al⁹ investigated 109 patients with acute urticaria and found only 1 patient to be allergic to food, with most of the remaining patients being idiopathic. Many reports have shown that 39% to 48% of children with acute urticaria have various types of infection, most of them caused by a virus^{5,6,9} commonly associated with upper respiratory tract infection symptoms, and that 44% of them had febrile episodes,⁸ suggesting that infection might play an important role in the etiology of acute urticaria in children. This study is the first, to our knowledge, to find that almost one-third of Taiwanese children with urticaria had *M pneumoniae* infection. It is highly unlikely that such a high rate of *M pneumoniae* infection in urticaria patients, as noted from the results of serologic tests, is due to an epidemic outbreak of *M pneumoniae* because the percentage of positive test results (*Mycoplasma* IgM) during February 1, 2006, through July 31, 2007, was lower than the percentage of positive test results during the following 16 months from August 1, 2007, through December 30, 2008 (12.34% vs 14.25%, $P = .04$).

M pneumoniae is an important bacterial agent that causes pneumonia in pediatric patients. Extrapulmonary complications of *M pneumoniae* infections are frequent and varied, notably dermatologic with cutaneous vasculitis, such as immune complex-mediated vasculitis, erythema multiforme, or even Stevens-Johnson syndrome. The precise mechanism of *M pneumoniae* associated with cutaneous manifestations is thought to be the result of immune complex-mediated injury or cytotoxic T-cell-mediated immune responses rather than action of the organisms themselves.¹⁰⁻¹² In addition, cytokine and chemokine release might also be involved in some phases of the immune responses because mycoplasmal lipopeptides

have been shown to activate macrophages and monocytes to release the proinflammatory cytokines, chemokines, and nitric oxide through toll-like receptor 2 with the MyD88-dependent signaling pathway.¹³

M pneumoniae infection induced erythema nodosum, anaphylactoid purpura, and acute urticaria in 3 members of a single family,⁷ suggesting that *M pneumoniae*-associated immune alteration might result from the differences in the hosts' immunologic responses to different pulmonary and extrapulmonary manifestations.

Diagnosis of acute *M pneumoniae* infection is challenging and is usually dependent mainly on positive serologic test results.¹⁴ However, the rapid cold agglutination test cannot be counted out as a means of diagnosis of this infection,¹⁵ especially when *M pneumoniae* IgM is undetectable or disappearing in the convalescent stage. Therefore, this study considers *M pneumoniae* infection to be detectable by an IgM antibodies (≥ 20 U/L) test or its equivalent, the *M pneumoniae* IgM test (10–20 U/L) coupled with a rapid cold agglutination test.

In clinical practice, acute urticaria in pediatric patients is often taken to be a commonly found but relatively benign disease, the symptoms of which might begin to diminish shortly after antihistamine treatment. To examine the veracity of this notion, this study analyzes the case of pediatric patients who were hospitalized because of severe urticaria, which was refractory to antihistamine treatment, and propounds that *M pneumoniae* infection might play an important role in the pathophysiology of pediatric urticaria, especially when urticaria is severe and refractory to usual medical treatment or when accompanied by fever or other upper respiratory tract symptoms. The acute urticaria in 32% of the cases in this study was found to be traceable to acute *M pneumoniae* infection. A macrolide (azithromycin) was prescribed to all patients who tested positive for *M pneumoniae* serologically. During 6 months of follow-up, none of these 65 patients progressed to chronic urticaria. This finding suggests that children with urticaria unresponsive to antihistamine treatment should be encouraged to undergo serologic examinations for *M pneumoniae* to diagnose this antibiotic-responsive disorder and to avoid or limit corticosteroid treatment. Currently, no clinical or laboratory features can distinguish *M pneumoniae* urticaria from non-*M pneumoniae* urticaria. The attempt to analyze the profiles of specific IgE directed against

common allergens to see whether they were different between urticaria patients with and those without *M pneumoniae* infection showed no difference between the 2 groups. However, this analysis needs further examinations on *Mycoplasma* IgE, *Mycoplasma* IgG, or *Mycoplasma*-specific T cells to investigate whether the pathogenesis of *M pneumoniae*-induced urticaria is IgE, immune complex, or T cell mediated.

The antibiotic azithromycin was prescribed to patients with serologic evidence of *M pneumoniae*. These patients responded to this treatment in 16 to 48 hours and had quicker convalescence and complete recovery from urticaria than urticaria patients without azithromycin treatment, implying that azithromycin treatment might effectively reduce the urticaria duration and symptoms. This was, however, a case-control study. Further prospective, randomized studies are needed to evaluate and corroborate the effectiveness of azithromycin as a worthwhile cure to *M pneumoniae*-related urticaria.

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