

Is Silent Sinusitis a Cause of Chronic Urticaria in Children?

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SUMMARY The etiologies of chronic urticaria (CU) comprise a wide variety of disorders including chronic infections. The association of sinusitis and CU is controversial due to the lack of a control group. The objective of this study was to investigate the role of silent sinusitis as a cause of CU in children. A sinus X-ray (SXR) was performed in 107 children with CU. SXR abnormalities were found in 52.3% of the patients. Nine patients (8.4%) had symptoms of sinusitis and were treated with amoxicillin/clavulanate. Five of these patients (55.6%) had CU remission. Forty-seven patients (43.9%) who had an abnormal SXR without sinusitis symptoms were randomized into treated (23 patients) and control (24 patients) groups. Eighteen patients (78.3%) in the treated group and 15 patients (62.5%) in the control group had CU remission ($p = 0.24$). These data did not support a causal relationship of sinusitis and CU in children.

Chronic urticaria (CU) is diagnosed when urticaria occurs on a regular basis for more than six weeks.¹ It affects 0.5–1% of the population and significantly impairs their quality of life.² The three main subtypes of CU are urticarial vasculitis (5%), physical urticaria (35–45%), and chronic idiopathic urticaria (CIU, 50–60%).³ Several studies attempted to identify the etiologies of CIU and revealed a wide variety of disorders as possible causes. These disorders were functional autoantibody to FcεRIα and IgE, thyroid autoimmunity, collagen vascular diseases, food or drug allergies, and chronic infections as well as parasitic infestation.^{4–16} Chronic infections from hepatitis B virus, hepatitis C virus, Epstein-Barr virus, cytomegalovirus, *Helicobacter pylori*, dental infections and sinusitis have been linked to CU at variable extents.¹⁷ Sinusitis was described as related to CU in both adults and children with inconsistent responses to antibiotics.^{4,6,11–13} The absence of a control group in most studies made it difficult to

conclude the causal relationship between sinusitis and CU.

In this study, we investigated 107 children with CU. A sinus X-ray (SXR) was performed in all patients and the responses to antibiotics were documented in a controlled method.

MATERIALS AND METHODS

Patients

The study was approved by the Institutional Review Board of Siriraj Hospital. Informed consent was obtained from the parents of the patients as the

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patients were less than 18 years of age. The study was conducted in the Pediatric Allergy Clinic, Siriraj Hospital, Mahidol University, Thailand, from March 2003 to February 2006. Children 4 - 15 years of age with chronic urticaria (CU, daily or almost daily urticaria lasting for more than six weeks) were asked to participate in this study. Patients with pregnancy, underlying diseases such as cardiovascular, hepatobiliary, and renal diseases were excluded.

Investigations and treatment

Complete history and physical examination were performed on all patients. Patients with a history of physical urticaria were excluded. SXR was performed in all patients and the results were interpreted by radiologists. The SXR abnormalities included opacification, air-fluid levels or mucosal thickening. The patients with symptoms and signs of subacute or chronic sinusitis such as mucopurulent nasal discharge, nasal obstruction, posterior nasal dripping, night-time cough, or facial pain for more than 30 days¹⁸ were treated with amoxicillin/clavulanate (60-80 mg/kg/day of amoxicillin) for at least two weeks and after the improvement of symptoms for another seven days. Patients without symptoms and signs of sinusitis, who had an abnormal SXR, were randomized into treated and control groups. Amoxicillin/clavulanate (60-80 mg/kg/day of amoxicillin) was given for two weeks to the treated group only. All patients were also treated with a second generation H₁-antihistamine (cetirizine or loratadine). They were initially followed every two weeks for one month and every two months thereafter. Patients were considered in remission if

the urticaria resolved within one month after the initiation of treatment and if symptoms did not recur for at least twelve months.

Data analysis

Data were expressed as individual values or the mean \pm SD for groups. Statistical analysis was performed using Fisher's exact test or the Chi-square test to compare the demographic data, SXR abnormalities and the treatment responses between treated and control groups where appropriate. Comparisons between the means of each group were done using the independent t-test. The differences between the groups were considered to be significant at a *p*-value of ≤ 0.05 .

RESULTS

One hundred and seven patients were recruited. Fifty-one children (47.7%) were male and 56 (52.3%) were female. The mean age was 9.0 ± 3.2 years (range 4-15 years). The mean CU duration was 18.1 ± 23.9 months (range 1.5-144 months). Forty-one (38.3%) and 55 (51.4%) patients had underlying allergic diseases and a family history of atopic diseases, respectively.

SXR abnormalities were found in 56 patients (52.3%) with CU. The most frequent abnormal sinus was the maxillary sinus (62.5%) followed by the ethmoid (26.79%), frontal (16.07%) and sphenoid sinuses (3.57%). Pan-sinusitis was found in 12.5% of the patients.

Table 1 Demographic data of the patients in the treated and control groups

Demographic data	Treated group n = 23	Control group n = 24	<i>p</i> -value
Age (mean \pm SD, years)	8.7 \pm 3.0	8.9 \pm 3.6	0.80*
Male (%)	11 (47.8%)	13 (54.2%)	0.66 ^a
Duration of urticaria (mean \pm SD, months)	14.3 \pm 20.5	18.8 \pm 17.5	0.41*
Personal history of atopy (%)	10 (43.5%)	11 (45.8%)	0.87 ^a
Family history of atopy (%)	11 (47.8%)	12 (50.0%)	0.88 ^a

*Independent *t*-test, ^aChi-square test

Table 2 The abnormalities in the sinus x-rays of the treated and control groups

Sinus abnormalities	Treated group n = 23	Control group n = 24	*p- value
Frontal sinusitis	5 (21.7%)	2 (8.3%)	0.25*
Maxillar sinusitis	14 (60.9%)	14 (58.3%)	0.86 ^a
Ethmoid sinusitis	7 (30.4%)	8 (33.3%)	0.83 ^a
Sphenoid sinusitis	0 (0.0%)	2 (8.3%)	0.49*
Pan-sinusitis	4 (14.7%)	3 (12.5%)	0.64 ^a

*Fisher's exact test, ^aChi-square test

Nine patients (8.4%) had symptoms of sinusitis and were treated with amoxicillin/clavulanate. Five of these patients (55.6%) had CU remission. Forty-seven patients (43.9%) who had an abnormal SXR without symptoms and signs of sinusitis, were randomized into treated (23 patients) and control (24 patients) groups. The demographic data and SXR abnormalities of both groups are shown in Tables 1 and 2, respectively. There was no difference in the demographic data and SXR abnormalities between the two groups. The CU remissions in the treated and control groups are shown in Table 3. Eighteen patients (78.3%) in the treated group and 15 patients (62.5%) in the control group had CU remission ($p = 0.24$).

DISCUSSION

Chronic urticaria in children is a challenge, especially its etiologies and investigations due to the limited data on this disease in the pediatric age group. Sinusitis was considered as one of the possible etiologies of CU in many adult and in a few pediatric studies. Radiographic sinusitis was described previously in 0.4-17.2% of unselected patients with CU.^{4,6,11-13} The impact of sinusitis treatment on the course of CU was still uncertain due to the limited number of patients and the lack of a control group. Harris *et al.*⁶ in a study of 94 CU children, found one patient with sinusitis who had complete CU remission after antibiotic and decongestant treatment. In contrast, Kulthanan *et al.*¹³ in a study of 450 adults with CU, revealed that antibiotic treatment in two patients with sinusitis could not resolve their CU. With these controversial results, sinusitis might be considered a coincidental finding in patients with

Table 3 Number of patients with remission from chronic urticaria in the treated and control groups

Remission	Treated group n = 23	Control group n = 24
Yes	18 (78.3%)	15 (62.5%)
No	5 (21.7%)	9 (37.5%)

*Chi-square test, $p = 0.24$

CU. A causal relationship of sinusitis as an etiology of CU can only be established if the treatment of sinusitis resulted in CU remission.

Our study was performed to determine whether there is a causal relationship between sinusitis and CU. We found a high proportion (52%) of abnormal SXR in CU children, after excluding physical urticaria. Only half of the patients who had symptoms of sinusitis and were treated with antibiotic were in CU remission. Silent sinusitis was found in 44% of our CU patients and the treatment of sinusitis in these patients did not induce a significantly higher rate of CU remission than in the control group. This finding was supported by a previous study. Nelson reported that out of 17 patients with CU and abnormal SXR, only three patients resolved from CU with sinusitis treatment, nine patients resolved from CU without sinusitis treatment, four patients had persistent CU despite sinusitis treatment and one patient resolved from CU with wheat elimination.¹⁹

Potential explanations for the limited effects of sinusitis treatment on CU remission are: 1) pa-

tients might have had not only sinusitis, but also other CU triggering factors (*e.g.* hypersensitivity reactions or autoimmunity); 2) sinusitis is not related to CU and all CU remissions were spontaneous; 3) SXR might not be the right tool to screen sinusitis in asymptomatic children; 4) treatment failure which was not documented as it was unethical to expose these children to another SXR to demonstrate the eradication of sinusitis.

In conclusion, our study did not support that sinusitis is an etiology of CU in children. SXR may be considered in some patients on an individual basis but there is no scientific evidence to recommend its general use in children with CU.

ACKNOWLEDGEMENTS

This study was supported by the Siriraj Grant for Research Development. The authors wish to thank Suthipol Udompunturak, M.Sc. (Applied Statistics) and Busaba Supawattanabodee, M.Sc. (Biostatistics) for their statistical advice.

REFERENCES

- Kaplan AP. Chronic urticaria and angioedema. *N Eng J Med* 2002; 346: 175-9.
- Powell RJ, Du Toit GL, Siddique N, *et al.* BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clin Exp Allergy* 2007; 37: 631-50.
- Greaves MW, Tan KT. Chronic urticaria: recent advances. *Clinic Rev Allerg Immunol* 2007; 33: 134-43.
- Jacobson KW, Branch LB, Nelson HS. Laboratory tests in chronic urticaria. *JAMA* 1980; 243: 1644-6.
- Boguniewicz M. Chronic urticaria in children. *Allergy Asthma Proc* 2005; 26: 13-7.
- Harris A, Twarog FJ, Geha RS. Chronic urticaria in childhood: Natural course and etiology. *Ann Allergy* 1983; 51: 161-5.
- Volonakis M, Katsarou-Katsari A, Stratigos J. Etiologic factors in childhood chronic urticaria. *Ann Allergy* 1992; 69: 61-5.
- Kemp AS, Schembri G. An elimination diet for chronic urticaria of childhood. *Med J Aus* 1985; 143: 234-5.
- Ghosh S, Kanwar AJ, Kaur S. Urticaria in children. *Pediatr Dermatol* 1993; 10: 107-10.
- Sackesen C, Sekerel BE, Orhan F, Kocabas CN, Tuncer A, Adalioglu G. The etiology of different forms of urticaria in childhood. *Pediatr Dermatol* 2004; 21: 102-8.
- Liutu M, Kalimo K, Uksila J, Kalimo H. Etiologic aspects of chronic urticaria. *Int J Dermatol* 1998; 37: 515-9.
- Buss YA, Garrelfs UC, Sticherling M. Chronic urticaria – which clinical parameters are pathogenetically relevant? A retrospective investigation of 339 patients. *J Dtsch Dermatol Ges* 2007; 5: 22-9.
- Kulthanan K, Jiamton S, Thumpimukvatana N, Pinkaew S. Chronic idiopathic urticaria: prevalence and clinical course. *J Dermatol* 2007; 34: 294-301.
- Fiebiger E, Maurer D, Holub H, *et al.* Serum IgG autoantibodies directed against the α chain of Fc ϵ RI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? *J Clin Invest* 1995; 96: 2606-12.
- Niimi N, Francis DM, Kermani F, *et al.* Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. *J Invest Dermatol* 1996; 106: 1001-6.
- Levy Y, Segal N, Weintrob N, Danon YL. Chronic urticaria: association with thyroid autoimmunity. *Arch Dis Child* 2003; 88: 517-9.
- Wedi B, Raap U, Kapp A. Chronic urticaria and infections. *Curr Opin Allergy Clin Immunol* 2004; 4: 387-96.
- American Academy of Pediatrics. Subcommittee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: management of sinusitis. *Pediatrics* 2001; 108: 798-808.
- Nelson HS. Routine sinus roentgenograms and chronic urticaria. *JAMA* 1984; 251: 1680-1.