Clinical Communications

Children with chronic spontaneous urticaria: Recurrence after remission and its predictors

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Clinical Implications

- About a fifth of children with chronic spontaneous urticaria have recurrence and some factors such as thyroid autoantibodies, age at symptom onset, and omalizumab usage may be associated with recurrence and time of recurrence.

TO THE EDITOR:

Chronic spontaneous urticaria (CSU) has a favorable prognosis and remission is seen in half the children with CSU within 5 years.[1-3] However, some cases may recur over time, and knowledge of the recurrence rate after remission and risk factors that predict recurrence after remission are unclear in children and very limited in adults.[4]

In the present study, we aimed to determine risk factors for predicting the recurrence of CSU in children and to document the timing of recurrence and the impact of risk factors on the time to recurrence.

Children who were diagnosed with CSU with a symptom frequency of at least once per week were reevaluated and those with inducible urticaria and urticarial vasculitis were excluded. Patients who had reported clearance of urticarial lesions lasting more than 6 months were accepted as in remission, and reappearance of the symptoms after remission was considered recurrence of the disease.[4,5] Patients in remission were questioned for recurrence of the symptoms via telephone visits or e-mail and were invited to the clinic for reevaluation. Out of 86 children with CSU, 76 were reached and evaluated for recurrence (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). A number of risk factors for the recurrence of CSU in children were also analyzed by logistic regression analysis (Table I).

The median (interquartile range) age of patients was 16.0 (12.0-20.0) years and 44 (57.9%) of them were female. The median age at symptom onset was 9.0 (4.0-13.0) years and CSU lasted a median of 2.3 (1.0-4.0) years. During remission, the patients were followed for a median of 6.0 (5.0-10.0) years (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Thirteen patients (17.1%) had a recurrence. Recurrence was seen in 4.0%, 8.3%, and 17.1% of children with CSU after 1, 3, and 5 years, respectively. Ten of 13 recurring patients (76.1%) went into second remission within 6 months and the remaining 3 (23%) after a period of 2 years. One patient (1.3%) had a second recurrence and after 6 months his complaints returned. Nearly half the recurring children with CSU had recurrence within the first 2 years of remission (Figure 1, *A*). Within the recurrence group, children 10 years or older at initial symptom onset for CSU showed an earlier recurrence compared with those younger than 10 years at initial symptom onset ($P = .003$) (Figure 1, *B*). Similarly, those with thyroid autoantibody positivity compared with autoantibody-negative patients ($P = .018$) (Figure 1, *C*), and those who used omalizumab for the treatment of CSU showed earlier recurrence compared with patients who did not use omalizumab ($P < .001$) (Figure 1, *D*).

When the patients with and without recurrence were compared, there was no difference between recurring and nonrecurring patients with respect to sex, initial disease duration, type and duration of medical therapy, peripheral eosinophil numbers, and total IgE levels. However, in patients with recurrence, age at symptom onset was higher (11.5 years; 10.0-14.5 years) than in those without recurrence (8.0 years; 3.5-12.5 years) ($P = .034$), and there was a higher thyroid antibody positivity (3 of 13 [23.1%] vs 3 of 63 [4.8%]; $P = .05$), respectively (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

The age at symptom onset after age 10 years (odds ratio, 5.148; 95% CI, 1.229-33.124; $P = 0.038$) and thyroid autoantibody positivity (odds ratio, 3.979; 95% CI, 1.628-23.124; $P = .042$) were found to be independent risk factors for recurrence (Table I). The other risk factors that were investigated in the study group including sex, disease duration until remission, treatment duration, peripheral eosinophil counts, and total IgE levels were not found to be related to recurrence.

To our knowledge, the risk factors for recurrence of CSU and the prevalence of recurrence in children are described here for the first time in the literature. There are several studies that give information on risk factors for the persistence of CSU. In these studies some risk factors were identified for the persistence of symptoms, such as plasma prothrombin levels, D-dimer, C-reactive protein, using higher doses of antihistamines and/or combination therapies, autologous serum skin test negativity, and Urticaria Activity Score Over 7 Days (UAS7) higher than 28.[1,3,6,7] Some of these risk factors that were found to be associated with CSU persistence may be related to disease recurrence as well. In a recent study, Ferrer et al[8] reported that in patients with CSU treated with omalizumab, baseline disease severity (UAS7) and early treatment response may identify patients with CSU who are at risk of recurrence after stopping omalizumab treatment. In contrast, data on the prevalence of recurrence and the risk factors associated with recurrence are lacking. Recently, Kim et al[4] found a prevalence rate of 13.0% for the recurrence of CSU in adult patients and the only risk factor identified for recurrence was the use of alternative agents such as anti-inflammatories, immune suppressants, and omalizumab, apart from first-line antihistamines.[4] In our study, we found a recurrence rate of 17.1% in children with CSU. This prevalence rate is similar to that reported by Kim et al.[4] Nearly half the patients had a recurrence in 2 years. This finding may be important for the clinical follow-up of patients with CSU and in remission.

Previously, we showed that girls 10 years or older at symptom onset may have a worse prognosis and CSU may persist longer.[1] In this study, the comparison of groups with and without

TABLE I. Risk factors for the recurrence of CSU during childhood

	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Sex	1.800	0.501-6.463	.367			
Age at symptom onset ≥ 10 y	7.708	1.552-38.284	.013	**5.568**	**1.059-29.270**	**.043**
Disease duration until remission	0.735	0.461-1.171	.195			
Treatment duration	1.188	0.688-2.053	.536			
Thyroid autoantibody positivity	6.000	1.059-34.003	.043	**4.480**	**1.268-26.124**	**.025**
Rheumatologic autoantibody positivity	1.050	0.254-4.346	.946			
Omalizumab usage	17.7	1.671-187.523	.017			
Eosinophil number (mm^3)	1.000	0.995-1.005	.882			
Total IgE kU/L	0.998	0.991-1.004	.445			

OR, Odds ratio.
Bold indicates statistical significance ($P < .05$).

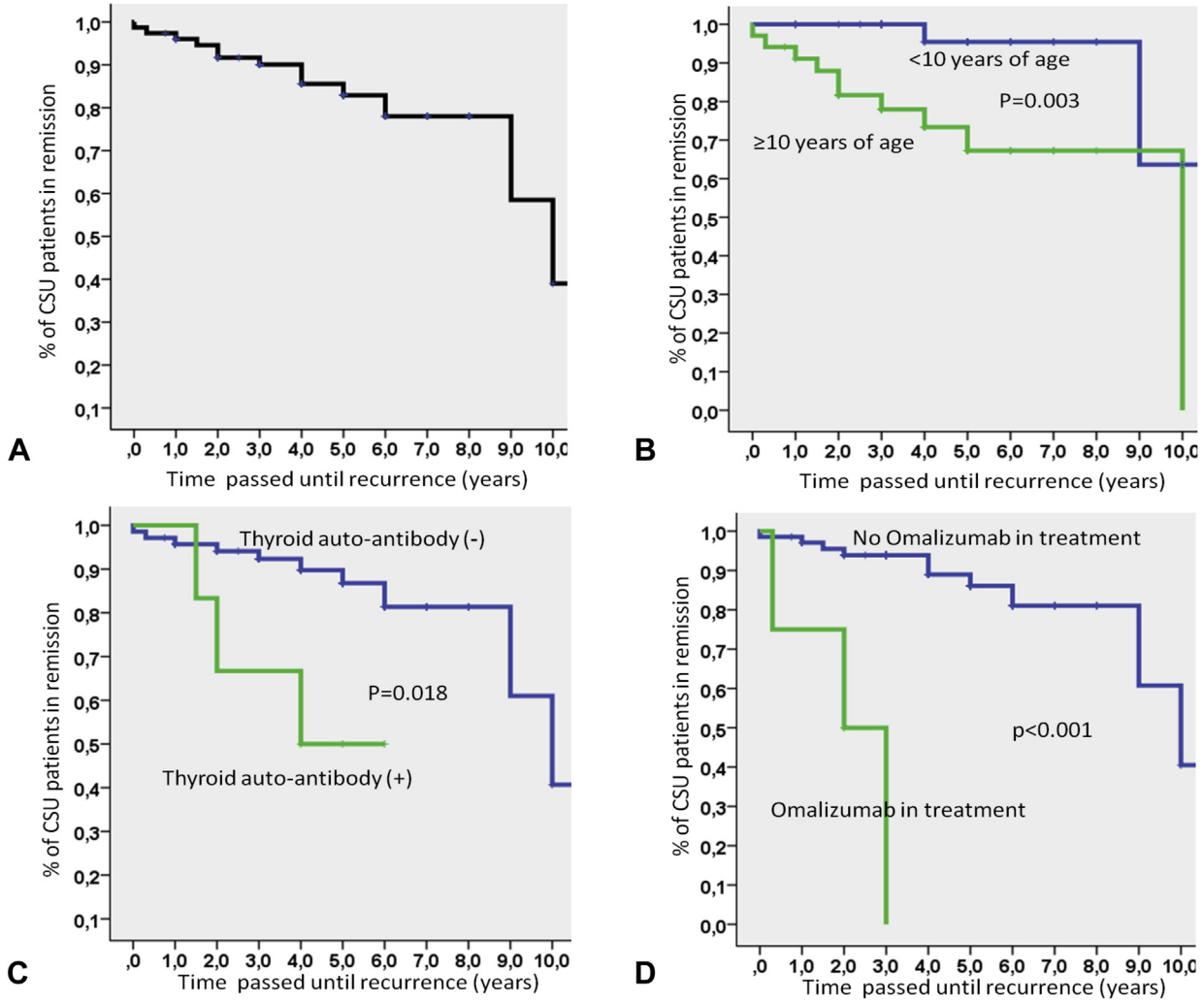

FIGURE 1. A, Percentage of children with CSU in remission by time. Comparison of the time for recurrence in children with CSU with respect to (**B**) age at symptom onset (<10 years vs ≥10 years), (**C**) thyroid autoantibody positivity, and (**D**) omalizumab usage.

recurrence showed no difference in sex distribution between groups, despite a slightly higher frequency of girls in the recurrent group than in the nonrecurrent group. However, the age at symptom onset was higher in the recurrent group than in the nonrecurrent group and those with a symptom onset after age 10 years had a recurrence earlier than the others. We do not know how disease-onset age may be important for both persistence and recurrence.

Another risk factor for the recurrence of the disease was thyroid autoantibody positivity. In the recurring group, the

frequency was significantly higher. In the study by Kim et al, some patients had autoantibody and basophil activation test positivity; however, they could not analyze the effect of these factors because of the retrospective nature of the study. In our study, the patients with thyroid autoantibody positivity also recurred earlier compared with the others. Despite the lack of knowledge about the association between thyroid autoantibody positivity and recurrence, some studies evaluated the relationship between CSU presence and thyroid autoantibodies mainly in adults.[5,7,9]

Kim et al found a higher recurrence rate in patients with CSU using omalizumab. In our study group, we identified omalizumab as a risk factor in univariate analysis but it lost its significance in multivariate analysis. However, in children with CSU who received omalizumab as an add-on therapy, we found an earlier recurrence time than in patients without omalizumab. One of the reasons for recurrence in these patients may be related to the severity of the disease, because omalizumab is used in cases that do not respond to classic antihistamine therapy and in more severe clinical situations. Previously, we have also found an association between UAS7, which indicates disease severity, and persistence of the disease in children with CSU.

The findings of this study may provide first answers to questions of who will have a recurrence, when will there be recurrence, and predictors of recurrence in children with CSU.

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REFERENCES

1. Sahiner UM, Civelek E, Tuncer A, Yavuz ST, Karabulut E, Sackesen C, et al. Chronic urticaria: etiology and natural course in children. Int Arch Allergy Immunol 2011;156:224-30.
2. Hiragun M, Hiragun T, Mihara S, Akita T, Tanaka J, Hide M. Prognosis of chronic spontaneous urticaria in 117 patients not controlled by a standard dose of antihistamine. Allergy 2013;68:229-35.
3. Chansakulporn S, Pongpreuksa S, Sangacharoenkit P, Pacharn P, Visitsunthorn N, Vichyanond P, et al. The natural history of chronic urticaria in childhood: a prospective study. J Am Acad Dermatol 2014;71:663-8.
4. Kim JK, Har D, Brown LS, Khan DA. Recurrence of chronic urticaria: incidence and associated factors. J Allergy Clin Immunol Pract 2018;6:582-5.
5. Harris A, Twarog FJ, Geha RS. Chronic urticaria in childhood: natural course and etiology. Ann Allergy 1983;51:161-5.
6. Arik Yilmaz E, Karaatmaca B, Cetinkaya PG, Soyer O, Sekerel BE, Sahiner UM. The persistence of chronic spontaneous urticaria in childhood is associated with the urticaria activity score. Allergy Asthma Proc 2017;38:136-42.
7. Rabelo-Filardi R, Daltro-Oliveira R, Campos RA. Parameters associated with chronic spontaneous urticaria duration and severity: a systematic review. Int Arch Allergy Immunol 2013;161:197-204.
8. Ferrer M, Gimenez-Arnau A, Saldana D, Janssens N, Balp MM, Khalil S, et al. Predicting chronic spontaneous urticaria symptom return after omalizumab treatment discontinuation: exploratory analysis. J Allergy Clin Immunol Pract 2018;6. 1191-7.e5.
9. Kasumagic-Halilovic E, Beslic N, Ovcina-Kurtovic N. Thyroid autoimmunity in patients with chronic urticaria. Med Arch 2017;71:29-31.

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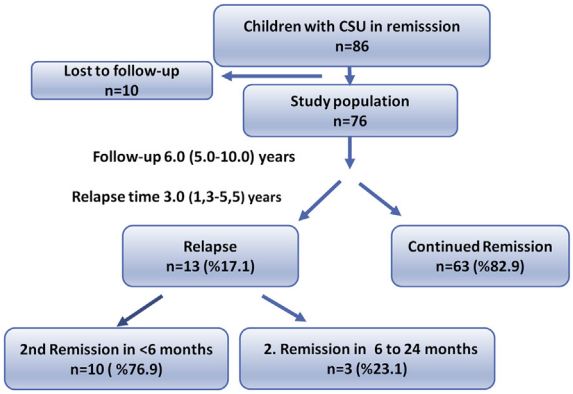

FIGURE E1. Flow-chart of the study population.

TABLE E1. Characteristics of the study population

Characteristic	No. of patients in remission (n = 76)
Current age (y)*	16.0 (12.0-20.0)
Age at symptom onset (y)*	9.0 (4.0-13.0)
Sex: male/female, n (%)	32 (42.1%)/44 (57.9%)
Patients with any allergic disease, n (%)	12 (15.8)
Eosinophil number (mm^3)	100 (100-200)
Total IgE (kU/L)*	94 (34-235)

*Median (interquartile range).

TABLE E2. Comparison of patients with CSU with and without relapse

Characteristic	Patients with relapse (n = 13)	Patients without relapse (n = 63)	*P* value
Current age (y)*	18.0 (15.5-21.5)	15.0 (11.0-19.0)	.038
Age at symptom onset (y)*	11.5 (10.0-14.5)	8.0 (3.5-12.5)	.034
Sex: female, n (%)	9 (69.2)	35 (55.6)	.363
Tiroid autoantibody positivity, n (%)	3 (21.4)	3 (4.8)	.050
Any autoantibody positivity, n (%)	5 (38.5)	16 (25.4)	.338
Eosinophil number (mm^3)	100 (50-200)	100 (100-200)	.994
Total IgE (kU/L*)	39 (11-220)	101 (39-239)	.292

*Median (interquartile range).