



Natural History and Predictors of recovery in Children with Chronic Spontaneous Urticaria

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Natural History and Predictors of recovery in Children with Chronic Spontaneous Urticaria

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Abstract:

Background: Limited data are available about the natural history of chronic spontaneous urticaria in children (CSU), and management guidelines are mostly extrapolated from evidence in adults.

Methods: The objective of this study was to evaluate the natural history of CSU in children and to identify predictors for remission. We performed an observational study, including patients aged 0 to 18 years with CSU diagnosed from January 2006 to July 2016. Disease activity was evaluated by the Urticaria Activity Score (UAS) and the Urticaria Activity Score 7 (UAS7); type of treatment and number of daily administrations were recorded.

Results: Eighty patients were included in the study. At 1, 3, and 5 years from the onset of symptoms, 29%, 55%, and 72% of the patients with CSU were in remission, respectively. A higher hazard ratio of non-remission both at 3 years (HR=1.7, 95%CI=1.2-2.4, p-value 0.004) and at 5 years (HR=1.7, 95%CI=1.2-2.7, p-value 0.001), was related to higher severity of CSU at the baseline. Remission rates were significantly higher in patients who used a single dose of antihistamine drug (89% vs. 54% and 67% at 5 years, p-value=0.0003). During follow-up, four patients experienced a relapse (6.9%). The distance of relapses from remission varied from 2 to 5 years without evidence of a correlation between the age at the onset and the duration of the disease (Spearman's coefficient=0.02; p-value=0.9).

Conclusion: High UAS score at onset is a prognostic factor for the persistence of symptoms, as well as the need for multiple antihistamine drug doses per day or second-line treatments.

Keywords: chronic spontaneous urticaria; children; natural course; remission; UAS; UAS7; treatment; autologous serum skin test; autoimmunity; predictive factors.

To the Editor,

Chronic urticaria (CU) is a relatively frequent disease with an estimated point prevalence of 0.7% around the world, subject to regional differences¹. Children seem to display a slightly higher frequency of the disease compared to adults, but to date, limited epidemiological data are available regarding the paediatric age, with only a few studies specifically examining the Caucasian population¹²³⁴.

Although it is considered a self-limited disease, CU often lasts for years. However, data on the natural history of CU are lacking, particularly in children, and frequently are not specific to the different CU subtypes. Finally, management recommendations are mostly extrapolated from evidence in adults.

We aimed to describe the natural history of Chronic Spontaneous Urticaria (CSU), the most frequent CU subtype, in a cohort of Caucasian children and to identify possible prognostic factors that could predict remission.

We performed an observational study at the Department of Paediatric Allergy and Immunology of the University teaching Tertiary Hospital, Institute for Maternal and Child Health IRCCS "Burlo Garofolo" of Trieste. The Internal Review Board approved the study. Patients aged 0 to 18 years with CSU diagnosed from January 2006 to July 2016 were included. Inducible urticaria, disease onset more than two years before the first examination or coexisting underlying conditions such as cardiovascular, hepatobiliary, and renal diseases were considered as exclusion criteria. Medical records were evaluated retrospectively, and the patients were eventually contacted by telephone to investigate their current CSU status. Remission was defined as an urticaria free period of at least three months without treatment, while reappearance of symptoms after remission was considered as a relapse. Patients were divided into three groups to evaluate the effect of the treatment regimen on the remission rate. They were assigned to the first group if they used a single dose of antihistamine drug, to the second group if they needed more than one daily dose (two, three or four doses per day), and to the third group if they used an adjunctive therapy, such as cyclosporin A or montelukast. An Autologous Serum Skin Test (ASST) was offered and performed in a subpopulation of patients who agreed to be tested³. Disease activity was assessed at the onset and during every control visit by the Urticaria Activity Score (UAS) and the Urticaria Activity Score 7 (UAS7)³. The specific methods of data recording and statistical analyses are described in *Appendix 1*.

The primary outcome was to assess the natural history of CSU. The secondary outcome was to identify likely predictors of disease duration.

A total of 86 patients were considered eligible, 6 of whom were lost to follow-up. The final population examined consisted of 80 patients, 41 females (51.3%), and 39 males (48.8%). The demographic and laboratory characteristics of the enrolled patients are reported in *Table 1*. Cetirizine was the second-generation H1-antihistamine drug of choice for all patients, with an average dose of

one per day (IQR: 1-2), being the sole treatment in 63 (78.8%) cases; overall 36 children (45%) took one dose per day of antihistamine and 27 (34%) more than one. An adjunctive therapy was recorded in 17 children (21.3%): all of them took corticosteroids, associated with another antihistamine in 2 cases (2.5%), ciclosporin in 1 case (1.3%) and montelukast in 1 case (1.3%).

An ASST was performed in 24 children (30.0%) with a positive result in 11 cases (45.8%). The result of the ASST did not affect the remission rates (*Table 2*).

Six patients (7.5%) presented elevated thyroid-stimulating hormone (TSH), despite normal free-T4 (fT4) with a median age at the finding of 9 years (IQR 4.75, 6.5-11.25), one patient (1.25%) had positive anti-TPO detected since the age of one year. The onset of comorbidities after the diagnosis of CSU was recorded in two patients (2.5%), consisting of celiac disease and hypothyroidism due to Hashimoto's thyroiditis, respectively, the latter presenting at the age of 16 years.

The median duration of CSU was 28 months (IQR: 9.0-50.0 months). At 1, 3 and 5 years of symptom onset, 29%, 55%, and 72% of CSU patients were in remission, respectively, with a cumulative remission rate of 78%.

Remission rate was significantly higher in the group of children who used a single dose of antihistamine drug per day than in the second and third group, respectively (81% vs. 30% and 44% at 3 years, p -value <0.0001 ; 89% vs. 54% and 67% at 5 years, p -value $=0.0003$) (*Figure 1a and 1b*).

The hazard ratio of the non-remission both at 3 years (HR=1.7, 95%CI=1.2-2.4, p -value 0.004) and 5 years from the onset of disease (HR=1.7, 95%CI=1.2-2.7, p -value 0.001), was higher for patients with a more severe UAS score at onset (*Table 2*). The median UAS score at onset was lower in the group of remission than in the group of non-remission both at 3 years (Median=2, IQR: 2 – 3 vs. Median=5, IQR: 4 - 5) and 5 years from the onset of disease (Median=3, IQR: 2 – 4 vs. Median=5, IQR: 4 - 5).

There was no evidence of a correlation between age at the onset and duration of the disease (Spearman's coefficient=0.02; p -value=0.9).

During the follow-up, four patients previously in disease remission had a relapse of CSU (6.9%). The distance of relapses from remission ranged from 2 to 5 years, while the relapse was protracted from 4 to 12 months.

Several studies have focused on the identification of factors that can predict the natural course of the disease, as desirable in long course conditions such as CSU¹⁻⁴.

We found a median duration of CSU of 28 months, consistent with that reported by Chansakulporn et al. of 33 months (2.7 years)³.

We identified a remission rate at 1, 3, and 5 years of 29%, 55%, and 72%, respectively, consistent with those found by Eser et al. (32.7% and 46.1% at 1 and 3 years, respectively)⁴, although they differ from those reported by Sahiner² and Chansakulporn³, which were both lower at one year. These data suggest a favorable trend of CSU in children, with the majority of patients reaching remission within five years. Although remission rates in adults are traditionally considered lower than in children, with

20% of patients with ongoing active disease at twenty years from onset⁵, according to recent studies, trends would be more consistent with those observed in the paediatric population^{6,7}.

The duration of CSU might be predicted at the onset by the severity of the UAS score; moreover, patients needing more than one dose of antihistamine drugs per day displayed a lower remission rate at 3 and 5 years when compared to patients using standard doses (*figure 1a and 1b*). These results are consistent with those reported by Eser⁴ and Yilmaz et al.^{8,9}. Rates of associated atopic disorders, family history of atopy, and possible autoimmune CSU etiology (as suggested by a positive ASST result) are similar to those reported in previous studies⁹. Nevertheless, none of these associated conditions seems able to impact on the remission rate. On the contrary, Netevhiporouk et al.¹⁰ found a higher resolution rate in cases of paediatric onset CSU with biomarkers of autoimmunity, such as positive results of a basophil activation test (BAT) using CD63 activation marker. Possibly, BAT may be a more specific biomarker for autoimmunity than ASST, and further studies should clarify this issue.

A limitation of our study is the relatively small sample size and missing evaluation of treatment compliance. No patients in this cohort used omalizumab, as the study was conducted mostly before its recent approval for use in children aged 12 and over in Italy¹¹.

In conclusion, this study showed that the prognosis of CSU is generally favourable in children, with a remission rate increasing up to 72% at 5 years after the onset of symptoms. Paediatric onset CSU is a benign entity, mostly easier to control by the first-line therapy than in adulthood, which instead requires second-line therapy in about two-thirds of the cases¹². Disease severity (elevated UAS score at onset as well as the need for adjunctive treatments) seemed to predict a more long-lasting disease. Relapses can occur later after the first remission and are not related to the age at the onset or the duration of the disease.

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Table1: Demographical and laboratory characteristics of the study population at enrollment.

	N. of patients (%) Total 80
Females	41 (51.2%)
Median age at onset	7
< 5 years	24(30%)
5-10 years	36(45%)
11-15 years	19(23.8%)
16-18 years	1(1.2%)
Median UAS score at onset	3.5 (IQR: 2.0-5.0)
Median UAS7 score at onset	25.0 (IQR: 16.0-34.5)
ASST (performed in 24 children, 30%)	11/24 (45.8%)
Personal history of atopy	24 (30.0%)
• food allergies	6 (7.5%)
• asthma	2 (2.5%)
• allergic rhinitis	16 (20.0%)
• atopic dermatitis	10 (12.5%)
Family history of atopy	33 (41.3%)
• food allergies	2 (2.5%)
• asthma	3 (3.8%)
• allergic rhinitis	28 (35.0%)

• atopic dermatitis	4 (5.0%)
• urticaria	2 (2.5%)
Elevated TSH with normal fT4	6 (7.5%)
Positive Anti-TPO titers	1 (1.3%)
Hashimoto's thyroiditis	1 (1.3%)
Positive Anti-TG titers	1 (1.3%)
Positive ANA titers	1 (1.3%)
IgA deficiency	1 (1.3%)

Table 2. Cox proportional hazard models of non-remission at 3 and 5 years from the onset of disease

Independent variables	Reference category	3 years			5 years		
		HR ¹	CI95% ²	P-value	HR ¹	CI95% ²	P-value
Personal atopy:							
Yes	No	1.3	0.6 - 2.7	0.5	1.3	0.5 - 3.0	0.6
Familial atopy:							
Yes	No	1.0	0.5 - 1.9	0.9	1.1	0.5 - 2.4	0.9
UAS Score at the onset		1.7	1.2 - 2.4	0.004	1.7	1.2 - 2.7	0.01
ASST Test:							
Not carried out	Negative	1.2	0.5 - 2.8	0.7	1.5	0.6 - 4.0	0.4
Positive		1.0	0.4 - 2.8	1.0	1.2	0.4 - 3.6	0.8
Therapy:							
More than 1 daily dose of AH ³	1 daily dose of AH ³	1.8	0.7 - 4.3	0.2	1.2	0.5 - 3.3	0.7
Adjunctive therapy	AH ³	1.2	0.4 - 3.3	0.8	1.0	0.3 - 3.4	1.0

¹HR=Hazard Ratio, ²CI95%= 95% Confidence Interval, ³AH=Anti-Histamine drug

Figure legend

Figure 1a. Kaplan-Meier curves for the probability of remission at 3 years from the onset of Chronic Urticaria, stratified by therapy. The remission rate was 81% for children who used a single dose of antihistamine per day, vs. 30% for children who used more than one dose of antihistamine per day, and 44% for children who used adjunctive therapy, p -value <0.0001 .

Figure 1b. Kaplan-Meier curves for the probability of remission at 5 years from the onset of Chronic Urticaria, stratified by therapy. The remission rate was 89% for children who used a single dose of antihistamine drug, vs. 54% for children who used more than one dose of antihistamine drug, and 67% for children who used adjunctive therapy, p -value=0.0003.

Note to figure 1c,1d: Therapy 1= one daily dose of anti-histamine drug; 2= More than one daily dose of anti-histamine drug; 3= Adjunctive therapy.

Appendix 1

Methods

Patients' follow up clinical data were collected: personal or family history of atopic diseases (such as atopic dermatitis, asthma, allergic rhinitis), connective tissue diseases or auto-inflammatory syndromes, drug intake, presence of angioedema, signs of infection, triggers of urticaria (such as cold, exercise, hot shower) and recent travel history.

Laboratory investigations included full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement, total immunoglobulins E (IgE), total immunoglobulins A (IgA), anti-transglutaminase antibody (tTG), antinuclear antibody (ANA), thyroid-stimulating hormone (TSH), free T4, anti-thyroid peroxisomal antibody (anti-TPO) and anti-thyroglobulin antibody (anti-TG) levels.

During their first evaluation, all children underwent a skin prick test for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria*, cat and dog epithelia, grass, tree, and weed pollens. Histamine (10 mg/ml of histamine phosphate) was used as a positive control and 0.9% sterile saline as a negative control. The skin prick test result was considered positive if the wheal diameter was 3 mm or higher compared with the negative control.

An Autologous Serum Skin Test (ASST) was offered and performed in a subpopulation of patients who agreed after patients and families granted the informed consent. It was executed using an intradermal skin test with 0.05 ml of sterile, fresh autologous serum. Histamine (10 µg/ml) and 0.9% sterile saline were used as positive and negative controls, respectively. The result was considered positive when the wheal diameter was 1.5 mm or higher, compared with the reaction elicited by a control saline solution 30 minutes after the intradermal injection.

According to the allergology unit, follow up protocol, disease activity was evaluated at the onset, and during every control visit by the Urticaria Activity Score (UAS) and the Urticaria Activity Score 7 (UAS7). In essence, they consist of a daily record of wheals number (range 0-3) and pruritus intensity (range 0-3), rated for one day (range 0-6) and seven consecutive days (range 0-42) respectively.

Statistical analysis:

Continuous variables were described as median and interquartile range while categorical variables were synthesized as frequency and percentage.

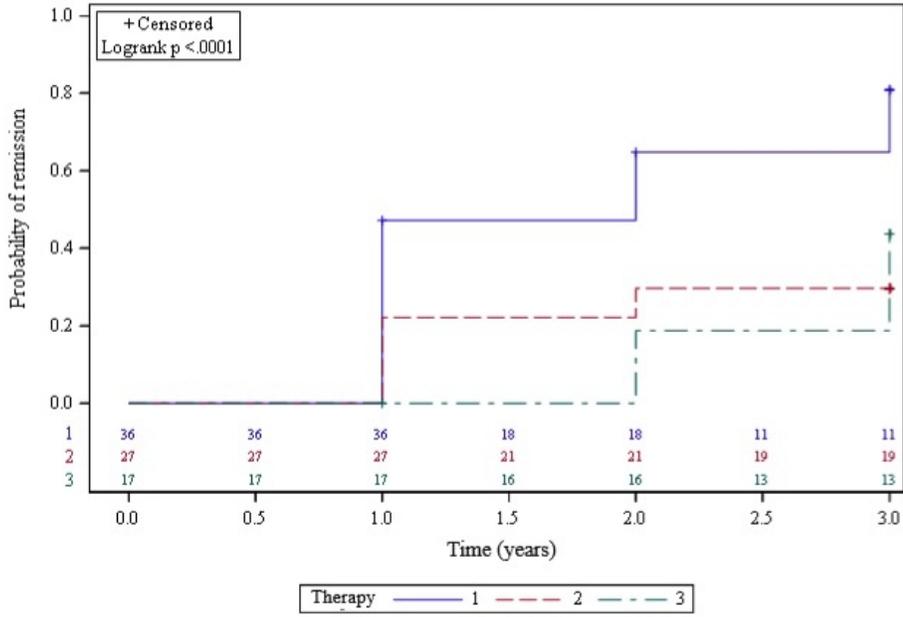
Spearman's test was used to establish the correlation between two continuous variables as the distributions were non-gaussian.

The Kaplan-Meier survival analysis was computed to evaluate the probability of remission at 1, 3 and 5 years from the onset of CSU, both in the entire population and in the treatment groups.

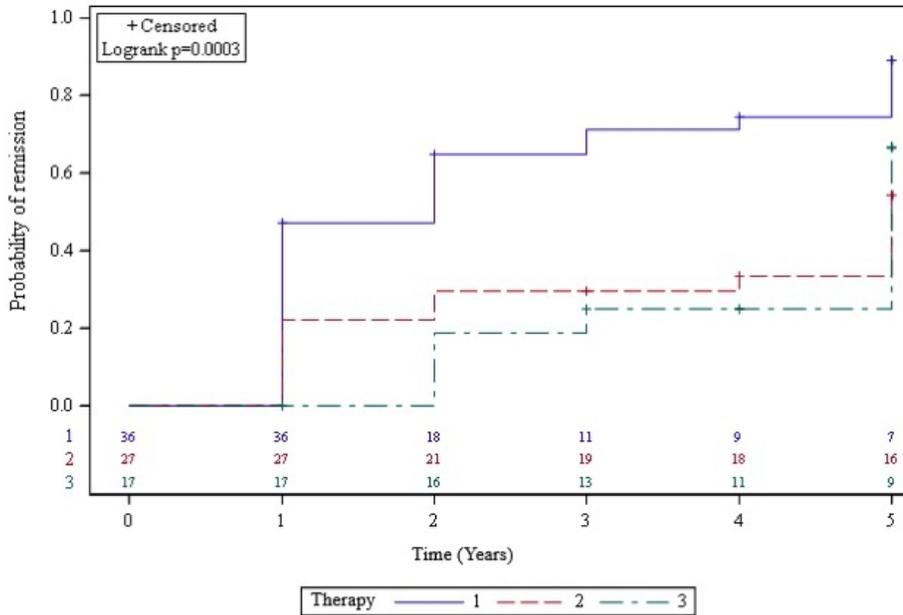
Patients were divided into three groups to evaluate the effect of the administered therapies on the remission rate: they were assigned to the first group if they used a single dose of an antihistamine drug, to the second group if they used more than one daily dose (2, 3 or 4 doses/day) and to the third group if they used an adjunctive therapy. The Log-rank test was used to determine the difference in the survival curves.

The proportional hazard Cox model was constructed to assess the relationship between the non-remission rate and independent variables as the personal history of atopy, family history of atopy, UAS score at the onset, ASST test and therapy. P-value <0.05 was considered statistically significant.

All analyses were performed using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC, USA).



1a



1b

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