

Investigation of Autoimmune Disease in Children with Chronic Spontaneous Urticaria

Chrysoula Kosmeri^a Ekaterini Siomou^b Anna Challa^c Sophia Tsaouri^b

^aDepartment of Pediatrics, University Hospital of Ioannina, Ioannina, Greece; ^bChild Health Department, Medical School, University of Ioannina, Ioannina, Greece; ^cPediatric Research Laboratory, Child Health Department, University of Ioannina, Ioannina, Greece

Keywords

Urticaria · Chronic spontaneous urticaria · Celiac disease · Autoimmune diseases · Child

important to test children with CSU for other autoimmune diseases. CD can be diagnosed in children with CSU even in the absence of other indicative signs.

© 2019 S. Karger AG, Basel

Abstract

Introduction: Chronic spontaneous urticaria (CSU) in childhood affects the quality of life of the patient and may be associated with other autoimmune diseases. The aim of this study was to investigate the association of autoimmune diseases with CSU in children. **Methods:** In a 3-year period, from 2015 to 2018, forty-nine children were diagnosed with CSU and monitored in the Outpatient Pediatric Allergy Clinic of the University Hospital of Ioannina in Northwestern Greece. The comorbidity with other autoimmune diseases was investigated in this population by autoantibody evaluation. **Results:** Of the 49 children with CSU, 1 had autoantibodies for celiac disease (CD), which was confirmed by duodenal biopsy via gastroscopy. Four children had high serum levels of anti-thyroid peroxidase antibodies but normal thyroid function. No other specific autoantibodies were detected. **Conclusion:** The prevalence of autoimmune diseases among our children with CSU was low. Nevertheless, we think it is

Introduction

Urticaria is a mast cell-driven disease of the dermis caused by various factors, though often the cause is unknown, and it is characterized by the development of hives or angioedema or both. When these symptoms persist for over 6 weeks, the condition is classified as chronic urticaria (CU), of which there are 2 forms, i.e., chronic spontaneous urticaria (CSU) and chronic inducible urticaria. CSU accounts for the majority of cases of CU [1] and, although it poses no threat to life, it has a profound impact on the physical and psychological state of the patients. In Europe, specifically in 5 European countries, the 1-year prevalence of CU and CSU in children has been

Edited by: H.-U. Simon, Bern.

reported to be 1.38 and 0.75%, respectively [2]. A population-based study of children from Korea showed that the prevalence of CU is 1.8% [3], while in the UK the prevalence has been reported to be 0.1–0.3% in children [4]. It should be noted that inducible forms of urticaria can coexist with CSU [1].

CSU is characterized by urticarial lesions occurring spontaneously, without any eliciting factor, on most days of the week and lasting 6 weeks or more. In children, CSU may persist for months or years. Reported resolution rates of childhood CSU, at 12, 36 and 60 months of follow-up, are 18.5, 54, and 67%, respectively [5].

Autoimmune activation of mast cells might be considered to be a contributor to the pathogenesis of CSU [6], described as IgE-mediated autoimmunity. It was recently found that subjects with CSU had more than 200 IgE autoantigens, while these were not present in healthy controls [7]. There are only a few studies showing that circulating IgG antibodies against the α subunit of the high-affinity IgE receptor (IgG anti-Fc ϵ R1 α) have been documented in 35–40% of patients, while a smaller proportion of them had IgG anti-IgE antibodies [8]. These induce a histamine release from blood basophils and cutaneous mast cells. One study showed low levels of functional autoantibodies against Fc ϵ R1 α in adult patients with CSU [9]. Therefore, there is not a consensus that autoimmune activation of mast cells contributes to CSU.

Many autoimmune disorders have been found associated with CSU, and a systematic review of CSU in children and adults revealed that autoimmune diseases occur in over 1% of these patients [10].

The aim of this study was to assess the presence of autoimmune disease in children with CSU diagnosed and monitored in the Outpatient Pediatric Allergy Clinic of the University Hospital of Ioannina, Greece.

Methods

During the 3-year period from 2015 to 2018, forty-nine children aged 1–15 years suffering from CSU were diagnosed and monitored in the Outpatient Clinic of Pediatric Allergy of the University Hospital of Ioannina, Greece, which is a referral center for children with allergic diseases of Northwestern Greece. The diagnosis of CSU was made when children had at least 2 admissions or outpatient visits for urticarial lesions arising spontaneously, with at least 6 weeks in between visits. In these children a diagnostic workup was conducted for known causes of urticaria [1].

A routine diagnostic assessment was conducted in all children, according to the recommendations for children with CSU of the Dermatology Section of the European Academy of Allergy and Clinical Immunology (EAACI), the European Union-funded

Network of Excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF), and World Allergy Organization (WAO) guidelines. This comprised the differential blood count, the erythrocyte sedimentation rate, and/or C-reactive protein [1]. However, a more extended workup for infectious diseases (e.g., *Helicobacter pylori*), functional autoantibodies (i.e., autologous skin serum testing), allergy (i.e., total serum IgE, skin prick tests, and/or allergen avoidance tests), severe systemic diseases, chronic inducible urticaria, stool assay for parasites and eggs, and serum antibodies for parasites was conducted for investigation of underlying causes or eliciting factors of urticaria.

The diagnostic procedure for autoimmune diseases included: anti-thyroglobulin, and anti-thyroid peroxidase (anti-TPO) antibodies, anti-tissue transglutaminase IgA, anti-endomysial IgA and anti-gliadin IgG antibodies, anti-nuclear antibodies, rheumatoid factor, anti-double-stranded DNA antibody, complement fractions C3 and C4, and measurement of total serum immunoglobulins, including IgA. Mean platelet volume (MPV) was assessed as a marker of inflammation. The normal range of MPV in adults is 7.5–11.5 fL, while a recent study in 98 healthy children found MPV of 9.9 ± 0.7 fL in toddlers and 10.6 ± 0.8 fL in schoolchildren [11].

The Urticaria Activity Score 7 (UAS-7) score was evaluated in all children on their first visit and 1 month after the initiation of antihistamine therapy. It was completed by the parents of the young children, while children aged 11 years or older completed this test on their own or with the help of their parents when needed. The Urticaria Activity Score (UAS) is a tool used in clinical practice to assess the activity of CSU (severity of pruritus and wheals) and the response to treatment. This score is estimated once or twice daily and the daily score can be summed over 7 days to create the UAS-7, which ranges from 0 to 42 [1, 12].

This study was approved by the ethical committee of the University Hospital of Ioannina. Written informed consent was provided by the parents for participation of their children in this study.

Results

The mean age of the 49 children was 8.8 years (range 1–15) and 23 (46.9%) were girls. The mean serum IgE level was 171.7 U/mL (range 5.5–1,670); 8 children had a serum IgE level above the upper normal limit for their age (the normal range in our hospital is 0–165 U/mL). The erythrocyte sedimentation rate and C-reactive protein were within the normal limits in all children, and the mean MPV level was 9.89 fL (range 8.7–12.1). Only 1 child had a level of MPV above the upper normal limit (MPV = 12.1 fL). The mean UAS-7 score of the children at the time of diagnosis of CSU was 13. All of the children were administered second-generation antihistamines in incremental doses, according to treatment guidelines [1].

Four of the 49 children (8.1%) had raised levels of anti-TPO antibodies, but as their levels of anti-thyroglobulin, TSH, and thyroid hormones were normal a diagnosis

of autoimmune thyroid disease was not established. Three children had serum levels of anti-nuclear antibody of 1/160 U/mL. Anti-DNA and ENA antibodies were negative. The results of autologous skin serum tests were all negative. However, even though the autologous skin serum test is the only available test to screen for autoantibodies against IgE or FcεRI, this is a nonspecific test as there are a number of factors in serum that could lead to mast cell degranulation.

In 1 child, antibodies for celiac disease (CD) were detected (anti-transglutaminase: positive >200 U/mL, anti-endomysial: positive, and anti-gliadin: positive >50 U/mL). This patient was an 11-year-old boy with a 5-year history of refractory CSU, with an urticarial rash distributed on the face, trunk, and extremities but without angioedema, and he was otherwise completely healthy. The UAS-7 score at his first visit was 31. His medical history was free of gastrointestinal symptoms such as diarrhea, constipation, or other symptoms. He had no anemia and no dermatitis herpetiformis, and his family history was negative for chronic diseases, autoimmune diseases, and gastrointestinal disorders. His body weight and height were consistently in the third to tenth percentile since birth, with no drop in the weight percentile, and his parents were also of low weight and height. The diagnostic workup for CSU, conducted according to EAACI/GA²LEN/EDF/WAO guidelines [1], was without pathological findings.

Further investigation was conducted, with gastroscopy and gastric and duodenal biopsies. The histopathological findings indicated CD, Marsh-Oberhuber type 3b, and Corazza-Villanacci grade B1. Following confirmation of CD, the child was put on a gluten-free diet. The child followed a strict gluten-free diet for 3 months (the parents confirmed compliance with this diet), after which partial clinical improvement of the CSU was observed and the UAS-7 score decreased to 5. Reassessment of antibodies for CD 10 months after the initiation of the gluten-free diet showed normalization of the CD antibodies. The endoscopy was not performed again in the child due to denial of parents despite the encouragement of doctors, so we cannot draw conclusions regarding histologic improvement along with improvement of urticaria symptoms. Nevertheless, after a year of a strict gluten-free diet, the patient's UAS-7 score continued to range between 3 and 10. It is of note that, while the clinical symptoms of urticaria improved with the gluten-free diet, complete remission of the symptoms was not achieved in this patient and he had relapses of urticaria symptoms after respiratory infections and under conditions of stress and therefore continued antihistamine treatment on alternate days.

The diagnostic workup was normal in the remainder of the children with CSU. No other autoimmune disease was diagnosed in the study subjects, who continue to be monitored.

Discussion

In our study, the assessment for the presence of autoimmune diseases among children with CSU showed that 1 child, who was otherwise apparently healthy, had CD and 4 children had positive anti-TPO antibodies, but with a normal thyroid function. No other autoimmune diseases were diagnosed.

Data on the coexistence of CU and CD are relatively limited. CD is an autoimmune disorder resulting from ingestion of gluten in genetically susceptible individuals (human leukocyte antigen class II genotypes defined as DQ2 or DQ8). A population-based study in North America documented an increase in the incidence of CD from 2000 to 2014 [13]. Children with CD are considered to be at increased risk of other autoimmune diseases [14].

Case reports of children with CU who were also diagnosed with CD have appeared over the years [15–17]. The first case, published in 1999 by Levine et al. [15], was of a girl with CU who had anti-thyroid and anti-nuclear antibodies and anemia. She reported no gastrointestinal symptoms, but eventually CD was diagnosed and after 12 months of a strict gluten-free diet she showed weight gain and normalization of hemoglobin but no improvement of her urticarial symptoms. Other case reports of children with CSU, otherwise asymptomatic, who are diagnosed with CD have shown that a gluten-free diet is associated with an improvement of their urticarial symptoms and normalization of CD autoantibodies [16–18].

Two large studies showed that the manifestation of CU preceded the diagnosis of CD. Specifically, in a case-control study of 79 children with CU and 2,545 control subjects without urticaria, CD was diagnosed more frequently in children with CU ($p = 0.0003$) [18]. A population-based cohort study of 28,900 individuals (both children and adults) with CD demonstrated that patients with CD were at a 1.5-fold increased risk of having urticaria and a 2-fold increased risk of having CU [19].

From the available data it is evident that there is an association between these 2 diseases, but the exact mechanism is as yet unknown and an etiopathogenetic relationship has not been established. One explanation giv-

en by some authors is that patients with CD demonstrate an increased mucosal permeability and, hypothetically, an increased passage of antigens is possible, with the subsequent formation of immune complexes [16, 19], which may contribute to an excess risk of urticaria [20].

In the majority of the case reports, a gluten-free diet was associated with improvement or remission of the urticaria [16, 17]. The mechanisms involved might be a decreased production of autoantibodies and a reduced permeability of antigens because of mucosal recovery [16, 17, 19]. In 1 case report, however, the CU was unresponsive to a gluten-free diet but continued to respond to antihistamine treatment [15]. In our patient, clinical improvement was observed after a gluten-free diet, without complete remission, and with a relapse of symptoms after upper respiratory infections. Levine et al. [15] concluded that the persistence of urticarial symptoms after a strict gluten-free diet, and even after the disappearance of anti-endomysial antibodies, excludes the possibility of an external antigen-induced urticaria via gastroenterology as a significant pathogenic etiology.

At present, no studies have concluded on whether CD is the triggering factor for CSU manifestation or if these 2 entities could be due to a shared susceptibility to autoimmune or chronic inflammatory processes. The increased incidence of a variety of other autoimmune diseases in children with CSU is noteworthy. In addition to CD, an increased prevalence of insulin-dependent diabetes mellitus, rheumatoid arthritis, psoriasis, Graves' disease, vitiligo, pernicious anemia, and Hashimoto's thyroiditis [10] in children and adults with CSU has been documented, and children with CU have a higher risk of systemic lupus erythematosus [21]. In our study, 4 children had raised levels of anti-TPO antibodies, but with a normal thyroid function. A systematic review in 2017 by Kolkhir et al. [22] reported a strong association between CSU and raised levels of IgG anti-thyroid antibodies, more commonly IgG anti-TPO antibodies, and concluded that anti-thyroid antibodies did not have a pathogenetic role in CSU but that their presence represents parallel auto-immune events. In a large population study, it was reported that autoimmune comorbidities of CU were independently diagnosed within 10 years of the diagnosis of CU, and not as part of the CU workup [23]. The aforementioned findings are in agreement with the results of our study. Hence, children with CSU should undergo long-term monitoring for possible development of other autoimmune diseases in the future.

Conclusion

The prevalence of autoimmune diseases among our children with CSU was low. Nevertheless, taking into account the rarity of CSU in childhood, physicians should be aware of the coexistence of CSU with other autoimmune diseases and for which children need to be tested additionally in the absence of any indicative symptom. When CD is diagnosed in children with CSU, a gluten-free diet should be applied, although remission or improvement of their urticaria is uncertain and they may continue to need antihistamine treatment. Future research should be focused on the underlying pathogenesis of the relationship between CSU and other autoimmune disorders, which could lead to the development of novel efficacious treatment of urticaria.

Statement of Ethics

This study was approved by the ethical committee of the University Hospital of Ioannina (protocol No. 547). Written informed consent was provided by the parents for participation of their children in this study.

Disclosure Statement

The authors have no conflict of interests to declare.

Funding Sources

No funding was received for this study.

Author Contributions

Chrysoula Kosmeri contributed to the design of this work and analysis of data for this work, participated in drafting this work, approved the final version to be published, and agreed to be accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ekaterini Siomou made substantial contributions to the design of this work and interpretation of data for the work, participated in drafting this work, approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Anna Challa contributed to the conception of this work and to analysis of data for this work, participated in revising it critically for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work

in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Sofia Tsabouri contributed to the design of this work and interpretation of data for this work, participated in drafting this

work, approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

- 1 Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al.; Endorsed by the following societies: AAAAI, AAD, AAIITO, ACAAI, AEDV, APAAACI, ASBAI, ASCIA, BAD, BSACI, CDA, CMICA, CSACI, DDG, DDS, DGAKE, DSA, DST, EAACI, EIAS, EDF, EMBRN, ESCD, GA2LEN, IAACI, IADVL, JDA, NVvA, MSAI, ÖGDV, PSA, RAACI, SBD, SFD, SGAI, SGDv, SIAAIC, SIDEmaST, SPDV, TSD, UNBB, UNEV and WAO. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018 Jul;73(7):1393–414.
- 2 Balp MM, Weller K, Carboni V, Chirilov A, Papavassilis C, Severin T, et al. Prevalence and clinical characteristics of chronic spontaneous urticaria in pediatric patients. *Pediatr Allergy Immunol*. 2018 Sep;29(6):630–6.
- 3 Lee SJ, Ha EK, Jee HM, Lee KS, Lee SW, Kim MA, et al. Prevalence and Risk Factors of Urticaria With a Focus on Chronic Urticaria in Children. *Allergy Asthma Immunol Res*. 2017 May;9(3):212–9.
- 4 Khakoo G, Sofianou-Katsoulis A, Perkin MR, Lack G. Clinical features and natural history of physical urticaria in children. *Pediatr Allergy Immunol*. 2008 Jun;19(4):363–6.
- 5 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 Oct;71(4):663–8.
- 6 Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immunol*. 2017 Jun;139(6):1772–1781.e1.
- 7 Kaplan AP. Chronic Spontaneous Urticaria: Pathogenesis and Treatment Considerations. *Allergy Asthma Immunol Res*. 2017 Nov;9(6):477–82.
- 8 MacGlashan D. Autoantibodies to IgE and FcεRI and the natural variability of spleen tyrosine kinase expression in basophils. *J Allergy Clin Immunol*. 2019 Mar;143(3):1100–1107.e11.
- 9 Schmetzer O, Lakin E, Topal FA, Preusse P, Freier D, Church MK, et al. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2018 Sep;142(3):876–82.
- 10 Kolkhir P, Borzova E, Grattan C, Asero R, Pogorelov D, Maurer M. Autoimmune comorbidity in chronic spontaneous urticaria: A systematic review. *Autoimmun Rev*. 2017 Dec;16(12):1196–208.
- 11 Knoefler R, Hackel S, Staechle J, Lohse J, Range U, Suttorp M, et al. Evaluation of Platelet Parameters in Children. *Blood*. 2017;130 Suppl 1:4842.
- 12 Hollis K, Proctor C, McBride D, Balp MM, McLeod L, Hunter S, et al. Comparison of Urticaria Activity Score Over 7 Days (UAS7) Values Obtained from Once-Daily and Twice-Daily Versions: results from the AS-SURE-CSU Study. *Am J Clin Dermatol*. 2018 Apr;19(2):267–74.
- 13 Almallouhi E, King KS, Patel B, Wi C, Juhn YJ, Murray JA, et al. Increasing Incidence and Altered Presentation in a Population-based Study of Pediatric Celiac Disease in North America. *J Pediatr Gastroenterol Nutr*. 2017 Oct;65(4):432–7.
- 14 Assa A, Frenkel-Nir Y, Tzur D, Katz LH, Shamir R. Large population study shows that adolescents with celiac disease have an increased risk of multiple autoimmune and nonautoimmune comorbidities. *Acta Paediatr*. 2017 Jun;106(6):967–72.
- 15 Levine A, Dalal I, Bujanover Y. Celiac disease associated with familial chronic urticaria and thyroid autoimmunity in a child. *Pediatrics*. 1999 Aug;104(2):e25.
- 16 Peroni DG, Paiola G, Tenero L, Fornaro M, Bodini A, Pollini F, et al. Chronic urticaria and celiac disease: a case report. *Pediatr Dermatol*. 2010 Jan-Feb;27(1):108–9.
- 17 Meneghetti R, Gerarduzzi T, Barbi E, Ventura A. Chronic urticaria and coeliac disease. *Arch Dis Child*. 2004 Mar;89(3):293.
- 18 Caminiti L, Passalacqua G, Magazzù G, Comisi F, Vita D, Barberio G, et al. Chronic urticaria and associated coeliac disease in children: a case-control study. *Pediatr Allergy Immunol*. 2005 Aug;16(5):428–32.
- 19 Ludvigsson JF, Lindelöf B, Rashtak S, Rubio-Tapia A, Murray JA. Does urticaria risk increase in patients with celiac disease? A large population-based cohort study. *Eur J Dermatol*. 2013 Sep-Oct;23(5):681–7.
- 20 Abenavoli L, Proietti I, Zaccaro V, Gasbarrini G, Addolorato G. Celiac disease: from gluten to skin. *Expert Rev Clin Immunol*. 2009 Nov;5(6):789–800.
- 21 Lin CH, Hung PH, Hu HY, Chung CJ, Chen TH, Hung KY. Clinically diagnosed urticaria and risk of systemic lupus erythematosus in children: A nationwide population-based case-control study. *Pediatr Allergy Immunol*. 2018 Nov;29(7):732–9.
- 22 Kolkhir P, Metz M, Altrichter S, Maurer M. Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: A systematic review. *Allergy*. 2017 Oct;72(10):1440–60.
- 23 Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. *J Allergy Clin Immunol*. 2012 May;129(5):1307–13.