© Pediatr Med Rodz 2019, 15 (2), p. 198–202
DOI: 10.15557/PiMR.2019.0035

Received: 03.10.2018
Accepted: 17.12.2018
Published: 31.07.2019

Anna Góra, Majka Jaszczura, Małgorzata Morawiecka-Pietrzak, Edyta Machura

Infection focus as a potential cause of chronic urticaria – a case of a 12-year-old boy and the review of literature

Ognisko infekcji jako potencjalna przyczyna pokrzywki przewlekłej – opis przypadku 12-letniego chłopca i przegląd piśmiennictwa

Department of Paediatrics, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia in Katowice, Zabrze, Poland
Correspondence: Anna Góra, Department of Paediatrics, 3 Maja 13-15, 41-800 Zabrze, Poland, tel.: +48 32 370 42 83, fax: +48 32 370 42 92, e-mail: a.szczepanek@o2.pl

Abstract

Chronic urticaria is a rare disease in the paediatric population. It is characterised by the presence of blebs, angioedema or the coexistence of these changes for a period of more than 6 weeks. It is assumed that the aetiology of the disease is multifactorial, but in many cases it remains undetermined. The development of urticaria depends on the activation of mast cells. High significance in the development of chronic urticaria is attributed to autoimmune mechanisms. The patients with urticaria reveal the presence of infection foci usually located in the head, including the upper respiratory tract. Pathogenic microorganisms can lead to the development of systemic reactions. Limited data on the causes of chronic urticaria among children triggers diagnostic and therapeutic concerns. Patients with chronic urticaria often require complex diagnostics and long-term treatment. Chronic urticaria significantly reduces the quality of life of patients and the pharmacotherapy used is fraught with the risk of side effects. This paper presents a case report of a 12-year-old boy with a 5-year history of chronic urticaria with a complete remission of skin lesions after adenotonsillectomy.

Keywords: urticaria, infection, bacteria, children, tonsillectomy

Streszczenie

Pokrzywka przewlekła jest rzadką chorobą w populacji pediatrycznej. Charakteryzuje się występowaniem bąbli, obrzęku naczynioruchowego lub obu wymienionych zmian jednocześnie przez okres ponad 6 tygodni. Przypuszcza się, że etiologia choroby jest wieloczynnikowa, jednak w wielu przypadkach pozostaje nieustalona. Rozwój pokrzywki zależy od aktywacji komórek tucznych. Duże znaczenie w rozwoju pokrzywki przewlekłej przypisuje się mechanizmom autoimmunologicznym. U chorych z pokrzywką stwierdza się obecność ognisk infekcyjnych zlokalizowanych najczęściej w obrębie głowy, w tym górnych dróg oddechowych. Drobnoustroje chorobotwórcze mogą prowadzić do rozwoju reakcji ogólnoustrojowej. Ograniczone dane na temat przyczyn pokrzywki przewlekłej spontanicznej wśród dzieci sprzyjają wątpliwościom diagnostycznym i terapeutycznym. Pacjenci obciążeni pokrzywką przewlekłą często wymagają złożonej diagnostyki i długotrwałego leczenia. Schorzenie to znacząco obniża jakość życia chorych, a stosowana farmakoterapia jest obarczona ryzykiem wystąpienia działań niepożądanych. W niniejszej pracy przedstawiono opis przypadku 12-letniego chłopca z 5-letnim wywiadem pokrzywki przewlekłej spontanicznej, u którego odnotowano całkowitą remisję zmian skórnych po adenotonsylektomii.

Słowa kluczowe: pokrzywka, infekcja, bakterie, dzieci, tonsylektomia

© Medical Communications Sp. z o.o. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (CC BY-NC-ND). Reproduction is permitted for personal, educational, non-commercial use, provided that the original article is in whole, unmodified, and properly cited.

INTRODUCTION

Urticaria is characterised by the development of blebs, angioedema, or both. The specific picture of the urticaria bleb consists of sudden local swelling of the skin, pruritus, transient nature and remission without leaving a trace, usually within 24 hours. In most cases, the symptoms disappear spontaneously after a few or a dozen or so days. If they persist for more than 6 weeks, then the urticaria is chronic[1]. The chronic form is present in 0.6% of the Polish population[2]. Chronic urticaria is divided into spontaneous and induced (associated with the action of known and repetitive triggers)[1].

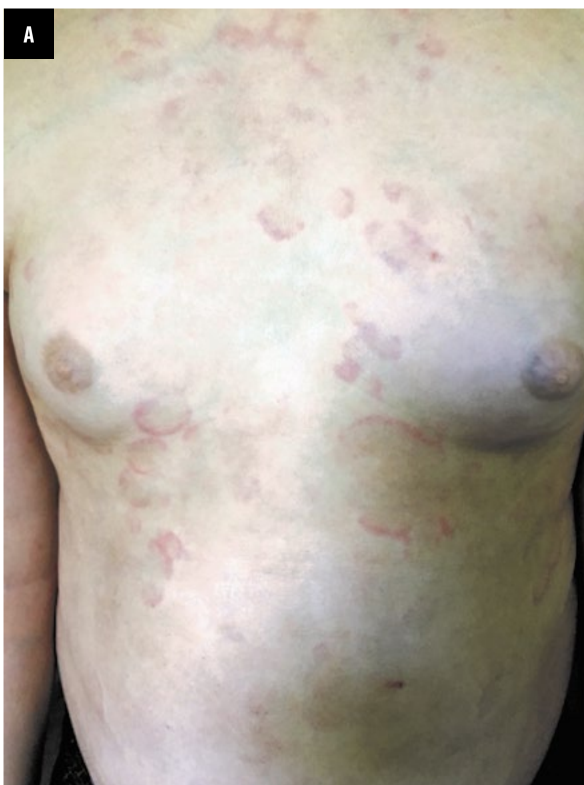
Chronic urticaria occurs in nearly 1.8% of the paediatric population, which makes it a rare disease in children and adolescents[3]. Despite this, it creates great diagnostic difficulties (up to 50% of idiopathic cases[4,5]) and the therapy does not often bring the desired result. Deterioration of the quality of life of patients affected by recurrent symptoms, often of an unknown cause, has an adverse psychological effect and arouses understandable anxiety of the whole family[1,3,6].

We are presenting the case of a 12-year-old boy with spontaneous chronic urticaria, who has been subjected to an ineffective therapy for many years, and the most probable cause of skin lesions was chronic inflammation of the upper respiratory tract.

CASE DESCRIPTION

A 12-year-old boy with a 5-year history of chronic spontaneous urticaria was hospitalised three times in the General-Paediatric Ward with the Sub-Department of Allergology, Pulmonology and Paediatric Immunology due to exacerbation of skin lesions. Before the second year of his life, he had been treated due to recurrent obstructive bronchitis; he had been permanently under the care of the Allergy Clinic, where IgE-dependent allergy had been excluded. The boy suffered from spontaneously appearing blebs on the lower and upper limbs and on the torso of variable severity, with persistent pruritus, subdued spontaneously for 2 to 3 days (Fig. 1 A, B). Physical examination revealed obesity (body mass index, BMI = 29 kg/m^2), concave back, valgus knees, adenoidal face and hypertrophic palatine tonsils. In UAS-7 (urticaria activity score), the activity of urticaria was evaluated at 17–26 points, which was a sign of moderate intensity of lesions[1].

Diagnostics were carried out according to the guidelines[1]. Normal results of routine and additional diagnostic tests were obtained, i.e. morphology with smear, ESR, C-reactive protein (CRP), D-dimers, absolute eosinophils, thyroid-stimulating hormone (TSH), free thyroxine (fT4), thyroid peroxidase antibodies (anti-TPO), IgA class antibodies to tissue transglutaminase (anti-tTG IgA), concentration and activity of C1-esterase inhibitor, IgM, IgA, IgG,



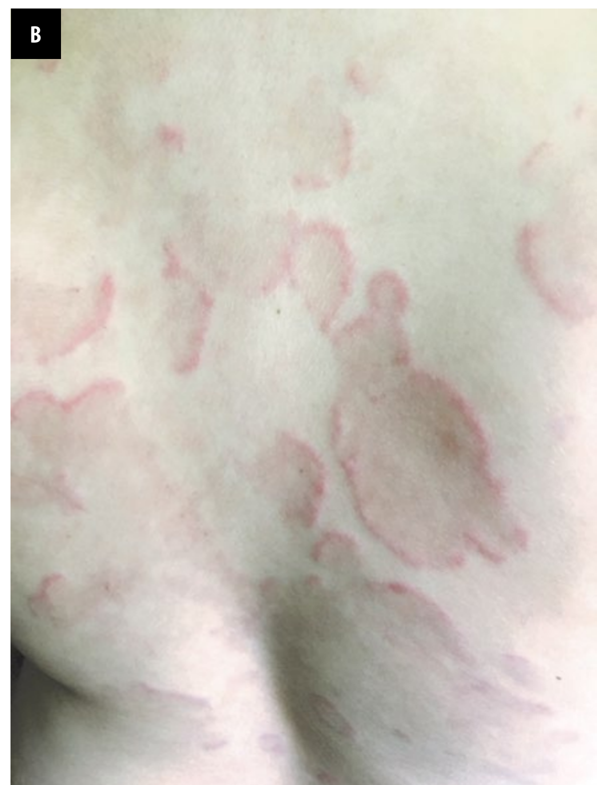


Fig. 1 A, B. Zmiany pokrzywkowe na tułowiu przed zabiegiem adenotonsylektomii

 DOI: 10.15557/PiMR.2019.0035

specific IgE (norm <0.35 kU/L – panel of 40 inhalation and food allergens), ANA profile, parasitological tests, general urine and chest X-ray examination. A tests for the presence of *Helicobacter pylori* antigen in faeces revealed negative results.

The following abnormalities were noted: high concentration of total IgE – 1,161 IU/mL (norm 2.9–103.5)[7], hypercholesterolaemia of low density lipoprotein (LDL) – 3.05 mmol/L (norm <2.8), hypertriglyceridemia – 2.04 mmol/L (norm <1.7), low concentration of vitamin D_3 – 5.67 ng/mL (norm 30–80), high anti-streptolysin O (ASO) titre – 245 IU/mL (norm 0–150), presence of *Staphylococcus aureus* in the swab from throat and *Staphylococcus epidermidis* in the nasal swab and urine culture (titre 10^3). The ultrasound examination of the abdominal cavity revealed liver steatosis.

Psychological examination revealed a significantly elevated level of anxiety in the boy, apathy, excessive sleepiness and difficulty in concentrating.

Due to the hypertrophy of the pharyngeal tonsil and chronic inflammation of the palatine tonsils, the laryngologist qualified the boy for adenotonsillectomy, which was performed only at the age of 12 (the procedure was put off three times due to acute respiratory infections and herpes labialis). After the surgery, complete remission of urticaria was observed (Fig. 2 A, B).

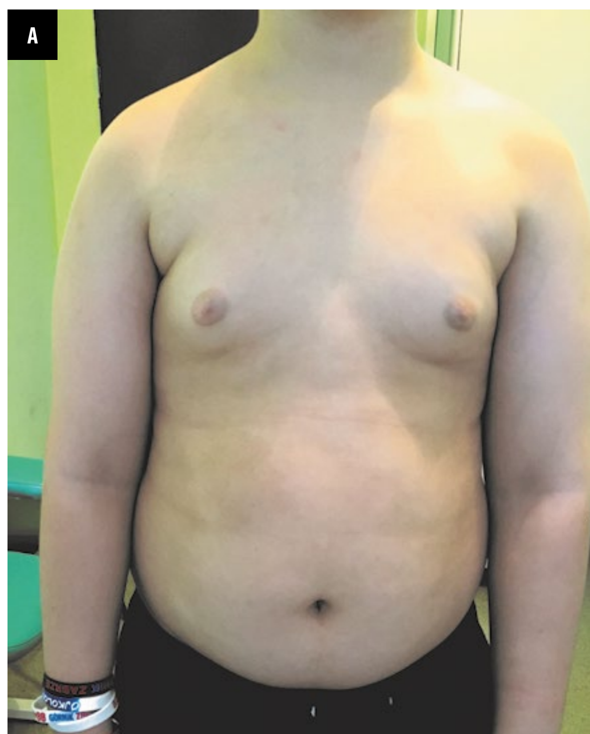
While anticipating the surgery, the boy was treated for 5 years with antihistamines of the first and second generation (levocetirizine, clemastine, fexofenadine), hypoallergenic and low-calorie diet, supplementation of vitamin D_3 – without improvement. During periods of exacerbation of the urticarial changes, treatment with oral prednisone preparations and eucerin-based cooling ointments was applied. The boy was treated with antibacterial (amoxicillin and clavulanate, clarithromycin, cotrimoxazole) and antiparasitic (mebendazole) drugs several times with transient reduction of skin lesions.

Within 10 months after the surgery, urticaria recurrence was not observed. In control tests, the concentration of total IgE – 339.5 IU/mL (norm 2.9–103.5)[7] was found; skin prick tests (SPT) and a re-made panel of specific IgE were negative.

DISCUSSION

It is thought that the aetiology of chronic urticaria in children, like in adults, is multifactorial[8]. However, currently available data on the paediatric population are scarce[3,9,10]. The causative factors include: food and inhalation allergies, non-allergic hypersensitivity to food additives and drugs, air pollution, thyroid disease, connective tissue diseases, stress[5,9]. It is estimated that in 30–50% of cases, chronic urticaria is of an autoimmune origin[4] and in 1–17% the background is related to drugs[10]. In most cases, the aetiology of the disease remains undetermined[5].

Although infections play a predominant role in the development of acute urticaria in children, the relationship between infectious agents and chronic urticaria remains unclear[6,11,12].



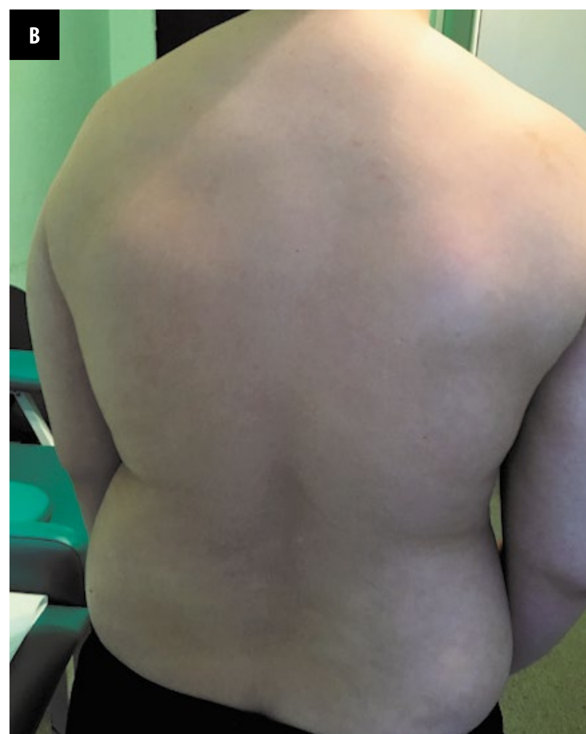


Fig. 2 A, B. Skóra pacjenta po zabiegu

DOI: 10.15557/PiMR.2019.0035 PEDIATR MED RODZ Vol. 15 No. 2, p. 198–202

Factors potentially related to the development of chronic urticaria include: *Streptococcus*, *Staphylococcus*, *Borrelia*, *Yersinia*, *Salmonella*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Helicobacter pylori*, *Mycobacterium leprae*[8,12], as well as viruses: human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), parvovirus B19, norovirus[1,6]. Urticarial changes on the background of urogenital infections and fungal infections have also been reported[8]. The causal relationship between parasitic infection and chronic urticaria has not been confirmed[9].

In the Polish population, the presence of an infectious focus was noted in nearly 36% of patients with chronic urticaria[11]. In over 90% of cases, the foci of infection are localized within the head, most often within the teeth, periodontium, paranasal sinuses, nose, ear and throat[11]. Elevated antistreptolysin O (ASO) were documented in 37% of patients[8], while antistaphylolysin antibodies (ASTA) were detected in the serum of 1–10% of patients[6]. The incidence of *Staphylococcus aureus* carriage in the nasal cavity of patients with chronic urticaria is higher than in healthy subjects (53% vs. 13%)[12,13]. The presence of this pathogen was also confirmed in our patient.

In the population of chronic urticaria patients, specific IgE is present against enterotoxin of *Staphylococcus aureus* (SEA – staphylococcal enterotoxin A, SEB – staphylococcal enterotoxin B) and against toxin TSST-1 (toxic shock syndrome toxin-1)[14]. The titre of reagin against staphylococcal enterotoxin B correlates with the total IgE titre and the degree of activity of spontaneous chronic urticaria. Therefore, it cannot be ruled out that the high concentration of total IgE in the presented case may be related to the presence of *Staphylococcus aureus* in the upper respiratory tract, especially that the boy was not found to have specific IgE for environmental allergens (foods, inhalation allergens). It is worth emphasising, however, that atopic disease in children with urticaria is more common than in the general paediatric population and may affect 28% of patients[3].

The pathomechanism of the influence of microorganisms on urticarial changes remains unexplained. The theory of infection focus assumes the occurrence of local, usually asymptomatic, inflammatory changes which, acting via the immunological mechanisms, cause a systemic effect[8,11]. The possibility of direct interaction of the pathogen on the skin (*Borrelia*, *Mycobacterium leprae*), bacterial toxins (*Staphylococcus aureus*) or activation of the complement through immune complexes are also indicated[12].

As we know, the development of urticaria changes depends, among other things, on the activation of mast cells of the skin. The process is achieved by combining specific IgE with the high affinity IgE receptor (FcεR1) present on the surface of the mastocyte. In the case of chronic urticaria, reagins arise not only in response to typical exo-allergens, but also in response to unknown antigens[14]. In about 30–50% of patients with chronic urticaria, autoantibodies against FcεR1 or IgE are detected, which may be reflected in the positive results of the autologous serum skin test (ASST)[11].

In the presented case, the attempts to perform SPT and ASST before adenotonsillectomy were unsuccessful due to the presence of active urticarial lesions and the lack of the possibility of withdrawal of antihistamines.

The diagnosis of chronic urticaria is based on the history and physical examination[1]. The panel of additional tests should be selected individually depending on the clinical picture[1,4,6]. Routine tests include peripheral blood count with smear, CRP and/or red blood cell count (ESR). In the case of patients with long-term and uncontrolled urticaria, it is recommended to carry out diagnostics for infectious diseases, presence of autoantibodies, thyroid diseases, allergies and non-allergic hypersensitivity reactions, coexistence of chronic induced urticaria, severe systemic diseases, celiac disease, cryopyrinopathy (e.g. Muckle–Wells syndrome)[1,4,8].

Due to the prevalence of psychiatric disorders in patients with chronic urticaria more frequent than in the general population, it is advisable to refer the patient for psychological consultations[15].

Treatment of chronic urticaria includes avoidance of exposure to known etiological factors and symptomatic pharmacotherapy.

Pharmacotherapy is based on the supply of second-generation antihistaminic drugs which block the H1 receptor. The group of drugs tested for efficacy and safety in children includes e.g. cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine and rupatadine[1,4]. Treatment of the next relapse consists in increasing the daily dose of antihistamines by up to four times, and in the case of no improvement – administration of omalizumab, cyclosporin, and in special cases – tumour necrosis factor α (TNF-α) receptor antagonists, and intravenous immunoglobulin preparations[1]. In patients with exacerbation of urticarial lesions, a short, maximum 10-day oral steroid therapy is allowed[1]. It is recommended to treat bacterial infections located in the nasopharyngeal cavity and eradicate *Helicobacter pylori*. In many cases, psychotherapy is indispensable[1].

It is worth mentioning that commonly used antihistamines of the second generation may cause side effects in the form of headaches, drowsiness, aggression, agitation, arrhythmias[16] and may promote the development of obesity and insulin resistance[17].

It is suggested that patients with spontaneous chronic urticaria are more prone to metabolic syndrome, hyperlipidaemia[18], vitamin D_3 deficiency[3] and depressive and anxiety disorders[15]. The abnormalities mentioned above largely concerned our patient. The child's drowsiness and anxiety diagnosed by the psychologist may have resulted from the course of the disease or administered medications and could strengthen the perception of somatic symptoms.

As already mentioned, the pharmacotherapy, diet and supplementation of vitamin D_3 used in our patient did not bring any effect, what is more, the continuation of the supply of antihistamines could exacerbate the metabolic and emotional disorders in the child and lead to the development of other side effects.

PEDIATR MED RODZ Vol. 15 No. 2, p. 198–202 DOI: 10.15557/PiMR.2019.0035

After the adenotonsillectomy, the urticaria remission occurred. During the 8-month follow-up period, there was no recurrence of skin lesions, and antihistamines were discontinued. Drowsiness and anxiety disorders were resolved, motor activity increased, and the boy's weight decreased, which significantly improved his quality of life.

The time relation of the remission of skin lesions with the performed procedure and the antibiotic therapy used may suggest the involvement of an infectious agent or changes in the functioning of the immune system, however, spontaneous remission of the disease cannot be unequivocally ruled out.

CONCLUSIONS

In summary, despite the constantly growing knowledge about chronic urticaria, its aetiology remains largely unknown. Individual approach to the diagnosis of the patient, active search and elimination of potential (including infectious) causes of chronic urticaria seem to be essential elements of the diagnostic and therapeutic process.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations that could adversely affect the content of the publication and claim the right to publish it.

References

1. Zuberbier T, Aberer W, Asero R et al.; Endorsed by the following societies: AAAAI, AAD, AAIITO, ACAAI, AEDV, APAAACI, ASBAI, ASCIA, BAD, BSACI, CDA, CMICA, CSACI, DDG, DDS, DGAKI, 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; 73: 1393–1414.
2. Raciborski F, Kłak A, Czarnecka-Operacz M et al.: Epidemiology of urticaria in Poland – nationally representative survey results. Postepy Dermatol Alergol 2018; 35: 67–73.
3. Cornillier H, Giraudeau B, Munck S et al.: Chronic spontaneous urticaria in children – a systematic review on interventions and comorbidities. Pediatr Allergy Immunol 2018; 29: 303–310.
4. Powell RJ, Leech SC, Till S et al.; British Society for Allergy and Clinical Immunology: BSACI guideline for the management of chronic urticaria and angioedema. Clin Exp Allergy 2015; 45: 547–565.
5. Caffarelli C, Cuomo B, Cardinale F et al.: Aetiological factors associated with chronić urticaria in children: a systematic review. Acta Derm Venereol 2013; 93: 268–272.
6. Wedi B, Raap U, Wieczorek D et al.: Urticaria and infections. Allergy Asthma Clin Immunol 2009; 5: 10.
7. Kendziorek A, Bobilewicz DM: Wartość oznaczeń immunoglobulin w różnych grupach wiekowych. In Vitro Explorer – Przegląd Medycyny Laboratoryjnej 2006; 1 (5): 12–17.
8. Wedi B, Raap U, Kapp A: Chronic urticaria and infections. Curr Opin Allergy Clin Immunol 2004; 4: 387–396.
9. Arik Yilmaz E, Karaatmaca B, Sackesen C et al.: Parasitic infections in children with chronic spontaneous urticaria. Int Arch Allergy Immunol 2016; 171: 130–135.
10. Machura E, Jońska-Golus M, Krakowczyk H et al.: Etiologia i przebieg kliniczny pokrzywki u hospitalizowanych dzieci. Dev Period Med 2013; 17: 64–71.
11. Brzewski PŁ, Spałkowska M, Podbielska M et al.: The role of focal infections in the pathogenesis of psoriasis and chronic urticaria. Postepy Dermatol Alergol 2013; 30: 77–84.
12. Minciullo PL, Cascio A, Barberi G et al.: Urticaria and bacterial infections. Allergy Asthma Proc 2014; 35: 295–302.
13. Ertam I, Biyikli SE, Yazkan FA et al.: The frequency of nasal carriage in chronic urticaria patients. J Eur Acad Dermatol Venereol 2007; 21: 777–780.
14. Altrichter S, Hawro T, Liedtke M et al.: In chronic spontaneous urticaria, IgE against staphylococcal enterotoxins is common and functional. Allergy 2018; 73: 1497–1504.
15. Hergüner S, Kiliç G, Karakoç S et al.: Levels of depression, anxiety and behavioural problems and frequency of psychiatric disorders in children with chronic idiopathic urticaria. Br J Dermatol 2011; 164: 1342–1347.
16. de Vries TW, de Langen-Wouterse JJ, van Puijenbroek E et al.: Reported adverse drug reactions during the use of inhaled steroids in children with asthma in the Netherlands. Eur J Clin Pharmacol 2006; 62: 343–346.
17. Ratliff JC, Barber JA, Palmese LB et al.: Association of prescription H1 antihistamine use with obesity: results from the National Health and Nutrition Examination Survey. Obesity (Silver Spring) 2010; 18: 2398–2400.
18. Zbiciak-Nylec M, Wcisło-Dziadecka D, Kasprzyk M et al.: Overweight and obesity may play a role in the pathogenesis of chronic spontaneous urticaria. Clin Exp Dermatol 2018; 43: 525–528.

DOI: 10.15557/PiMR.2019.0035