



Submitted on: 11/29/2016  
Approved on: 02/05/2017

ORIGINAL ARTICLE

## Acute urticaria as a manifestation of viral infections in childhood

Bruna Piassi Guaitolini<sup>1</sup>, Priscilla Filippo Alvim de Minas Santos<sup>2</sup>, Gabriela Dias<sup>3</sup>, Denise Pedrazzi<sup>4</sup>, Eduardo Costa<sup>5</sup>

### Keywords:

urticaria,  
child,  
viruses.

### Abstract

**Objective:** To report serial cases of acute urticarial associated with viral infections. **Material and Methods:** Serial report cases of children diagnosed with acute urticaria associated with viral infections and literature review. **Results:** Seven patients were evaluated, three of them female, with an average age of 3 years. Three patients had urticarial lesions, without other associated symptoms. The remaining patients presented a previous characteristic of upper airways. All were evaluated in emergency service, medicated with antihistamines and referenced for evaluation by specialist in allergy and immunology. The urticaria remission period ranged from 5 to 15 days. In the diagnostic investigation, two children presented reactive IgM for Parvovirus B19, three presented reactive IgM for Epstein Barr virus (EBV), one presented reactive IgM for EBV and for Herpes Simplex virus I and II, and one had reactive IgM for Herpes Simplex I and II. **Conclusion:** Acute urticaria is a common childhood disease with detailed clinical history and physical examination essential for the etiological diagnosis. The pediatrician should be aware of the main triggering factors, including viral infections.

<sup>1</sup> Resident Physician in Pediatrics at the Central Military Hospital - Resident in Pediatrics in the Central Military Hospital (Hospital Central do Exército) Rio de Janeiro, RJ, Brazil.

<sup>2</sup> Master's Student of the Graduate Program in Medical Sciences - Rio de Janeiro State University - Specialist in Allergy and Immunology at Jesus City Hospital, Rio de Janeiro, RJ, Brazil.

<sup>3</sup> Master of Medical Sciences from the Federal University of Rio de Janeiro - Specialist in Allergy and Immunology at the Pedro Ernesto University Hospital and the Piquet Carneiro Clinical Center of Rio de Janeiro State University, Rio de Janeiro, RJ, Brazil.

<sup>4</sup> Specialist in Allergy and Immunology at the Pedro Ernesto University Hospital and the Piquet Carneiro Clinical Center of Rio de Janeiro State University Eduardo Costa: Ph.D. in Medical Sciences from Rio de Janeiro State University - Head of the Allergy and Immunology Department of the Pedro Ernesto University Hospital and the Piquet Carneiro Clinical Center of Rio de Janeiro State University, Rio de Janeiro, RJ, Brazil.

<sup>5</sup> PhD in Medical Sciences from Universidade do Estado do Rio de Janeiro (UERJ). Head of Allergy and Immunology Department of Hospital Universitário Pedro Ernesto and Policlínica Piquet Carneiro (UERJ). Rio de Janeiro, RJ, Brazil.

### Correspondence to:

Priscilla Filippo Alvim de Minas Santos.

Avenida Rio Branco, nº 185, Sala 429, Centro, Rio de Janeiro, RJ, Brazil. CEP: 20040-007. E-mail: pri.80@globo.com

## INTRODUCTION

Urticaria is a common clinical manifestation in children. It is characterized by papular, erythematous, and pruritic lesions that vary in size and sometimes cause a burning sensation. The lesions are transient in nature, with the skin usually returning to its normal appearance within one to 24 hours<sup>1</sup>. Urticaria is classified as acute when the duration of symptoms is less than six weeks and chronic when they last for more than six weeks. Episodes of acute urticaria in children are usually mild and self-limiting<sup>2</sup>. Acute urticaria is the most common type of urticaria in childhood. It may be associated with angioedema, which is characterized by edema of the subcutaneous tissue, predominantly in the eyelids and lip, but also in other mucous membranes. Remission occurs within 72 hours. In some cases, when other systems such as the cardiovascular, respiratory and/or gastrointestinal systems are also involved, the manifestations of urticaria may progress to an anaphylactic reaction. Physicians should be aware of this possibility.

Acute urticaria in childhood may be triggered by numerous factors such as food, medications, insect bites, chemical contrasts, physical stimuli, and infections (viral, bacterial, parasitic, and fungal), although in many cases the identification of the causal agent is not possible. Reports state that 79.5% of cases of acute urticaria are associated with viral infection<sup>3</sup>. In children, infections associated with acute urticaria are most commonly caused by the herpes virus, whereas in adults, they are most often caused by the hepatitis virus<sup>3</sup>. The treatment of acute urticaria consists of reducing symptoms and treating the underlying issue if it has been identified.

The aim of this article is to report a series of cases of acute urticaria associated with viral infections caused by the Epstein Barr virus, the herpes simplex virus, and parvovirus B19.

## METHODS

A retrospective and descriptive study was conducted with children treated in a private practice by an allergy and immunology specialist in the city of Rio de Janeiro, Brazil. The medical records of patients with a diagnosis of acute urticaria associated with viral infections (serological diagnosis) who were treated between January 2013 and January 2016 were analyzed. Age, sex, history of acute diseases before urticaria, the use of medications, associated symptoms, presence of angioedema, treatment of urticaria, and duration of the disease were all assessed.

## RESULTS

The study included seven patients, three of whom were female. The mean age was three years (with a range of 2 to 7 years). With regard to previous history of diseases at the onset of symptoms, four patients exhibited clinical evidence of upper respiratory tract infection.

There were no reports of vaccinations or use of medications in any of the cases. The patients did not exhibit urticaria-associated angioedema.

All patients were seen in the emergency department, treated with antihistamines, and referred for assessment by a specialist in allergy and immunology. The remission period of the urticaria manifestations varied between five and 15 days. All patients underwent thorough anamnesis, general physical examination, and complementary tests, including full blood count, reactive C protein levels, erythrocyte sedimentation rate, immunoglobulin levels (IgG, IgM, IgA, and total IgE), antinuclear factor, kidney and liver function tests, IgM and IgG serology for the Epstein Barr virus (EBV), parvovirus B19, cytomegalovirus (CMV), herpes simplex 1 and 2, and herpesvirus 6, as well as serology for hepatitis A, B and C, urine and stool tests (three stool samples for parasitology).

The laboratory analyses showed that two children had IgM-positive serology for parvovirus B19, three had IgM-positive serology for EBV, one was IgM positive for EBV and IgM positive for herpes simplex 1 and 2, and one was IgM positive for herpes simplex 1 and 2. Only one patient exhibited recurrent acute urticaria (Table 1).

**Table 1.** Characteristics of the patients assessed.

Case	Sex	Age (Years)	Duration (Days)	Previous clinical manifestation	Associated infection	Antihistamine prescribed in the emergency dept.
1	F	2	7	URTI	PB19	Hydroxyzine
2	M	7	5	URTI	PB19	Hydroxyzine
3	F	5	5	URTI	EBV	Hydroxyzine
4	F	3	9	NO	EBV	Dexchlorpheniramine
5	M	6	10	NO	EBV	Dexchlorpheniramine
6	M	3	6	NO	EBV and HS I and II	Fexofenadine
7	M	2	15	URTI	HS I and II	Hydroxyzine

IVAS: upper respiratory tract infection; PB19: Parvovirus B19; EBV: Epstein Baar virus; HS: Herpes simplex.

## DISCUSSION

Acute urticaria affects 15% to 25% of people at some point during their lives<sup>5</sup>, but its estimated prevalence in children and adolescents is between 2.1% and 6.7%<sup>6</sup>. Urticaria can be triggered by both immune and non-immune responses. Acute urticaria is often caused by an allergic mechanism mediated by immunoglobulin E. When an allergen activates previously sensitized skin mast cells and basophils (with IgE specific to

the allergen in question bound to their membranes), there is a release of vasoactive mediators (histamine, leukotrienes, and prostaglandins) that cause capillary dilatation. This leads to erythema, axon reflexes with an increase in capillary permeability, and subsequent papule formation. Non-immune reactions involve products that result from the activation of mast cells mediated by innate immunity or by the direct activation of these cells, without the participation of allergens or IgE<sup>6</sup>.

Chronic urticaria may be the initial manifestation of chronic systemic diseases or of an autoimmune phenomenon in which mast cell activation depends on autoantibodies and fragments of the activated complement system. There are also reports of bacterial and parasitic infections being the primary cause<sup>4</sup>.

The association between acute urticaria and foods and/or medications is common in children and frequently leads to food restrictions and discontinuation of medications. Anamnesis ruled out these hypotheses in the cases considered herein. The identification of the causal factor is important for the management and prognosis of urticaria. It has been reported that 37% to 58% of cases of acute urticaria are associated with infections and with upper respiratory tract infections in particular, but also with infections of the gastrointestinal and urinary tracts<sup>3,7</sup>. In the present series, only four of the seven children exhibited symptoms of upper respiratory tract infection before the appearance of lesions, a finding which indicates the possibility of an infectious cause even in the absence of suggestive clinical manifestations.

The herpes viruses include herpes simplex virus 1 and 2, herpesvirus 6, Epstein Bar virus, and cytomegalovirus.

The herpes virus alternates between latency and reactivation both in primary infection and in reactivation of the infection and may be associated with acute urticaria or recurrent acute urticaria<sup>5</sup>. Five of the cases considered herein were associated with infection by herpesvirus (EBV and herpes simplex I and II). Marieri et al.<sup>5</sup> assessed 37 children with urticaria and 37 healthy children and confirmed the association between acute urticaria and infection by the herpes virus through laboratory tests<sup>4</sup>. The viruses that are most commonly associated with urticaria in childhood are the cytomegalovirus, herpesvirus 6, and Epstein Barr virus, whereas the hepatitis viruses are those most commonly associated with the disease in adults<sup>4</sup>. Other viruses are also associated with the disease, such as adenovirus, respiratory syncytial virus, rotavirus, parvovirus B19, and the hepatitis A, B and C viruses<sup>7</sup>. When the infection is resolved, the skin symptoms also tend to disappear.

Several hypotheses have been proposed to explain the association between viral infections and urticaria: Chin et al. and Arias-Santiago et al. have suggested a cross-reaction between viral IgM and IgG and mast cell IgE that favors mast cell degranulation and the formation of urticarial plaques<sup>4</sup>; Leiste et al. and Griffin et al. have suggested that circulating immune complexes and complement activation stimulate both

the production of vasoactive amines and the activation of the complement by basophils, a process which increases vascular permeability<sup>4</sup>. Although several pathogenic mechanisms have been suggested, the precise role of infection in the development of urticaria is still unclear.

Bacterial infection by *Helicobacter pylori*, *Streptococcus* spp., *Staphylococcus* spp., *Mycoplasma pneumoniae*, *Salmonella* spp., *Chlamydia pneumoniae*, *Brucella* spp., *Borrelia* spp., *Yersinia enterocolitica*, and *Mycobacterium leprae* should also be considered as potential causes of urticaria<sup>8</sup>.

Detailed clinical history and physical examination are important to determine whether complementary tests are required. Acute urticaria is usually self-limiting and rarely requires further investigation. These patients were investigated because they were referred to a specialist by a pediatrician with the aim of assessing the potential causes of the disease.

The treatment of urticaria is based on the removal of the causal agent, when it is triggered by a specific food or medication, and when the patient is on medication for symptoms. Second-generation antihistamines are the first-line treatment, and their combination with other drugs may be necessary in refractory cases.

We noted that, although second-generation antihistamines were the first therapeutic option, 85% of the patients were given first-generation antihistamines in the emergency department. This practice runs contrary to current guidelines on urticaria treatment, which contraindicate the use of these antihistamines because they have a sedative effect and impair cognitive function<sup>9,10</sup>.

All patients were treated with antihistamines in the emergency department and were sent home with a prescription for antihistamines, but no patient was prescribed corticosteroids, which may be indicated for short periods in the initial management of cases of refractory acute urticaria or when urticaria is associated with angioedema from the onset.

## CONCLUSION

Urticaria is still a challenge for pediatricians and allergists. It is a common childhood disease. Detailed clinical history and physical examinations are essential for its etiological diagnosis. Pediatricians should be aware of the main triggering factors, which include viral infections. Clinical manifestations may be clearly present in anamnesis.

## REFERENCES

1. Lima SO, Rodrigues CS, Camelo-Nunes IC, Solé D. Urticárias físicas: revisão. Rev Bras Alerg Immunopatol. 2008;31(6):220-6.
2. Roxo-Júnior P. Diagnóstico e tratamento de doenças alérgicas em pediatria. São Paulo: Atheneu; 2011.
3. Huang SW. Acute urticaria in children. Pediatr Neonatol. 2009;50(3):85-7. PMID: 19579753 DOI: [http://dx.doi.org/10.1016/S1875-9572\(09\)60041-3](http://dx.doi.org/10.1016/S1875-9572(09)60041-3)

4. Imbalzano E, Casciaro M, Quartuccio S, Minciullo PL, Cascio A, Calapai G, et al. Association between urticaria and virus infections: A systematic review. *Allergy Asthma Proc.* 2016;37(1):18-22. DOI: <http://dx.doi.org/10.2500/aap.2016.37.3915>
5. Mareri A, Adler SP, Nigro G. Herpesvirus-associated acute urticaria: an age matched case-control study. *PLoS One.* 2013;8(12):e85378. DOI: <http://dx.doi.org/10.1371/journal.pone.0085378>
6. França AT, Valle SOR. *Urticária e Angioedema: diagnóstico e tratamento.* 3a ed. Rio de Janeiro: Revinter; 2014.
7. Pite H, Wedi B, Borrego LM, Kapp A, Raap U. Management of childhood urticaria: current knowledge and practical recommendations. *Acta Derm Venereol.* 2013;93(5):500-8. PMID: 23546182 DOI: <http://dx.doi.org/10.2340/00015555-1573>
8. Minciullo PL, Cascio A, Barberi G, Gangemi S. Urticaria and bacterial infections. *Allergy Asthma Proc.* 2014;35(4):295-302. PMID: 24857191 DOI: <http://dx.doi.org/10.2500/aap.2014.35.3764>
9. Mathur AN, Mathes EF. Urticaria mimickers in children. *Dermatol Ther.* 2013;26(6):467-75. DOI: <http://dx.doi.org/10.1111/dth.12103>
10. Pastorino AC. Revisão sobre a eficácia e segurança dos anti-histamínicos de primeira e segunda geração. *Rev Bras Alerg Imunopatol.* 2010;33(3):88-92.