

Association between urticaria and virus infections: A systematic review

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ABSTRACT

Background: The association between urticaria and virus infections has rarely been reported in the literature. The lack of reported cases is probably due to the difficulty in establishing a cause-and-effect relationship. It is not possible to challenge the patient with an etiologic agent.

Objective: The purpose of this work was to perform a systematic review on the association between urticaria and virus infections.

Methods: This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched for articles from January 1, 2008, through May 2015, by using two key terms related to urticaria and virus diseases, "urticaria" and one key term related to virus infections, "virus disease," then "urticaria" and the name of each virus family, and of the most representative virus serotypes.

Results: We reported cases of patients affected either by acute or chronic urticaria with a concurrent virus infection. Previous other causes of urticaria had to be excluded. Herpesviridae infections and urticaria were the most frequently reported associations in children. However, hepatitis virus infections would appear to be the most-frequent cause of urticaria in adults.

Conclusions: Data obtained indicated viral infection as a potential trigger and sometimes as the main etiologic agent in causing acute or chronic urticaria. In every case, urticarial manifestation cleared up after either healing or controlling of the viral infection. However, prospective studies and well-structured research is needed to better clarify the role of viruses in the pathogenesis of urticaria and their relative prevalence.

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As defined by the most-recent European Academy of Allergy and Clinical Immunology position paper, "urticaria is a disease with a severe impact on patient's quality of life, characterized by the onset of wheals, angioedema, or both. Wheals have a central swelling of variable size, often surrounded by a reflex erythema. These lesions are associated with itching or a burning sensation and have a fleeting nature. Angioedema is described as a sudden, pronounced erythematous or skin-colored swelling of the lower dermis and subcutis with frequent involvement below mucous membranes and sometimes pain rather than itching and frequent involvement below mucous membranes.

Its resolution time is longer than that necessary for wheals (up to 72 hours)."^{1,2}

Urticaria is classified by duration as acute urticaria (AU) if the disease lasts <6 weeks, and as chronic urticaria (CU) if it lasts ≥6 weeks. A further classification is based on the presence or absence of inducing factors (induced versus spontaneous).³ During the past few years, many advances have been made in detecting the cause of different types of urticaria. Collecting a patient's history is the main part in identifying the etiology of the disease. In accordance with European Academy of Allergy and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum, and World Allergy Organization guidelines, the second step for achieving a diagnosis is a physical examination of the patient. After this, if the history is suggestive, then a provocation test is recommended. Based on the patient's history, other factors should be investigated, such as type I allergy, pseudo-allergic (nonallergic hypersensitivity reactions) to non-steroidal anti-inflammatory drugs, food, or food additive allergies; screening for malignancies or antinuclear antibody test might also be useful and, only if the patient's history indicates it, screening for autoantibodies against either immunoglobulin E (IgE) or high-

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affinity receptor for the Fc region of IgE, and physical stimulation tests.

Infections may have a pathogenic role in urticaria, and, in a previous review, we noted bacterial infections as possible triggers or causes of AU and CU. In addition, viral, parasitic, and fungal infections have been implicated as underlying causes of chronic spontaneous urticaria but with mechanisms that are still unclear^{1,2,4}; a direct link is difficult to establish because it is not possible to challenge patients with the suspected etiologic agent.^{1,2} The purpose of this work was to perform a systematic analysis of the published cases of urticaria associated with virus diseases.

METHODS

Research Strategy

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines⁵ by using the MEDLINE data base. We searched for articles on this Web site from January 1, 2008, through May 2015, by using two key terms related to urticaria and virus diseases: "urticaria" and one key term related to virus infections, "virus disease," then "urticaria," and the most common name associated with each virus family.

It was decided to use the abstracts of articles whose titles indicated that they might have examined the association between urticaria and virus diseases as a rule of thumb for articles to be read. The entire article was read if the abstract indicated that the article potentially met the inclusion criteria. Also, we reviewed and searched references of the selected articles.

Study Selection

Articles were included in the present review according to the following inclusion criteria: English language, publication in peer-reviewed journals, year of publication of 2008 or later. Articles were excluded by title, abstract, or full text for irrelevance to the topic in question. A further exclusion criterion was review article.

Data Extraction

Two authors (M.C., S.Q.) performed the initial search and independently reviewed and selected the references based on the inclusion and exclusion criteria. The data derived from our research of articles included the following: study author names, publication dates, study design (*i.e.*, case control, cross-sectional, longitudinal), groups studied, clinical and biologic variables, outcome of interest of the study. Principal outcome of interest included case reports on human (adult and child) cases of urticaria related to a viral infection. Given the considerable heterogeneity of the etiologic agents and difficulty in detecting a certain causal effect,

characteristics of the studies and protocols were summarized and the study outcome was reported by using descriptive statistics without conducting any meta-analyses.

RESULTS

The literature search consisted of scanning virus families and of focusing attention on case reports that associated urticaria and virus infections. There was an almost equal distribution between AU and CU reports. Due to the lack of case reports on this association, and to facilitate the finding of a possible etiologic agent by the reader, we decided to group the cases by virus family. This outline also follows our previous paper "Urticaria and bacterial infections."⁶

Herpesviridae

Herpesviridae includes herpes simplex virus 1 (HSV-1), HSV-2, human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). A total of five studies focused on the association between urticaria and Herpesviridae infections. Mareri *et al.*⁷ tried to find an association between herpesvirus infections and urticaria by analyzing the cases of 37 children affected by urticaria and by evaluating 37 healthy children. By performing a set of laboratory tests, they proved that the start of AU was associated with a herpesvirus infection.

Arias-Santiago *et al.*⁸ reported the case of a young girl who developed facial wheals and pruritus after bathing in the sea. Due to the onset, 2 weeks previously, of exudative pharyngitis, fever, and submandibular lymphadenopathies, she was tested for EBV antibodies. EBV IgM was positive. Cold urticaria in the patient improved after 8–9 weeks, which coincided with seroconversion to EBV IgG,⁸ which confirmed what had been observed in a previous study.⁹

Chin *et al.*¹⁰ reported the case of a 22-year-old boy who was diagnosed with idiopathic pure sudomotor failure and a cholinergic urticaria that occurred after mononucleosis infection (EBV). There are no other previous cases reported; according to the researchers, the pathogenic mechanism remains unknown.¹⁰

Zawar *et al.*¹¹ described two cases of CU associated with an HSV-2 infection. In the first case, a 52-year-old man had been affected by CU for 4 years. No drug or food allergies were found to be associated with the urticaria. Because he presented with herpetic genital lesions, he was treated with acyclovir. Urticaria symptomatology ceased after antiviral therapy. As in the first case reported, a 42-year-old man was diagnosed with chronic idiopathic urticaria. Wheals on his trunk and legs coincided with contemporary genital herpes on the prepuce. Urticarial resolution was obtained after antiviral therapy was administered (acyclovir).¹¹

A case of a neonate (18 days old) affected by neonatal urticaria multiforme was studied by Borghesi *et al.*¹² Other possible causes that led to this kind of urticaria were excluded. The researchers reported the presence of HHV-6 by reverse transcription polymerase chain reaction, which indicates an acute viral infection. Data appeared to point to HHV-6 as a possible etiology of urticaria multiforme.

Parvoviridae (parvovirus B19)

Soldo-Juresa *et al.*¹³ described an episodic acute intermittent angioedema and urticaria in a 47-year-old woman. A biopsy specimen of the skin lesions demonstrated the presence of lymphocytic lichenoid vasculitis. In serum, parvovirus B19 IgG was highly positive, and parvovirus B19 DNA was detected by polymerase chain reaction in bone marrow. The researchers concluded that the acute infection of parvovirus B19 was a trigger for reactive macrophage activation syndrome and, consequently, for the skin lesions.¹³

Caliciviridae (norovirus)

Two cases were reported by Leiste *et al.*¹⁴ that associated urticaria and virus disease. A 50-year-old man developed AU 2 weeks before hospital admission. He had had diarrhea for three weeks. The only alteration detected by laboratory examinations was the presence of human norovirus in the patient's stool. Leiste *et al.*¹⁴ concluded that the virus was the only possible cause of urticaria. In the second case, a 45-year-old woman with chronic recurrent urticaria since 1993 had repeated episodes of vomiting and diarrhea. During hospitalization for generalized urticaria, vomiting, and diarrhea, other causes of urticaria were excluded. The only abnormal finding was the detection of human norovirus in stool samples.¹⁴

Picornaviridae (hepatitis A virus)

Griffin *et al.*¹⁵ describe a case of a middle-aged woman with acute hepatitis. The woman had serologic positive hepatitis A virus-IgM and hepatitis A virus-IgG. Ten days after the onset of disease, she developed wheals on both legs and arms for >6 weeks.¹⁵

Flaviviridae (hepatitis C virus)

A case of a 47-year-old patient affected by positive hepatitis C virus (HCV) results and alcohol-correlated cirrhosis was reported by Chiba *et al.*¹⁶ During hospitalization, the patient had increased bilirubin, worsening of the general clinical condition, and a rash with yellowish lesions. According to the researchers, it was hyperbilirubinemia by increased vascular permeability, which caused the urticaria. Because hyperbilirubinemia was due to HCV infection, it seemed plausible to link this case of urticaria to the viral infection.¹⁶

Pinto-Almeida *et al.*¹⁷ observed a case of a 49-year-old woman with a 1-year history of wheals and purpuric macules. Laboratory examinations showed increased liver enzymes, positive anti-HCV values, and low complement levels. The patient was diagnosed with hypocomplementemic urticarial vasculitis. Symptomatic and conservative treatment of hepatitis C was initiated, with progressive improvement of the skin condition.

Foschi *et al.*¹⁸ reported the case of a 77-year-old woman with HCV-related chronic hepatitis accompanied by cutaneous wheals and pruritus, probably related to mixed cryoglobulinemia resistant to antihistamines. The patient was treated with interferon and ribavirin, with an optimal response associated with the resolution of both cryoglobulinemia and cutaneous symptoms. After treatment, HCV replication relapsed, but skin lesions did not recur.¹⁸

Hepadnaviridae (hepatitis B virus)

Approximately 31 years after one of the first reports of urticaria associated with hepatitis B virus (HBV),¹⁹ Van Aalsburg *et al.*²⁰ reported a 34-year-old patient with giant wheals and periorbital edema. A retrospective analysis of stored samples revealed that these signs were prodromal manifestations of an acute HBV infection. The skin lesions reverted when the HBV infection was cleared.²⁰

DISCUSSION

Urticaria is often coupled with allergic diseases, but only in a small percentage is this association correct. Above all, with the chronic type, it is more often linked to a systemic disease. During the past few years, CU has been associated with bacterial and parasite infections. However, the exact role of infections in the development of urticaria is not clear and needs further studies.^{6,21-23} According to the current update, "The diagnosis and management of acute and chronic urticaria," published in *The Journal of Allergy and Clinical Immunology*, some cases of chronic infectious processes have been reported in the literature as causes of CU.²⁴ Although the incidence of each of these has not been well established, some of the reported cases include viral infections caused by HBV, HCV, EBV, and HSV.²⁴

In our review, we aimed to associate urticaria and virus diseases by an attentive search of the literature to look for case reports that sustained this hypothesis. What emerged was a total of 50 cases (37 summarized in a pediatric prospective study) distributed equally for sex and age. For obvious reasons, the occurrence of Herpesviridae (HSV, HHV-6, EBV, CMV) infections in children was more frequent. CMV, HHV-6, and EBV infections were the most frequently concurrent with

AU in children. Once the infection cleared up, wheals and pruritus recovered.

In adults, according to data shown previously, hepatic viruses were the most common likely cause of urticaria. It is not the first time that this association has been reported. Since 1978, researchers have linked hepatitis virus infections and urticaria, and tried to speculate on pathogenic mechanisms.²⁵ Although ap- pertaining to different families (Flaviviridae, Hepadna- viridae, Picornaviridae), HCV, HBV, and hepatitis A virus infections have frequently been associated with skin lesions. In all the cases reported, AU was resolved either after therapy or by spontaneously clearing up of the virus. A Parvoviridae (parvovirus B19) infection produced the same symptoms (AU) until intravenous immunoglobulin therapy was administered. The only virus infections that led to CU were HSV-2 (Herpes- viridae) and norovirus (Caliciviridae).

It is important to emphasize that, at the time of the occurrence of the urticaria, none of these patients was on chronic therapies. For these reasons, drug adverse events can be excluded as a possible trigger of skin lesions. Except for the case of mixed cryoglobulinemia urticaria, antihistamines were effective in controlling symptoms. However, urticaria was resolved definitively only after treatment of the viral infections. In most of the cases, either symptomatic or conservative treatment led to patient recovery from urticarial symp- toms. However, chronic diseases had to be treated for a definitive urticaria withdrawal (*i.e.*, hepatitis B and C or genitalis HSV infections).^{11,18,20}

As explained in the reviewed cases, multiple mech- anisms were hypothesized as being involved in trig- gering urticaria. Sometimes more than one mechanism combined in augmenting vascular permeability. Chin *et al.*¹⁰ and Arias-Santiago *et al.*⁸ tried to explain wheal growth by hypothesizing a cross reaction between viral IgM and IgG with mast cell IgE. According to their interpretation, this link favored mast cell degranula- tion.^{8,10} However, Leiste *et al.*¹⁴ and Griffin *et al.*¹⁵ mentioned circulating immune complexes, which stim- ulated basophils in producing vasoactive amines and activating complement. Both these pathways resulted in increased vascular permeability.^{14,15} According to Chiba *et al.*,¹⁶ it might be possible that hyperbiliru- binemia increases vascular permeability and, therefore, be a causal factor for urticaria. Finally, already several years ago, Patella *et al.*²⁶ investigated the mechanism through which a protein, largely secreted in the intes- tinal tract during hepatitis viral infections, induced the release of proinflammatory mediators (superantigen theory). This mediator secretion resulted in an aug- mentation of vascular permeability.²⁶ Although not being exhaustive, these hypotheses bring us closer to a better comprehension of the etiopathogenetic mecha- nisms of AU and chronic "idiopathic" urticaria.

CONCLUSION

The quality of life in patients affected by spontane- ous urticaria with uncontrolled symptoms is quite low and comparable with patients affected by congenital types of angioedema.^{27,28} It is important to identify more etiologic agents to find more-effective therapies.

As mentioned in the introduction, a direct link is difficult to establish because it is not possible to chal- lenge patients with the suspected etiologic agent. Data obtained seemed to indicate viral infections as poten- tial triggers and sometimes as a main etiologic agent in causing AU and CU. Because herpesvirus is the most common probable etiopathologic agent, researchers should focus on identifying the most frequently asso- ciated symptoms during history collection. In adults, hepatitis virus screening could be useful and, accord- ing to patient history, in some cases, should be per- formed. Once an acute infection or a relapse has been diagnosed during urticaria, antiviral therapy appears to be effective in inducing definitive wheal remission. However, there is no report of antihistamine resistance.

In all probability, multicenter systematic studies that assess an etiologic association between virus infections and both AU and CU will help in better understanding current data. Moreover, these studies could help in deriving a pathogenic theory on idiopathic and chronic spontaneous urticaria.

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