

Acute urticaria in the infant

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Abstract

Urticaria is a mast cell-driven disease presenting with wheals, angioedema, or both. Acute urticaria (AU) lasts < 6 weeks. AU is a not common condition in newborns and infants since they are showing an immune system functionally insufficient. In newborns and infants, AU is typically generalized and featured by large, annular, or geographic plaques, often slightly raised. The clinical features of the disease depend on the peculiar structure of neonatal and infant skin. A careful morphological examination of the lesions is essential to differentiate AU from other skin eruptions that may have overlapping features and to treat it adequately. The second-generation antihistamines are the first-line treatment of AU; however, only antihistamines with proven efficacy and safety should be used in newborns and infants. Corticosteroids may be added in severe cases.

KEYWORDS

acute urticaria, angioedema, diagnosis, differential diagnosis, infant, newborn

1 | INTRODUCTION

Urticaria is a common disease characterized by the development of wheals (hives), angioedema, or both.¹ Urticaria can either occur acutely or evolve in a chronic form. By the duration of illness, it is classified into acute urticaria (AU), lasting less than six weeks, or chronic urticaria (CU), lasting more than six weeks. AU is a not common condition in newborns and infants since they are showing an immune system functionally insufficient. Epidemiological data report a prevalence of AU ranging from 1% to 16.2%.^{2,3} However, they do not provide reliable indications for the infant since the current literature data include pediatric patients of various age of life despite the causes and clinical characteristics of the AU are different in infants and young children. Moreover, AU in infants must be differentiated from other skin eruptions that may have overlapping features and, therefore, be diagnosed and treated adequately.

2 | ETIOLOGY AND PATHOPHYSIOLOGY

Several mechanisms have been recognized to be involved into the etiology of AU in newborns and infants, including direct mast cell activation, innate immunity (eg, complement, Toll-like receptors, cytokines, chemokines, opioids) involvement, immunoglobulin E (IgE)-mediated reactions, and immune events mediated by xenobiotics (haptens, drugs).^{4,5} Mast cell activation leads to the release of histamine and other inflammatory mediators, thus, resulting in sensory nerve stimulation (pruritus), vasodilatation (erythema), extravasation (edema), and recruitment of other immune cells (infiltrate). Urticaria or itch without angioedema may be caused by non-histaminergic autoinflammatory mechanisms involving the cryopyrin and interleukin (IL)-1 pathway. Non-histaminergic angioedema is related to bradykinin and fibrinolytic dysregulation, as well as primary defects in vascular integrity.^{4,5}

Common causes or triggers of AU in children include infections, allergic reactions, physical stimuli, and systemic diseases.¹ Mild

infections, often associated with drug therapy, appear to be the most frequent causes of AU in infants, as documented in over 40% of the cases. The infectious agents commonly associated with AU are mainly viruses such as *Rhinovirus*, *Rotavirus*, *Epstein-Barr*, *Adenovirus*, *Hepatitis virus* (A, B, C) *Herpes simplex*, *Human Immunodeficiency Virus* but also bacteria such as *Mycoplasma pneumonia* and *Chlamydia pneumonia*.¹

Less frequently, foods such as milk, egg, peanut, wheat, soy, fish, and shellfish can cause AU in sensitized infant and young child, and, sometimes, AU can be part of a more serious anaphylactic reaction. Even β -lactams and non-steroidal anti-inflammatory drugs and vaccines are referred to as triggers of AU in both infants and children.¹

3 | CLINICAL PRESENTATION

Acute urticaria in infants is typically generalized and featured by large, annular, or geographic plaques, often slightly raised.⁶ Moreover, edema is commonly found in the dermal layer.⁶ In this regard, angioedema, defined as a sudden, pronounced swelling of the submucosal or subcutaneous tissue, involving areas such as the lips, eyelids, auricles, scrotum, throat, back of the hands and feet, is commonly associated with AU up to 50% of cases.⁵ Angioedema may sometimes be painful but not itching, and its resolution is slower than wheals, lasting up to 72 hours.⁵ The clinical presentation of the disease depends on the structure and peculiar characteristics of the skin of neonate and infant.⁶ It is usually soft and smooth, thin, and lacking protective flora. The microvasculature network is poorly developed, and a decreased cohesion between epidermis and dermis, as well as low content in collagen and elastic fibers, has been also detected.⁶ Therefore, functionally, the skin is predisposed to higher heat, transepidermal water loss, and drug and toxin absorption.⁶ A careful morphological examination of the lesions is essential to make the diagnosis and to differentiate the AU from other similar clinical pictures as acute hemorrhagic edema of infancy, urticaria multiforme, erythema marginatum, erythema multiforme, serum sickness-like reaction, chronic infantile neurologic cutaneous and articular (CINCA) syndrome, and sweet syndrome.⁷⁻⁹

Acute hemorrhagic edema of infancy, or Finkelstein's or Seidlamayer's disease, is a small vessel leukocytoclastic vasculitis that is typically associated with target-like or cockade appearance plaques, red to purpuric lesions with a necrotic or bullous center. The cutaneous manifestations appear predominately over the ears, cheeks, and extremities.^{8,9}

The acute and transient onset of blanchable, annular, polycyclic, erythematous, itching wheals with ecchymotic centers in association with angioedema are suggestive of urticaria multiforme, a benign cutaneous hypersensitivity reaction predominantly histamine-mediated.^{8,9}

Erythema marginatum is a non-painful, transient, migrant, rarely pruritic rash. It occurs over the trunk and in the upper arms and thighs, but never on the face. Erythema marginatum is characteristic of rheumatic fever and can also precede or accompany hereditary angioedema, although it can also occur independently.^{8,9}

Key messages

Acute urticaria (AU) is a not common condition in newborns and infants since they are showing an immune system functionally insufficient. Compared to the pediatric population, the causes and clinical characteristics of AU are different in infants and young children. AU in infants must be differentiated from other skin eruptions that may have overlapping features and to be diagnosed and treated adequately. The second-generation antihistamines are the first-line treatment of AU. Corticosteroids may be added in severe cases. Parents need reassurance that AU is not a life-threatening disease, and the prognosis is generally good.

Differently to AU, erythema multiforme is not itchy and shows persistent target lesions with a central papule, blister, purpura, or ulcer.^{8,9}

Serum sickness-like reactions (SSLRs) refer to hypersensitivity reaction that has symptoms similar to those of serum sickness but in which immune complexes are not found. Similarly to AU, the skin eruption presents erythematous, annular, and edematous plaques. Generally, it occurs in preschool children. The onset of symptoms ranges from several days up to three weeks after taking medications, and it is accompanied by systemic symptoms such as fever, arthralgia, and lymphadenopathy. The drugs most commonly associated with this condition are cefaclor and other cephalosporins, penicillins, sulfonamides, and macrolides.^{8,9}

An urticarial rash starting at a very early age, non-pruritic, fluctuating irregularly, and unresponsive to antihistamine therapy can be the first sign of chronic infantile neurologic cutaneous and articular (CINCA) syndrome.^{8,9}

The sweet syndrome is a neutrophilic dermatosis caused by a type IV immune-mediated reaction and triggered by infections or medications. This condition is a reactive process characterized by the abrupt onset of tender, erythematous papules that coalesce to form plaques, often associated with fever. The pathogenesis of sweet's syndrome is multifactorial and remains to be definitively established. In children, it has been more commonly associated with bacterial or viral upper airway infections. The sweet syndrome can also be a sign of immunodeficiency or autoinflammatory disease. Histopathology demonstrates dermal edema, a neutrophil-predominant infiltrate, and leukocytoclastic without true vasculitis.¹⁰

4 | DIAGNOSIS AND TREATMENT

In addition to an accurate anamnesis, a careful morphological examination of the characteristics of wheals, typically itchy, migrating, fading with finger pressure, duration and pattern of recurrence of lesions (less than 24 hours with episodes lasting less than six weeks), the

number, shape, size, site, and distribution of lesions are essential to making the correct diagnosis. Laboratory tests should be performed only when history and clinical data suggest an eliciting trigger or an underlying disease, to avoid re-exposure to relevant causative factors and/or confirm their role in the pathogenesis.¹ The second-generation antihistamines are the first-line treatment of au, but only antihistamines with proven efficacy and safety should be used in newborns and infants. In severe cases, corticosteroids such as prednisone or prednisolone may be added for a few days to control symptoms.¹

5 | CONCLUSIONS

Urticaria/angioedema in the newborn and infant is not a life-threatening disease, and the prognosis is generally good, but it can significantly impair the quality of life for patients and their families. Careful anamnestic evaluation and an accurate physical examination of the patient are necessary to recognize the similarities and differences with other clinical pictures that can mimic AU in this age of life. If most of these conditions are benign and self-limiting, other diseases can lead to severe outcomes if not promptly recognized, so early diagnosis is essential.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTION

Sara Manti: Writing-original draft (equal). **Domenico Minasi:** Conceptualization (equal); Supervision (equal). **Fernanda Chiera:** Writing-original draft (equal). **Gian Luigi Marseglia:** Supervision (equal). **Amelia Licari:** Writing-review & editing (equal).

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