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Urticaria and angioedema in children and adolescents: diagnostic challenge

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Abstract
Urticaria diagnosis may be challenging in children since it can be triggered or related to numerous conditions. In this paper, we reviewed the main aspects regarding the diagnosis of urticaria in the pediatric population. Acute urticaria is often due to viral infections. However, other culprits, including foods, insect stings, drugs, contrast media, vaccination, latex, and medical diseases, may account for acute patterns. Laboratory tests and confirmatory allergy tests should be individualized and guided by history. Chronic urticaria (CU) is defined when hives and/or angioedema last for more than 6 weeks. The most common type of chronic urticaria in children is chronic spontaneous urticaria (CSU). Chronic inducible urticaria (CindU) is less common but is important to diagnose in order to manage appropriately and reduce the risk of severe reactions. Inducible forms in children are often diagnosed with specific provocation tests similar to the tests used in adults. Given that chronic urticaria could rarely be a presentation of vasculitis, systemic-onset juvenile idiopathic arthritis, or auto-inflammatory syndromes, it is important to rule out these conditions. It is crucial to differentiate cases of chronic urticaria from mastocytosis and Bradykinin-mediated angioedema, given that treatment may differ. The management of chronic urticaria in children has improved over the last decade because of the development of both clear management guidelines and new effective drugs. It is crucial to increase awareness for appropriate diagnosis and new available treatment to improve the management of chronic urticaria in children.

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Introduction

Urticaria is a mast cell-mediated disease that presents with wheals, angioedema, or both. Acute urticaria is reported in 3.4–5.4% of children in European countries.[1-3] The point prevalence of chronic urticaria in children is 1.43%, and some data have expressed an increasing incidence during the last decade.[4,5] Diagnosis of urticaria is essentially clinical, but finding its etiology could be a challenging task. A complete workup comprising detailed clinical history and physical examination, basic tests, and a limited laboratory investigation is of utmost importance to exclude other diagnoses, identify underlying causes and comorbidities, and assess predictors of the course of disease and response to treatment.[3] In this paper, we reviewed the main aspects regarding the diagnosis of urticaria in the pediatric population.

Acute urticaria

Diagnostic approach

The diagnosis of urticaria is usually clinical. Given that numerous conditions may present with hives/hives-like lesions, the first step to identify correctly a case of acute urticaria is to have a good history and perform complete physical examination, including morphological characteristics of lesions.

Urticaria is a condition that typically presents with intensely pruritic, circumscribed, erythematous raised wheals, with central pallor often surrounded by erythema, that blanch with pressure. It appears on any part of the skin, grows rapidly, coalesce, and individual lesions typically disappear within 24 h. Urticaria could be associated with angioedema, and is classified as acute if it lasts for less than 6 weeks.[6,7]

Patients should be queried on onset of lesions, frequency and duration, diurnal variation, timing (if an allergen culprit is suspected), distribution, shape and size of wheals, associated symptoms (which may suggest anaphylaxis or infectious etiology), and medication and supplement use (especially, new or recently changed dosages). It is also important to assess patients for known allergies, recent infections/risk of infections (including transfusion history), family history of urticaria and angioedema, and conduct complete systems review.[3,7-9]

Laboratory tests should be guided by history elements, as acute urticaria does not require a diagnostic workup because it is usually self-limited.[3] However, if a type I hypersensitivity (Immunoglobulin E [IgE]-mediated) in sensitized patients or the presence of other eliciting factors, such as nonsteroidal anti-inflammatory drugs (NSAIDS), are suspected, then appropriate confirmatory tests (including skin tests/specific IgE or challenges) should be considered.[3,10] If an inflammatory or infectious cause is suspected, then a full blood count and inflammatory biomarkers (e.g., C-reactive protein [CRP], and erythrocyte sedimentation rate [ESR]) are recommended.[10]

Causes of acute urticaria

Acute urticaria and angioedema are often related to mast cell and basophil activation from multiple triggers, which could be IgE- or non-IgE-mediated.[11]

The most common cause of acute urticaria is viral infections, especially of the upper respiratory tract. It accounts for 40% of acute urticaria cases in adults and children.[10,12,13] Recently, with the COVID-19 pandemic, it has been reported that acute urticaria may occur prior or in association with symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection.[14,15] Other virus, bacteria, and parasitic infections associated with acute urticaria are elaborated in Table 1.[6-8,10,13,16]

More rare culprits of acute urticaria include foods, insect stings, medications and therapeutic agents, contrast media, vaccination, latex, and underlying medical diseases (Table 1). About 30–40% of acute urticaria patients are idiopathic and called acute spontaneous urticaria.[6-8,10,12,13,16] Up to 36% of these patients can progress to chronic spontaneous urticaria (CSU).[17]

Infections

Infections are the most common cause of acute urticaria in children. An observational study performed in 10 emergency departments in Italy established that 43.9% of children admitted with acute urticaria had an associated infectious disease.[1] Techasatian et al. reported that infections were responsible for urticaria in 51.26% of pediatric patients seen at an emergency department in Thailand, especially respiratory (36.74%) and gastrointestinal (31.82%)

Table 1 Causes of acute urticaria.

Idiopathic
Infection
• Viral (adenovirus, rhinovirus, cytomegalovirus, enterovirus, Epstein–Barr virus [EBV], Hepatitis A, B, C, herpes simplex, influenza A, parvovirus B19, respiratory syncytial virus, rotavirus, varicella/zoster, human immunodeficiency virus [HIV]).
• Bacteria (Group A beta-hemolytic streptococcus, *Haemophilus influenzae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Helicobacter pylori*)
• Others: Helminthic, *Anisakis simplex*, *Blastocystishominis*, malaria, scabies
Medications and therapeutic agents
• Penicillins, cephalosporins, sulfonamides, chemotherapy, transfusion products, angiotensin-converting enzyme inhibitors, NSAIDS, aspirin, opiates, radiocontrast media, neuromuscular blocking agents.
Vaccination
Food
• Cow's milk, egg, peanut, fish, seafood, tree nuts, wheat, soy, yeast, fruits, and legumes and other vegetables.
Insect bite or stings
• Wasps, hornets, bees, yellow jackets, fire ants
Latex
Underlying medical diseases
• Systemic mastocytosis, serum sickness, systemic lupus erythematosus, malignancy, cutaneous vasculitis associated with connective tissue disorders.

infections.[18] In both studies, infections related to acute urticaria were more common in children aged up to 6 years.[1,18] However, data may vary in different regions, as in Portugal just 22% of children with acute urticaria had an infectious etiology in a retrospective analysis of patient's charts.[19] Infection-induced urticaria in children can last for several days, developing at the time of the infection, or days or weeks later, and fever may not be present concomitantly with cutaneous symptoms.[18]

In a systematic review of the association of urticaria and virus infections, *Herpesviridae* infection was frequently reported in children. Still, an association has also been reported with *Streptococcus pyogenes*, *Mycoplasma pneumoniae*, and parasites.[20,21] Recently, during the pandemic, prevalence of urticaria in patients with SARS-Cov-2 infection was reported as 3.4–14.8%.[22] Urticaria could be an early clinical feature of COVID-19 in children, and it is not uncommon to be the only symptom without other classical features of SARS-Cov-2 infection.[15,22]

Food and additives

Recent studies report that 2.52–14% of pediatric patients of acute urticaria in an emergency unit are related to foods.[1,18,19,23] Shrimp (2.4%), egg (2%), milk (1.6%), fruits (1.2%), fish (1.2%), meat (1.2%), and peanut (0.8%) were the most common food-related allergens observed in one of these studies.[19] Aydoğan et al. evaluated 212 children with suspected food-induced acute urticaria, of which 84.4% had a definitive diagnosis of food allergy; cow's milk (56.4%), egg (35.2%), and nuts (19%) were the most common causes.[24] Evaluation of food allergy includes specific serum IgE antibody test, basophil activation test (BAT; if available), skin tests, and oral food challenge.[25] In established cases of food allergy, avoidance is the main treatment with prescription of an epinephrine auto-injector. Oral immunotherapy can be considered in specific cases.[25,26]

Additives are substances added to food for coloring, sweetening, enhancing flavor, or preservation.[27] There are currently more than 3000 substances listed as food additives, but few studies have assessed the prevalence of food additives' adverse reactions, which is estimated to be 1–2% in children. IgE-mediated mast cell activation and degranulation can induce urticaria to natural dyes (e.g., carmine red dye). However, other mechanisms are also involved, such as sodium metabisulphite-induced urticaria and angioedema.[28] It is unlikely that a small molecule such as tartrazine plays a major role in acute urticaria.[29]

Diagnosis of an adverse reaction to food additives starts with a detailed medical history, ruling out other possible hidden causes of urticaria and angioedema. *In vitro* specific IgE assays and skin tests are limited for natural dyes. An additive-free diet for up to 4 weeks helps to reinforce or exclude the possibility of involvement of a specific substance in the reaction. The double-blind placebo-controlled food challenge is the gold standard to confirm diagnosis.[28] Patients with a confirmed diagnosis must follow a specific diet to avoid the ingestion of culprit additive.[27]

Drugs

According to three recent studies, wheals and/or angioedema as an isolated manifestation of a drug hypersensitivity reaction accounts for 3.5–8.0% of children admitted in different emergency departments.[1,18,19] Data of 178 children with a suggestive history of drug hypersensitivity in Latin America demonstrated that urticaria was the only clinical manifestation in more than 50% of patients. NSAIDs were the most common implicated group, followed by beta-lactam antibiotics (BLA).[30] Nevertheless, any drug could be considered when evaluating a child with acute urticaria, including those for treating rare diseases.[31] Moreover, urticaria is a frequent manifestation of drug-induced anaphylaxis in children, and other symptoms should always be evaluated.[32]

Urticaria induced by drugs is generally an IgE-mediated reaction, as in BLA hypersensitivity, but other mechanisms may be involved.[33] Nonselective hypersensitivity is the most relevant phenotype of NSAID hypersensitivity, and its mechanism involves COX-1 inhibition.[34] A complete workup is recommended for diagnosing drug hypersensitivity, as clinical history solely is not reliable and may lead to a false label of allergic manifestations, affecting individual treatment options.[35] Akcal et al. recently demonstrated the importance of a complete evaluation of children with suspected immediate-type beta-lactam hypersensitivity (58.3% with urticaria/angioedema), as only 21 out of 48 patients had proven BLA allergy.[36]

Protocols for investigating a drug hypersensitivity reaction vary according to suspicious drug and mechanism of reaction, and must be individualized. Drug-specific IgE *in vitro* assays are not available for many drugs and their variable sensitivity and specificity limit their use in clinical practice. Skin test concentrations have been determined for many drugs and are recommended when an IgE-mediated reaction is suspected. Drug provocation test is still considered the gold standard for identifying culprit drug, especially when skin tests are negative or unavailable, or to exclude cross-reactivity.[33]

Acute urticaria versus anaphylaxis

Acute urticaria and angioedema must be differentiated from anaphylaxis to reduce the risk of death.[11]

In 2020, the World Allergy Organization redefined anaphylaxis criteria to identify these cases in an effective manner. Acute onset of an illness, with involvement of the skin, mucosal tissue, or both, associated with involvement of at least one system (respiratory, cardiovascular, or gastrointestinal) is highly probable to be anaphylaxis. Therefore, a complete review of systems is mandatory for evaluating a patient with acute urticaria.[37]

However, anaphylaxis may occur in the absence of skin involvement or cardiovascular shock, and such presentation is common in fatal cases. Skin manifestations are absent in 10–20% of anaphylaxis reactions, resulting in delay in recognition.[38] Acute onset of hypotension, bronchospasm, or laryngeal involvement after exposure to a known or highly probable allergen, even in the absence of typical skin involvement, is suggestive of anaphylaxis.[37]

The allergens commonly involved in anaphylaxis are very similar to those cited for acute allergic urticaria: mainly, food, medications, and venom. Some cases are idiopathic, when no apparent trigger could be identified.[37] Mast cell disorders should also be ruled out, especially when there is recurrent anaphylaxis or after *hymenoptera* sting-induced anaphylaxis.[39]

It is also essential to assess cofactors, which can influence the onset and severity of an allergic reaction. Endogenous factors include underlying diseases, such as systemic mastocytosis, uncontrolled asthma, or hormonal status. Exogenous factors include physical exercise, infections, psychological burden, sleep deprivation, alcohol intake, and medications such as beta-blockers and angiotensin-converting enzyme inhibitors. The role of cofactors in anaphylaxis is allergen- and age-dependent, but they should always be considered in history to reduce future risks.[40,41]

Chronic urticaria (CU)

Natural history of chronic urticaria in children

A meta-analysis determined that the point prevalence of chronic urticaria in children is 1.43% compared to 0.86% in adults. As opposed to chronic urticaria in adults, which is more common in females, the prevalence is similar in male and female children aged less than 15 years.[4] The median age of onset of pediatric chronic urticaria is 5–9 years.

The resolution of pediatric chronic urticaria is often defined as 1 year without symptoms in the absence of treatment.[42] Chronic urticaria in adults is reported to resolve spontaneously within 5 years in only 30–55% of patients.[43] Data on the natural history of chronic urticaria and its subtypes in children are scarce. Studies suggest that in children, 45.3% cases of chronic inducible urticaria (CIndU) resolve in 6 years,[44] and 50% CSU cases resolve in 5 years.[45] A recently conducted Canadian study has reported that mean age at onset of disease was 6.7±4.7 years (range: 0–17 years). Similar to adult studies, the resolution rate was low, 10.3 per 100 patients per year. The most common type of chronic urticaria was CSU (78%). A quarter of patients had concomitant angioedema symptoms.[42]

Previous studies conducted in adults reported that resolution was less probable in females, cases of long duration of the disorder at initial examination, angioedema patients, and in CIndU.[46] Factors associated with a higher resolution rate in children included CD63 antigen upregulation on basophil measured by BAT and absence of peripheral blood basophils.[42] Similar findings were reported in a study conducted on adults having chronic urticaria, where the 1-year resolution was 56.5% in autoimmune forms versus 34.5% in idiopathic forms.[47]

Diagnostic approach

Diagnosis of chronic urticaria is a diagnosis of exclusion. In general, a history of hives/angioedema or both that occurs most days of the week for more than 6 weeks with no clear trigger is highly supportive of the diagnosis of CSU. Sometimes, the hives merge to form target-like lesions. It is important to rule out inducible forms through questions on flares associated with heat, cold, sun, pressure, vibration, water, or exercise. Inducible forms in children are often diagnosed with specific provocation tests similar to tests used in adults (Figure 1).[3,48]

Up to 10% of chronic urticaria cases in children in endemic areas are related to intestinal parasite infections, mainly strongyloidiasis and blastocystosis.[49,50] It is also important to quarry families traveling to endemic areas and to assess for parasites in those living or traveling to these regions.

Studies suggest that almost a quarter of children and adolescents with CSU can experience aggravation of symptoms when exposed to aspirin and other NSAIDs.[51] This clinical characterization is known as aspirin-exacerbated cutaneous disease. Hence, it is important to ask about potential exposure to NSAIDs.

Given that chronic urticaria can rarely be a presentation of vasculitis, systemic-onset juvenile idiopathic arthritis, or auto-inflammatory syndromes,[52,53] it is important to rule out history of arthritis, recurrent fever, and the presence of similar symptoms in family members. In case of other family members presenting with hives, it is important to rule out Hereditary Alpha Tryptasemia that has an autosomal dominant inheritance and is reported to affect up to 6% of the population.[54]

In cases presenting with angioedema only, it is crucial to rule out hereditary angioedema.[55] Unlike chronic urticaria, these patients usually present with intermittent angioedema during childhood or adolescence that could be life-threatening, for which treatment differs substantially. Hence, it is important to rule out symptoms of laryngospasm, abdominal pain, and a family history of angioedema.

Chronic urticaria is not considered an allergic assumption, and extensive blood work or skin tests are not indicated as routine examinations. A complete blood count and sedimentation rate/CRP, total IgE levels, and anti-thyroid peroxidase antibodies are often the only indicated tests.[56]

Figure 1 Positive provocation by a pulse-controlled ergometry test in adolescent with cholinergic urticaria.[42]

Role of infection and allergens in chronic urticaria in children

Chronic spontaneous urticaria has been associated with infectious diseases in adults, especially *H. pylori* and nasopharynx bacteria. However, results of conducted studies are conflicting, with methodological issues not allowing definitive conclusions regarding a direct cause-effect relationship.[3] Pediatric data regarding infections and CSU are scarce. A systematic review on etiological factors associated with CSU in children demonstrated that infections could be associated with 1% of cases, and with parasites in 3.5% patients.[57]

Prevalence of parasitic infections in children ranges from 0% to 37.8%.[50] Vezir et al. analyzed the frequency of parasites in children and adults with CSU in Turkey, and compared them with healthy controls. No significant difference was observed in the incidence and parasite species in both groups. Nonetheless, 57% of patients improved their urticaria after anti-parasitic therapy.[58]

In general, any suggestive history of infection in patients with CSU must be investigated and appropriately treated. Still, symptoms are not resolved in the majority of cases even after eradication of infection.[3,21] On the other hand, viral infections exacerbate CSU. During the COVID-19 pandemic, one in three patients with CSU reported exacerbations due to SARS-Cov-2 infection, especially those with more severe COVID-19.[59,60]

Allergens, such as food and inhalants, are an uncommon cause of CSU, and only should be investigated if the clinical history is consistently suggestive in up to 5% of CSU pediatric patients.[57] Drugs, especially NSAIDs, could be both a cause and an aggravating factor of CSU. Elimination would block symptoms in the first case but not in the latter.[3]

Chronic Inducible Urticaria

Chronic inducible urticaria is characterized by the development of wheals and/or angioedema started by definite and specific triggers and can affect 30% of pediatric patients with chronic urticaria.[44,61] Frequency of its subtypes varies in different regions. Miles et al. reported cold chronic urticaria (60.3%) and cholinergic chronic urticaria (41.3%) as the most common subtypes in 64 children presenting CIndU in Montreal, Canada.[44] On the other hand, symptomatic dermographism was reported in 50%, followed by cold chronic urticaria in 25%, of 118 patients with CIndU aged less than 14 years in Naples, Italy.[61]

CIndU subtypes should be investigated with specific tests depending on patient's history. The current guidelines recommend performing the same tests in children as in adults to diagnose CIndU.[48] However, some tests may be challenging, as triggering cholinergic urticaria in a treadmill, especially in young patients. Different subtypes of CIndU and its specific tests are shown in Table 2.

Among the different subtypes of CIndU in children, cold chronic urticaria and dermographism have been explored in an effective manner. A retrospective chart review of 415 patients with acquired cold urticaria, aged less than 18 years, was performed at Boston Children's Hospital. The study suggested that cold induced urticaria was associated with atopy in 78% of patients. Moreover, 25% of patients had other subtypes of urticaria. Two-third of patients presented with mild localized symptoms but 18.6% experienced anaphylaxis. Cold stimulation was positive in 70% of the patients tested and associated with increased risk of anaphylaxis, highlighting the importance of adequate investigation in these patients (Figures 2A and B).[62]

Table 2 Recommended diagnostic tests in CindU subtypes.

Cold urticaria	Cold provocation and threshold test
Delayed pressure urticaria	Pressure test and threshold test
Heat urticaria	Heat provocation and threshold test
Solar urticaria	Ultraviolet (UV) and visible light of different wave lengths and threshold test
Symptomatic dermographism	Elicit dermographism and threshold test
Vibratory angioedema	Test with vibration (e.g., Vortex mixer)
Aquagenic urticaria	Provocation testing
Cholinergic urticaria	Provocation and threshold testing
Contact urticaria	Provocation testing

A recently conducted study compared dermatographism with urticaria in 100 children and the same number of controls tested with Fric Test 4.0 (Moxie, Berlin, Germany). Dermatographism was elicited in 51% in the first group and 22% in the latter. Of the patients with urticaria and positive Fric Test 4.0, almost half had acute urticaria. The authors concluded that dermographism could be related to urticaria *per se* and not only to chronic inducible form.[63]

Avoidance of specific and definite triggers of CIndU helps to reduce the occurrence of wheals and angioedema, but is usually not sufficient to control the disease and comes with a substantial burden. Patients must be provided with information that helps them to recognize and minimize relevant trigger exposure. Patients with delayed pressure urticaria, for example, must be informed that pressure is defined as force per area and simple measures, such as broadening the handle of heavy bags, could help in preventing symptoms. Similar considerations apply to cold urticaria, where the impact of chill factor of cold winds needs to be considered. In case of solar urticaria, exact identification of the range of eliciting wavelengths is important for appropriate selection of both sunscreens and light bulbs with a UV-A (320–400 nm) filter. However, the relevant physical trigger threshold is low in many patients, and total avoidance of symptoms is virtually impossible.[3]

Auto-immunity

Studies suggest that autoimmunity plays a major role in the pathogenesis of chronic urticaria. The autoimmune pathways accounting for development of chronic urticaria are subdivided into two main types: (i) In type I, IgE auto-antibodies against self-antigens are hypothesized to play a major role. In adults, these auto-antibodies are reported to target mainly interleukin 24 (IL-24).[64] (ii) Type IIb pathways

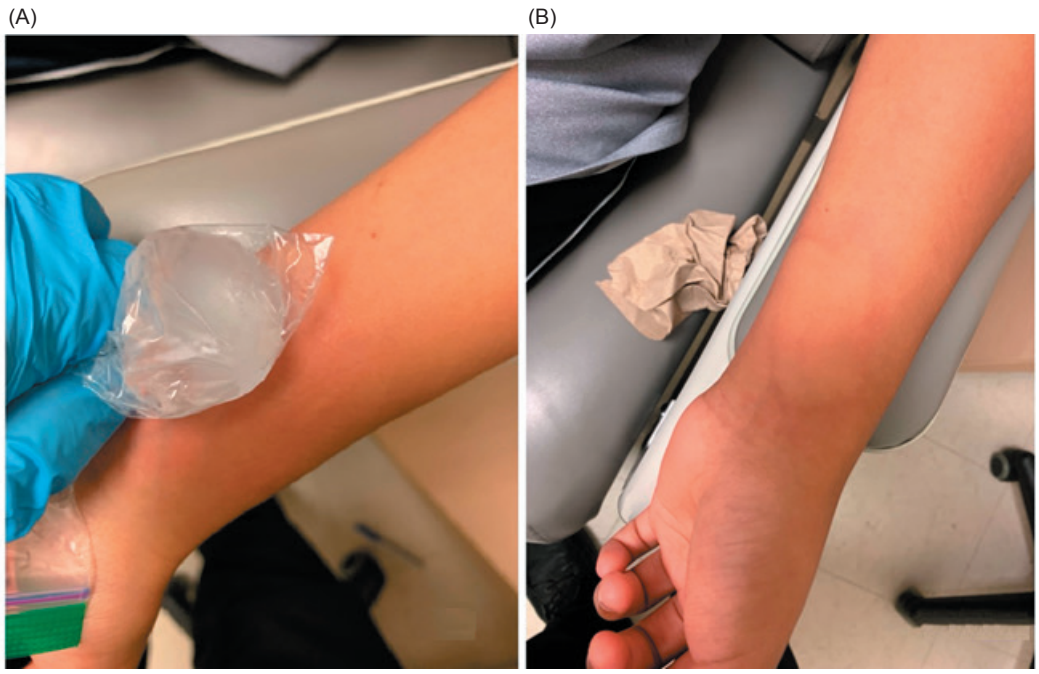

Figure 2 (A) Ice cube test in a patient with cold-induced urticaria. (B) Hives induced by cold after 5 min of ice cube test.

involve IgG antibodies against the constant region of IgE or IgE receptor.[65] The pathogenesis of pediatric CSU is thought to be similar to adult CSU, although little data are available on chronic urticaria's pathogenesis in children. An autoimmune etiology is suggested in approximately half of the children whereas the remaining cases are thought to be idiopathic.[66]

In line with autoimmune hypothesis, a meta-analysis of studies measuring the prevalence of autoimmunity in adults with CSU reported that the prevalence of autoimmune thyroiditis, pernicious anemia, vitiligo, type I diabetes mellitus, Graves' disease, celiac disease, and rheumatoid arthritis is increased compared to the general population.[67] However, at this point no similar studies have been conducted in children.

Patients can be screened for the presence of these autoantibodies either *in vivo* using the autologous serum skin test (ASST) or *in vitro* via BAT measuring the levels of CD63 or CD203 on healthy donor basophils incubated with serum from the patient.[68] Studies revealed that autologous serum skin test results were positive in 53.5% of children with CSU.[69] It was reported that children with CSU have high CD63 BAT and high levels (>1.8% of basophils) or absence of basophils was associated with earlier disease resolution.[70] However, currently, the use of BAT is limited to research and is not offered in clinical practice as a routine.

Autoinflammatory diseases

Urticaria and urticaria-like lesions can be a part of several syndromes. In patients with recurrent or persistent fever accompanied by an array of inflammatory symptoms, the possibility of an autoinflammatory disease resulting from inappropriate activation of innate immunity should be considered. Urticarial rashes are characteristic features of five autoinflammatory syndromes: the 3 cryopyrin-associated periodic syndrome (CAPS), Schnitzler's syndrome, and familial cold autoinflammatory syndrome-2 (FCAS2).[71]

The 3 cryopyrin-associated periodic syndrome is a rare heterogeneous disease entity. It encompasses a group of three allelic disorders inherited in an autosomal dominant manner and caused by a gain-of-function mutation in *NLRP3* gene, resulting in increased secretion of IL-1.[72,73] It presents as a clinical spectrum of three disorders with several shared features that differ in severity: familial cold inflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and chronic infantile neurological cutaneous articular syndrome (CINCA), also known as neonatal onset multisystem inflammatory disease (NOMID).[72] FCAS is the least aggressive syndrome and resolves after approximately 12 h. MWS is similar to FCAS, but has more severe clinical outcomes, and the attack can last for 1–3 days. Finally, CINCA is the severest syndrome, marked by neonatal onset and chronicity with flares lasting for 1–3 days.[72,74]

Diagnosis of CAPS is often arrived at early in life, although some patients develop symptoms at or even before birth. CAPS is characterized by recurrent episodes of urticaria-like rashes (often the first symptom), with a neutrophilic infiltrate on biopsy, arthralgia, myalgia, headache, and fever. Conjunctivitis, keratitis, and uveitis are observed in all three subtypes. Attacks may be triggered by exposure to cold, minor trauma, or emotional stress. Some patients develop sensorineural hearing loss during adolescence or adulthood. At the most severe clinical spectrum (CINCA), there are central nervous symptoms (chronic headache, hydrocephalus, seizures, developmental delay, and elevated intracranial pressure) and arthropathy with dysmorphic features.[71,72,74-76]

The diagnostic criteria for CAPS include the presence of raised inflammatory markers and at least two of the five conditions: urticarial rash, cold/stress-triggered episodes,

sensorial hearing loss, chronic aseptic meningitis, and skeletal abnormalities (epiphysial overgrowth/frontal bossing).[73,75] Higher morbidity is associated with evolution to amyloidosis in all three subtypes.[74]

Schnitzler's syndrome is a rare acquired autoinflammatory disease whose pathophysiology has not been elucidated yet. It is characterized by recurrent febrile urticarial eruptions (often with neutrophilic dermal infiltrate on skin biopsy); joint and/or bone pain, with or without abnormal bone remodeling; enlarged lymph nodes; hepatomegaly and/or splenomegaly; and elevated markers of inflammation, such as CRP and leukocytosis.[77] Presence of monoclonal gammopathy, IgM or IgG (less common), is a defining criterion.[78] Angioedema is rare, and some patients report worsening of skin lesions after exposure to heat or cold, ingestion of alcohol, or physical exercise. Frequency of episodes ranges from daily to monthly, and the onset of symptoms is in the fifth decade, with slight predominance in males.[71,76]

There is no gold standard to diagnose Schnitzler's syndrome, and several diseases must be ruled out before considering the diagnosis, including CAPS, adult-onset Still's disease (AOSD), and lymphoma. The main complication is the onset of blood dyscrasia in 20% of patients, especially Waldenstrom's disease.[76,77]

Familial cold autoinflammatory syndrome-2 is an autoinflammatory disease that shares most features of CAPS; but the mutation is in the *NLRP12* gene, which has structural similarities with *NLRP3* gene. Its manifestations are episodic fever, arthralgia, and myalgia that appear in the first days of life. Most patients have urticarial rashes, which exacerbate following exposure to cold.[71]

Other mast cell activation diseases (Mast Cell Activation Syndrome [MCAS], mastocytosis)

According to recent consensus statements, all mast cell activation disorders are defined when the following three criteria are met:

1. Clinical symptomatology that is in keeping with the disorder (e.g., hives and flushing).
2. A transient, measurable increase in either serum tryptase or other markers of mast cell mediators.
3. Response to agents that interfere with mast cell mediators (such as cetirizine).[79]

Clonal MCAS include mastocytosis and monoclonal mast cell syndromes (rarely reported in children).

Mastocytosis refers to a group of myeloproliferative disorders characterized by excessive proliferation and accumulation of mast cells in tissues. It affects 1 in 10,000 individuals.[80] Cutaneous mastocytosis (CM) is limited to the skin, while systemic mastocytosis (SM) develops in extracutaneous organs, with or without skin involvement.[81,82] Childhood onset of mastocytosis is assumed to be mostly cutaneous and hence is the main focus of this section.[81,83] Urticaria pigmentosa (UP), diffused cutaneous mastocytosis (DCM), and mastocytoma (MS) of the skin are the three major forms of cutaneous mastocytosis.[81]

Cutaneous mastocytosis is diagnosed through collaboration of clinical findings and laboratory tests (mainly, elevated baseline tryptase levels). Mechanical irritation may cause reddening and urticarial swelling of the lesions—Darier's sign—and is often used to diagnose cutaneous mastocytosis in the clinical context. Lesional skin biopsy specimens exemplifying mast cell hyperplasia confirm the diagnosis of cutaneous mastocytosis.[82] Typical urticaria pigmentosa lesions consist of red brown to yellowish long-lasting macules, papules, or nodules (Figure 3). It is important to note that urticaria pigmentosa lesions may present as either a monomorphic variant with small maculopapular lesions, typically seen in adult patients, or a polymorphic variant with larger lesions of variable sizes and shapes, typically seen in pediatric patients. If monomorphic variant develops in children, it often persists into adulthood, whereas polymorphic variant may resolve around puberty.[84] Clinical features of DCM include diffused skin infiltration and spontaneous blistering with erosions and crusts, various degrees of erythroderma, prominent dermographism, and pruritus.[85]

Mastocytoma is defined by the presence of one or several brownish red plaques or nodular lesions, usually 4–5 cm in diameter.[86] Of the three variants, urticaria pigmentosa is the most common type and represents approximately 65% of all pediatric cases.[81,84] Cutaneous mastocytosis is associated with gain-of-function mutations of the c-*kit* gene in approximately 60–80% patients. Children with typical cutaneous lesions require bone marrow biopsy only if there is extra cutaneous involvement, for instance, hepatosplenomegaly, lymphadenopathy, or peripheral-blood abnormalities.[87]

Two large studies have reported that anaphylactic reactions to *hymenoptera* venom occur in 6–27% of adult mastocytosis, mainly systemic mastocytosis. *Hymenoptera* stings

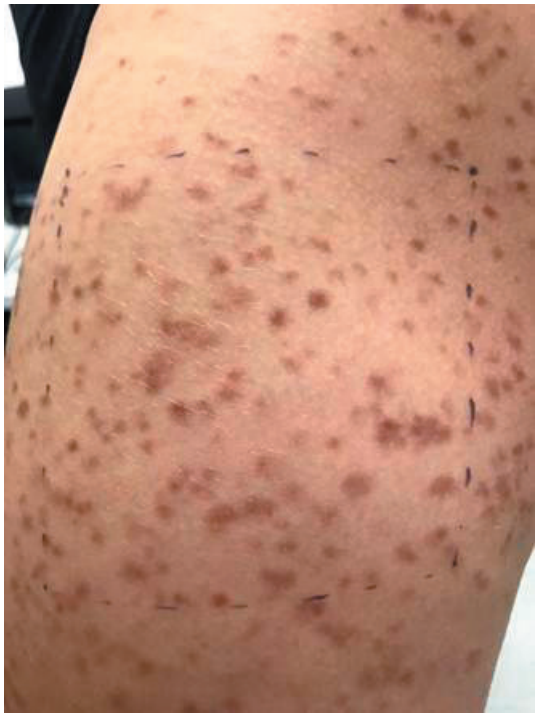

Figure 3 Typical red brown macules in a patient with cutaneous mastocytosis.

played no role in eliciting anaphylaxis in children with mastocytosis. Only one case of anaphylaxis to fire ant was reported in a 4-year-old girl with urticaria pigmentosa.[88]

Nonclonal MCAS is of two types: the first is secondary to mast cell activation via a known trigger such as IgE-mediated stimulation. The second is idiopathic, in which the etiology of factor(s) activating mast cells is not known.[79] The latter is often referred to as MCAS, which is reported to present at a median age of 9 years.[89] It is important to appropriately diagnose MCAS according to the above-discussed three criteria, as it is often misdiagnosed and inappropriately managed in clinical practice.[90]

Biomarkers of chronic urticaria in children

A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic response to a therapeutical intervention." Several reports have suggested clinical and blood biomarkers associated with urticaria diagnosis, activity monitoring, duration, and response to treatment.[91] However, little data are available on specific pediatric populations with chronic urticaria.

Karaman and Turedi reported that younger age is associated with good prognosis, but elevation in absolute neutrophil count and neutrophil:lymphocyte ratio was associated with poor prognosis of chronic urticaria in children.[92] Netchiporouk et al. analyzed data from 139 children with chronic urticaria and observed that basopenia and positive results of BAT (CD63 level > 1.8%) were associated with higher resolution rate.[42]

Matrix-metalloproteinase-9 (MMP-9) enhances migration of inflammatory cells and regulates chemokines function, having a potential role in urticaria pathogenesis. Dilek et al. observed that MMP-9 levels in children are associated with urticaria activity score, indicating that it could be used as a biomarker of disease activity in this age-specific population.[93] Similarly, mean platelet volume (MPV) has been used as an inflammatory marker of various diseases. A prospective study involving 40 children with chronic urticaria demonstrated that these patients had lower MPV values than healthy controls, suggesting that MPV could be a potential marker of inflammation in chronic urticaria.[94]

Other potential urticaria biomarkers frequently reported in adults, such as D-dimer, total IgE, and anti-thyroperoxidase antibodies, are still insufficiently explored in children, and data available in this population are mandatory.

Recurrent angioedema without wheals

Bradykinin-mediated recurrent angioedema

Bradykinin-mediated recurrent angioedema occurs in rare diseases, including hereditary angioedema (HAE) and acquired angioedema (AAE), including angiotensin-converting enzyme-induced angioedema; the latter two are primarily seen in adults and rarely in children.[95]

Hereditary angioedema is an autosomal dominant disease, with symptoms commencing during childhood in most of the patients, and not in prepubertal stage. It is most often caused by quantitative and/or functional deficiency in C1-esterase inhibitor (C1-INH) protein, activating the complement, contact, and fibrinolysis systems, with increased production of bradykinin. The diagnosis should be guided by characteristic symptoms and family history, and confirmed by laboratory tests. HAE lasts longer than histaminergic angioedema and affects the gastrointestinal system, resulting in severe abdominal pain. Erythema marginatum is present in 60% of patients but not urticaria.[96-98]

In children, the most frequent phenotype of HAE is a quantitative and/or functional deficiency of C1-INH. However, there is a third type of HAE with normal C1-INH, which is less frequent at this age. In these cases, diagnostic criteria depend on clinical aspects and the presence of Factor XII (FXII) mutations, which represent less than 20% of pediatric patients. Other mutations associated with HAE with normal C1-INH have been studied, but Factor XII are the most reported mutation until now.[99]

Angiotensin-converting enzyme (ACE) is the most important peptidase responsible for the breakdown of bradykinin. ACE inhibitors precipitate sudden worsening of HAE, or occasionally trigger angioedema in patients without HAE (ACE inhibitor-induced angioedema). Although these drugs are not used frequently in children, in cases of renal disease and hypertension, this mechanism of angioedema should be remembered, especially if the angioedema not responding to antihistamines, corticosteroids, and adrenaline.[96] Also, acquired angioedema due to C1-INH deficiency occurs if there are nonhereditary, quantitative, or functional deficiencies of C1-INH. The most common conditions associated with this type of angioedema are autoimmunity and B-cell lymphoproliferative disorders, and the development of angioedema can precede diagnosis of the disease.[100]

An evaluation of 95 children and adolescents (mean age: 7 years) followed up in 18 reference centers for the diagnosis and treatment of HAE demonstrated that 84% were symptomatic, with onset of symptoms at 3.3 years of age. Attacks of angioedema affected the extremities (73.5%), gastrointestinal tract (57%), face (50%), lips (42.5%), eyelids (23.7%), genitals (23.7%), upper airways (10%), and tongue (6.3%). Family history was present in 84% of patients (Figure 4).[101] In the United Kingdom, pediatricians reported that 6.3% of children with HAE had life-threatening edema attacks.[102] Fatal crises are rare in children, and in a series of 70 deaths, three were under the age of 21 years.[103]

The current guidelines recommend initial screening with serum or plasma levels of component C4 of the complement. Almost all the patients with HAE have low levels of C4. If the level is below 50% of the reference value, C1-INH antigenic level must be measured along with C1-INH activity if necessary. If C4 level is normal, the test must be repeated during an angioedema attack, especially when the history is strongly suggestive of HAE.[97] Special care must be taken when diagnosing children with HAE, as C4 and C1-INH levels, and C1-INH activity, are physiologically low during childhood, reaching adult levels between 6 and 12 months of age for C1-INH, and 2 years for C4. Thus, C4 levels are not a valid screening test for HAE in children in the first year of life.[98]

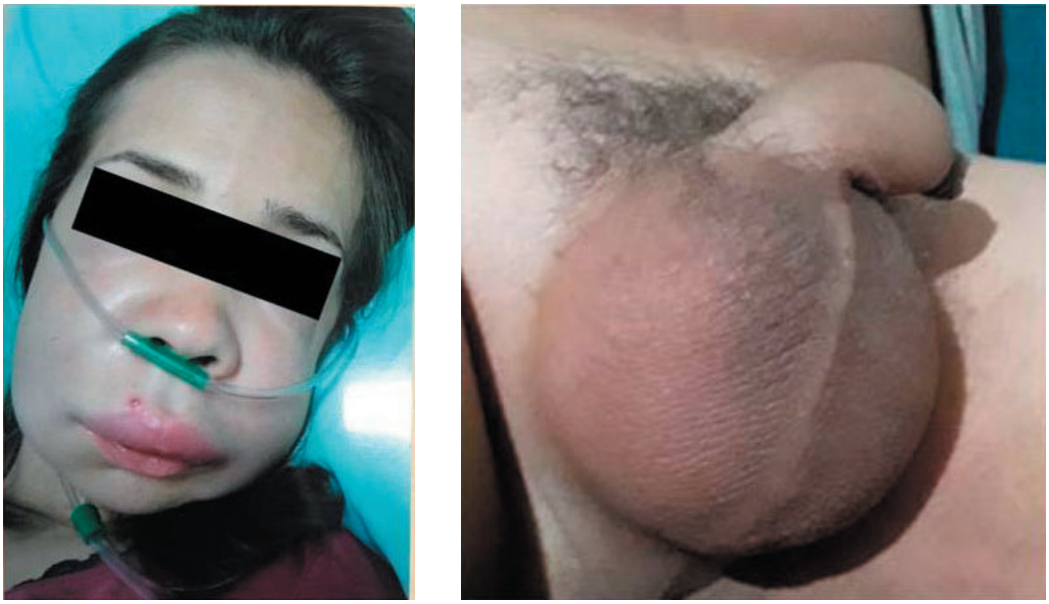

Figure 4 A female adolescent with facial HAE attack, and a male adolescent with genital attack.

Diagnosing comorbidities in chronic urticaria

One of the objectives of CSU investigation is to check for comorbidities. The most common comorbidities are CIndU, autoimmune diseases, and allergies, but may vary according to different populations. Mental disorders (i.e., depression and anxiety, and sleep disturbances) are frequent with considered consequences.[3,104,105]

A systematic review of nine reports, including 633 individuals, analyzed data on comorbidities in children aged less than 12 years with CSU. A prevalence of atopy was observed in 28% patients—asthma in 15.4% and allergic rhinitis in 13.8% patients. Autologous serum skin test (ASST) was positive in 36.8%, antinuclear antibodies in 10.4%, and thyroid antibodies in 6.4% patients. *H. Pylori* was detected in 21%, vitamin D deficiency in 69.1%, and psychiatric disorders in 70.4% patients.[106] Every finding from the patient's medical history, physical examination, or basic tests that indicates comorbidity or consequence of CSU must be investigated.[3]

Assessment of disease activity, impact, and control

Patient-reported outcome measures (PROMs) to assess disease activity (Urticaria Activity Score [UAS7] and Angioedema Activity Score [AAS]), quality of life (Chronic Urticaria Quality of Life Questionnaire [CU-Q2oL]), and control (urticaria control test [UCT] and angioedema control test [AECT]) are available in a wide range of languages.[3] Although these tools have been validated in adults with chronic urticaria, older children and adolescents usually indicate no difficulties in understanding and using most of them. Alternative tools validated in the pediatric population are the Children's Dermatology Life Quality Index (CDLQI), which is not specific for urticaria but for dermatological diseases, and the Pediatric Itch Severity Scale (ISS-Ped).[107,108] Thus, development and validation of PROMs for the pediatric population will fill a significant gap useful for both clinical practice and research.

Future perspectives

Chronic urticaria in children has some differences when compared to that in adults. Advances in differential diagnosis, use of biomarkers, and patient reported outcomes are expected for the upcoming years. Thus, it is mandatory to come up with more data in the pediatric population in order to set specific recommendations for the diagnosis and management of this age group.

Conclusions

Urticaria is a common clinical consideration in children. Both acute and chronic subtypes affect the quality of life and may be associated with other disorders. Identification of underlying causes helps to prevent the future episodes. An appropriate evaluation and diagnosis are decisive for therapeutic success.

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