An Approach to Urticaria

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Urticaria is one of the most common skin diseases. It occurs in patients of all ages and is estimated to develop in 20% of the population at some time.[1-3]Although urticaria has a characteristic clinical morphology, it can be challenging to diagnose, particularly given the evanescent nature of the lesions, which often are not present at the time of the clinic visit. Furthermore, hives are elicited by triggers that the patient may have trouble identifying, which can lead to an obscured history, inadequate trigger recognition and avoidance, poor disease control, and frustration for both the patient and physician.

Despite these challenges, urticaria and many of its causes usually can be diagnosed by a detailed history, review of systems, and physical examination, with studies showing a limited role for laboratory evaluation.[4,5] Although causative factors frequently are not found, certain etiologies are more common in acute and chronic forms of the disease, and particular clues in the history or physical examination may help to elicit a trigger or suggest an underlying cause (Table 1). Accordingly, this column will provide residents with an overview of several etiologies of this sometimes challenging condition, tips for identifying triggers or underlying causes, and key elements of the patient's history and physical examination.

ETIOLOGIES AND CLUES

Urticaria can be caused by IgE-mediated mast cell degranulation, direct mast cell release, complement activation with or without immune complex deposition, autoantibodies, physical factors, alterations in prostaglandin synthesis, and a variety of other known and unknown pathways.[6] Regardless of the mechanism of histamine release, urticaria broadly is categorized as either acute or chronic; the acute variety of urticaria is defined by the occurrence of lesions for less than 6 weeks and the chronic form is present for more than 6 weeks. Although largely arbitrary, this distinction may be useful during the initial evaluation; it may help to clarify the underlying cause and the best diagnostic and therapeutic approach as well as direct patient counseling.

Acute Urticaria

Acute urticaria most frequently occurs in the pediatric population, often in association with atopy, with common causes including viral infections, medications, foods, insect bites and stings, or contact allergens.[4,7] In approximately 50% of cases, the cause of acute urticaria is unknown and 20% to 30% of all cases may progress to chronic urticaria.[8-10]

Although all medications can cause urticaria, antibiotics, especially β-lactam antibiotics, are the most common triggers.[1,11] Other commonly implicated agents include radiocontrast dye, opioids such as codeine, and nonsteroidal anti-inflammatory drugs such as aspirin, with 9% of all cases of acute urticaria associated with medication exposure.[1,4] When evaluating patients with acute urticaria, it is important to pay close attention to their medication list and note any new medications that were initiated prior to the eruption. Furthermore, physicians must keep in mind that hives can arise from minutes to days to weeks after administration of a drug, and a review of all medications taken over the month prior to the eruption is important. Urticaria that occurs weeks after drug exposure also may be a manifestation of a serum sickness or serum sickness–like reaction, which would be associated with fever, lymphadenopathy, angioedema, and arthralgia (Figure 1).[11,12]

Food sources have been shown to be responsible for only 1% of cases of acute urticaria, though the actual percentage is probably higher due to the

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Table 1.

Summary of Triggers for Urticaria

Category	Comments
Infections	Acute urticaria: associated with mild viral illnesses caused by *Rhinovirus* and *Rotavirus*, hepatitis, herpes simplex virus, *Mycoplasma*, streptococcal pharyngitis; chronic urticaria: chronic sinusitis, tooth abscesses, hepatitis, endocarditis, *Helicobacter pylori*, parasitic infections
Foods and supplements	All foods possible triggers (milk, soy, wheat, egg, peanuts, tree nuts, and fish most common); hives occur within minutes to an hour after consumption; reproducible with each exposure
Drugs	All medications possible triggers (β-lactam antibiotics most common); can develop minutes to days to weeks after drug exposure
Bites and stings	Bites or stings of mosquitoes, fleas, mites, lice, or bedbugs; "meal cluster" (breakfast, lunch, and dinner) pattern of lesions; symmetrically distributed on exposed skin
Autoimmune and idiopathic causes	Most common causes of chronic urticaria; autoimmune cases due to circulating autoantibodies to IgE or IgE receptor on mast cells; autoimmune cases can be confirmed by autologous serum skin testing
Physical causes	Various physical stimuli to the skin; subtypes include dermatographism, delayed pressure urticaria, solar urticaria, cholinergic urticaria, cold urticaria, aquagenic urticaria, and vibratory urticaria; wheals occur within 15 minutes, lasting <2 hours for most (except delayed pressure urticaria)
Underlying disease	Least common cause of chronic urticaria; causes include chronic infection, thyroid disease, connective-tissue disease, or malignancy

number of individuals who self-diagnose their condition.[4] Similar to medications, all foods have the potential to induce urticaria, but certain foods are more common. In children, the most common causative foods include milk, soy, wheat, egg, peanuts, tree nuts, and fish, whereas adults tend to react to peanuts, tree nuts, and fish. Unlike medications, hives caused by food tend to occur within minutes to less than an hour after ingestion, and urticaria that occurs more than 2 hours after ingestion may be suggestive of an alternate cause.[1] The regularity of hives also can be a clue, and causative foods typically should initiate a reaction each time they are ingested rather than sporadically.

Acute urticaria also can be triggered by infections, particularly mild viral upper respiratory infections caused by *Rhinovirus* and *Rotavirus*.[4] Hives in these patients can occur either at the same time as the illness or following its resolution, and patients should be asked to report any prior or current viral symptoms. Reports also have shown an association of acute urticaria with hepatitis, herpes simplex virus, *Mycoplasma*, and streptococcal pharyngitis.[1,11]

Exposure to mosquitoes, fleas, mites, lice, or bedbugs also can induce another form of acute urticaria called papular urticaria. This condition is characterized by eruptions of intensely pruritic papules, vesicles, and wheals in response to biting or

Figure 1. Serum sickness–like reaction with urticaria, fever, and arthralgia in a 3-year-old girl following cefaclor administration.[12]

Figure 2. Papular urticaria on the leg.[14]

stinging insects (Figure 2).[13,14] The presence of lesions in a linear fashion or in a "meal cluster" described as breakfast, lunch, and dinner can be a useful clue to confirm this diagnosis. The lesions tend to occur symmetrically on exposed skin; tend to spare the genital, perianal, and axillary regions; and may be recurrent or chronic.[14] Important clues in the patient's history include the presence of a flea-infested dog or cat at home, a history of pet exposure outside the primary dwelling (ie, while visiting a relative or friend), exposure to mosquitoes during outside play, or residence in crowded lodges that experience frequent turnover rates and may contain bedbugs (eg, homeless shelters, hotels, dormitories). Additionally, it is not unusual for only a single family member to be affected, as the condition is caused by hypersensitivity and some individuals react while others do not.[13]

Contact urticaria is another form of acute urticaria characterized by the localized development of urticarial lesions at the site of exposure to certain externals agents. IgE-mediated contact urticaria develops in individuals sensitized to environmental or occupational allergens including foods, animals, grass, or latex. IgE-independent contact urticaria occurs via direct effects of urticants on blood vessels, with common causes including cinnamic aldehyde in cosmetics and the stinging nettle weed, which contains tiny spines containing histamine.[6]

Chronic Urticaria

Chronic urticaria is defined by the spontaneous development of hives on a regular basis for more than 6 weeks, often without an identifiable cause. The condition occurs more often in women than men (2:1 ratio) and commonly develops between 20 and 40 years of age.[4,15-18] Chronic urticaria can be difficult to treat and symptoms may persist for years to decades.[11] An epidemiologic study in Spain (N=5003) revealed that 11.3% of affected patients still had urticaria after more than 5 years, and in many cases, chronic urticaria caused severe detrimental effects on quality of life.[19,20]

Chronic urticaria can be divided into 3 subtypes including autoimmune and idiopathic urticaria, physical urticaria, and chronic urticaria secondary to an underlying condition.

Autoimmune and Idiopathic Urticaria—Autoimmune and idiopathic causes of chronic urticaria are the most common and occur in 70% of cases.[1] Half of these patients have the autoimmune type, with autoantibodies to the α-chain of the IgE receptor on mast cells or IgE itself, resulting in chronic stimulation

and release of vasoactive mediators from mast cells.[1,6] The other half of patients have an idiopathic form of disease. Autoimmune cases can be distinguished from idiopathic disease with autologous serum skin testing. This test involves injecting the patient's own serum intradermally into uninvolved skin on the forearm, in addition to saline- and histamine-injected controls. The test is considered positive for autoimmunity if a wheal is formed at the serum-injected site that is 1.5 mm greater than the bleb at the saline-injected site. Although the results do not necessarily change medical management, it can be helpful to provide a diagnosis for the patient and to monitor the disease course.[1,6]

Physical Urticaria—Physical urticaria is a less common form of chronic urticaria, though quality of life tends to be more severely affected in these individuals.[4] It results from a variety of physical stimuli to the skin, producing wheals that typically occur within 15 minutes following the stimuli and last for less than 2 hours, with the exception of delayed pressure urticaria.[6,11,21] Subtypes of physical urticaria include dermatographism, delayed pressure urticaria, solar urticaria, cholinergic urticaria, cold urticaria, aquagenic urticaria, and vibratory urticaria.

Dermatographism is the most common form of physical urticaria and is characterized by wheal and flare formation following firm stroking of the skin (Figure 3).[22] Patients will report that within 15 minutes of stroking or scratching the skin, linear edema, erythema, and pruritus will develop, with erythema alone being insufficient for a diagnosis of true dermatographism. Dermatographism may be the only manifestation of chronic urticaria but is more often present in the setting of chronic urticaria due to other causes.

Figure 3. Dermatographism with linear erythematous and edematous papules and plaques.[22]

Delayed pressure urticaria results in hive formation or angioedema on body parts that have been exposed to pressure. Clinically, hive formation tends to be delayed, often developing at least 4 to 6 hours after pressure is applied, even up to 24 hours later.[1] These patients may report the development of lesions at sites of tight clothing including along the waistline, where the elastic bands of socks make contact with the legs, or on the buttocks after prolonged periods of sitting.[6]

Solar urticaria is an uncommon manifestation of physical urticaria and is characterized by the development of hives after exposure to light wavelengths ranging from 280 to 760 nm.[23] These lesions tend to develop within minutes of sun exposure, occurring mostly on sun-exposed skin, with resolution in 1 to 3 hours.

Cholinergic urticaria is induced by an increase in core body temperature and occurs following exercise, hot showers, sweating, fevers, emotional stress, or consumption of spicy foods. It is responsible for approximately 30% of all cases of physical urticaria and characteristically results in smaller punctate urticarial lesions that are 1 to 3 mm in size, most commonly in teenagers and young adults. These lesions often begin on the trunk and spread distally to the face and extremities. They may be associated with severe pruritus, tingling, or burning sensations.[11]

Cold urticaria results in the rapid development of urticarial lesions following exposure to cold stimuli (Figure 4).[24] It typically occurs on regions of the body that have been exposed to the cold and may develop while outdoors on a cold day, when touching cold objects, or when swimming in cold water.[11]

Aquagenic urticaria occurs following exposure to water of any temperature and results in small wheals that can be reproduced by applying water to the skin. Vibratory urticaria results in localized hives at the site of vibratory stimuli.

Chronic Urticaria Secondary to an Underlying Condition—The least common subtype of chronic urticaria is urticaria secondary to an identifiable underlying condition. This subtype is rare and occurs in only 10% of cases, with the most common underlying disorders including infection, thyroid disease, connective-tissue disease, and malignancy.[1] Infections that have been associated with chronic urticaria include chronic sinusitis; tooth abscesses; hepatitis; endocarditis; *Helicobacter pylori* infection; and parasitic infections, such as strongyloidiasis in endemic regions.[21] Clues that support this diagnosis include a history of fever, diarrhea, nausea, chronic pharyngitis, cough, and sinus-related symptoms.[1] Hypothyroidism also can be associated with chronic urticaria as well as hyperthyroidism, though less commonly.[25-27] Connective-tissue diseases, including lupus

Figure 4. Cold urticaria in a patient after an ice cube wrapped in plastic was applied to the skin for 5 minutes.[24]

Figure 5. Urticaria associated with small cell carcinoma of the lung.[28]

erythematosus, scleroderma, rheumatoid arthritis, and mixed connective-tissue disease, can be associated with chronic urticaria and these patients would likely have other signs and symptoms to suggest one of these underlying disorders. Malignancy is argued by some to be associated with chronic urticaria, most commonly in elderly patients, with underlying conditions found to include lymphoma, leukemia, and myeloma, as well as solid tumors of the colon, rectum, liver, lung (Figure 5), ovary, and testicles.[1,28] Notably, the association with malignancy is debatable, as a large epidemiologic study examining 1155 patients with chronic urticaria found an underlying malignancy in 36 patients, while the expected number of patients affected was 41.[29]

Accordingly, a detailed patient history is crucial and often is all that is necessary to confirm a diagnosis of urticaria. The importance of a thorough history was confirmed in a prospective study of 220 patients with chronic urticaria, which revealed that the use of a detailed questionnaire in combination with limited laboratory investigations (complete blood cell count and erythrocyte sedimentation rate) was nearly as successful in revealing an underlying cause as a detailed questionnaire plus a more extensive screening program (eg, chemistry profile, allergy testing, complement levels, infectious screening, autoimmune disease screening, malignancy screening, physical examination, provocative tests).[30] Some useful questions to ask patients when urticaria is suspected are listed in Table 2, and a printable patient questionnaire also can be downloaded from the Internet.[31]

APPROACH TO THE PHYSICAL EXAMINATION

A complete dermatologic physical examination should be performed on all patients with urticaria, including a comprehensive skin and lymph node examination, which can help to identify the characteristics of the urticarial lesions as well as any underlying cause. Simple challenge testing also can be performed in the office during the examination to confirm the presence of physical urticaria. For example, dermatographism can be easily detected by stroking the skin

Table 2.

Important Questions to Ask Patients[31]

If acute or chronic urticaria is suspected, ask patients:

- When did the hives start?
- What do the hives feel like (eg, itchy, burning, painful)?
- How big are the hives?
- Where on the body do the hives occur?
- How frequently do the hives occur?
- Can you identify any exacerbating factors?
- Have you taken any new prescription or over-the-counter medications in the days or weeks prior to the eruption?
- Is there a temporal and reproducible relationship to certain foods?
- Was there a preceding or current illness? Have you experienced any fever, malaise, diarrhea, or recurrent or chronic sinusitis?
- Have you recently traveled internationally?
- Have you had any known exposures to stinging or biting insects?
- Are the lesions present or exacerbated following physical stimuli (eg, stroking the skin, tight clothing, vibration, cold, heat, water, sunlight, exercise)?
- Are you experiencing any joint pain, swelling, or stiffness?
- Have you experienced any photosensitivity or oral ulcerations?
- Is your age-appropriate cancer screening up-to-date? Have you experienced any unexplained fevers, night sweats, fatigue, or weight loss?
- Do lesions last more than 24 hours?

with a firm object such as a tongue blade. The diagnosis of cold urticaria can be confirmed by placing an ice cube in a sealed plastic bag on the patient's skin for 5 to 10 minutes, which should result in rapid hive development over the exposed area. Aquagenic urticaria can be confirmed by applying a warm compress against the skin or by immersing a body part in warm water. Pressure urticaria can be detected by applying a weight to the patient's thigh. Solar urticaria can be confirmed by challenging the skin with various wavelengths of light.

FURTHER EVALUATION

The most important evaluation in patients with urticaria is a comprehensive history, review of systems, and physical examination. However, when other signs and symptoms are noted, further testing may be necessary to determine an underlying cause, including a complete blood cell count with differential, comprehensive metabolic panel, thyroid function testing, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody testing, complement levels, serum protein electrophoresis, antineutrophil cytoplasmic antibody testing, urinalysis, stool analysis, skin biopsy, and chest radiography. When the clinical history suggests a type I hypersensitivity reaction, specialized allergy testing can be performed to confirm the reaction, including radioallergosorbent testing or skin prick (scratch) testing. If the patient history does not suggest a specific causative agent, random skin testing generally is not necessary.[21] If the lesions are not visible at the time of the clinic visit, it may be helpful to have the patient bring photographs to confirm the diagnosis or to keep a journal at home that documents the settings in which the condition flares. Overall, physicians should explain to patients that most cases of chronic urticaria are autoimmune or idiopathic in etiology and an underlying cause typically is not found.

Although rarely needed, a skin biopsy may play a role in the evaluation of urticaria in more complex or unclear cases. A biopsy should be considered when urticarial lesions last more than 24 hours to rule out urticarial vasculitis, when other signs or symptoms are present to suggest an underlying causative process or mimicking condition, or when the lesions fail to respond to appropriate therapies.

Notably, angioedema may frequently occur in association with acute and chronic urticaria. When angioedema occurs in isolation, however, acquired or hereditary causes should be considered and evaluated, as described at length by Volcheck.[1]

INTERVENTIONS

A search for an etiology is critical and will help determine the best treatment strategy such as allergen avoidance; treatment of underlying infection, autoimmune disease, or malignancy; or initiation of pharmacologic therapy for symptom control in chronic idiopathic urticaria. Although beyond the scope of this article, there are excellent reviews describing a stepwise approach to the treatment of acute and chronic forms of disease.[1,6]

FINAL THOUGHTS

It should be kept in mind that urticaria can occur in a number of other settings not mentioned above,

including as part of Schnitzler syndrome, Muckle-Wells syndrome, pruritic urticarial papules and plaques of pregnancy, urticarial vasculitis, and in the urticarial phase of bullous pemphigoid, among others. Nonetheless, the information provided here should be a good starting point for residents who are confronted with a new diagnosis of urticaria and should serve you well in the majority of cases encountered.

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