

# Idiopathic Recurrent Angioedema

Evangelo Frigas, MD\*, Miguel Park, MD

*Division of Allergic Disease and Internal Medicine, Mayo Clinic College of Medicine,  
200 First Street SW, Rochester, MN 55905, USA*

Angioedema is a constellation of syndromes characterized by swelling of the deeper layers of the skin or submucosa (or both). Although any part of the body may be affected by angioedema, the face and extremities are most commonly involved. The swellings develop from extravasation of plasma in the affected areas. The extravasation is due to transient increase in endothelial permeability caused by vasoactive substances produced locally. Episodic abdominal pain arising from swelling of the submucosa of any portion of the gastrointestinal tract may occur without swelling of the skin; therefore, angioedema should be included in the differential diagnosis of intermittent, unexplained abdominal pain.

In some cases of angioedema, it has been shown that the extravasation of plasma is caused by vasoactive substances secreted from activated mast cells and eosinophils or by inappropriate activation of the complement and kinin systems, which may be either hereditary or acquired. However, in most clinical presentations of angioedema, the pathogenetic mechanism is unknown. About 50% of the cases of angioedema are accompanied by urticaria and pruritus.

The diagnosis of idiopathic recurrent angioedema is made after a comprehensive evaluation has ruled out the known causes of angioedema. Currently, the prevalence, natural history, and prognostic variables of idiopathic recurrent angioedema are unknown.

Taking a comprehensive personal and family history, performing a physical examination, and compulsively monitoring the response to therapy are the most beneficial and cost-effective diagnostic and treatment tools. All patients with idiopathic recurrent angioedema should be reevaluated once a year or more often if deemed necessary by their primary care physicians,

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\* Corresponding author.

E-mail address: [frigas.evangelo@mayo.edu](mailto:frigas.evangelo@mayo.edu) (E. Frigas).

with the intent of identifying the pathogenesis and optimizing treatment. Diligent and knowledgeable follow-up spares patients costly or unnecessary tests and ineffective or harmful treatment. This is best achieved by close collaboration between the patient's primary care physician and an allergist or dermatologist in an academic medical center that has a clinical, research, and education program in angioedema where innovative treatments and research protocols may be used effectively and safely for the patient. Currently, the treatment of idiopathic recurrent angioedema with or without urticaria is difficult and frustrating for patients and their physicians because it is often only partially effective and is labor-intensive, lengthy, and expensive.

The term angioedema is used to define a localized, sudden, transient, and often recurrent swelling of the skin or submucosa (or both). It is caused by vasoactive substances that produce a transient increase in endothelial permeability [1,2]. In the skin, the nonpitting swellings are accompanied by the cardinal signs of inflammation, namely, rubor and calor, whereas dolor and functio laesa appear when angioedema involves the throat or gastrointestinal tract [3]. These swellings usually last from a couple of hours to a few days and resolve spontaneously. About 50% of cases are accompanied by urticaria and pruritus [3].

The term idiopathic recurrent angioedema is used when three or more episodes of angioedema have occurred within a period of 6 months to 1 year without any cause being identified after an initial comprehensive medical evaluation and periodic reevaluations and treatment trials. This category of angioedema is not only the most common of the cases of recurrent angioedema referred to a tertiary medical center, but it is also among the most distressing for the patient and the most challenging for the medical profession. In our experience, the amplified morbidity from severity and chronicity of symptoms, secondary chronic anxiety, depression, and side effects of the medications used for treatment requires a systematic and comprehensive approach. An essential component of this approach is close collaboration between the patient's primary care physician and a specialist in allergy or dermatology who practices in a tertiary referral medical center that has a program in patient care, education, and research in angioedema. This approach best addresses the needs of these patients for periodic reevaluation in search of the pathogenesis, the effectiveness of the therapy used, careful and safe testing of innovative treatments, and research protocols.

The purpose of this manuscript is to share our experience in the Urticaria/Angioedema Clinic at Mayo Clinic in the care of patients with idiopathic recurrent angioedema and to review the literature on the subject.

## **Epidemiology**

The epidemiology of idiopathic recurrent angioedema is not well known. For the past 50 years, it generally has been reported that urticaria,

angioedema, or both, will affect 10% to 20% of people worldwide at least once in their lifetime [4]. Women are affected slightly more often than men, and at presentation 50% of patients are found to have both urticaria and angioedema [4]. In a recent study of 107 patients with chronic urticaria, angioedema occurred much more often, affecting 83% of the patients studied [5]. With regard to the etiology, it has been reported and reiterated in a recent symposium on urticaria and angioedema that most of the cases are idiopathic [6,7].

### **Clinical presentations and endoscopic and radiographic findings**

Angioedema of the skin is typically nonpitting, with ill-defined margins. The skin is swollen, tender, and warm. Frequently, a burning sensation is described by patients, and pruritus is present when there is urticaria. Attacks of recurrent angioedema may last from hours to a few days and usually resolve spontaneously [3]. Occasionally, physical trauma or stress may be the precipitating factor. Angioedema may affect any part of the gastrointestinal tract. Angioedema of the wall of the bowel may cause obstruction as well as nausea, vomiting, and abdominal pain.

The radiographic findings in angioedema of the gastrointestinal tract may consist of dilated loops of bowel, obliteration of the normal contour of the mucosa, "thumbprinting sign," narrowing of the lumen, and ascites [3]. Unless there is a high degree of awareness of patients who present repeatedly to an emergency department with recurrent abdominal pain without angioedema of the skin, the diagnosis of gastrointestinal angioedema is easily missed [3]. The abdominal symptoms from recurrent angioedema may be attributed to anxiety and somatization, which may lead to a psychiatric evaluation. Fever and leukocytosis are unusual in recurrent angioedema. Cases of cerebral angioedema leading to migraine and transient ischemic attacks have been described [8].

There are no distinguishing radiologic or endoscopic findings that may differentiate idiopathic, recurrent angioedema from any of the other categories of chronic recurrent angioedema. Angioedema due to hereditary deficiency of the C1 esterase inhibitor is not accompanied by urticaria and pruritus.

### **Pathogenesis**

Excessive production or decreased catabolization of molecules that increase vascular permeability cause extravasation of plasma under the skin or the submucosa, and this produces the swellings of angioedema. The best known and most frequently cited vasoactive molecules are histamine, tryptase, prostaglandin  $F_{2\alpha}$  from mast cells, and bradykinin from inappropriate and excessive activation of the complement and kallikrein systems [1–3,9,10].

Food allergens (especially shellfish, nuts, and peanuts), latex, and insect venoms as well as several medications can release histamine from sensitized mast cells and may produce angioedema on an IgE-mediated basis. Some medications (narcotics, polymyxin, *d*-tubocurarine) may cause angioedema owing to their ability to cause direct mast cell degranulation in the absence of IgE antibodies against the drug. Nonsteroidal anti-inflammatory drugs, oral contraceptives, and estrogen replacement medications have all been associated with angioedema, although the mechanisms of their effects have not been clearly established [2,3,9]. Angiotension II inhibitors, such as losartan and angiotensin-converting enzyme (ACE) inhibitors, such as captopril, can cause angioedema in a subset of patients taking these drugs [2,3,9]. Angioedema develops in 1% to 5% of patients who take ACE inhibitors, and it is indistinguishable from any other form of angioedema [2,3]. Although most cases of angioedema caused by ACE inhibitors occur during the first week of therapy, symptoms of angioedema have occurred after a patient has taken the medication for several years [2,3]. It has been proposed that ACE-induced angioedema may be caused by either an increase in the production of bradykinin [9,10] or a decrease in its catabolization [1].

In susceptible persons, physical agents such as cold, pressure, vibration, and ultraviolet radiation can produce angioedema, which usually is associated with urticaria [11]. The ice-cube test is used to rule out a cold-induced pathogenesis. Cold-induced angioedema and urticaria have been reported in association with cryoglobulins, cold agglutinin disease, cryofibrinogenemia, and paroxysmal cold hemoglobinuria [12].

The pathogenetic mechanisms of recurrent angioedema from inherited and acquired deficiencies of the C1 esterase inhibitor of the complement and kallikrein systems have been well studied. In these categories of angioedema, the swellings are suspected to be due to increased local production of various kinins, especially bradykinin and kallidin [2,3,13] (see article by Davis elsewhere in this issue).

About 20 years ago, it was first reported that occasionally autoimmune thyroid disease, recurrent angioedema, and urticaria are associated [14]. Consequently, antithyroid autoantibodies, such as the antimicrosomal and antithyroglobulin autoantibodies associated with Hashimoto thyroiditis, were singled out as a possible autoimmune cause in a subset of patients with angioedema and urticaria [15]. Gruber and colleagues [16] proposed that possibly anti-IgE autoantibodies have a role in autoimmune urticaria and angioedema, and Grattan and colleagues [17] researched the identification of these autoantibodies by performing an autologous skin test. They reported a 30% incidence of positive skin test reactions in patients with chronic urticaria [17]. Hide and colleagues [18] published evidence of a histamine-releasing IgG anti-high-affinity IgE receptor (anti-FcεR1) autoantibody and proposed it as a cause for autoimmune urticaria and angioedema. The presence of IgG autoantibodies in the sera of certain patients with chronic urticaria against the alpha chain of FcεR1 has been confirmed

by others as well [19–23]. According to this autoimmune model, the pathogenetic mechanism is mediated by specific IgG autoantibodies that bind and cross-link adjacent FcεR1 receptors or the Fc portion of adjacent IgE molecules, leading to mast cell activation and the release of vasoactive substances that cause angioedema or urticaria (or both). In this pathogenetic model, a synchronous activation of the complement system with the production of C5a may augment the reaction in some patients [24,25].

Most recently, it has been reported that normal serum has a natural autoantibody (anti-FcεR1a) against the α subunit of the IgE receptor [26,27]. It has been hypothesized that through an abnormal control mechanism these anti-receptor autoantibodies may lead to mast cell activation and development of angioedema [26,27]. Yet another autoimmune model has been suggested that does not involve immunoglobulins, in which the release of vasoactive mediators in patients with idiopathic chronic urticaria and angioedema may be mediated by aberrant regulation of the intracellular signal transduction of the p21ras pathway [28]. An autoimmune model for the pathogenesis of angioedema appears to be supported by reports on the benefits of plasmapheresis in patients with severe chronic urticaria [29], on intravenous immunoglobulin for chronic autoimmune urticaria [30], on cyclosporine for chronic idiopathic urticaria [31], and on methotrexate for chronic idiopathic urticaria [32].

In summary, the pathogenesis of idiopathic recurrent angioedema with or without urticaria is not known. The great variety of clinical presentations and the large number of patients with angioedema recalcitrant to therapy suggest that the pathophysiologic mechanisms are more complex than has been reported. Multicenter, large, double-blind, placebo-controlled clinical studies with well-selected patients may provide reliable and useful information on the treatment of idiopathic recurrent angioedema.

### **Initial evaluation, diagnosis, and differential diagnosis at an allergy specialty clinic**

All patients who have chronic recurrent angioedema (ie, three or more episodes within 3 to 6 months) with or without chronic urticaria or who have recurrent abdominal pain that is unexplained after adequate evaluation and treatment by their primary care physician or gastroenterologist should have a work-up for angioedema by a specialist, usually an allergist or dermatologist. On the basis of our experience, we propose the algorithm in Fig. 1 for the systematic evaluation of patients with recurrent angioedema with or without urticaria. In the Urticaria/Angioedema Clinic, which was established in the Division of Allergic Diseases and Internal Medicine at Mayo Clinic Rochester in 1995, we evaluate approximately 300 to 400 patients annually, most of them referred by their primary care physicians.

Our work-up often consists of a comprehensive physical examination, a detailed personal and family history, and skin biopsy for standard light microscopic direct and indirect immunofluorescence when needed, especially

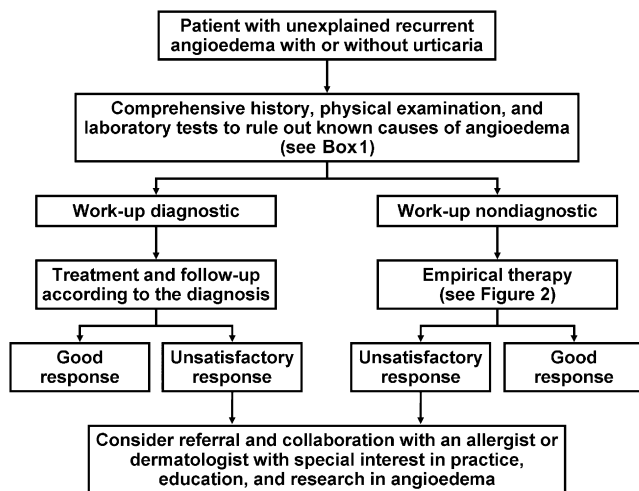


Fig. 1. Proposed algorithm for the evaluation and follow-up of patients with recurrent angioedema.

if there is coexisting urticaria or if vasculitis is suspected. The importance of a comprehensive general medical evaluation for these patients cannot be overemphasized. As appreciated by others, the benefits from the history and physical examination outweigh the contribution of laboratory tests [33]. Special attention must be directed to confirming the patient's description of symptoms and time course. Is what the patient describes as swelling angioedema? Carefully look for any relationship between the patient's symptoms and activities, eating, and medication use. Is the patient's angioedema caused by medications taken? The inquiry about medications used by the patient should include asking about over-the-counter preparations, herbs, vitamins, and supplements, which patients often do not consider as medications and therefore do not mention them unless asked. Often, this relationship between medication and angioedema is not self-evident. Discontinuation of the medication(s) may be necessary to clear this possibility. In addition to the medications, any skin products and cosmetics used by the patient must be identified. The initial work-up includes the following laboratory tests: complement C4, C1q, CH50, C1 esterase inhibitor by functional and quantitative assays, and a panel for mast cell-mediator screening, which includes measurements of tryptase and calcitonin in the serum and histamine, *N*-methylhistamine, and prostaglandin  $F_{2\alpha}$  in a 24-hour urine collection. The following are also part of the work-up if they have not been performed recently: a complete blood count, chemistry group, serum protein electrophoresis, total serum IgE, erythrocyte sedimentation rate, and a thyroid cascade, which includes testing for antithyroid antibodies. When warranted by the patient's history, allergy skin tests or specific IgE blood tests are performed to rule out latex and food allergy.

In our experience, the most common initial diagnosis is idiopathic recurrent angioedema with or without urticaria, for which antihistamine therapy prescribed by the referring physicians usually has been partially beneficial. Almost all the patients report a beneficial effect from treatment with systemic glucocorticoids, but the beneficial effect vanishes as soon as the glucocorticoid therapy is stopped. Some patients are not able to discontinue the glucocorticoid therapy because of intolerable angioedema, urticaria, and pruritus. We have not identified the large number of patients with recurrent angioedema due to C1 esterase inhibitor deficiency that authors from other tertiary medical centers have reported [34]. Also, we have not encountered the high incidence of angioedema reported to be caused by oral contraceptives, estrogen replacement therapy, ACE inhibitors, and associated autoimmune thyroid disease [5,35–37]. Annually, about 1% of the patients we evaluate have swelling that masquerades as angioedema, such as allergic or contact dermatitis, folliculitis, cellulitis, acne rosacea associated with lymphedema, angioedema associated with eosinophilic panniculitis [38], idiopathic cyclic edema, angioedema associated with hypereosinophilia [39], granulomatous cheilitis, and superior vena cava syndrome.

Since we started testing with the panel for mast cell mediators in the late 1990s, we have found several patients with chronic idiopathic recurrent angioedema with or without urticaria who have an isolated elevation of prostaglandin  $F_{2\alpha}$  in the urine but normal levels of the other mediators. These patients are not atopic and have no clinical evidence of localized or systemic mastocytosis. The biopsy of the bone marrow is normal and there is no increase in the number of mast cells. In our experience, these patients may benefit from treatment with aspirin. We have also noted that the increase in prostaglandin  $F_{2\alpha}$  in the urine returns to normal after aspirin has been added to their treatment.

After the initial clinical evaluation and laboratory work-up, the patient's case is assigned to one of the diagnostic categories listed in **Box 1**. The diagnosis of idiopathic recurrent angioedema is the most common. Whenever possible, these patients are scheduled for reevaluation in 3 to 4 months, or more often if necessary, with 30-minute visits to determine whether any new symptoms warrant further investigation and to reappraise the benefits and side effects of therapy. Furthermore, once a year, a general medical examination is repeated with the same components as described above to search for the pathogenesis and to reassess the effectiveness of therapy. We have found that frequent communication and supportive collaboration among the specialist, patient, and patient's primary care physician are essential for the success of the treatment.

## Treatment

Treatment and follow-up depend on the diagnosis. Angioedema caused by medications, allergens, or physical agents is treated by eliminating the

**Box 1. Diagnostic categories of recurrent angioedemas**

Idiopathic angioedemas with or without urticaria (the most common category)  
Medication induced  
Allergen induced  
Physically induced  
Associated with autoimmune disease of the thyroid  
Combination of 2 or more of the above  
From deficiency of C1 esterase inhibitor of the complement and kallikrein systems (C1 INH)  
Hereditary C1 INH deficiency  
Variant 1: 80%–85% of cases of hereditary angioedema  
Variant 2: 10%–15% of cases of hereditary angioedema  
Variant 3: percentage of cases of hereditary angioedema unknown  
Acquired with C1 INH deficiency  
Variant 1: associated with malignancies, mainly lymphoproliferative  
Variant 2: caused by anti-C1 INH autoantibodies  
Pseudoangioedemas

causative agent. Hereditary angioedema, which often requires lifelong treatment and careful monitoring, is best treated by referral to a specialist in the management of this disease. Idiopathic, chronic, recurrent angioedema may require treatment and follow-up for several years. Depending on where the patient lives and the resources available in the area, the best care is provided by effective collaboration between the patient's primary care physician and a specialist in a clinic with a program for treatment, education, and research in angioedema and urticaria. In our Urticaria/Angioedema Clinic, we offer patient education, treatment, and research studies.

For general patient education, patients with idiopathic angioedema are given the same instructions as for other categories of angioedema and urticaria. Specifically, patients are given instructions for skin care, primarily the avoidance of dryness. Patients are advised to avoid cosmetic creams, perfumes, and deodorants when these items are suspected to cause flares of symptoms. They also are advised to avoid any medication that has caused or is suspected to cause an exacerbation of their symptoms. Often this information is not self-evident to patients. For example, patients sensitive to aspirin may use a product that contains aspirin; thus, these patients should be given a list of commonly used products and medications containing aspirin. Other factors reviewed with patients are diet, exercise, and stress. Patients with a history of angioedema of the throat are provided with an action

plan to use in case of recurrence. This includes instructions on how to use epinephrine, systemic glucocorticoids, and antihistamines; wearing an identification bracelet; and telephone numbers for immediate access to care.

For medications, we often follow a stepwise ladder approach as shown in Fig. 2. The benefit of antihistamine therapy for patients with idiopathic angioedema varies, but these medications are almost always helpful. In step 1, we usually start with a nonsedating or less-sedating antihistamine, such as fexofenadine, cetirizine, loratadine, or desloratadine, taken during the daytime. Often, as has been reported, we have found off-label dosage beneficial, especially when there is coexisting urticaria [2]. For example, we have prescribed fexofenadine 180 mg, cetirizine 10 mg, or loratadine 10 mg twice daily instead of once daily with good results, provided the agent is needed, well tolerated, and does not interfere with the other medications the patient is taking. If this treatment is not satisfactory, we proceed with step 2 by adding a sedating antihistamine such as doxepin, hydroxyzine, or diphenhydramine, usually taken at bedtime. The dose of the sedating antihistamine should be titrated according to its effectiveness in controlling the patient's symptoms, provided of course it is well tolerated and does not interfere with the rest of the medications the patient is taking. For example, we have often noted the need for increasing the nightly dose of doxepin from 10 mg up to 150 mg to adequately control the patient's symptoms. We have also noted that increasing the dose of doxepin above 150 mg adds no further improvement in symptom control. Other authors have reported very good results with higher doses of sedating antihistamine (specifically diphenhydramine) taken during the daytime [2]. They have noted that the patient's sedation and somnolence from diphenhydramine wears off after 1 week of treatment [2]. They also noted benefit from combining H<sub>1</sub> with H<sub>2</sub> antihistamines and a leukotriene antagonist [2].

When the antihistamine therapy in step 2 is only partially effective (often the case for our patients with idiopathic angioedema), we proceed with step 3, in which, in addition to the antihistamines, we prescribe treatment trials with other medications we or others have found helpful in this setting. Review of the literature shows that patients with severe angioedema with or without urticaria that is not responding to antihistamine therapy have

|                           |                           |                                      |
|---------------------------|---------------------------|--------------------------------------|
|                           |                           | Additional medications<br>(see text) |
|                           |                           | Sedating antihistamine               |
| Nonsedating antihistamine | Nonsedating antihistamine | Nonsedating antihistamine            |
| Step 1                    | Step 2                    | Step 3                               |

Fig. 2. Algorithm for a stepwise ladder approach in the treatment of angioedema with or without urticaria. For detailed description of the medications used in steps 1, 2, and 3, see the text in the "Treatment" section.

been treated with a wide variety of medications. In a double-blind randomized study, cyclosporine was found to be effective in patients with chronic idiopathic urticaria and angioedema [31]. Our experience with cyclosporine has been limited because of concerns about the potential for severe side effects and the benefit often encountered with drugs with fewer side effects. In another double-blind randomized study, nifedipine was found to be beneficial for patients with chronic idiopathic urticaria and angioedema [40]. In the few cases in which we have tried this medication, we have not noticed benefit. Other reported beneficial therapies include methotrexate [32,41], androgens with impeded androgenic action [42,43], and warfarin [44].

In our experience, treatment trials for 2 to 4 months with either colchicine 0.6 mg once or twice daily [45] or dapsone 25 mg twice daily and titrated up to 100 mg twice daily [46], or sulfasalazine 500 mg once or twice daily are often helpful [47,48]. We rule out glucose-6-phosphate dehydrogenase deficiency before initiation of therapy with dapsone. We also have noted benefit occasionally with recombinant interferon  $\alpha$ . We usually start at a dose of 3 million units subcutaneously 3 times weekly. At times, the addition of indomethacin (sustained release) 75 mg once or twice daily to the treatment with dapsone or interferon has been beneficial in improving the control of symptoms. We evaluate the benefit from any of the medication trials mentioned above after 2 to 4 months. During these trials, we closely monitor the patients with office visits and laboratory testing every 2 to 3 weeks to ensure there are no side effects from the treatment. In a subset of patients with idiopathic recurrent angioedema and increased urinary levels of prostaglandin  $F_{2\alpha}$ , we have noted benefit from adding aspirin to the treatment at any of the steps described above, provided the patients are not sensitive to aspirin. We usually start with 81 mg of aspirin, and if needed and tolerated by the patient, we gradually increase the dosage up to 1.5 to 2 g per day in divided doses.

Systemic glucocorticoids, although very effective for the majority of patients with recurrent angioedema, in our experience should not be used long-term because of their cumulative and severe side effects and the frequent development of dependence. Therefore, we use them sparingly and only in short courses (ie, prednisone 20 mg for 5 to 7 days usually without tapering), for treatment of protracted attacks of angioedema or after epinephrine has been used to treat a severe attack of angioedema or urticaria.

## Summary

The treatment of idiopathic, chronic, recurrent angioedema with or without urticaria is difficult, both for patients and their physicians, because treatment often is only partially effective and is labor-intensive, expensive, and lengthy. New medications for urticaria and angioedema that currently are being tested clinically may prove effective.

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