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Current treatment options for idiopathic angioedema

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ABSTRACT

Background: Idiopathic angioedema is defined as localized swelling of the cutaneous and mucosal tissue that occurs in episodes without a clear etiology. It can be problematic to treat when the underlying pathophysiology is not well understood.

Objective: To identify successful treatments of idiopathic angioedema reported in the literature.

Methods: A literature search was performed using PubMed. Published case reports and articles discussing treatment of idiopathic angioedema were used in the formulation of this review. In addition, 2 case reports are provided.

Results: Although there are no approved treatments for idiopathic angioedema, several medications used for the treatment of hereditary angioedema, such as bradykinin receptor antagonists (icatibant), kallikrein inhibitors (ecallantide), and C1 inhibitors, were successful in 10 patients. Anti-IgE monoclonal antibody (omalizumab) proved successful in 5 patients. The most widely used and successful medication was tranexamic acid (154 patients).

Conclusion: Despite an unknown etiology, this article highlights viable treatment options for idiopathic angioedema. More clinical trials and better markers identifying the cause of angioedema are needed.

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Introduction

Angioedema is defined as localized swelling of the cutaneous and mucosal tissue.¹ The swelling usually develops slowly, although a rapid onset is possible, with attacks lasting from a few hours to several days. Angioedema is usually self-limited but can be life-threatening if laryngeal swelling occurs, leading to occlusion of the airway. Potential causes of angioedema include hereditary, acquired, allergic, drug induced, and idiopathic. Several treatment options have been shown to be effective for many types of angioedema, including high-dose antihistamines, corticosteroids, and epinephrine. Removal of an offending medication or treatment of the underlying disease can be effective for drug-induced or acquired angioedema, respectively. In recent years, new therapeutic options have become available in the United States for hereditary angioedema (HAE) types I and II. These include replacement of C1 esterase inhibitor and blockers of bradykinin (icatibant) and kallikrein (ecallantide).

Idiopathic angioedema is most often defined as at least 3 episodes of angioedema within 6 to 12 months without a clear etiology.¹ A diagnosis of idiopathic angioedema is made after a thorough evaluation has been completed and other causes of angioedema have been excluded. In some cases, patients have had symptoms for

months or years before the diagnosis is made and have used multiple medications with little to no improvement. The goal of this article is to present 2 new cases of antihistamine-resistant idiopathic angioedema and to review previously published case reports and retrospective data to identify treatments that have been successful for the treatment of idiopathic angioedema.

Methods

A literature search of PubMed was performed using the search terms *angioedema*, *idiopathic*, and *idiopathic angioedema*. Then, the search was limited to case reports regarding treatment and excluded discussion of angioedema with associated urticaria or use of angiotensin-converting enzyme inhibitors. In addition, the authors present 2 cases reports from their institution.

Results

Case Reports

The authors present 2 case reports of antihistamine-resistant idiopathic angioedema in teenage girls to add to the existing literature.

Patient 1 was 15 years old at the time of presentation with a medical history of asthma and anxiety for which she was taking Zoloft (sertraline HCl; Pfizer, New York, New York) daily. She presented with a new onset of symptoms including orofacial edema, abdominal cramping, occasional swelling of the hands and feet, and a sensation of throat swelling, although throat swelling was never witnessed by

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Table 1
Description of previous reports of idiopathic angioedema

Study	Patients, n	Age (y)	Sex	Symptoms (n)	Episode frequency	Episode length	Unsuccessful treatments	Successful treatments
Ozturk and Kocaturk, ² 2014	1	47	M	orofacial and scrotal edema	weekly	NR	antihistamines, fluoxetine, prednisolone 0.5 mg/kg (initially worked but was stopped owing to side effects)	omalizumab 300 mg every 4 wk for 4 mo (IgE was 183 before treatment)
Stahl et al, ³ 2014	1	32	F	orofacial edema	several times a month	4 d	diphenhydramine 50 mg, prednisone 60 mg, epinephrine IM 0.3 mg, racemic epinephrine methylprednisolone 125 mg, danazol 200 mg bid, fexofenadine 180 mg bid, ranitidine 150 mg bid, montelukast, progestin, sulfasalazine, tranexamic acid, hydroxychloroquine	ecallantide, icatibant for acute episodes, Berinert 20 U/kg for acute episodes, Cinryze 1,000 U biweekly prophylaxis
Wintenberger et al, ⁴ 2014	19	52 (median)	8 M, 11 F	facial edema, abdominal pain	2–48 attacks in 6 mo	≥24 h	antihistamines	tranexamic acid 1–3 g/d prophylaxis (robust response in 12, moderate decrease in 4, 3 had no change in attacks)
Mansi et al, ⁵ 2014	70	38 (median; range 5–75)	36 M, 34 F	edema of face/perioral (57), oral mucosa (46), abdominal (14), limbs (38)	81% reported >5 attacks/y	48 h (median)	corticosteroids, antihistamines, adrenaline	tranexamic acid 1 g every 4 h acutely (13 of 24 reported positive response), tranexamic acid 3 g/d for prophylaxis (37 of 38 reported positive response), Berinert 1,000 U for acute episode in 1 patient
Berry and Firszt, ⁶ 2013	1	16	F	facial edema, severe abdominal pain	1–2 times/mo	3 d	fexofenadine 180 mg qd, hydroxyzine 100 mg qd, diphenhydramine 50 mg qid, cetirizine 10 mg qd, danazol 200 mg bid, Depo-Provera	ecallantide 30 mg for acute episodes
Montinaro et al, ⁷ 2013	1	50	M	facial edema	2–3 times/mo	36 h	levocetirizine 5 mg bid, antihistamines, corticosteroids, tranexamic acid 500 mg bid	icatibant 30 mg for acute episodes
Dy et al, ⁸ 2013	1	8	F	orofacial, laryngeal, extremity edema	several times a year	48 h	epinephrine, steroids, antihistamines	ecallantide 30 mg for acute episodes
Websky et al, ⁹ 2013	1	68	M	head and neck edema	weekly	NR	antihistamines, montelukast, corticosteroid pulse therapy (initially helpful but was stopped)	omalizumab 300 mg every 4 wk for 8 mo, then every 8 wk (IgE was 1,164 before treatment)
Del Corso et al, ¹⁰ 2012	1	48	M	orofacial, laryngeal edema	1–2 times/mo	NR	sedating and nonsedating oral antihistamines (given at off-label dosing), tranexamic acid, corticosteroids, anti-leukotrienes, cyclosporine, colchicine, high-dose methylprednisolone or hydrocortisone, chlorpheniramine maleate, epinephrine (inhaled and IV)	icatibant 30 mg and IV corticosteroids for acute episodes

Colas et al, ¹¹ 2012	1	26	F	edema of face, glottis, distal upper and lower extremity; prodromal palpitations, pharyngeal discomfort before onset of edema	≥2 times/wk	48–72 h	rupatadine 10 mg qd, dexchlorpheniramine 16 mg qd, ranitidine 150 mg qd, hydroxyzine 25 mg, prednisone 60 mg qd, dapsone 50 mg qd, ranitidine 150 mg qd, tranexamic acid 1 g tid (slight improvement), Berinert 500 IU (no response)	icatibant 30 mg for acute episodes
Ghazan-Shahi and Ellis, ¹² 2011	1	19	F	orofacial edema, hoarse voice (presumed laryngeal edema), presence of high-titer antinuclear antibody*	NR	NR	initially responded to high-dose antihistamine and epinephrine IM, cetirizine 20 mg bid (prophylactic), ranitidine 150 mg bid (prophylactic), montelukast, methylprednisolone 125 mg tid, steroid every 4–6 h, epinephrine IM 1–2 injections qd, C1 esterase inhibitor, hydroxychloroquine 200 mg bid, IVIG, dapsone	rituximab 560 mg/wk for 4 wk
Du-Thanh et al, ¹³ 2010	35	45.8 (mean)	21 M, 14 F	head and neck edema (35), headaches (35), digestive symptoms (8), dyspnea, cough, dysphonia, and/or undiagnosed chest pain (9)	averaged from daily to <1 episode/y	averaged 1 h to 4 d	antihistamines, corticosteroids	tranexamic acid 1 g during episodes (23 saw improvements), then transitioned to tranexamic acid 3 g qd prophylaxis (12 showed complete remission, 11 showed improvement, n = 23)
Sands et al, ¹⁴ 2007	3	50, 63, 65	M	orofacial, laryngeal, scrotal swelling, persistent asthma	years of episodes	NR	fexofenadine, cetirizine, ranitidine, prednisone	omalizumab 300 mg every 3 wk, omalizumab 375 mg every 2 wk, omalizumab 300 mg every 4 wk (IgE was 244, 510, and 62.4, respectively, before treatment)
Zingale et al, ¹⁵ 2006	40	8–75	M:F ratio 1.35	upper airway (14), abdominal pain (11)	NR	NR	cetirizine, desloratadine, hydroxyzine	tranexamic acid during episodes was used in milder cases (effective in 8, partial in 3), tranexamic acid prophylaxis was used for more severe cases (effective in 16, partial in 6)
Cicardi et al, ¹⁶ 1999	25	16–77	15 M, 10 F	edema of face, arms, legs and genitalia (21), only facial edema (4), swelling of larynx or pharynx swelling (13), bowel wall edema (5)	>12 attacks/y (16), 6–11 attacks/y (6), 1–5 attacks/y (3)	NR	hydroxyzine 100 mg qd, hydrocortisone up to 1 g/d for acute episodes (7 of 13 failed)	tranexamic acid 1 g tid, tapered to effectiveness as prophylaxis (15 with good response)

Abbreviations: bid, 2 times daily; F, female; IM, intramuscularly; IV, intravenously; IVIG, intravenous immunoglobulin; M, male; NR, not reported; qd, every day; qid, 4 times daily; tid, 3 times daily.

a medical provider. Swelling episodes were occurring 2 to 3 times per week for approximately 5 months. The patient had tried high-dose antihistamines initially, with the addition of ranitidine, montelukast, and prednisone, because she noted no improvement in symptoms. She also was prescribed injectable epinephrine for her complaint of throat swelling, which would temporarily relieve the sensation of throat swelling but symptoms would return within 1 hour. The patient noted using injectable epinephrine 15 times in 60 days. She was suspected of having vocal cord dysfunction or anxiety that was causing the subjective sensation of swelling, because it had never been directly visualized by a medical provider. Therefore, epinephrine was not the recommended treatment for her symptoms. An initial workup for HAE was completed, with normal C4 and C1 esterase function and concentration. There was a negative family history of angioedema. The patient was referred to speech therapy for evaluation and treatment of vocal cord dysfunction. Psychiatric evaluation also was recommended. Owing to symptoms refractory to antihistamines and corticosteroids, approval was obtained for icatibant during acute episodes. The patient used icatibant on 5 occasions, with decreased swelling within 45 minutes of administration. Swelling did reoccur 4 to 5 hours later, but in a milder state. Because the patient demonstrated improvement with icatibant and was continuing to have frequent episodes, approval was obtained for a trial of C1 esterase inhibitor prophylaxis (Cinryze; Shire, Lexington, Massachusetts). The patient also had a progesterone implant (Implanon; Merck, Kenilworth, New Jersey) placed for contraceptive purposes approximately 1 month before initiation of Cinryze therapy. With these interventions, the patient had a significant decrease in the frequency and severity of her angioedema attacks, with 1 to 2 acute episodes per month requiring administration of icatibant.

Patient 2 was 13 years old at the time of presentation with a medical history of exercise-induced bronchospasms and anxiety. She presented with a new onset of symptoms including lip swelling, occasional uvular and tongue swelling, and a sensation of throat swelling, although throat swelling during her attacks was never witnessed by a medical provider. The patient also had associated upset stomach and general malaise before the onset of swelling episodes. Her episodes were occurring 1 to 3 times per month for approximately 1 year. This patient had tried high-dose antihistamines, ranitidine, and prednisone, with no change in symptoms. She also used injectable epinephrine, with no improvement. On 2 separate occasions, she was given nebulized racemic epinephrine in the emergency department, which the patient found helpful for her throat symptoms, although this could have been a placebo effect. The patient had significant stressors in her personal life that were judged to contribute to the angioedema episodes. She also had started her menstrual cycle, which was considered as a possible trigger for episodes. Her initial workup for HAE was negative, with normal C4 and C1 esterase function and concentration. There was a negative family history of angioedema. Approval for icatibant was obtained for this patient and she reported improvement in symptoms within 45 minutes of use, although lip swelling did return within 24 hours of use. Owing to persistent symptoms despite treatment with icatibant, she was switched to off-label use of C1 inhibitor prophylactic treatment (Cinryze) for 4 to 6 months. The hope was that she would go into remission during that time. She responded well to this treatment with minimal swelling episodes. The patient also was referred to speech therapy for evaluation and treatment of vocal cord dysfunction. In addition, she was referred for psychiatric evaluation and gynecology for consideration of a progestin oral contraceptive.

Literature Review

The initial PubMed search identified more than 160 articles. The completed search included 20 case reports and articles relevant to

treatment of idiopathic angioedema (Table 1).^{2–16} In the cases reported, there were 201 patients, and approximately 53% of patients were male and 47% were female. The age of patients ranged from young children to adults (5–77 years), with most being adults. All patients had undergone evaluation for HAE and had normal C1 esterase inhibitor (concentration and function) and normal C4 levels before receiving the diagnosis of idiopathic angioedema. More than 50% of patients reported swelling of their face and throat. Some cases reported involvement of other body parts and/or abdominal symptoms before swelling episodes. All patients reported more than 3 attacks per year, with most having monthly episodes. The typical length of the angioedema episodes was 36 to 72 hours until resolution.

All patients had undergone treatment with multiple high-dose antihistamines. Sixty percent of patients tried additional medication, including, but not limited to, corticosteroids (oral and intravenous) and intramuscular epinephrine, but no decrease or remission of symptoms was reported. Of note, in the case report by Sands et al,¹⁴ 2 of 3 patients had persistent asthma for which they were started on omalizumab and their angioedema showed improvement. The third patient was started on off-label use of omalizumab and also had resolution of angioedema episodes. Prior to starting omalizumab, the patients' IgE levels were 244, 510, and 62.4 kU/L respectively.¹⁴ In the case presented by Ghazan-Shahi and Ellis,¹² the patient was responsive to steroids but was later found to have positive antinuclear antibodies for which treatment with rituximab, 560 mg/week for 4 weeks (a B-cell–depleting, monoclonal, anti-CD20 antibody) was effective.

Successful treatment strategies included icatibant for acute episodes (4 patients), ecallantide for acute episodes (3 patients), C1 esterase inhibitor (Cinryze) prophylaxis (1 patient), C1 esterase inhibitor (Berinert, CSL Behring, King of Prussia, PA) for acute episodes (2 patients), omalizumab (5 patients), and rituximab (1 patient). Tranexamic acid was the most widely used drug in 154 of potentially 189 patients. Tranexamic acid's success rate for acute use and as a prophylactic was 80%. It was reported that those who did not use the drug had contraindications or chose not to proceed with this therapy.^{4,5,13,15,16}

Since 2012, off-label use of inhibitors of the bradykinin pathway has been reported in the successful treatment of idiopathic angioedema. Although none of these patients had evidence of deficiency in their C1 inhibitor level or function, the effectiveness of these medications suggests that bradykinin could play a role in the pathophysiology of idiopathic angioedema.

Although not discussed in the case reports, an additional treatment option worthy of consideration is the use of progestin contraceptives in patients of childbearing age. A French retrospective study, reported on by Saule et al,¹⁷ identified 55 women with nonallergic angioedema including HAE who were treated with progestin contraceptives. Total or partial improvement of swelling episodes was observed in 81% of these women, with more success noted in the group on antigonadotropic progestin vs progestin-only pill. They concluded that antigonadotropic progestin could be recommended as an adjuvant treatment for women of childbearing age. Bork et al¹⁸ also found that angioedema episodes in women can be provoked or exacerbated by exogenous estrogen; therefore, treatment with progestin might be helpful.

Not included in Table 1, but worth including in this review, is a letter to the editor submitted by Feldman et al¹⁹ who reported on 4 patients with recurrent tongue swelling. All 4 were unresponsive to multiple medications and had negative workup for HAE or alternative diagnoses. Owing to the refractory nature of their angioedema and physical examination findings, they were diagnosed with factitious angioedema. Psychiatry services were recommended for all these patients, but only 2 pursued outpatient psychological services.¹⁹

Discussion

Idiopathic angioedema continues to be a difficult condition to manage. In 2014, Cicardi et al.²⁰ and the Hereditary Angioedema International Work Group published an excellent summary article discussing the various forms of angioedema and available treatment options. The report noted the limited existing literature discussing idiopathic non-histaminergic angioedema and the treatment summary stated that there is no conclusive evidence for the effective treatment of attacks. Zingale et al.¹⁵ devised a diagnostic flowsheet for angioedema without urticaria, with a recommendation to start antihistamines first and then, if symptoms are unresolved, to proceed with initiation of tranexamic acid therapy.

Cicardi et al.¹⁶ reported the successful treatment of idiopathic angioedema with tranexamic acid in 1999. Tranexamic acid is an antifibrinolytic agent that displaces plasminogen from fibrin, resulting in inhibition of fibrinolysis. Its mechanism of action also includes inhibition of the proteolytic activity of plasmin and decreased activation of complement and consumption of C1 esterase inhibitor, which might explain its effectiveness in the treatment of angioedema.²¹ Tranexamic acid is relatively inexpensive and comes in oral and intravenous preparations. It is generally well tolerated; however, in this review, 4 patients did not tolerate its use and therefore were switched to C1 esterase inhibitors. Although this might be an option for some patients, it is contraindicated in those with active thromboembolic disease, risk of thrombosis, and concurrent use of combination hormonal contraception.²¹ Other side effects include migraines, dizziness, gastrointestinal upset including diarrhea, and menstrual irregularities. If a patient cannot use tranexamic acid or it is believed that the patient's angioedema might be mediated by bradykinin, newer medications that block bradykinin and C1 esterase inhibitors might be better treatment options.

This review describes attempts to treat idiopathic angioedema using medications developed for other conditions, including HAE, asthma, urticaria, and autoimmune disease, with varying degrees of success. The greatest challenge with idiopathic angioedema is that the underlying cause of the angioedema is not known, so a pharmacologic mechanism for treatment cannot be predicted. What is surprising is that many reported treatments were found to be effective. For example, why would administration of C1 esterase inhibitor be effective in a patient who has normal concentration and function of this enzyme? This suggests that an unknown function of the enzyme is being replaced in patients with angioedema or that supraphysiologic levels can be used to block whatever pathophysiology is taking place. Because angioedema is mediated by histamine and/or bradykinin, it makes sense that treatment with antagonists for either mediator or the 2 mediators would be effective. What is lacking is a good test to measure production of these mediators as part of routine clinical care. One also must consider that not all chemical mediators and/or mechanisms of angioedema have been identified. In the meantime, the treatment of idiopathic angioedema is likely to remain by trial and error. Unfortunately, the medications being tried are very expensive and often off label, so this approach is not ideal. Until better markers for the cause of idiopathic angioedema can be identified, it appears to be the best available option.

Conclusion

Idiopathic angioedema is a diagnosis of exclusion. There have been 20 case reports and articles published on patients with idiopathic angioedema and the treatments used. Because the underlying cause of idiopathic angioedema is not fully understood, there

are no medications specifically designed to treat this condition. Antihistamines, corticosteroids, and epinephrine remain first-line therapies, but what can be used when these fail? Tranexamic acid continues to be a viable treatment option in some patients. In addition, newer medications for HAE such as human plasma derived or recombinant C1 esterase inhibitor, icatibant, and ecallantide have been reported to be successful in acute episodes of idiopathic angioedema, which suggests that bradykinin plays a role in this condition. Human plasma derived C1 esterase inhibitor (Cinryze) also has been reported to be successful in prophylactic management, which was the authors' experience with 2 patients. Omalizumab, which is currently approved for the treatment of asthma and chronic urticaria, should be considered a potential treatment option. If a patient is of childbearing age, then progestin contraceptives could be considered. Although this review highlights a small sample of successful treatment options, larger multisite clinical trials are needed for these medications to be approved as first-line therapy in cases of idiopathic angioedema.

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