

Angioedema with Normal Laboratory Values: The Next Step

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Abstract When faced with a patient with recurrent swelling, a thorough laboratory evaluation to determine the underlying etiology ensues. When the laboratory work-up is unrevealing, health care practitioners are frequently left in a quandary. This review will attempt to provide up-to-date information on how to approach the diagnosis and management of angioedema in a patient with normal laboratory values. The subtypes that will be reviewed in detail include: hereditary angioedema with normal C1 inhibitor (HAE with normal C1INH), drug-induced angioedema, and idiopathic angioedema. We present literature to aid the physician in the diagnosis and treatment of these disorders.

Keywords Angioedema · Hereditary angioedema · Hereditary angioedema with normal C1 inhibitor · Idiopathic angioedema · Drug-induced angioedema · Normal-complement levels · Treatment · Diagnosis · Bradykinin · Pathophysiology · Estrogen

Introduction

Angioedema is characterized by asymmetric, often recurrent and intermittent swelling of the deeper dermal tissues. Acute episodes can involve the face, tongue, gastrointestinal/genitourinary tracts, and larynx [1]. The two most widely recognized mediators to cause swelling are bradykinin and histamine. Clinically, patients may present with isolated angioedema or concomitantly with urticaria. The evaluation involves checking specific laboratory parameters to identify

an underlying diagnosis. In a patient with normal complement levels, the diagnosis is not straightforward and often involves a meticulous history of medication usage, family history, and response to treatment to narrow down the differential.

Known Mechanisms of Angioedema

In mast cell-mediated angioedema, inflammatory mediators such as histamine, heparin, leukotriene C4, and prostaglandin D2 lead to increased vascular permeability and swelling [2••]. Mast cell-mediated angioedema can further be broken down into three forms: allergic IgE-dependent mast cell degranulation, non-allergic direct mast cell degranulation, and leukotriene-mediated mast cell degranulation. These forms are typically associated with urticaria [1]. In contrast, bradykinin-mediated angioedema is caused by the increased production or decreased breakdown of bradykinin. A deficiency in C1INH protein or function results in unopposed activation of the contact and complement systems resulting in increased levels of bradykinin and decreased levels of complement proteins 2 and 4 (C2 and C4) [3]. Bradykinin causes an increase in vascular permeability by binding to B2 bradykinin receptors on endothelial cells resulting in edema [4].

Diagnostic Approach

Identifying the etiology of angioedema is often challenging for the health care provider (see Fig. 1). The most important aspect of the evaluation is a detailed history and physical exam. Questions should be directed at the patient's history of drug, food, occupational exposures, physical triggers, infectious exposures, and insect stings or bites. Physical exam should assess for the presence of hives, erythema marginatum, and obvious swelling. A detailed family history should be obtained to help differentiate hereditary forms. One should still note that 25 %

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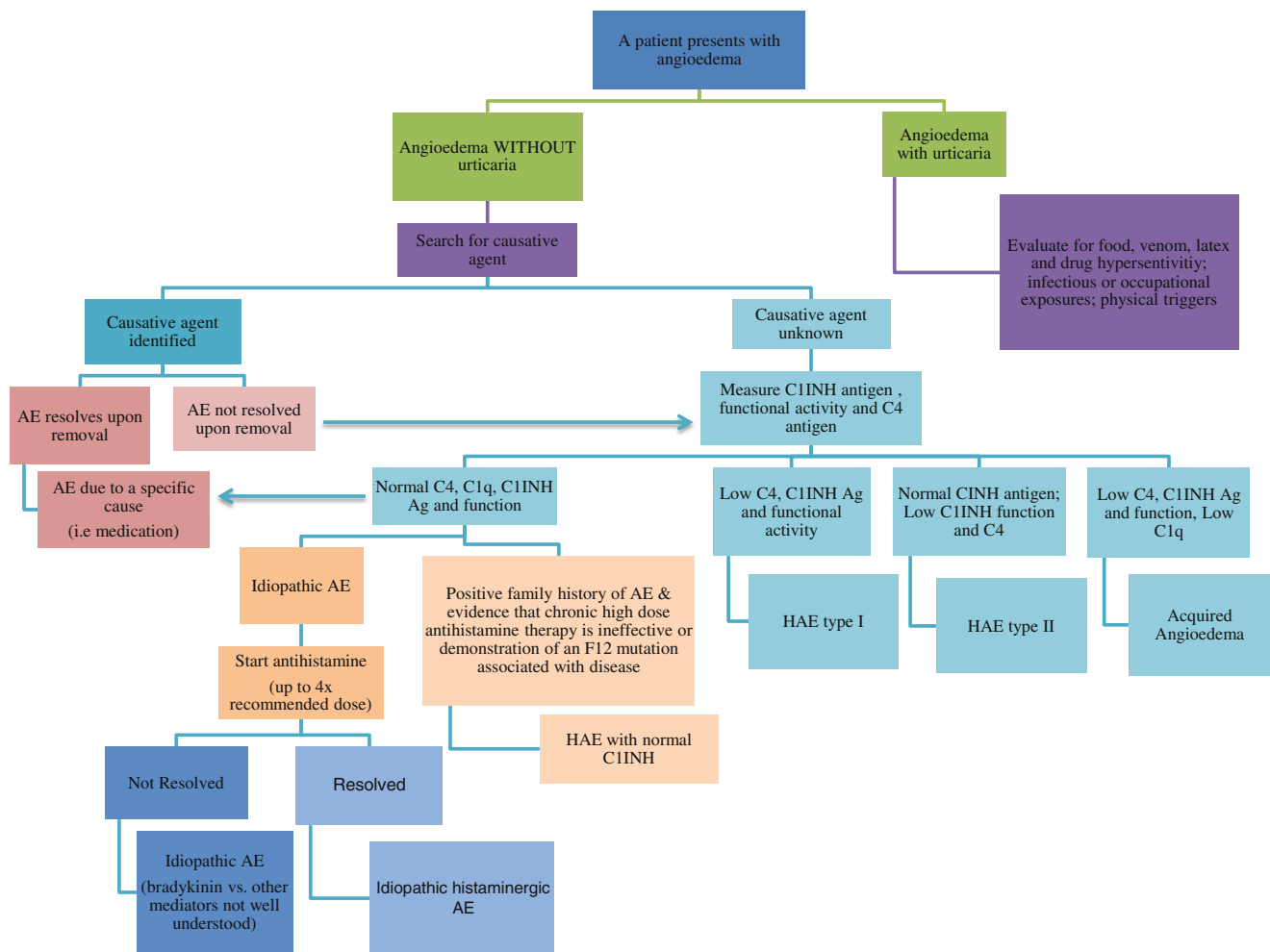


Fig. 1 Diagnostic approach to a patient with angioedema. AE, angioedema; HAE, hereditary angioedema; C1INH, C1esterase inhibitor (adapted from Zingale et al. [6])

of cases of HAE type I/II can occur from de novo mutations [5]. Urticaria is a histaminergic response, and thus, if urticaria is associated with angioedema, complement studies are not indicated. If urticaria is present, diagnostic testing should be limited and based on the patient's specific complaints. If patients have recurrent angioedema without concomitant urticaria or pruritis, they should be evaluated for hereditary forms of angioedema, acquired angioedema, drug-induced angioedema, and idiopathic angioedema. Complement levels (C4), C1 inhibitor protein and function, and C1q antibodies should be checked. If all of these values are normal, then hereditary angioedema with normal C1 inhibitor, drug-induced angioedema, and idiopathic angioedema moves to the forefront of diagnosis. Allergic angioedema can also have normal laboratory values as mentioned above; however, it usually occurs with concomitant urticaria and will not be discussed in detail in this review article. Lastly, idiopathic angioedema is a diagnosis of exclusion and should be considered after a thorough evaluation has been performed.

Differential Diagnosis of Angioedema

When approaching angioedema, the differential diagnosis is broad and should be initially differentiated by laboratory values (see Table 1). Venom hypersensitivity, aeroallergens, food, and drug and latex allergy cause swelling via an IgE-mediated mast cell degranulation and are often accompanied by itching or hives. In these cases, specific IgE antibodies to the individual implicated allergens will be positive [6, 7]. Non-allergic angioedema in which mast cells are indirectly stimulated to release their pro-inflammatory mediators include chronic autoimmune urticaria and angioedema, medication-induced (e.g., opiates, radiocontrast media) and physical urticaria/angioedema, and exercise-induced anaphylaxis [7]. Patients with chronic autoimmune urticaria may or may not have abnormal laboratory values.

Patients with bradykinin-mediated angioedema fall into a few major forms: hereditary angioedema (type I/II), HAE with

Table 1 Laboratory parameters in angioedema subtypes

Angioedema subtype	Abnormal laboratory values
Type I HAE	C4: ↓ C1INH (quant/func): ↓ C1q: nml
Type 2 HAE	C4: ↓ C1INH protein: nml C1INH func: ↓ C1q: nml
HAE with normal C1INH	C4; C1INH (quant/func): nml
Gleich's syndrome and NEAE	%eos: ↑; C4; C1INH (quant/func): nml
Allergic	C4; C1INH (quant/func): nml
AAE type I and II	C4: ↓ C1INH (quant/func): ↓ C1q: ↓
Drug-induced	C4; C1INH (quant/func): nml
Idiopathic	C4; C1INH (quant/func): nml
Idiopathic capillary leak syndrome (Clarkson syndrome)	CK: ↑; albumin: ↓; IgM: ↑ C4, C1INH (quant/func): nml

C1INH, C1 inhibitor; *HAE*, hereditary angioedema; *quant*, quantitative; *func*, functional; *NEAE*, non-episodic angioedema with eosinophilia

normal C1INH, acquired angioedema, ACE-inhibitor-induced (ACEI) angioedema, and idiopathic angioedema. Patients with HAE type I will have a decrease in C1INH protein (quantitative and functional). In HAE type II, patients will have a normal C1INH protein level but a low functional activity. In both HAE type I and II, complement C4 levels will be low [8•]. Acquired angioedema is a result of the rapid consumption of C1 inhibitor and/or loss of inhibition of the complement cascade. There are two described subtypes: types I and II. Type I is typically associated with paraneoplastic processes or lymphoproliferative disease, whereas type II is secondary to autoimmune mechanisms [9]. Patients with acquired angioedema have a marked reduction in C4, C1q, and C1INH proteins and/or function. Abnormal laboratory values in the complement system are not usually seen with ACEI angioedema [10]. Lastly, HAE with normal C1INH, idiopathic angioedema, and episodic (Gleich's syndrome) and non-episodic angioedema with eosinophilia (EAE and NEAE, respectively) are rare forms of angioedema with an unclear pathophysiologic mechanism. Both HAE with normal C1INH and idiopathic angioedema will have normal laboratory values. A very rare disease, idiopathic capillary leak syndrome (Clarkson syndrome), will frequently have elevated

creatinine kinase levels, decreased serum albumin levels and a monoclonal gammopathy [11, 12].

Thus, although there are many different types of angioedema, only a small subset lack concomitant urticaria and have normal laboratory parameters. These forms, HAE with normal C1INH, medication-induced angioedema, and idiopathic angioedema will be discussed in greater detail in the remainder of the review.

Angioedema with Normal Laboratory Parameters

HAE with Normal C1INH

A new form of hereditary angioedema with normal C1 inhibitor levels was described in 2000 by Binkley and Bork [13, 14]. A landmark consensus report published in 2012 established guidelines for the nomenclature, diagnostic criteria, unique clinical features, pathophysiology, and therapeutics of this relatively new disease entity [15•]. We will focus on these aforementioned areas and discuss how they compare to other forms of angioedema with normal laboratory parameters.

Nomenclature

Several different names have been used to describe the familial form of hereditary angioedema with normal C1 inhibitor levels leading to misunderstanding and frustration among physicians and patients. A multitude of names have been used to characterize this condition, including type III HAE, estrogen-dependent HAE, HAE with normal C1 inhibitor, and new HAE among others. The consensus report identified the need for standardization in terminology and concluded the name of this disease to be termed “HAE with normal C1INH” [15••]. Standardizing the name of this condition will help physicians and patients to communicate about this disease and to develop targeted therapeutic strategies.

Clinical Features

Subtle but significant differences in the symptomatology, patient demographics and genetic penetrance can help differentiate HAE with abnormal laboratory values from HAE with normal C1 inhibitor. The location of swelling attacks can help distinguish between these two conditions. For example, those with HAE with normal C1INH do not often experience multiorgan attacks, whereas these are commonly seen in those with C1INH antigen deficiency [16]. Moreover, in patients with HAE type I/II, abdominal swelling is almost ubiquitous, while only 50 % of patients with HAE with normal C1INH will describe this type of swelling [16]. Those with HAE with normal C1INH are more likely to be female and develop symptoms in their 3rd decade. Patients with HAE type I/II tend to develop onset of symptoms earlier, in their 1st or 2nd decade, and males and females are equally affected. Table 2 summarizes the clinical features that help distinguish HAE with normal C1 inhibitor from HAE due to C1 inhibitor deficiency. Lastly, those with HAE with normal C1 inhibitor do not experience a prodromal erythema marginatum

prior to onset of symptoms as seen in HAE type I and II, and the disease-free interval can be considerable [16].

Pathophysiology

Factor12 Mutation Over the past 7 years, two primary mutations have been found in protein factor 12 (FXII) in those with HAE with normal C1INH. Both occur at the proline-rich region of FXII. The production of bradykinin is modulated by this important protease. Current literature suggests that the inheritance pattern is autosomal dominant with incomplete penetrance as studies have shown asymptomatic individuals who were heterozygous for the mutation [17]. Although a significant discovery concerning the genetic basis of HAE with normal C1INH, these mutations are exceedingly rare in the US patient population. Most of the mutations have been seen in the European cohort of patients with up to 25 % occurring in European patients with HAE with normal C1INH [17]. To date, no differences in clinical presentation exist between those with HAE with normal C1INH with this mutation and those without this mutation.

Estrogen Effect Overall the impact of female sex hormones, namely estrogen, has had a variable effect on disease activity in HAE with normal C1INH [13, 14, 18–20]. Originally, Binkley and Davis [13] reported a family of women that only swelled during states of increased estrogen exposure. In contrast, Bork et al. [14] reported that estrogen worsened swelling attacks in women but swelling still occurred when estrogen levels were not elevated. More recently, estrogens have not been shown to have an impact on many women with reported HAE with normal C1INH [21–23]. Pregnancy can have a variable effect on disease severity in HAE with normal C1INH [18, 20, 24–30]. Steady-state levels of C1INH decrease during pregnancy, even in normal women [18]. Therefore, it is not surprising that some women with HAE with normal C1INH experience an increase in the number of angioedema attacks

Table 2 Clinical characteristics of HAE with normal C1INH versus HAE type I/II

Clinical characteristics	HAE with normal C1INH	HAE type I/II
Gender	Females affected more than males	Males and females affected equally
Location of attacks	50 % experience abdominal attacks Face, tongue: common	Abdominal attacks: vast majority Face: occasional Tongue: uncommon
Prodromal erythema marginatum	Not seen	Common
Attacks affecting multiple organs	Uncommon	Common
Interval between attacks	May be high	Typically short (2–3 days)
Symptom onset (average)	26.8±14.9 years	11.7±7.7 years

C1INH, C1 inhibitor; HAE, hereditary angioedema (adapted from Zuraw et al. [15••])

during gestation [30, 31]. Shortly after delivery, the functional activity of C1 inhibitor returns to baseline.

Both murine and human studies have demonstrated that estrogen increases quantitative and functional levels of factor XII [32–36]. In 1985, Gordon et al. observed increased functional activity and protein levels of factor XII in rats treated with estrogen [35]. Later, in 1991, Ratnoff showed enhanced expression of factor XII in estrogen and prolactin treated rats [36]. Subsequently, studies have demonstrated increased levels of factor XII in the plasma of women treated with exogenous estrogens [32, 34].

Diagnostic Criteria of HAE with Normal C1INH Despite the recent advances in our current understanding of HAE, the diagnosis of HAE with normal C1INH remains difficult. However, during the consensus of an international expert panel on HAE in 2012, Zuraw et al. [15•] outlined specific diagnostic criteria to overcome the challenges of proper diagnosis. Patients should be classified as HAE with normal C1INH only if they meet certain well-defined criteria. First, they must have a history of recurrent angioedema without urticaria or a medication known to cause angioedema. Second, there should be a documented normal or near normal C1INH antigen, function, and complement C4 level. Given the potential for laboratory error when testing for C1INH function and C4 level in the US, it may be necessary to repeat the functional assay and C4 level testing during an angioedema attack to confirm accuracy [37]. Lastly, one should have either a positive family history of angioedema and evidence that chronic high-dose antihistamine therapy is ineffective or demonstration of an F12 mutation that is associated with disease. This last statement is important because HAE with normal C1INH is often misdiagnosed as idiopathic angioedema.

Drug-Induced Angioedema Angioedema is a well-known side effect of a number of medications, particularly ACEI. Therefore, it is critical to obtain a detailed medication history of any patient presenting with angioedema, especially those with normal laboratory parameters (C4, C1 inhibitor function, antigen, and C1q). Investigation into prescription and over-the-counter medications as well as herbal remedies should be obtained as they can all lead to angioedema. Although ACE-inhibitors are well known to cause angioedema, other medications reported to cause swelling include non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin II receptor antagonists, antibiotics, radiocontrast media, proton pump inhibitors, statins, fibrinolytic agents, estrogens, diuretics, calcium channel blockers, beta-blockers, and psychotropic drugs [38]. Drug-induced angioedema can present as swelling alone or concomitantly with urticaria. Over the past 30 years since their introduction, ACEIs have been widely implicated in their ability to cause angioedema. Swelling occurs in about 0.1–2.2 % of patients taking ACEI and can occur at any time from starting the

medication [39–41] with the highest incidence of swelling during the first month of therapy [42]. In a study conducted by Banerji et al. [43], facial swelling, shortness of breath, lip swelling, tongue swelling, and laryngeal edema were the most common presenting signs of ACEI angioedema, though abdominal, peripheral, and urogenital swelling has also been reported [44–46]. Recently, sitagliptin, a dipeptidyl peptidase-IV (DPP-IV) inhibitor, has been reported to cause angioedema [47–49]. DPP-IV inhibitors cause increased vascular permeability and swelling by decreasing the breakdown of inflammatory mediators, such as substance P. In a meta-analysis of phase III trials, there was an increased risk of angioedema in those patients taking an ACEI concurrently with vildagliptin. However, the authors found that there was no association between vildagliptin use alone and angioedema [48]. Therefore, it seems that DPP-IV inhibitors increase the risk of angioedema when taken with ACE-inhibitors and should be considered in the differential of drug-induced angioedema.

Idiopathic Angioedema Without Urticaria Idiopathic angioedema is defined as three or more episodes of swelling in a period of 6–12 months without a clear etiology after a thorough evaluation [50]. To date, the frequency of this type of angioedema is unclear as epidemiologic studies are lacking. In patients presenting with recurrent swelling without urticaria, it is important to evaluate for acquired and hereditary angioedema by checking a complete blood count with differential, C4, C1 esterase inhibitor (quantitative and functional studies), and C1q [1]. It is paramount to rule out all of the known causative entities of angioedema before labeling a patient as having idiopathic angioedema. Treatment of idiopathic angioedema is largely empiric and often based on control of clinical symptoms rather than targeting specific pathological mechanisms.

Treatment/Therapeutics

HAE with Normal C1INH Our current knowledge about treatment for HAE with normal C1INH is based on anecdotal data and observational studies. To date, there are no randomized controlled clinical trials for treatment of this condition. Icatibant®, adrenalin, corticosteroids, C1 inhibitor, Kalbitor®, and antihistamines have all been used for the treatment of acute attacks of hereditary angioedema with normal C1INH with varying efficacy [14, 31, 51–53]. Icatibant was recently shown to be effective for acute swelling episodes in three patients with HAE with normal C1INH in Europe. In those patients, it took about 1–2 h for symptoms to abate [54]. Another study from the same year found that six of seven patients treated with C1-INH concentrate (Berinert®, CSL Behring, Inc., Marburg, Germany) had a resolution of an acute attack [51]. Unanimously, corticosteroids, adrenalin, or antihistamines in varying dosages for treatment of acute attacks of HAE with normal C1INH were ineffective [13, 14, 51, 55]. A

significant reduction in swelling attacks has been shown with prophylactic treatment with danazol, progesterone, and/or tranexamic acid. Two recent case reports showed that danazol, at doses ranging from 100 to 600 mg daily, could induce remission in three separate patients with HAE with normal C1INH. One patient was able to titrate the dose over several weeks to 50 mg twice a week and remained symptom free for 2 years at the time of the publication [51, 55]. Similar results have been shown in a small number of case reports using tranexamic acid as prophylactic treatment. Similar to the effect seen in HAE due to C1 INH deficiency, progesterone has shown promise in the role of a long-term prophylaxis agent in HAE with normal C1INH. In a combined retrospective and prospective analysis of thirty-five patients with HAE with normal C1INH by Bork et al. [51], 8/35 (23 %) women were symptom free while taking exogenous progesterone for a range of 1 to 6 years, 27 years in total. Additionally, in a case series by Bork et al., one woman had resolution of symptoms and was symptom free after switching from an estrogen-containing pill (ethinylestradiol and levonorgestrel) to a progesterone-only-containing pill (desogestrel) [22]. Overall, studies are demonstrating that danazol, progesterone, and tranexamic acid are effective prophylaxis agents in HAE with normal C1INH, whereas corticosteroids, adrenalin, and antihistamines are ineffective treatment or prophylactic agents. However, current literature on treatment and prophylaxis in HAE with normal C1 inhibitor should be interpreted with caution given the lack of randomized controlled trials comparing the efficacy of currently available medications.

Drug-Induced Angioedema The first step in the treatment of drug-induced angioedema is to discontinue the implicated agent. Treatment with antihistamines, corticosteroids, and epinephrine are generally not helpful for ACEI-induced angioedema, although they are often administered in the emergency room and inpatient setting. Angiotensin II receptor blockers (ARBs) may be an alternative class of medications in patients who have experienced ACE-I-induced angioedema, although some patients (<10 %) will develop angioedema after ARB intake. Therefore, ARBs may be reserved for patients with high therapeutic need for angiotensin inhibition [10]. This stance has been widely adopted by both the National Kidney Foundation and the ACC/AHA guidelines [56, 57]. Recurrent chronic angioedema may occur after discontinuation of an ACEI. In a large European retrospective study by Beltrami et al. [58], 46 % of patients had a recurrence of swelling, and of those, a vast majority developed swelling within the first month after discontinuation of ACEI.

Idiopathic Angioedema

The treatment of idiopathic angioedema is similar to that of chronic urticaria. Daily second-generation H-1 anti-histamines

(e.g., fexofenadine, desloratadine, loratadine, cetirizine) should be initiated as prophylactic treatment. Patients should be reevaluated after 4 weeks, and dosing should be increased appropriately to prevent recurrent swelling. First-generation sedating antihistamines, H2 receptor blockers, and leukotriene receptor antagonists can be added if symptoms are not controlled with H1 antihistamines at four times the recommended dose [59]. Oral corticosteroids can be used for treatment of acute attacks unresponsive to antihistamines but their use for long-term therapy should be limited secondary to their side effect profile. Improvement with an adequate dose of antihistamines/leukotriene antagonists suggests a histamine-mediated pathophysiology. Patients with bradykinin-mediated angioedema typically do not respond to short- or long-acting antihistamines or corticosteroids and respond minimally to epinephrine. A successful trial of purified C1INH, ecallantide, icatibant, danazol, or tranexamic acid would also support a bradykinin-mediated mechanism of disease. However, the cost, acquisition, and method of delivery make this trial challenging in clinical practice.

Conclusions

Angioedema can represent a diagnostic challenge to physicians. A thorough evaluation to look for known causes of angioedema is essential. When complement levels and serum studies are unrevealing, it is necessary to assess for factors in the history that will help delineate an underlying diagnosis. If a family history of swelling is notable and no medications are implicated, HAE with normal C1INH should be considered, and the diagnosis should be confirmed by the guidelines outlined in the international consensus article by Zuraw et al. In those patients with a diagnosis of idiopathic angioedema, a systematic approach to treatment is warranted as previously outlined in this article. Anecdotal, off-label use of various medications has been used with varying success in the treatment of this disease. However, since the efficacy of these therapies has not been validated by randomized, placebo-controlled trials, use of these medications cannot be recommended as standard of care therapy. Novel diagnostic tools are needed to uncover the mechanism of idiopathic swelling and to better direct treatment modalities.

Compliance with Ethics Guidelines

Conflict of Interest Mark Davis-Lorton is on the speaker's bureau for and has served as a primary investigator for clinical trials sponsored by Dyax Corp. and Viropharma Inc.

Janelle Sher declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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