



Letter

Characterization of idiopathic angioedema in a university-based allergy/immunology practice

Angioedema without urticaria is a disease with multiple phenotypes, of which several have been studied during the last few decades, notably the types of hereditary angioedema.¹ However, a sizeable portion of patients with angioedema cannot be easily placed into existing categories because often no trigger is identifiable. These patients are classified as having idiopathic angioedema. The prevalence of angioedema without urticaria was first reported in a cohort of 776 patients from 1993 to 2003.² In this cohort, 41% were found to have idiopathic angioedema, with 81% of these patients deemed to be histaminergic given their clinical response to antihistamines. Response to antihistamine therapy contrasts strongly with other forms of bradykinin-mediated processes, such as hereditary or angiotensin-converting enzyme inhibitor–related disease, but bears a striking similarity with chronic spontaneous urticaria (CSU). Our aim was to identify a cohort limited to patients with idiopathic angioedema to further elucidate natural history and response to treatment. We hypothesized that if these factors were similar to those of CSU, perhaps isolated idiopathic angioedema could be managed under similar guidelines.

In an institutional review board–approved protocol, the University of Wisconsin School of Medicine and Public Health electronic medical record (EMR) was accessed to identify patients who received an *International Classification of Diseases, Ninth Revision* code of angioneurotic edema without a concomitant code for urticaria or chronic urticaria during a 5-year period (2009–2014) and were seen at least once by a practitioner at 1 of 2 university-based allergy clinics in Madison, Wisconsin. A total of 250 patients were initially identified, and relevant EMRs were accessed, including allergist and primary care physician notes as well as laboratory results. We excluded those who had an alternative diagnosis to angioedema or a clearly identifiable cause (angiotensin-converting enzyme inhibitor, acquired, hereditary, allergic disease). In addition to historical data, captured diagnostic testing included C4, C1 inhibitor studies, C1q, tryptase, erythrocyte sedimentation rate, and C-reactive protein. A total of 157 of the 250 patients (63%) identified were included in our cohort of idiopathic angioedema. Data were collected with respect to the duration and frequency of symptoms, anatomical location of episodes, and medications administered. A subset of patients with recurrent symptoms started on a long-acting daily histamine₁ (H₁)–antihistamine at the time of initial allergy clinic evaluation were specifically identified. Of 68 patients with recurrent angioedema, 47 had follow-up data (with an allergist or primary care physician). Angioedema was classified as histaminergic if there was an

absolute decrease in frequency of episodes from initial evaluation to date of last contact. Statistical analyses were performed as categorical comparisons using the χ^2 test (SigmaPlot 13.0, Systat, Chicago, Illinois).

At the initial allergy appointment, 22 patients (14%) had only a single documented episode, whereas an equal number had recurrent episodes that lasted less than a year. A total of 87 patients (55%) had recurrent episodes ongoing for more than a year. A total of 88 patients (57%) reported no current symptoms as of most recent documentation. A total of 48 patients (31%) were lost to follow-up. There were equal numbers of patients (6%) who continued to have yearly or greater than yearly symptoms. The most common site affected was the face, which was seen in 117 patients (75%), whereas 90 (57%) had involvement of the oral cavity. Less commonly affected sites included the limbs (17%) and abdomen (3%).

A total of 68 of the 87 patients with recurrent angioedema were prescribed long-acting H₁-antihistamine controller therapy, but 21 patients were lost to follow-up. Mean follow-up was 4.06 years, and median follow-up was 3.81 years (range, 0–13.8 years). Frequency of episodes at baseline and last known follow-up visit for the 47 patients is shown in Figure 1. Of these 47 patients, 91% had a decrease in frequency of symptoms ($P < .001$). Only 4 patients (9%) reported no decrease in the frequency of episodes and were deemed nonhistaminergic.

One of the striking features of the natural history of idiopathic angioedema was the trend toward cessation of symptoms despite a significant frequency of episodes on initial evaluation. This finding suggests that idiopathic angioedema is self-limited and spontaneously resolves or that medication management significantly improves symptoms. The predominance of facial and oral involvement in our cohort is similar to what is typically observed in angiotensin-converting enzyme inhibitor–induced disease.^{3,4} On the other hand, the low prevalence of gastrointestinal symptoms (only 3%) in our cohort contrasts strongly with what is typically seen with hereditary angioedema attacks.^{5–7}

Ninety-one percent of patients with recurrent angioedema prescribed long-acting H₁-antihistamines were found to have a statistically significant decrease in the frequency of episodes, suggesting a histaminergic disease process. This percentage is similar to what has been seen previously with respect to idiopathic angioedema.² The response rate to H₁-blocker controller therapy is also similar to that observed in CSU, which has often been characterized as a similar disease, with the distinction being noted in the layer of dermis that is affected. All the above findings have led to the notion that angioedema may merely be a form of urticaria and could be treated with current CSU guidelines.⁸ Furthermore, perhaps omalizumab may provide similar benefits in refractory

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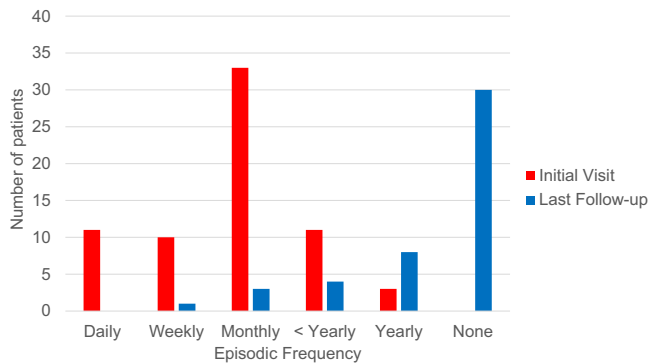


Figure 1. Change in frequency of angioedema episodes. The frequency of angioedema episodes at baseline was compared with the frequency at last contact with a health care professional. The number of patients with corresponding angioedema episode frequencies at the initial visit and last follow-up visit are shown in categories of daily, weekly, greater than once per year, yearly or less, and none.

idiopathic angioedema, although data showing improvement are currently limited to smaller case series.⁹

The main limitation of our study was the retrospective nature of EMR analysis. There was no previously existing protocol to rule out alternative causes, necessitating some subjectivity in inclusion criteria for patients. Assessing response to treatment was challenging because of missing follow-up data and lack of objective measures, such as an Angioedema Activity Score.¹⁰ Dosing of the antihistamines over time was not consistently reported in clinical notes and therefore had to be captured as a categorical yes or no.

Idiopathic angioedema tends to be a persistent and often severe disease that mainly affects the face and oral cavity. However, a significant proportion of these patients may ultimately experience cessation of symptoms in the span of months to years, and most have histaminergic disease that responds to long-acting

H₁-antihistamine therapy. Overall, idiopathic histaminergic angioedema may be categorized as a form of urticaria with a similar natural course and medication response pattern.

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