

anaphylactic reactions without seeing systemic reactions. The validated chlorhexidine nonirritating concentration is 5 mg/mL; therefore, it is highly unlikely that inferior concentrations pose a potential risk for anaphylaxis. In vitro test (IgE determinations and BATs) results were all positive, revealing the usefulness of these tools to obtain an accurate diagnosis, as previously described.^{5,6} The BAT in both patients was performed under 2 different conditions to determine the optimal basophile activation concentration for each sample. There is lack of a dose response in the BATs done in case 2. In our opinion, with the lowest pharmaceutical concentration, you can see basophile activation. On the contrary, with the highest concentration, you can see cytotoxic effects or unspecific basophile activations, causing technical interpretation problems. The elevated serum tryptase level in our patients was indicative of mast cell degranulation during the episode.

True incidence of chlorhexidine allergy is unknown because chlorhexidine is an underestimated antigen of anaphylactic reactions. Although rarely described, it can also appear in children. Increased awareness of the risk of this widely used antiseptic is needed, especially at all emergency departments, perioperative environments, and intensive care units.

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References

- [1] Calogiuri GF, Di Leo E, Trautmann A, et al. Chlorhexidine hypersensitivity: a critical and updated review. *J Allergy Ther.* 2013;14:141.
- [2] Silvestri DL, McEnery-Stonelake M. Chlorhexidine: uses and adverse reactions. *Dermatitis.* 2013;24:112–118.
- [3] Nishioka K. Histamine release in contact urticaria. *Contact Dermatitis.* 1984;11:191.
- [4] Ferrarini A, Baggi M, Flückiger R, Bianchetti MG. Intraoperative anaphylaxis to a chlorhexidine polymer in childhood. *Paediatr Anaesth.* 2006;16:705.
- [5] Opstrup MS, Malling HJ, Kroigaard M, et al. Standardized testing with chlorhexidine in perioperative allergy: a large single-centre evaluation. *Allergy.* 2014;69:1390–1396.
- [6] Ebo DG, Bridts CH, Stevens WJ. IgE-mediated anaphylaxis to chlorhexidine: diagnostic possibilities. *Contact Dermatitis.* 2006;55:301–302.
- [7] Brockow K, Garvey LH, Aberer W, et al; ENDA/EAACI Drug Allergy Interest Group. Skin test concentrations for systemically administered drugs: an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy.* 2013;68:702–712.
- [8] Hoffmann HJ, Santos AF, Mayorga C, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. *Allergy.* 2015;70:1393–1405.
- [9] Antunes J, Kochuyt AM, Ceuppens JL. Perioperative allergic reactions: experience in a Flemish referral centre. *Allergol Immunopathol.* 2014;42:348–354.
- [10] Aalto-Korte K, Mäkinen-Kiljunen S. Symptoms of immediate chlorhexidine hypersensitivity in patients with a positive prick test. *Contact Dermatitis.* 2006;55:173–177.

Manifestations of hereditary angioedema



Hereditary angioedema (HAE) is characterized by sudden edema of the larynx, lips, oropharynx, periorbital tissues, abdomen, or limbs.¹ Episodes of severe headaches and visual disturbances are also commonly seen in patients with HAE. Symptoms usually resolve within minutes to hours. Neurologic manifestations of HAE are more rare, but there have been case reports in the literature involving cerebral edema^{2,3} and stroke-like episodes.⁴ Local cerebral edema has been implicated in transient ischemic attacks (TIAs); although the mechanism is not well delineated, rapid onset of edema might temporarily reduce blood flow in certain blood vessels, leading to TIA symptoms, which resolve as the edema resolves.

We report the cases of 3 patients who have been diagnosed with HAE type 1 and who have neurologic manifestations of this disorder (Table 1). Patient 1 is a 27-year-old white woman who was diagnosed with HAE type 1 at 26 years of age. Her symptoms included swelling of the limbs and abdomen, severe fatigue, chronic migraine, dizziness and poor balance, recurrent episodes of cognitive problems, and severe bouts of opsoclonus and myoclonus. The latter resulted in blurry vision and, on some occasions, double vision and involuntary twitches of the muscles of her shoulders, arms, and sometimes legs. These symptoms were having a markedly detrimental effect on the patient's quality of life as she was attending medical school and facing enormous challenges because of the symptoms mentioned above. Brain magnetic resonance imaging (MRI) was performed in November 2010, but the results were essentially normal. On the basis of her clinical presentation and neuroimmune markers, she was initially treated

with intravenous immunoglobulin (IVIG; 380 mg/kg every 2 weeks) for the symptoms of opsoclonus and myoclonus and had some improvement. She also received 2 doses of intravenous rituxan (1 g, with the same dose repeated after 4 months) and again had some mild improvement in her symptoms. However, the patient had the most improvement after she was prescribed an C1-esterase inhibitor (human) (Berinert), with 500 U administered intravenously twice weekly. After 4 C1-esterase inhibitor infusions, the patient's symptoms of edema, recurrent migraines, severe fatigue, vision, and balance problems resolved almost completely and did not recur for the last 5 months she was undergoing treatment. She has reported a marked improvement in her overall quality of life and has been able to continue her studies in medical school.

Patient 2 was diagnosed with HAE type 1 at 48 years of age, but the patient reported that her attacks had been ongoing intermittently for years, with continued swelling of her face, abdomen, knees, and elbows, resulting in extreme discomfort and affecting her ability to work and her quality of life. Further symptoms included red painful rashes, severe migraine headaches, hearing loss, tinnitus, and dizziness, as well as nausea and vomiting. These symptoms did not respond to steroids, antihistamines, IVIG infusions, or omalizumab and had resulted in visits to numerous medical specialists and numerous emergency department visits with no improvement. In January 2014, the patient applied for disability because she was unable to work, illustrating how severe and pervasive her symptoms were. The patient underwent brain MRI on 2 separate occasions, but the imaging only revealed minimal white matter changes in the frontal lobes of dubious clinical significance. She was evaluated for HAE based on her abdominal

Table 1
Characteristics of Patients With HAE Type 1

Patient No.	Age, y	Sex	C1-INH function	C1-INH serum	Neurologic symptoms	HAE symptoms	Treatment
1	27	F	28	11	Oposclonus, muscle twitch, poor balance	Swelling of the limbs and abdomen, severe migraine	Started with C1-esterase inhibitor (Berinert), 500 U twice daily, and moved to C1-esterase inhibitor (Cinryze), 1,000 U twice a week, icatibant (Firazyr) as needed
2	48	F	10	14	Hearing loss, tinnitus, and dizziness	Swelling of face and abdomen, severe migraine	C1-esterase inhibitor (Cinryze), 1,000 U twice weekly, and icatibant (Firazyr) as needed
3	38	F	38	16	Motor and sensory deficit of her left side, TIA-like presentation	Facial and laryngeal swelling, abdominal swelling	C1-esterase inhibitor (Cinryze), 1,000 U twice weekly, and icatibant (Firazyr) as needed

Abbreviations: C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; TIA, transient ischemic attack.

and facial swelling and migraines. The patient was then treated with C1-esterase inhibitor (human) (Cinryze), 1,000 units twice a week, and experienced almost immediate relief of some of her symptoms, with the severity and intensity of HAE flares decreasing and a marked improvement in the frequency and severity of migraines. The patient also reported a marked improvement in her overall quality of life and in her ability to function on a day to day basis.

Patient 3 is a 38-year-old white woman who was diagnosed with HAE type 1. Her symptoms consisted of facial, laryngeal, abdominal, and limb swelling, which would occur at random and would last several hours before resolving. Symptoms were unresponsive to steroids and antihistamines. The patient also experienced recurrent episodes in which she experienced sudden development of muscle weakness on one side of the body, with motor and sensory deficits, resulting in an inability to move her arm or leg and with severe numbness over the limbs on one side of the body. Symptoms closely resembled those of a TIA and were strokelike; however, MRI and computed tomography of the head performed shortly after these episodes did not reveal any pathologic findings, and the results were essentially normal. The patient also experienced recurrent and frequent severe migraine headaches, which were unresponsive to medications, such as ibuprofen, acetaminophen, propranolol, and eletriptan hydrobromide. The patient had a concomitant diagnosis of primary immune deficiency and was being treated with IVIG (533 mg/kg every 3 weeks), which was effective in reducing recurrent upper respiratory tract infections attributable to the underlying immune deficiency but was not effective against the angioedema manifestations. The patient was treated with C1-esterase inhibitor, 500 U intravenously twice a week for 3 months, and during this period experienced almost complete relief of her angioedema symptoms, including a marked improvement in the frequency and severity of her migraines.

This was the first time that she had experienced some relief from migraines. The patient also had no motor or sensory neurological deficits while she was being treated with the C1-esterase inhibitor. This patient had to relocate because of family reasons, and so close monitoring of her outcomes is no longer possible.

It is well known that patients with HAE have a propensity to develop autoimmune disease.⁵ The 3 cases reported here illustrate some of the important neurologic symptoms that can occur with hereditary angioedema. We believe that angioedema is often not recognized as the cause of several neurologic signs and symptoms, and we think it is important to bring our findings to the attention of the medical community.

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References

- [1] Cugno M, Zanichelli A, Foiemi F, Caccia S, Cicardi M. C-1 inhibitor deficiency and angioedema: a molecular mechanisms and clinical progress. *Trends Mol Med*. 2009;15:69–78.
- [2] Hoxha M, Meta D, Kalo T. Hereditary angioedema as a potential cause of cerebral edema. *Otorhinolaryngologia*. 2013;51:31–34.
- [3] Sunder TR, Balsam MJ, Vengrow MI. Neurological manifestation of angioedema: report of two cases and review of the literature. *JAMA*. 1982;247:2005–2007.
- [4] Bonnaud I, Rouaud V, Guyot M, et al. Exceptional stroke-like episodes in a patient with type 1 autosomal angioedema. *Neurology*. 2012;78:598.
- [5] Nielsen EW, Gran JJ, Straume B, et al. Hereditary angioedema: new clinical observations and autoimmune screening, complement, and kallikrein-kinin analyses. *J Intern Med*. 1996;230:11–130.

Eosinophilic esophagitis as possible complication of aspirin treatment in patient with aspirin-exacerbated respiratory disease



A 44-year-old African American woman with severe, persistent asthma and chronic rhinosinusitis with nasal polyposis due to aspirin-exacerbated respiratory disease (AERD) and allergic rhinoconjunctivitis presented to an outpatient allergy clinic with

chief symptoms of epigastric pain and dysphagia while taking aspirin for AERD. The patient was diagnosed with asthma and rhinosinusitis at 31 and 34 years of age, respectively. She initially had symptoms compatible with AERD at 38 years of age when she first reacted to ibuprofen and was diagnosed with sinonasal polyposis. AERD diagnosis was confirmed 3 years later with a positive challenge result to aspirin. She continued aspirin treatment, 650 mg twice daily, for 3 years. She had remarkable clinical improvement in rhinitis and asthma symptoms; her forced expired volume

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Disclosures: Authors have nothing to disclose.