

TABLE I. Proposal of classification for vibratory urticaria/angioedema

Types	Subtypes	Pathogenesis	Clinical course	Clinical features
Hereditary vibratory urticaria/angioedema	Hereditary vibratory angioedema (Patterson type ²)	Hereditary (autosomal dominant): unknown mutation(s)	Chronic	Angioedema (hours)
	Hereditary vibratory urticaria (Boyden type ³⁻⁵)	Hereditary (autosomal dominant): ADGRE2 mutations (Lebanese families)	Chronic	Hives (<1 h)
Acquired vibratory urticaria/angioedema	Acquired vibratory angioedema	Idiopathic	Chronic	Angioedema (hours)
	Secondary acquired vibratory urticaria ^{6,7}	Self-limited and triggered by an identifiable cause (infection, <i>Hymenoptera</i> sting)	Acute/subacute (symptoms triggered by vibratory stimuli last until the primary condition is resolved)	Hives (<1 h)/anaphylaxis

from quality-of-life impairment, had ever consulted a physician, or required any treatments. In our opinion, further studies are needed to determine whether these 35 individuals truly correspond to pathological cases of acquired vibratory angioedema or rather exacerbated physiological responses to vibratory stimuli.

We agree with our colleagues that vibratory urticaria/angioedema should be correctly diagnosed, and we encourage others to share their experience in the published literature.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication January 25, 2021; accepted for publication February 9, 2021.

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REFERENCES

- Kulthanan K, Ungprasert P, Tapechum S, Rujitharanawong C, Kiratiwongwan R, Munprom K, et al. Vibratory angioedema subgroups, features, and treatment: results of a systematic review. *J Allergy Clin Immunol Pract* 2021;9:971-84.
- Patterson R, Mellies CJ, Blankenship ML, Pruzanski JJ. Vibratory angioedema: a hereditary type of physical hypersensitivity. *J Allergy Clin Immunol* 1972;50:174-82.
- Boyden SE, Desai A, Cruse G, Young ML, Bolan HC, Scott LM, et al. Vibratory urticaria associated with a missense variant in ADGRE2. *N Engl J Med* 2016;374:656-63.
- Boyden SE, Metcalfe DD, Komarow HD. Vibratory urticaria and ADGRE2. *N Engl J Med* 2016;375:94-5.
- Kaplan AP, Greenberger PA, Geller M. Vibratory urticaria and ADGRE2. *N Engl J Med* 2016;375:94-5.
- Rose MH. Vibratory urticaria associated with bladder-wall infection with the yeast *Torulopsis glabrata*. *J Allergy Clin Immunol* 1989;84:408.
- Astarita C, Savoia A, De Bartolomeis F. Venom-dependent vibration-induced anaphylaxis: a new hazard following large local reactions from hymenoptera stings. *J Investig Allergol Clin Immunol* 2014;24:282-3.

- Vergara-de-la-Campa L, Gatica-Ortega ME, Pastor-Nieto MA, Molina-Figueras E, Pérez-Mesonero R, Luna-Bastante L, et al. Vibratory urticaria-angioedema: further insights into the response patterns to vortex provocation test. *J Eur Acad Dermatol Venereol* 2020;34:e699-701.

- Zhao Z, Reimann S, Wang S, Wang Y, Zuberbier T. Ordinary vibratory angioedema is not generally associated with ADGRE2 mutation. *J Allergy Clin Immunol* 2019;143:1246-8.e4.

<https://doi.org/10.1016/j.jaip.2021.02.036>

Reply to "Proposal for a new classification of vibratory urticaria/angioedema"



To The Editor:

We thank Dr. Pastor-Nieto for her interest in our recent publication of a systematic review of vibratory angioedema (VA) and proposal for its classification.^{1,2}

In line with Dr. Pastor-Nieto's suggestion to subclassify hereditary VA (HVA), we distinguish 2 HVA subgroups, that is, due to a mutation in adhesion G protein-coupled receptor E2 (ADGRE2; 24 cases) and due to unknown cause (4 cases not investigated for their underlying genetic mutation).² ADGRE2-mediated HVA manifests with transient whealing (<1 hour),^{3,4} whereas HVA patients with unknown mutation have angioedema (hours to days).⁵ This may suggest that HVA in the latter patients is not due to ADGRE2, but does not exclude this. Further analyses of these and other HVA patients are needed to understand if the described ADGRE2 mutation is the only mutation that drives HVA. Until further information becomes available, we prefer to subclassify HVA as "due to ADGRE2 mutation" and "due to unknown cause."

Acquired vibratory angioedema (AVA) can present with wheals, angioedema, or both, and disease activity ranges from mild to severe. AVA may, therefore, be subclassified by clinical phenotypes or by disease activity. Dr. Pastor-Nieto's suggestion to subclassify AVA as primary and secondary, that is, AVA without and with an underlying cause, respectively, is interesting. Two of 55 AVA patients (3.6%) had a potential cause, that is, a *Candida glabrata* urinary tract infection⁶ and a *Hymenoptera* sting.⁷ Secondary cases of cold urticaria, a form of chronic inducible urticaria (CIndU) like AVA, have been described, anecdotally, but this is not very helpful.⁸ The pathogenesis and cause(s) of CIndU

including AVA are currently unclear. Insect stings, infections, and other events or conditions that occur at the time of onset of CIndU or shortly before may be coincidental or may have triggered the development of CIndU without being responsible for its persistence. Even in cases where CIndU patients were treated for a “cause,” for example, a chronic infection, and experienced remission of their CIndU, this does not prove a causal relationship. CIndU remission may have occurred spontaneously, or the antibiotic treatment may have cured the CIndU by eradication of another infection or by off-target effects. Most suspected causes of CIndU, insect stings for example, cannot be eradicated and are, therefore, not of therapeutic relevance. A search for underlying mechanisms, in the management of patients with CIndU including AVA, does not usually benefit patients, but rather raises false hopes of a possible cure, incurs costs, may lead to ineffective treatment, and can delay appropriate treatment. We suggest to consider all cases of AVA, until we know the cause(s) of this disease, as primary.

VA is a rare form of CIndU. The global chronic urticaria registry (CURE, www.urticaria-registry.com) of the GA²LEN network of urticaria centers of reference and excellence (UCAREs, www.ga2len-ucare.com) can help to collect more cases of VA and to increase our knowledge of VA.^{9,10} Identifying and characterizing the underlying causes and pathogenesis of CIndUs including AVA is of the highest priority and may allow for the development of novel and better treatments including curative treatments. When we have more data and a clear understanding of the etiopathogenesis of VA, revising its classification may be possible and helpful.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication February 6, 2021; accepted for publication February 9, 2021.

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REFERENCES

- Pastor-Nieto MA, Gatica-Ortega ME, de-la-Campa LV, Gimenez-Arnau AM. Proposal for a new classification of vibratory urticaria/angioedema. *J Allergy Clin Immunol Pract* 2021;9:2542-3.
- Kulthanan K, Ungprasert P, Tapechum S, Rujitharanawong C, Kiratiwongwan R, Munprom K, et al. Vibratory angioedema subgroups, features, and treatment: results of a systematic review. *J Allergy Clin Immunol Pract* 2021;9:971-84.

- Boyden SE, Desai A, Cruse G, Young ML, Bolan HC, Scott LM, et al. Vibratory urticaria associated with a missense variant in ADGRE2. *N Engl J Med* 2016;374:656-63.
- Epstein PA, Kidd KK. Dermo-distortive urticaria: an autosomal dominant dermatologic disorder. *Am J Med Genet* 1981;9:307-15.
- Patterson R, Mellies CJ, Blankenship ML, Pruzansky JJ. Vibratory angioedema: a hereditary type of physical hypersensitivity. *J Allergy Clin Immunol* 1972;50:174-82.
- Rose MH. Vibratory urticaria associated with bladder-wall infection with the yeast *Torulopsis glabrata*. *J Allergy Clin Immunol* 1989;84:408.
- Astarita C, Savoia A, De Bartolomeis F. Venom-dependent vibration-induced anaphylaxis: a new hazard following large local reactions from hymenoptera stings. *J Investig Allergol Clin Immunol* 2014;24:282-3.
- Maltseva N, Borzova E, Fomina D, Bizjak M, Terhorst-Molawi D, Košnik M, et al. Cold urticaria—what we know and what we do not know. *Allergy*. 2021;76:1077-94.
- Maurer M, Metz M, Bindslev-Jensen C, Bousquet J, Canonica GW, Church MK, et al. Definition, aims, and implementation of GA2LEN Urticaria Centers of Reference and Excellence. *Allergy* 2016;71:1210-8.
- Weller K, Giménez-Arnau A, Grattan C, Asero R, Mathelier-Fusade P, Bizjak M, et al. The Chronic Urticaria Registry: rationale, methods and initial implementation. *J Eur Acad Dermatol Venereol* 2021;35:721-9.

<https://doi.org/10.1016/j.jaip.2021.02.037>

Thoracic conidiobolomycosis: Invasive or allergic?



To the Editor:

Yeoh et al¹ describe a challenging case of invasive conidiobolomycosis managed with mepolizumab. However, the index case described by the authors appears to be an allergic inflammatory response to *Conidiobolus*. A Th2 response to the fungi (elevated eosinophils and total IgE), histopathology showing eosinophil-rich inflammation, a prolonged course lasting for nearly a year, and a good response to glucocorticoids and mepolizumab suggest an allergic inflammation. Also, a lack of progression of invasive infection despite high-dose glucocorticoids and mepolizumab therapy implies otherwise.² The clinical and radiologic presentation described by the authors probably represents bronchocentric granulomatosis. However, the authors have not presented computed tomography images.

The authors rightly cite the example of allergic bronchopulmonary aspergillosis,³ wherein such presentations are previously described.⁴ *Aspergillus fumigatus* is the most extensively studied of the environmental fungi pathogenic to humans. A spectrum of manifestations can occur in humans (saprophytic colonization, allergic response, and invasive) depending on the fungal burden and the host immune response. A similar allergic reaction to fungi other than *A. fumigatus* has been well described.⁵ Although the clinical presentation and available investigations suggest an allergic response to *Conidiobolus*, the performance of skin testing or demonstration of IgE against the culture filtrate antigens of the *Conidiobolus* isolate would help in confirming the allergic nature.⁶

The distinction between allergic and invasive forms is important because high doses of glucocorticoids and immunomodulatory treatments may be harmful in the invasive variety of thoracic or disseminated conidiobolomycosis.

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