

(reviewed by Fang et al¹¹). It has been reported to have an antiviral effect against SARS-CoV-2.¹² Several reports have shown beneficial responses using inhaled NO therapy in COVID-19 patients.^{13,14} Atopic asthmatic patients have higher inducible NO synthase and exhaled NO, which correlate with sputum eosinophil levels.¹⁵ Kimura et al¹⁶ reported reduction of angiotensin-converting enzyme 2 gene expression in asthmatic patients with the Th2 phenotype. Thus, could the connection between the Th2 phenotype and exhaled NO contribute to less severe COVID-19 in asthmatic patients?¹⁷

Contributions to endotheliopathy of factors antecedent to infection versus the infection itself remain inconclusive. Certainly, risk and genetic factors can increase susceptibility to endothelial damage upon infection. However, hyperinflammatory and a disordered humoral response to SARS-CoV-2 infection itself significantly contribute to severe COVID-19.

Mark Ballow, MD^a
Christopher L. Haga, PhD^b

^aDepartment of Molecular Medicine, Scripps Research Institute, Jupiter, Fla

^bDivision of Allergy and Immunology, Department of Pediatrics, Morsani College of Medicine, University of South Florida, St Petersburg, Fla.

C. L. Haga has received funding from the Schacknow Family Foundation, Inc and previously served as a consultant for the purification of adenovirus-based therapeutics including vaccines for various companies. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication March 12, 2021; accepted for publication March 15, 2021.

Corresponding author: Mark Ballow, MD, Division of Allergy and Immunology, Department of Pediatrics, University of South Florida, Johns Hopkins All Children's Hospital, Children's Research Institute, 140 7th Ave South, 4th FL, CRI, St Petersburg, Fla 33701-4899. E-mail: mballow@usf.edu, markbal.aired@gmail.com.

REFERENCES

- Tricarico G, Travagli V. Patient variability in severity of COVID-19 disease. Main suspect: vascular endothelium. *J Allergy Clin Immunol Pract* 2021;9:2540-1.
- Ballow M, Haga CL. Why do some people develop serious COVID-19 disease after infection, while others only exhibit mild symptoms? *J Allergy Clin Immunol Pract* 2021;9(4):1442-8.
- Hadi HAR, Suwaidi JA. Endothelial dysfunction in diabetes mellitus. *Vasc Health Risk Manag* 2007;3:853-76.
- Konukoglu D, Uzun H. Endothelial dysfunction and hypertension. *Adv Exp Med Biol* 2017;956:511-40.
- Avogaro A, de Kreutzenberg SV. Mechanisms of endothelial dysfunction in obesity. *Clin Chim Acta* 2005;360:9-26.
- Ungvari Z, Tarantini S, Kiss T, Wren JD, Giles CB, Griffin CT, et al. Endothelial dysfunction and angiogenesis impairment in the ageing vasculature. *Nat Rev Cardiol* 2018;15:555-65.
- Wu S-C, Arthur CM, Wang J, Verkerke H, Josephson CD, Kalman D, et al. The SARS-CoV-2 receptor-binding domain preferentially recognizes blood group A. *Blood Advances* 2021;5:1305-9.
- Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020;383:120-8.
- Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and anti-phospholipid antibodies in patients with Covid-19. *N Engl J Med* 2020;382:e38.
- Velásquez M, Rojas M, Abrahams VM, Escudero C, Cadavid AP. Mechanisms of endothelial dysfunction in antiphospholipid syndrome: association with clinical manifestations. *Front Physiol* 2018;9:1840.
- Fang W, Jiang J, Su L, Shu T, Liu H, Lai S, et al. The role of NO in COVID-19 and potential therapeutic strategies. *Free Radic Biol Med* 2021;163:153-62.
- Akerström S, Mousavi-Jazi M, Klingström J, Leijon M, Lundkvist A, Mirazimi A. Nitric oxide inhibits the replication cycle of severe acute respiratory syndrome coronavirus. *J Virol* 2005;79:1966-9.
- Ignarro LJ. Inhaled NO and COVID-19. *Br J Pharmacol* 2020;177:3848-9.
- Zamanian RT, Pollack CV Jr, Gentile MA, Rashid M, Fox JC, Mahaffey KW, et al. Outpatient inhaled nitric oxide in a patient with vasoreactive idiopathic pulmonary arterial hypertension and COVID-19 infection. *Am J Respir Crit Care Med* 2020;202:130-2.
- Yamamoto M, Tochino Y, Chibana K, Trudeau JB, Holguin F, Wenzel SE. Nitric oxide and related enzymes in asthma: relation to severity, enzyme function and inflammation. *Clin Exp Allergy* 2012;42:760-8.
- Kimura H, Francisco D, Conway M, Martinez FD, Vercelli D, Polverino F, et al. Type 2 inflammation modulates ACE2 and TMPRSS2 in airway epithelial cells. *J Allergy Clin Immunol* 2020;146:80-8.e8.
- Ferastraoru D, Hudes G, Jerschow E, Jariwala S, Karagic M, de Vos G, et al. Eosinophilia in asthma patients is protective against severe COVID-19 illness. *J Allergy Clin Immunol Pract* 2021;9:1152-62.e3.

<https://doi.org/10.1016/j.jaip.2021.03.031>

Proposal for a new classification of vibratory urticaria/angioedema



To the Editor:

We have read with interest the article published by Kulthanan et al¹ regarding the results of the systematic literature review on vibratory angioedema. The article shows a complete analysis of the published literature and proposes a classification of vibratory angioedema in 2 variants, namely hereditary and acquired. According to the authors, the hereditary forms significantly show wheals compared with the acquired forms.

Hereditary vibratory angioedema was originally described in 1972 by Patterson et al² in a family whose members were diagnosed with angioedema on vibratory stimuli shortly after they were born. Boyden et al³ described several members of 3 Lebanese families carrying the *ADGRE2* (adhesion G protein-coupled receptor E2) mutation in whom hives on vibratory stimuli predominated in the clinical picture and referred to the condition as vibratory urticaria. These authors intended to study the *ADGRE2* mutation in Patterson's family members but were unable to contact them. In their opinion, based on the clinical manifestations, Patterson's patients and their own likely suffered from different conditions.^{4,5} Both being hereditary, in Patterson's cases, lesions consisted of cutaneous/subcutaneous angioedematous lesions lasting hours to days,² and in Boyden's cases, lesions consisted of evanescent hives lasting less than 1 hour.³⁻⁵ Thus, we propose to subclassify the hereditary variants into 2 subtypes: the hereditary vibratory angioedema (Patterson type) and the hereditary *ADGRE2*-related vibratory urticaria (Boyden type).

Regarding the acquired cases, they could be subclassified into 2 subtypes: the more frequent acquired vibratory angioedema, characterized by a sustained history of angioedema on vibratory stimuli without hives that may last months or years, and the rare secondary acquired vibratory urticaria,^{6,7} described only twice in relation to *Candida glabrata* infection⁶ and *Hymenoptera* sting.⁷ In the latter, lesions consist of hives; a primary condition is necessary for it to develop and evolution is transient (symptoms triggered by the vibratory stimulus last until the primary condition is resolved).

On the basis of these observations, we believe that vibration can induce a heterogeneous set of diseases defined as vibratory urticaria or angioedema and propose a modification on the Kulthanan classification to incorporate some data included in the clinical descriptions of the cases (Table I).

In addition, Kulthanan et al¹ included the 12 volunteers working in 2 dermatology departments in Spain that we reported⁸ as well as the population of 7 Chinese and 18 German medical students studied by Zhao et al.⁹ These individuals had a previous history of symptoms on vibratory stimuli according to questionnaires and usually different degrees of alteration of the vortex provocation test. To the best of our knowledge, none suffered

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.

Maria Antonia Pastor-Nieto, MD^{a,b}
Maria Elena Gatica-Ortega, MD^c
Laura Vergara-de-la-Campa, MD^c
Ana Maria Gimenez-Arnau, MD^d

^aDermatology Department, University Hospital of Guadalajara, Guadalajara, Spain

^bMedicine and Medical Specialties Department, Faculty of Medicine and Health Sciences, University of Alcalá de Henares, Alcalá de Henares, Spain

^cDermatology Department, Hospital Complex of Toledo, Toledo, Spain

^dDermatology Department, Hospital del Mar IMIM, Universitat Autònoma, Barcelona, Spain.

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.

Corresponding author: Maria Antonia Pastor-Nieto, MD, Dermatology Department, Hospital General Universitario de Guadalajara, Calle Donantes de Sangre s/n, Guadalajara 19002, Spain. E-mail: mapastornieto@gmail.com.

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