

**Title:**

**PROPOSAL FOR A NEW CLASSIFICATION OF VIBRATORY URTICARIA/ANGIOEDEMA**

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## **PROPOSAL FOR A NEW CLASSIFICATION OF VIBRATORY URTICARIA/ANGIOEDEMA**

To the Editor,

We have read with interest the article published by Kulthanan et al.<sup>1</sup> regarding the results of the systematic literature review on Vibratory Angioedema. The paper shows a complete analysis of the published literature and proposes a classification of vibratory angioedema in two 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 al.<sup>2</sup>, in a family whose members were diagnosed with angioedema upon vibratory stimuli shortly after they were born. Boyden et al.<sup>3</sup> described several members of 3 Lebanese families carrying the *ADGRE2* (Adhesion G Protein-Coupled Receptor E2) mutation in whom hives upon 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<sup>4-5</sup>. Both being hereditary, in Patterson's cases lesions consisted of cutaneous/subcutaneous angioedematous lesions lasting from hours to days<sup>2</sup> and, in Boyden's cases, lesions consisted of evanescent hives lasting less than 1 hour<sup>3-5</sup>. Thus, we propose to subclassify the hereditary variants into two 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 two subtypes: the more frequent Acquired Vibratory Angioedema, characterized by a sustained history of

angioedema upon vibratory stimuli without hives that may last months or years, and the rare Secondary Acquired Vibratory Urticaria<sup>6,7</sup> described only twice in relation to *Candida glabrata* infection<sup>6</sup> and *Hymenoptera* sting<sup>7</sup>. 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).

Based on 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 in order to incorporate some data included in the clinical descriptions of the cases. (Table 1).

Additionally, Kulthanan et al.<sup>1</sup> included the 12 volunteers working in two Dermatology Departments in Spain that we reported<sup>8</sup> as well as the population of 7 Chinese and 18 German medical students studied by Zhao et al.<sup>9</sup> These individuals had a previous history of symptoms upon vibratory stimuli according to questionnaires and usually different degrees of alteration of the vortex provocation test. To the best of our knowledge, none suffered from quality of life impairment, had ever consulted a physician nor 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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**TABLA 1. PROPOSAL OF CLASSIFICATION FOR VIBRATORY URTICARIA/ANGIOEDEMA**

Subtypes		Pathogenesis	Clinical course	Clinical features
<b>Hereditary Vibratory Urticaria/ Angioedema</b>	<b>Hereditary Vibratory Angioedema (Patterson type<sup>2</sup>)</b>	Hereditary (Autosomal dominant): Unknown mutation(s)	Chronic	Angioedema (hours)
	<b>Hereditary Vibratory Urticaria (Boydén type<sup>3-5</sup>)</b>	Hereditary (Autosomal dominant): ADGRE2 mutations (Lebanese families)	Chronic	Hives (<1 hour)
<b>Acquired Vibratory Urticaria/ Angioedema</b>	<b>Acquired Vibratory Angioedema</b>	Idiopathic	Chronic	Angioedema (hours)
	<b>Secondary Acquired Vibratory Urticaria<sup>6,7</sup></b>	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 hour)/ anaphylaxis