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## Need to define a subgroup of patients with idiopathic mast cell activation syndrome



### To the Editor:

We applaud Gülen et al<sup>1</sup> for their recent publication on selecting the right criteria and proper classification to diagnose mast cell activation syndromes (MCAS). Confusion among health professionals and patients rests primarily with the definition of idiopathic MCAS.

It remains unexplained why two important aspects of the original description of MCAS by Akin et al<sup>2</sup> have been dropped: (1) inclusion of neurologic symptoms, and (2) elevated 24-hour urine mast cell mediator metabolites. The latter exclusion is particularly puzzling because Ravi and colleagues<sup>3</sup> reported that of 25 patients with MCAS, urinary 11beta-prostaglandin-F2alpha was more frequently elevated than N-methyl histamine (two of 25 patients) and serum tryptase (10 of 25 patients). Because the diagnosis of those MCAS patients was stringent, one wonders whether the requirement for tryptase measurements may be justified or practical, because few emergency rooms or clinical sites are able to measure tryptase associated with an acute episode, even in the setting of anaphylaxis. In fact, elevated levels of another mast cell-derived mediator, platelet activating factor (PAF), were reported to be more strongly associated with the severity of anaphylaxis than either histamine or tryptase.<sup>4</sup>

Increasing evidence suggests that many patients thought to have MCAS along with neurologic and cognitive symptoms have extreme sensitivity to odors and stress, are resistant to treatment with antihistamines, omalizumab, or both, and do not have elevated serum levels of tryptase (Table I). This should not be surprising because mast cells can be stimulated by many neuroimmunomodulatory triggers, leading to the release of mediators other than histamine or tryptase.<sup>5</sup>

The review by Gülen et al<sup>1</sup> provides a useful breakdown of MCAS, but it does not discuss triggers that may contribute to idiopathic MCAS. Instead, any known trigger (eg, stress) is combined into the category of secondary MCA with no explanation. Does this mean that as more mast cell triggers are identified, they, too, will be relegated to secondary MCA? That would imply that idiopathic MCAS will never be associated with triggers of its own unless it is limited by default to innate and not external triggers.

Many idiopathic MCAS patients describe sudden mast cell reactivity to multiple triggers (old and new) after a catastrophic event such as a death in the family, major surgery, or extensive trauma: in other words, physical or emotional stress. Hence, a possible innate trigger of mast cells could be the key stress mediator, corticotropin-releasing hormone, the main receptor for which (CRHR-1) was shown to be expressed and functional on

**TABLE I.** Proposed subgroup of neurosensitive mast cell activation syndrome patients

|                                                                                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------|
| Presence of neurologic and cognitive symptoms                                                                                    |
| Extreme sensitivity to odors and stress                                                                                          |
| Resistance to treatment with antihistamines, omalizumab, or both                                                                 |
| Absence of serum tryptase elevation                                                                                              |
| Potential serum elevation of corticotropin-releasing hormone, platelet activating factor, and vascular endothelial growth factor |

human mast cells, leading to selective release without tryptase or vascular endothelial growth factor.<sup>6</sup>

Maybe we should consider a distinct subgroup of neurosensitive MCAS patients in whom the criteria of a positive response to antihistamines and elevated serum tryptase levels do not necessarily apply (Table I). An analogous case would be that of chronic spontaneous urticaria patients, because as many as 40% are resistant to treatment with antihistamines and are characterized by elevated levels of PAF.<sup>7</sup> Potentially useful new serum biomarkers that would need to be validated could include corticotropin-releasing hormone, PAF, and vascular endothelial growth factor (Table I).

There should be renewed efforts to identify useful biomarkers for MCAS that also may lead to different treatment approaches. For instance, rupatadine (which is available in Canada and is mentioned in Table I in Gülen et al<sup>1</sup>) is a potent histamine-1 receptor antagonist, but it also has anti-PAF and mast cell blocking actions. Diagnostic criteria should characterize patients more accurately, but they should also reflect the realities of patients, who have often guided the health profession toward new or more refined diagnostic entities.

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## Reply to “Need to define a subgroup of patients with idiopathic mast cell activation syndrome”



### To the Editor:

We thank Theoharides<sup>1</sup> for the positive statement referring to the diagnostic approach to mast cell activation syndromes (MCAS) presented in article.<sup>2</sup> In his letter, Theoharides raises several issues for discussion, which we welcome the opportunity to address.

We mentioned measuring urinary mediators and would include their metabolites, but also noted that they are less specific than serum tryptase in documenting mast cell activation. It is also true that measurement of urinary mediators might have some utility, particularly if tryptase measurement at the right time has not been possible. However, we would also note that their measurement must involve careful collection and measurement in association with an event, and this may also be generally unavailable.

By definition, MCAS is classified as idiopathic when there is no identifiable primary or secondary associated diagnosis that in itself helps explain the event identified by consensus criteria. Theoharides notes that some individuals with idiopathic MCAS may report some sensitivity to odors or stress with the onset of an episode of MCAS. If such an association is reproducible, an argument may be made to reclassify the individual as having secondary MCAS, insight into the underlying pathology aside. However, in the absence of meeting consensus criteria, such an individual should not be given the diagnosis of MCAS, although a search should be made to understand the basis of such observations, including the possibility of some underlying involvement, such as with specific cell types including mast cells (MCs) or lymphocytes, or an underlying neurologic abnormality. Certainly, as research identifies new triggers and mechanisms of MC activation, the number of individuals identified with idiopathic MCAS will decrease.

Furthermore, we absolutely agree with Theoharides that there is a substantial need to identify additional biomarkers specific for documenting involvement of MCs in the evaluation of MCAS.

Theoharides mentions that neurologic symptoms are lacking in MCAS diagnostic criteria. As we noted in our article, neurologic symptoms may occur with an MCAS event. What remains to be

determined is whether, as Theoharides suggests, “many patients suspected of MCAS present with neurocognitive symptoms” and also are sensitive to odors, for example, which he suggests may be a distinct subgroup of “neurosensitive” patients with MCAS. This brings up the question, and to which we agree, that sometimes, the possibility exists that MC activation may be less severe or may involve a single organ system, so that not all MCAS criteria are fulfilled, and the patient may still experience MC activation-related symptoms, because mast cell activation disorders are a heterogeneous group of conditions.<sup>3</sup> We note that such individuals may be more appropriate for the International Classification of Diseases, 10th Revision diagnostic coding of “mast cell activation, unspecified”, rather than the syndromic presentation meeting all criteria for MCAS, although precise guidance to diagnose this category is currently lacking and is challenging in the critical need of further understanding.

On behalf of all authors for Gülen et al.<sup>2</sup>

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