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Letter to the Editor

"The Role of the Autonomic Nervous System in Epilepsy and Migraine: A Narrative Review"- Authors' Reply

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We sincerely thank you for taking the time to read our narrative review, "The role of the autonomic nervous system in epilepsy and migraine: A narrative review" [1]. We greatly value your insightful comments and suggestions, which have provided valuable opportunities to reflect further on the topics discussed in the review. Regarding your specific points, we would like to offer the following clarifications:

Our review was a narrative review and not a systematic review [1]. We therefore expected that it may not have addressed all autonomic-system involvements in epilepsy and headache, given their complexity and breadth. The purpose of the review was not to cover all aspects systematically, but rather to focus on more frequent or impactful manifestations.

Regarding Takotsubo syndrome (TTS) [2,3], although we recognize its relevance, it was excluded due to its rarity. Other similarly rare autonomic involvements were also excluded for this reason, consistent with the narrative nature of our review.

With respect to neurogenic pulmonary edema [4,5], this condition represents acute respiratory distress caused by severe central nervous system (CNS) compromise. The condition may involve autonomic-system imbalance caused by brain damage, in which sympathetic hyperactivity triggers excessive catecholamine release, leading to significant hemodynamic changes and pulmonary edema. Additionally, vagus-nerve inhibition may contribute to neurogenic pulmonary edema through an abnormal inflammatory response [6]. Although other pathogenic mechanisms have been proposed, a detailed discussion of these falls outside the scope of this review, though we remain open to further exploration of the topic.

Regarding malignant cardiac arrhythmias [7], we note that these were indeed addressed in the article. For example, in section "3.4 Autonomic Dysfunctions in developmental epileptic encephalopathies (DEE)" [1], we discussed the role of cardiac dysautonomia and arrhythmias in conditions such as Rett syndrome and Cyclin-dependent kinase-like (CDKL5) Deficiency Disorder [8–10].

Regarding coronary spasm, although it may occasionally complicate seizures, the case [11] cited in your letter involves a seizure that was secondary to a subarachnoid hemorrhage, which we consider a significant limitation in drawing broader conclusions. Moreover, a clear causal relationship between seizures, autonomic involvement, and coronary spasm has not been established in the literature.

On the topic of genitourinary and gastrointestinal involvement, we believe these aspects were adequately discussed in the review. For example, in section "3.1 Autonomic Changes in the Ictal Phase" [1], we described symptoms such as urinary incontinence and gastrointestinal manifestations during seizures. We also detailed the contribution of brain regions such as the anterior cingulate and insular cortex to these dysfunctions.

The authors of the Letter to the Editor noted that seizures typically activate sympathetic nervous system activity, resulting in increased heart rate and blood pressure. However, parasympathetic activation or sympathetic inhibition may predominate in focal seizures. Moreover, seizures can impair autonomic respiratory reflexes in the postictal phase, potentially contributing to Sudden Unexpected Death in Epilepsy (SUDEP), as thoroughly discussed in Chapter 3, particularly in Section 3.1 [12].

Finally, concerning autonomic involvement in headaches, we recognize that some details may not have

been sufficiently emphasized. However, Chapter 2 of our review [1] was dedicated to that topic. For example, we discussed blood pressure fluctuations that are linked to secondary headaches, and the role of the baroreflex system, in maintaining cerebral blood flow [13]. Additionally, we reviewed the vasodilatory effects of neuropeptides such as Calcitonin gene-related peptide (CGRP) and substance P [14,15]. That said, we agree that reduced blood-pressure variability and increased diastolic blood pressure at rest in migraine patients, could have been highlighted further.

In conclusion, we greatly appreciate your thoughtful observations and the opportunity to clarify these points. We hope that our responses address your concerns comprehensively, and we remain open to further discussion or constructive feedback.

Author Contributions

DDA, FC, AF, EC, GT, AS, VR, VS, PP drafted the manuscript. DDA, FC, AF, SLC, EC, GT, AS, GB, VR, VS, PP performed the literature searches. DDA, AF, AS, VR, VS and PP critically revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare no conflict of interest.

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