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LETTER

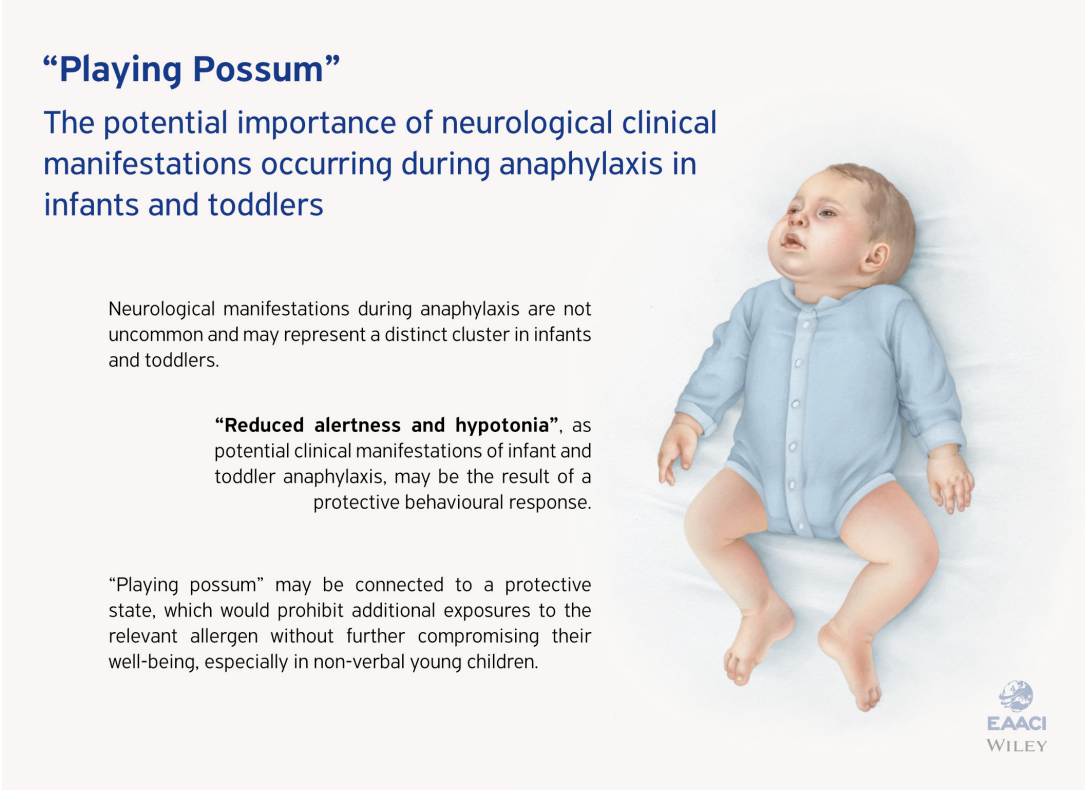
WILEY

"Playing possum": The potential importance of neurological clinical manifestations occurring during anaphylaxis in infants and toddlers

To the Editor,

According to the definition of the European Academy of Allergy and Clinical Immunology, anaphylaxis is a severe systemic hypersensitivity reaction that can be life-threatening. It is characterized by a rapid onset of clinical manifestations of multiple organ systems, which can lead to potentially fatal systemic compromise; therefore, it is considered a medical emergency.[1] Given the multisystem nature of anaphylaxis, the clinical manifestations can vary enormously between and within patient episodes. Compilating this further, anaphylaxis can have age-based presentation differences, in particular between infants and toddlers compared with older children and adults.

Cardiovascular manifestations are more common in adults and respiratory manifestations more common in younger children. The European Anaphylaxis Registry had noted vomiting as a predominant clinical manifestation in preschool children compared with nausea in adolescents. As well, cough is a more common sign in children under 10 years of age, with throat and chest tightness symptoms more common over 10 years. Finally, cardiac and



circulatory signs/symptoms manifest mostly with presyncope and hypotension in adolescents and adults, whereas infants and toddlers can have more nonspecific neurological manifestations such as fussiness, clinginess, behavioral changes, and "reduced alertness".[2] The pathophysiology of such neurological manifestations in this younger age demographic is poorly understood.

Pouessel et al.[3] performed a retrospective study of 1951 food anaphylaxis cases registered by the Allergy Vigilance Network, which included data on anaphylaxis cases comparing infants (≤12 months) with preschool children (1–6 years). The authors described that hypotension, neurological manifestations, and more specifically, "hypotonia" were more likely to occur in infants compared with preschool-aged children (21% vs. 9%, $p = .004$; 26% vs. 11%, $p = .002$; 15% vs. 2%, $p = .002$, respectively). The authors noted that cardiovascular manifestations were rarely reported in infants and young children, but they acknowledged that this may be due to underdiagnosis and poor recognition. Anaphylaxis often occurs outside of a monitored medical setting, where blood pressure either is not measured or cannot be reliably measured in the pretreatment phase of an acute episode. Therefore, the authors recognized the possibility of omission bias and selection bias within their analysis, where cases were based on voluntary notification and a likelihood that severe cases with cardiovascular involvement might have been more likely to be registered than less severe cases.

Samady et al.[4] performed a retrospective study of 357 children with food-induced anaphylaxis who were seen at a large, urban US children's hospital emergency department. The authors noted that cardiac manifestations with hypotension were uncommon and occurred in only 2% of children <12 months old, 2% of children 12–23 months old, 1% of children 2–6 years old, and 2% of children >6 years old (trend not statistically significant) compared with other clinical manifestations across all age cohorts in the dataset. Jeon et al.[5] performed a retrospective study examining 338 cases of food-induced anaphylaxis in infants aged 0–2 years old, noting neurological manifestations in 11.9% of the cases.

While not representative of the total picture of infant and toddler anaphylaxis, the data from these studies suggest that neurological manifestations during anaphylaxis are not uncommon and may represent a distinct cluster in infants and toddlers. Earlier work to provide a foundation to the approach to infant and toddler anaphylaxis did not try to address such clinical manifestations phenotype or even suggest specific criteria for these ages.[6]

Neurological manifestations may arise due to different underlying pathophysiological mechanisms particular to the infant and toddler, including cerebral hypoperfusion secondary to cardiovascular compromise occurring during anaphylaxis. However, data suggest that hypotension is rarely documented in infants and toddlers in the acute anaphylaxis setting, and in the absence of accurate blood pressure monitoring in this age group, it is difficult to be certain of a precise underlying mechanism. An alternate hypothesis is that the neurological signs/symptoms seen during anaphylaxis may represent isolated neurological responses. There is evidence to suggest that allergic inflammation, through its mediators, may lead to the modification of the functions of neurons as a form of allergen-induced neuromodulation and allergic reactions may be increasingly considered an immune-neuronal condition.[7] Both mast cells and eosinophils may release mediators that can be neurotoxic, and the degree that such mediators cross the blood–brain barrier in the acute setting of anaphylaxis is uncertain.

Of note, young children who suffer from acute food protein-induced enterocolitis syndrome, which is not IgE mediated but is an immunologically mediated adverse reaction to food, very characteristically are described as, e.g., lethargic, floppy, withdrawn, and sleepy.[8] While to some degree this may be the result of hypovolemia from protracted emesis, it may also be a clinical manifestation of a poorly understood neuro-enteric mechanism that has shown some evidence of response to 5-HT3 antagonists such as ondansetron.

Regardless of the underlying pathophysiology, we suggest that "reduced alertness and hypotonia", as potential clinical manifestations of infant and toddler anaphylaxis, may be the result of a protective behavioral response. "Playing possum" is an idiomatic phrase which means "pretending to be dead," and it comes from a characteristic of the Virginia opossum (*Didelphis virginiana*), which are famous for pretending to be dead when threatened. In infants and toddlers, "playing possum" may be connected to a protective state, which would prohibit additional exposures of the relevant allergen, without further compromising their well-being, especially in nonverbal young children.

A challenge in the area is the descriptive nature of many studies looking at infant and toddler anaphylaxis. Such series often focus on patient observations after the administration of adrenaline rather than emergent from the start of anaphylaxis, as the early signs and symptoms may not always be immediately recognized. Data regarding directly observed clinical manifestations of anaphylaxis, including vital sign monitoring from the start of reactions by healthcare professionals is lacking. Further investigation of this will help to identify food allergic anaphylaxis phenotypes in children, but this would require, for example, pooling of datasets, incorporation of

potential biomarkers that may inform the underlying pathophysiology indicating mast cell mediator release and techniques such as cluster or latent class analysis to help aggregate clinical manifestations patterns. We suggest accurately observing and measuring physiological signs/symptoms of anaphylaxis during oral food challenges (OFC) in infants and toddlers,[9] and if possible, consider studies that use noninvasive monitoring of cerebral perfusion. This would give us greater insight into pathophysiological changes, including neurological manifestations, that occur during severe allergic reactions and help gather evidence concerning this "playing possum" phenomenon commonly observed by clinicians of young children, without otherwise compromising their well-being. Obtaining better understanding of the immunological features behind this process will aid in our ability to manage anaphylaxis in infants and toddlers.

AUTHOR CONTRIBUTIONS

Mattia Giovannini: Conceptualization; writing – original draft; writing – review and editing; formal analysis; data curation. **Ru-Xin Foong:** Writing – review and editing; formal analysis; data curation; writing – original draft. **Matthew Greenhawt:** Writing – review and editing; supervision; formal analysis; data curation. **George du Toit:** Conceptualization; writing – review and editing; formal analysis; data curation; supervision.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest to disclose in relation to this paper.

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