

Clinical Communications

The association between anaphylaxis and post-traumatic stress disorder in subjects with Hymenoptera venom allergy

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Clinical Implications

- Patients who experience anaphylaxis due to Hymenoptera venom allergy disclose susceptibility to post-traumatic stress disorder. Therefore, routine evaluation of emotional symptoms by the treating allergist is recommended in these individuals.

TO THE EDITOR:

Post-traumatic stress disorder (PTSD) occurs after exposure to emotionally stressful events. It can evolve into a chronic disease, accompanied by depression, unemployment, and physical disabilities, thereby constituting a public health concern. Traumatic events that cause this disorder are invariably characterized by a threat to physical integrity. PTSD has been investigated in association with a variety of medical conditions including cardiac arrest, newly diagnosed cancer, and childbirth.¹

Anaphylaxis represents a severe, and occasionally life-threatening, form of the immediate-type, or IgE-mediated, allergy. Nevertheless, it appears that there are limited data on the etiologic role of anaphylaxis in PTSD. In this study, we evaluated a population of patients with a history of a systemic allergic reaction to Hymenoptera venom in an attempt to delineate the interaction between traumatic life events, anaphylaxis, and PTSD.

This study evaluated PTSD symptoms in adult patients presenting with Hymenoptera insect stings who were referred to 2 medical centers in Jerusalem, Israel, between 2008 and 2018. Medical records were reviewed independently by 2 allergy specialists for demographic and clinical data, eligibility for recruitment, and assessment of allergic reactions: anaphylaxis or local reaction (LR). Subjects were asked to fill out the following questionnaires: (1) Life Events Checklist (LEC-5), a 17-item self-report questionnaire that assesses prior exposure to potentially traumatic events²; (2) PTSD Checklist (PCL-5), a 20-item self-report questionnaire, assessing symptoms according to DSM-5.³ Inclusion criteria were age >18 years at the time of recruitment; a history of Hymenoptera insect sting with ensuing systemic or local responses; and informed consent. No exclusion criteria were employed. The study was approved by the local institutional ethics committees of Hadassah Medical Center and Shaare-Zedek Medical Center in keeping with the principles of the Declaration of Helsinki (applications 0517-16

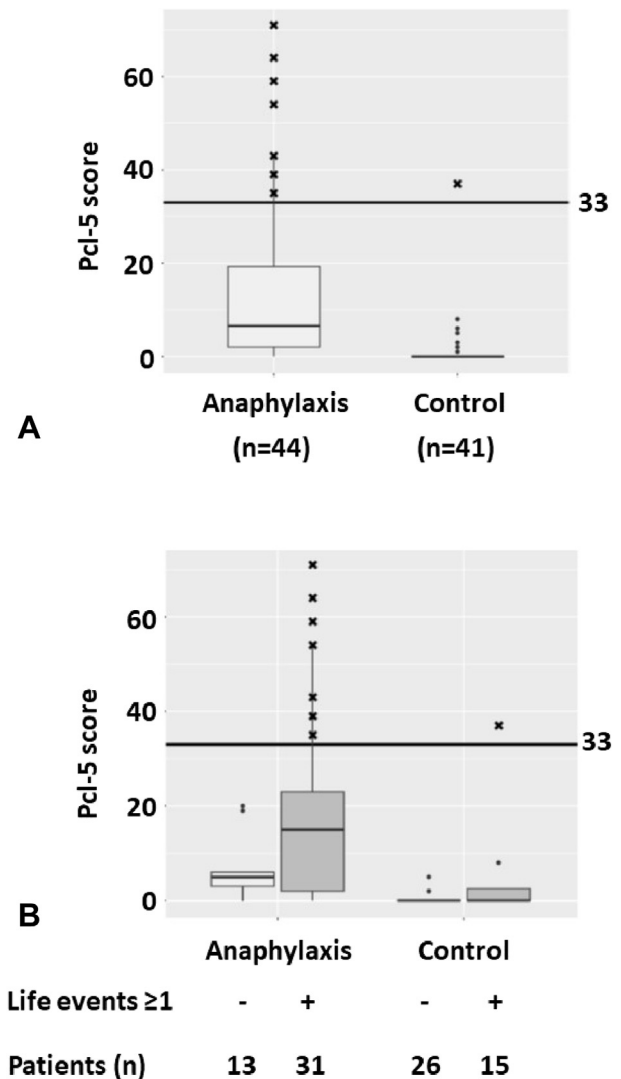


FIGURE 1. PTSD and previous traumatic life events in subjects with Hymenoptera venom allergy after anaphylaxis or local reaction. **A**, When compared with the local-reaction subjects (right panel), the postanaphylaxis patients (left panel) have an increased prevalence of PTSD (15.9% vs 2.4%; $P < .05$) and higher mean PCL-5 scores (15.2 ± 18.5 vs 1.6 ± 5.9 ; $P < .001$). **B**, The average of previous traumatic life events in the anaphylaxis group (left panels) is higher compared with the local reaction control group (1.9 ± 2.7 vs 0.78 ± 1.4 ; $P < .05$). All postanaphylaxis patients with PTSD had at least 1 previous traumatic life event (average of 4). The horizontal line indicates the cutoff score of 33 points for probable PTSD. PCL-5, PTSD Checklist; PTSD, post-traumatic stress disorder.

and 0239-16, respectively). All analyses were carried out with SPSS (version 23.0; IBM Corp, Armonk, NY). Differences between study groups were examined using Student t -tests, with significance set at $P < .05$. Probable PTSD was determined by a cutoff of 33 on the PCL-5 questionnaire. The χ^2

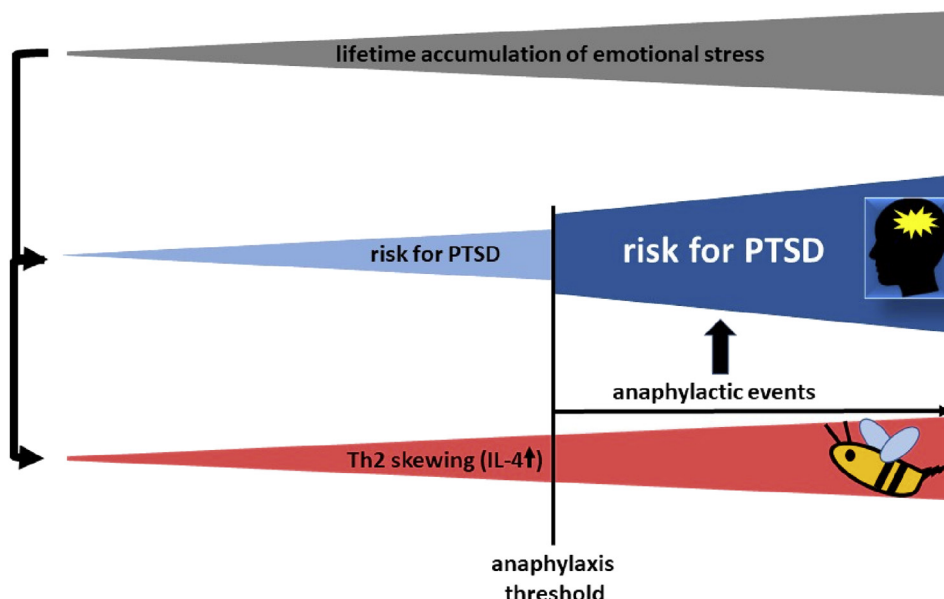


FIGURE 2. The association between chronic emotional stress, anaphylaxis, and PTSD. Chronic emotional stress both increases the risk for PTSD and disrupts the Th1/Th2 balance, thus creating susceptibility to severe allergic reactions. The latter is thought to be mediated, in part, by excessive IL-4. This effect consequently leads to a threshold beyond which insect venom can induce anaphylaxis. This life-threatening allergic event constitutes a “last straw” that, in turn, increases the risk for PTSD in a previously susceptible individual. *PTSD*, Post-traumatic stress disorder.

test was used to examine relationships between categorical variables.

A total of 440 medical records were retrieved, with a diagnosis of insect sting. Eighty-five individuals (19.3%) were recruited, after the exclusion of subjects with mosquito or spider bites ($N = 75$) and those who did not meet the study criteria or declined enrolment ($N = 280$). The study group comprised 44 with documented Hymenoptera-induced anaphylaxis and 41 with LR. The anaphylaxis and LR groups were similar in terms of gender (52.3% vs 58.5% males), age (mean, 41.2 ± 16.4 vs 36.8 ± 13.8 years), age at the time of an allergic event (30.5 ± 15 vs 25.6 ± 11.9 years), asthma (4.5% vs 7.3%), and comorbid allergic diseases (15.9% vs 9.8%).

The postanaphylaxis group obtained higher PCL-5 scores, compared with subjects with LR, indicating increased PTSD-related symptoms (mean, 15.2 ± 18.5 vs 1.6 ± 5.9 ; $P < .001$) (Figure 1, A). Accordingly, there was a higher rate of probable poststing PTSD when the allergic response involved anaphylaxis rather than an LR (15.9% vs 2.4%; $P < .05$). Intriguingly, the occurrence of PTSD did not seem to correlate with the severity of the allergic reaction as evaluated by both the Brown⁴ and Mertes⁵ anaphylaxis grading scores. However, in the anaphylaxis/PTSD group, 86% of the subjects experienced a feeling of suffocation compared with 54% in the anaphylaxis/non-PTSD group.

In order to collect data on prior exposure to traumatic events, subjects were asked to answer the LEC-5 questionnaire. As expected, all patients with PTSD had 1 or more previous traumatic life events according to the LEC-5 questionnaire. Those belonging to the anaphylaxis group ($N = 7$) reported a mean of 4 events, whereas the single nonanaphylaxis subject reported 2 events. Interestingly, traumatic events were reported at a higher

rate in the anaphylaxis group (31 of 44; 70%) compared with the LR group (15 of 41; 36.5%) (Figure 1, B), regardless of PTSD. Consequently, the relative risk for anaphylaxis after at least 1 traumatic life event was calculated to be 2.02 (1.24-3.29; 95% confidence interval).

In this study, we analyzed self-reported PTSD symptoms after anaphylaxis in response to Hymenoptera sting. The data presented herein show that both the symptom levels and the prevalence of probable PTSD are significantly higher in subjects with a history of anaphylaxis (Figure 1, A). This observation implies that anaphylaxis is an important traumatic event that contributes to the etiology of PTSD. Our data show no significant association between the intensity of anaphylaxis and the likelihood of subsequent PTSD. We did observe, however, that affected patients reported a feeling of suffocation, which may have created a perception of imminent death, thus increasing the probability of PTSD.

In addition to the fact that anaphylaxis may precede PTSD, we also noted that traumatic life events are associated with increased risk for anaphylaxis (relative risk = 2.02). This association was retained even when a comparison between the 2 study groups was made after exclusion of patients with PTSD. Previous works showed that chronic stress correlates with the severity of Th2-mediated disease, such as atopic dermatitis,⁶ chronic urticaria,⁷ and asthma,⁸ and animal models lend further support to this hypothesis.⁹ A possible mechanistic explanation for this observation is provided by studies showing that traumatic events and emotional stress disrupt the Th1/Th2 balance, thus stimulating IL-4 production and increased Th2 response.¹⁰ Additional potential players may include various other cytokines, changes in serum cortisol, and neuroimmune mechanisms.

This study presents several limitations. Our data were obtained from questionnaires rather than clinical interviews. This methodology limits the collection of findings that are relevant to diagnosis of PTSD, characterization of the traumatic event, and identification of other psychiatric disorders. Furthermore, a large proportion of subjects declined recruitment, and this may possibly entail a patient-selection bias. Therefore, the observations presented herein may not completely reflect the entire population of patients with Hymenoptera venom allergy in Israel or in other countries.

On the basis of our findings and previous reports, we propose the following model (Figure 2). Lifetime emotional stress increases the risk for both PTSD and anaphylaxis. This traumatic allergic response constitutes a “last straw” that, in turn, considerably increases the risk to develop PTSD in a previously susceptible individual.

In summary, we show a link between traumatic life events, anaphylaxis, and PTSD. It is, therefore, recommended that evaluation of emotional stress and PTSD symptoms should be part of the routine medical intake in patients with systemic anaphylaxis.

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REFERENCES

1. Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, et al. Post-traumatic stress disorder. *Nat Rev Dis Primers* 2015;1:15057.
2. Weathers FW, Blake DD, Schnurr PP, Kaloupek DG, Marx BP, Keane TM. The Life Events Checklist for DSM-5 (LEC-5). Washington, DC: US Department of Veteran Affairs; 2013. Available from: ptsd.va.gov/professional/assessment/documents/LEC5_Standard_Self-report.PDF. Accessed April 13, 2018.
3. Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP. The PTSD Checklist for DSM-5 (PCL-5). Washington, DC: US Department of Veteran Affairs; 2013. Available from: ptsd.va.gov/professional/assessment/documents/PCL5_Standard_form.PDF. Accessed April 13, 2018.
4. Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;114:371-6.
5. Mertes PM, Alla F, Trechot P, Auroy Y, Jouglu E. Groupe d'Etudes des Réactions Anaphylactoides Peranesthésiques. Anaphylaxis during anesthesia in France: an 8-year national survey. *J Allergy Clin Immunol* 2011;128:366-73.
6. Peters EM, Michenko A, Kupfer J, Kummer W, Wiegand S, Niemeier V, et al. Mental stress in atopic dermatitis—neuronal plasticity and the cholinergic system are affected in atopic dermatitis and in response to acute experimental mental stress in a randomized controlled pilot study. *PLoS One* 2014;9:e113552.
7. Varghese R, Rajappa M, Chandrashekar L, Kattimani S, Archana M, Munisamy M, et al. Association among stress, hypocortisolism, systemic inflammation, and disease severity in chronic urticaria. *Ann Allergy Asthma Immunol* 2016;116:344-8.
8. Rosenberg SL, Miller GE, Brehm JM, Celedón JC. Stress and asthma: novel insights on genetic, epigenetic, and immunologic mechanisms. *J Allergy Clin Immunol* 2014;134:1009-15.
9. Palermo-Neto J, Guimarães RK. Pavlovian conditioning of lung anaphylactic response in rats. *Life Sci* 2000;68:611-23.
10. Shalev A, Benarroch F, Goltser-Dubner T, Canetti L, Saloner C, Roichman A, et al. Long-term immune alterations accompanying chronic posttraumatic stress disorder following exposure to suicide bomb terror incidents during childhood. *Neuropsychobiology* 2017;76:130-5.