VIEWPOINT

Adverse Childhood Experiences, Toxic Stress, and Trauma-Informed Neurology

Robin Ortiz, MD, MSHP
ACEs Aware Initiative, Aurrera Health Group, Sacramento, California; Department of Pediatrics, Grossman School of Medicine, New York University, New York City; and Department of Population Health, Grossman School of Medicine, New York University, New York City.

Rachel Gilgoff, MD
ACEs Aware Initiative, Aurrera Health Group, Sacramento, California; and Office of the California Surgeon General, California Health and Human Services Agency, Sacramento.

Nadine Burke Harris, MD, MPH
Office of the California Surgeon General, California Health and Human Services Agency, Sacramento.

Corresponding Author: Robin Ortiz, MD, MSHP, Department of Pediatrics, Grossman School of Medicine, New York University, 180 Madison Ave, New York, NY 10016 (robin.ortiz@nyulangone.org).

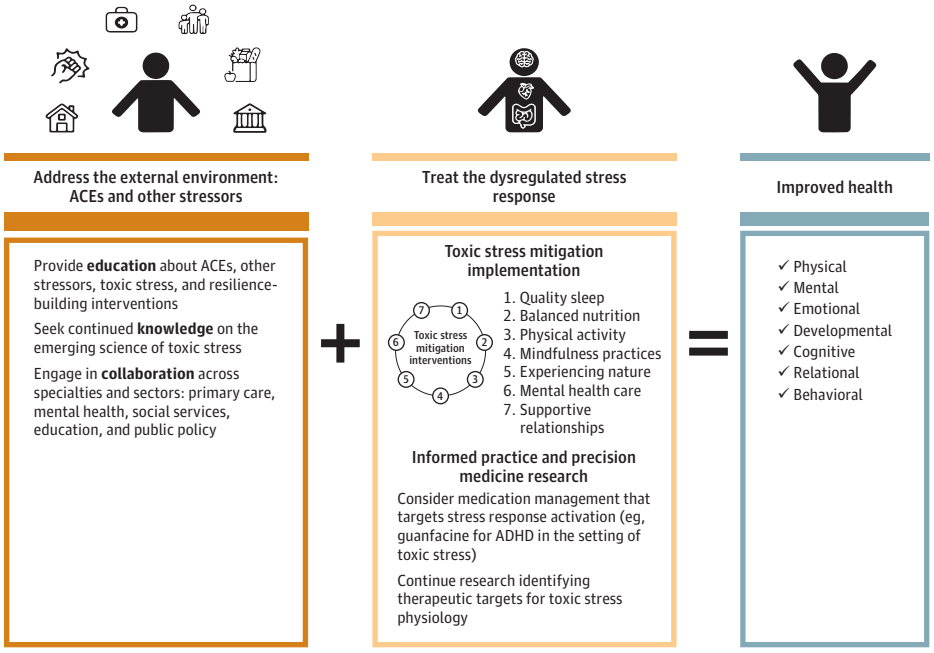
The COVID-19 pandemic has substantially increased stress globally. It has and is expected to continue to increase rates of stress-related disease and cognitive impairment without appropriate interventions. Much of what we know about how stress changes our biology comes from the body of work related to the Adverse Childhood Experiences (ACE) study published by the US Centers for Disease Control and Prevention and Kaiser Permanente.[1] ACEs include child abuse (emotional, physical, or sexual), neglect (physical or emotional), and household challenges (household incarceration, mental illness, substance use, intimate partner violence, or parental separation or divorce) experienced by 18 years of age.[1] ACEs are associated in a dose-dependent way with over 60 mental and physical health outcomes and premature death,[2] including many of the leading causes of death in the US, such as heart disease, cancer, unintentional injuries, stroke, chronic lower respiratory disease, diabetes, kidney disease, and suicide.[1-3] ACEs are also associated with common neurological and neuropsychiatric conditions, including dementia and memory impairment, epilepsy or seizure disorder, attention-deficit/hyperactivity disorder (ADHD), and headaches, in addition to sleep disturbances, developmental delay, learning or behavioral problems, autism spectrum disorders, mood disorders and posttraumatic stress disorder, and chronic pain.[2-4] It is inevitable that clinicians and investigators across the discipline of neurology will regularly encounter individuals with ACEs and their health outcomes. In one assessment, an estimated two-thirds of US individuals have experienced at least 1 ACE, and 1 in 4 have experienced 2 or more.[1]

ACEs lead to short- and long-term ill health through prolonged activation of the biological stress response and associated disruption of neurologic, endocrine, immune, metabolic, genetic, and genetic regulatory systems, a condition now known as the toxic stress response.[3,5] Decades of research have clarified the mechanisms by which ACEs, acting through toxic stress, pose population-wide health risks.[1-8] The stress response involves a complex set of neurological structures and networks, including the amygdala, hippocampus, prefrontal cortex, hypothalamic-pituitary-adrenal axis, and sympatho-adreno-medullary-axis, leading to release of cortisol, noradrenaline and adrenaline among other neuropeptides, hormones, and immune modulators.[5-7] Early life stressors and the associated prolonged activation of the stress response system may alter brain structure, function, and connectivity (eg, altered pain and reward processing, autonomic imbalance, impaired cognition and memory, and accelerated aging), affecting behavioral and cognitive abilities and increasing biological susceptibility to adverse health outcomes into adulthood.[5,7,8] For example, childhood adversity has been associated with alterations in corticolimbic and corticostriatal circuitry involving the prefrontal cortex, ventral striatum, and nucleus accumbens that may impact reward processing, potentially leading to increased risk for impulsivity and addictive behaviors.[8] ACEs have also been associated with altered amygdala reactivity, downregulation of glucocorticoid receptors, and impaired immune function and glucose metabolism.[5,8]

The emerging evidence for an underlying toxic stress response as a treatable physiologic association between ACEs and common neurological presentations should serve as a call to action. While potential causal mechanisms between toxic stress and neurological (and nonneurological) symptoms or conditions are still being investigated, the discipline of neurology is strategically placed to advance the clinical applications of ACEs and emerging toxic stress science to more accurately assess and treat the root neurobehavioral causes for these health conditions. A trauma-informed, toxic stress–responsive approach is one in which the clinician recognizes how early adversity or trauma may physiologically contribute to a health condition and respond with supportive, evidence-based care that avoids retraumatization.[9] Understanding how to recognize and best respond to stress-related clinical impacts in neurological practice may inform treatment for conditions spanning from ADHD to COVID-19–related spikes in stress-related disease, including stroke and dementia.

Medication management for ADHD exemplifies how accounting for the biology of toxic stress is important in clinical decision-making and highlights the need for ongoing research. ACEs and other childhood adversities are associated with greater odds of ADHD,[3,7] and patients with ADHD who also have a history of ACEs often exhibit a poorer response to stimulant treatment. In classic ADHD, stimulants counteract deficits in circuits involving the neurotransmitters norepinephrine and dopamine, effectively improving attention, working memory, and executive function.[10] However, excessive catecholamine activity is also associated with executive functioning deficits. For individuals with ACEs who may be experiencing prolonged activation of the stress response, α2-adrenergic agonists, like guanfacine, are increasingly being used in pediatric centers to help regulate catecholamine signaling, thereby improving prefrontal processes like executive function and attention.[10] Treatment for ADHD in the setting of toxic stress should also include behavioral therapy to reduce environmental risk factors and address underlying toxic stress physiology by using stress-buffering strategies.[9]

Figure. A Call to Action for Trauma-Informed Neurology



Adverse childhood experiences (ACEs) are associated with increased morbidity and mortality throughout the life course, including clinical sequelae prevalent in neurology practice. Neurologists should continue to learn and collaborate in advancing research around toxic stress and practice trauma-informed neurology to recognize, respond to, and avoid retraumatization with respect to ACEs-related experiences and life course outcomes.

Trauma-informed neurology can center patient experiences, more effectively treat toxic stress-associated health impacts, and inform future research (**Figure**). Neurologists stand poised to help patients understand the role that toxic stress physiology may play in the clinical presentation or severity of neurological condition(s)—and in effective treatment thereof. Such an approach can aid clinicians in more specifically managing clinical conditions associated with ACEs when toxic stress is suspected by incorporating interventions targeted at regulating stress physiology, and help reduce blame, shame, and stigmatization patients often feel in connection with early adversity and/or toxic stress symptomatology. Interventions to regulate and counter stress physiology include routine physical activity, antiinflammatory diets, supportive relationships, experiencing nature, quality sleep, mindfulness practices, and mental health treatment.[9]

Neurologists can consider such interventions collaboratively with specialties, such as primary care and mental health, toward building more targeted and patient-centered care systems. Further, researchers should prioritize investigation into toxic stress mechanisms and physiologically responsive interventions. Together, neurologists and neuroscientists are uniquely positioned to lead these vital advancements in the prevention, recognition, and treatment of toxic stress and associated health impacts and to catalyze breakthroughs in addressing the health and societal risks posed by ACEs and stress induced by the COVID-19 pandemic.

ARTICLE INFORMATION

Published Online: April 25, 2022. doi:10.1001/jamaneurol.2022.0769

Conflict of Interest Disclosures: Dr Ortiz reports personal fees from Aurrera Health Group. Dr Gilgoff reports personal fees for serving as a consultant/advisor for Aurrera Health Group and the ACEs Aware initiative of the Office of the California Surgeon General and having stock in Stronger Brains, Inc. No other disclosures were reported.

Additional Contributions: The authors thank Devika Bhushan, MD, Office of the California Surgeon General, for her contribution to the manuscript, and Nicolette Ricker, BS, Aurrera Health Group, for her contribution to the formatting design of the figure. They were not compensated for their contributions.

REFERENCES

1. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the Adverse Childhood Experiences (ACE) study. *Am J Prev Med*. 1998;14(4):245-258. doi:10.1016/S0749-3797(98)00017-8

2. Hughes K, Bellis MA, Hardcastle KA, et al. The effect of multiple adverse childhood experiences on health. *Lancet Public Health*. 2017;2(8):e356-e366. doi:10.1016/S2468-2667(17)30118-4

3. Nelson CA III, Gabard-Durnam LJ. Early adversity and critical periods: neurodevelopmental consequences of violating the expectable environment. *Trends Neurosci*. 2020;43(3):133-143. doi:10.1016/j.tins.2020.01.002

4. Sterling S, Chi F, Lin J, et al. Physical, mental health and developmental conditions, and sociodemographic characteristics associated with adverse childhood experiences among young children in pediatric primary care. *J Pediatr Health Care*. 2021; 35(5):491-499. doi:10.1016/j.pedhc.2021.04.009

5. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities. *JAMA*. 2009;301(21):2252-2259. doi:10.1001/jama.2009.754

6. Bucci M, Marques SS, Oh D, Harris NB. Toxic stress in children and adolescents. *Adv Pediatr*. 2016;63(1):403-428. doi:10.1016/j.yapd.2016.04.002

7. Sarkar T, Patro N, Patro IK. Cumulative multiple early life hits—a potent threat leading to neurological disorders. *Brain Res Bull*. 2019;147:58-68. doi:10.1016/j.brainresbull.2019.02.005

8. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging. *Psychol Bull*. 2011;137(6):959-997. doi:10.1037/a0024768

9. Gilgoff R, Singh L, Koita K, Gentile B, Marques SS. Adverse childhood experiences, outcomes, and interventions. *Pediatr Clin North Am*. 2020;67(2):259-273. doi:10.1016/j.pcl.2019.12.001

10. Arnsten AF, Scahill L, Findling RL. Alpha2-adrenergic receptor agonists for the treatment of attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2007;17(4):393-406. doi:10.1089/cap.2006.0098