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GUEST EDITORIAL

The relationship of childhood adversity and migraine and the value of prospective studies

The first report of a link between childhood maltreatment and recurrent headache appeared over 30 years ago, in a small study of adult women recounting a history of childhood sexual abuse.[1] Several studies confirming an association of headache and contact (sexual and/or physical) abuse followed,[2–5] but it was another 20 years before the scope of investigation of this particular association was expanded to include emotional childhood abuse, as well as exposure to traumatizing household dysfunction (family member substance abuse, mental illness, incarceration, witnessing maternal battering, and parental separation/divorce).[6] The results from the 2010 analysis of the large, landmark Adverse Childhood Experiences (ACE) study dataset demonstrated that frequent headache was associated with each of the eight types of ACEs evaluated, particularly emotional abuse, and that there was a dose-response relationship between cumulative ACE score and prevalence/risk of headache in adults.[6] The American Migraine Prevalence and Prevention study that followed in 2015,[7] was the first publication to use International Classification of Headache Disorders criteria in a nationally representative sample evaluating the maltreatment–headache link while also controlling for depression and anxiety. The queries on maltreatment only encompassed emotional neglect, emotional abuse, and sexual abuse, but, nevertheless, results demonstrated that, compared with adults with episodic tension-type headache, adults with migraine were more likely to recall abuse and neglect in childhood. The American Migraine Prevalence and Prevention study,[7] most preceding it,[1–6] and two large adult population-based studies that followed it,[8,9] corroborated the associations of adverse childhood events with adult headache/migraine. All, however, have been limited by their retrospective design, and with this the looming specter of recall bias, particularly given the advanced age of some participants, the prevalent histories of past and current disordered psychological states, and the stigma of victimization. Further limitations among the morass of cross-sectional studies in adults included incomplete characterization of types, frequency, and temporal sequence of ACEs and headache. Studies of ACEs and headache in children and adolescents are fewer,[10–17] and although they minimize some of the limitations of adult studies, potential obstacles to getting valid information remain. Youthful participants, for instance, may be reluctant to report abuse due to fear of punishment or rejection, and their parents may deny maltreatment because they are unaware, or wish to shield themselves or perpetrators in the household from blame, thus leading to underestimation of the prevalence of ACEs. Many surveys in young populations have not explicitly asked about physical, emotional, and sexual maltreatment but recent data suggest that it has a greater impact on pain than does exposure to household dysfunction.[18,19]

The study published in the current edition of *Headache*, ACE and Onset of Migraine in Canadian Adolescents: A Cohort Study, is a rare find on this topic, a prospective study following participants from infancy to adolescence.[20] The dataset of the National Longitudinal Survey of Children and Youth (NLSCY) included responses about the child from the parent (or person most knowledgeable) regarding exposure at ages 4/5 and 6/7 years to 14 ACEs, at 8/9 years on symptoms of depression and anxiety, and at 14/15 years on migraine, as diagnosed by a health professional. In addition, at this age, the adolescent self-reported on the presence or absence of non-migraine frequent headache. The results showed that migraine, but not non-migraine frequent headache, is associated with ACEs, and that the effect is not dependent on depression and anxiety. Despite the striking differences in methodology and limitations between prospective and retrospective studies, this cohort study corroborates the ACE–migraine link found in cross-sectional studies. This corroboration is foreshadowed by a 2015 investigation on the associations of migraine and stressful childhood events in prospective (NLSCY) compared to retrospective (National Population Health Survey) assessment.[21] Results in that comparison showed that the link of early life stress and migraine did not depend on the method of assessment, thus downplaying the role of recall bias.

Another important contribution of this prospective study is the finding that the relationship of ACEs and migraine were direct, and not mediated by depression and anxiety, thus strengthening the case for causality. These findings differ from those of the investigators' 2019 study of the NLSCY data set evaluating migraine and early life stressors (related to household dysfunction and different than the 14 ACEs in the current study), which showed the relationship of stressors to migraine was mediated by depression and anxiety.[22] The relationship was, however, similar to that found in the retrospective National Longitudinal Study of Adolescent to Adult Health (Add Health) data set, where structural equation modeling of data from young adults suggested that childhood physical, sexual, and emotional abuse had a direct relationship to migraine, as well as to depression and to anxiety, and that depression and anxiety did not mediate the link between abuse and migraine.[23]

The studies performed by these investigators using data from the prospective NLSCY[20–22] have great value, but, as they acknowledge, the definitive epidemiological study on these relationships has yet to be performed. When it comes to toxic stress in childhood and migraine, we still know too little about the impact of the specific headache type,

as well as of the abuse type, severity, duration, critical periods in development, relationship with perpetrator, support systems, and resilience. It is also time for further investigations that deepen our understanding of the neurobiological effects of toxic stress, including stress-induced epigenetic modifications, structural and functional limbic system alterations, and the interaction of hypothalamic-pituitary-adrenal responsivity with endocannabinoid, monoaminergic, oxytonergic, and immune/inflammatory systems that influence pain.[24] Migraine is just one of the many diseases influenced by ACEs. Given the high prevalence of childhood adversity, and the wide range of serious effects it has on mental and physical health throughout one's life, preventing ACEs, identifying early those at risk of the sequelae of exposure to adversity, and intervening with effective therapies hold the promise of improving health and longevity, both on an individual and a global scale.

CONFLICT OF INTEREST

The author reports no relevant conflict of interest.

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