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Childhood Abuse and Migraine: Epidemiology, Sex Differences, and Potential Mechanisms

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Abstract

Migraine and maltreatment are both common conditions that are more prevalent in women. Epidemiological evidence supports an association between childhood abuse and headache, as well as pain in general, although some controversy exists based on methodological concerns of studying the influence of remote, traumatic, stigmatizing events in an often depressed population. There is a growing scientific body of knowledge regarding the neurobiological effects of abuse on brain function and structure that suggest a possible role of early life stress in the pathogenesis of migraine, and a differential impact based on sex. Advances in our understanding of the basic mechanisms by which an adverse environment interacts with and changes the genome, may suggest new treatment strategies.

Keywords

headache; migraine; childhood maltreatment; abuse

Migraine is up to 3 times more common in women than in men,¹ and the divergence in prevalence between the sexes that occurs after puberty suggests that gonadal hormones likely have a substantive role. There are, however, other factors that may be at play in determining sex-based differences in migraine prevalence, including being the victim of abuse, neglect, or other stress-inducing adverse experiences during childhood. In this review we will first discuss the prevalence of maltreatment in children and adults with the emphasis on childhood maltreatment. We will then discuss the current literature suggesting an association between maltreatment and migraine, highlighting the differences between men and women. Finally, we will discuss the neurobiological changes associated with maltreatment that may impact migraine and be amenable to treatment.

PREVALENCE OF CHILDHOOD MALTREATMENT

Throughout the world, childhood maltreatment is a major public health problem, with implications for both physical and mental health that extend into adulthood.² In this too often silent epidemic it is estimated that the true burden may be 5- to 10-fold higher than the nearly 1 million cases that are substantiated each year in the USA.³ Parents are the

perpetrators in about 80% of cases; and girls are the victims more frequently than boys (51.3% vs 48.3%).⁴

Although there is some variation between studies, sexual abuse usually is defined as being touched or fondled or made to touch another in a sexual way, being made to view sexual material, or being the victim of attempts or of actual oral, anal, or vaginal intercourse by an individual at least 5 years older. Physical abuse includes having a parent or household adult push, grab, slap, or throw something at one, as well as being hit hard enough to leave marks or cause injury. Physical neglect encompasses not having enough to eat, being made to wear dirty clothes, not receiving medical attention, and not being taken care of or protected. Emotional abuse includes being sworn at, insulted, put down, humiliated, or threatened with physical violence. Emotional neglect encompasses not being loved, not being emotionally supported, or made to feel unimportant, by other family members. Epidemiological studies estimate the prevalence of childhood maltreatment to range from 25% to 45%.⁵

There are significant differences in prevalence between the sexes based on abuse type. Childhood sexual abuse, for example, is more commonly perpetrated on girls than boys. Based on survey studies in adults, 15–30% of girls and 5–15% of boys experience some type of sexual abuse in childhood, and it is penetrative in about a third of these cases.³ Similarly, emotional abuse is also more common in girls, with large population-based self-report studies in the UK and USA showing that 8–9% of women and about 4% of men reported exposure to severe psychological abuse during childhood.^{3,6,7} Childhood physical abuse, by contrast, is more commonly reported to occur to boys, but at least in some studies the differences in prevalence between the sexes are less striking. In the Adverse Childhood Experiences (ACE) Study, for instance, childhood physical abuse was reported by 21.7% of men and 19.7% of women ($P < .02$).⁶ All other adverse experiences, which included sexual and emotional abuse, as well as parental separation, violence, mental illness, and drug abuse, were more common in women.⁶ Women were also more likely than men to report having experienced a greater number of different types of abuse, which may have health implications.⁶

The prevalence of childhood physical and sexual abuse among persons seeking treatment for physician-diagnosed migraine, as determined by 2 headache clinic-based survey studies, was on par with the prevalence reported in community and health maintenance organization (HMO)-based populations.^{8,9} In the migraine population, however, the prevalence of emotional abuse appears to be nearly 4-fold higher, and it, like sexual abuse, was more common in women.⁹ Given the differences between the sexes in abuse prevalence, particularly based on abuse type, and number of different types experienced, the question arises as to whether childhood maltreatment factors into the sex-based differences in migraine prevalence.

PREVALENCE OF MALTREATMENT IN ADULTS

The prevalence of intimate partner violence is difficult to determine with certainty, but according to the World Report on Violence and Health, 22% of women in the USA report having been physically assaulted by an intimate partner at some point in their lives.¹⁰ Additionally, the National Violence Against Women Survey reported that 26% of women and 8% of men in the USA have suffered from maltreatment by intimate partners in the form of physical assault, rape, or stalking.¹¹ Victimization in adulthood has been strongly tied to abuse during childhood.^{12,13} While maltreatment as an adult is unfortunate and sometimes tragic, there is evidence that childhood is an especially vulnerable time period from a neurobiological perspective with potentially greater health-related consequences.

MALTREATMENT AND MIGRAINE

In the current literature on maltreatment and headache, there is limited data specific to migraine, diagnosed using standardized International Headache Society (IHS) criteria.¹⁴ In adults there are 4 studies that specifically address the lifetime prevalence of self-reported physical or sexual abuse in migraineurs diagnosed using IHS criteria.^{8,15–17} The first was a retrospective chart analysis of over 160 adult headache clinic patients, in which 40% of chronic daily headache (CDH) and 27.3% of episodic migraine patients reported a lifetime history of physical and/or sexual abuse.¹⁵ The second study, a multi-center headache clinic-based survey study of 949 adult female migraineurs, reported a lifetime prevalence of 24% for self-reported physical abuse and of 25% for sexual abuse.⁸ In the third study, also a multicenter headache clinic-based survey, of over 750 adults with migraine, 30.8% with CDH and 26.1% with episodic migraine reported physical abuse, while 27.7% with CDH and 29.4% with episodic migraine reported sexual abuse at some point in their lifetime.¹⁶ In the most recent study, in which 2066 post-partum Peruvian women were interviewed, women with lifetime experiences of sexual or sexual violence had increased odds of having migraine meeting IHS criteria (adjusted odds ratio [aOR] 1.44, 95% confidence interval [CI] 1.19, 1.75) and the odds were increased further in those with symptoms of depression (aOR 2.25, 95% CI 1.75, 2.28).¹⁷

A number of practice-based^{18,19} and population-based studies^{20–26} have demonstrated at least a modest association between headache and childhood abuse, although many are limited to women or to 1 abuse type (Table). In the ACE Study, participants of both sexes were queried regarding 8 types of adversity, including emotional, sexual, and physical abuse. Participants were, however, asked only 1 headache-related question, “Are you troubled by frequent headaches?” Frequent headache was nearly 3-fold more common in women than men and associated with each separate type of adversity.²⁶ Furthermore, there was a positive correlation between the number of adverse childhood events (ACE score) and the prevalence of frequent headache. Despite the higher ACE scores in women, the dose–response relationship was present in both sexes, suggesting that the link of abuse and headache was not sex-dependent (Figure).

Not only does headache appear to be related to childhood maltreatment, headache in the abused is more disabling and frequent, including being more likely to be continuous and to “transform” from episodic to chronic.²⁷ At least for emotional abuse, these associations with a more severe headache phenotype appear to be independent of other factors, including depression, anxiety, lower educational attainment, obesity, smoking, that are associated with both chronic headache frequency and childhood maltreatment. In this context, it is interesting to note that although emotional abuse has received less scientific and public attention, it may have more lasting consequences and be particularly deleterious when combined with other abuse types.²⁸

There has been a growing interest in the relationship of childhood maltreatment and a variety of pain disorders related to migraine. Overall, studies suggest an association between maltreatment and painful disorders,²⁹ but many factors play into the strength of the association including abuse type, timing, intensity, duration, and relationship of the victim to the perpetrator. The finding that with a greater number of different types of abuse experienced in childhood, the greater the likelihood of multiple pain disorders in adulthood³⁰ supports a link between abuse and pain, but controversy still exists.^{31,32}

Limitations of Past Research

The use of self-report of past events introduces the limitation of an individual’s memory, and the influence of disease status, such as depression, on the memory process. These

factors may introduce what is referred to as recall bias into a study, particularly those with a retrospective case-control design.³³ Reluctance to report embarrassing behaviors may lead to intentionally incorrect responses to a personal history questions, a phenomenon known as response bias. When studying childhood trauma in an adult population, the physical and psychologically traumatizing nature of the event, the time elapsed between the event and the interview, the stigma attached to being a victim, and the current psychological state (eg, depression) could each play a role in memory and perception. In the case of depression which is associated with both abuse and pain, 4 studies from general populations^{25,34–36} have established that although depression influences (to a degree varying between 0% and 33%) the strength of the abuse-pain association, an independent relationship exists.

Despite these caveats, studies in healthcare-seeking populations, with persons who may be more prone to have a condition but also to give positive responses to questions, have similar results to those from non-clinical students and general populations. Furthermore, results from 3 prospective studies support the abuse-pain relationship. One demonstrated that abused children were at increased risk to develop pain later during childhood.³⁷ Another found that in adults who were pain-free at study enrollment, those who reported having been sexually abused in childhood were more likely to report back pain, and related physical limitations, on 2-year follow-up.³⁸ A third study using longitudinal data of over 9000 persons from the National Population Health Survey in Canada identified a moderate relationship between arthritis pain developing in adulthood and psychological trauma in childhood or adolescence.³⁹ The debate regarding the abuse-pain relationship is mainly fuelled by the negative findings from 2 prospective case-control studies^{36,40} in which adults, interviewed regarding pain complaints years after court-documented evidence of abuse as children, reported no increase in pain prevalence. One possible explanation for the discrepancy between results of prospective and retrospective studies is that identification of abuse during childhood leads to treatment that dampens the future effects on health. It is also possible that the use of court documents to define an individual as abused is inaccurate because of the fact that abuse is an under-reported event. This second explanation is supported by the finding that when childhood abuse was defined by self-report rather than by court document,⁴⁰ some in the “non-abused” control group (ie, without court-documented abuse) reported having been abused, thus becoming cases. In the analysis of the redefined groups, a relationship of abuse with pain emerged.

THE NEUROBIOLOGY OF CHILDHOOD MALTREATMENT

As we have outlined, epidemiological studies demonstrate that (1) women are more likely than men to experience childhood maltreatment; (2) childhood maltreatment is associated with painful conditions, including migraine. In the following paragraphs, we will explore the evidence that childhood maltreatment leads to neurobiological sequelae, some with sex-specific differences, that support the plausibility of a causal link to headache pain.

Functional Changes

Under normal circumstances, stress precipitates a constellation of adaptive responses in the neuroendocrine and autonomic systems that at a central level enhance arousal and cognition, and at a peripheral level modulate immune and cardiovascular function.⁴¹ The neuroendocrinological response to stress is characterized by hypothalamic release of corticotrophin-releasing hormone (CRH), the key mediator to the anterior pituitary's production and release of adrenocorticotrophin (ACTH), which in turn stimulates production and release of glucocorticoids from the adrenal cortex. Systemically circulating glucocorticoids regulate the (hypothalamic-pituitary-adrenal) HPA stress response via negative feedback to the hypothalamus, anterior pituitary and hippocampus. A decrease in

glucocorticoid levels or impaired glucocorticoid receptor function might then lead to increased stress responsiveness.

There is considerable preclinical and clinical evidence that chronic early life stress results in long-term changes in HPA axis function and regulation typified by hypersecretion of CRH and ACTH.⁵ The initial hypersecretion of cortisol may over time lead to blunting of the cortisol response to CRH and ACTH⁴² and relative glucocorticoid resistance.⁴³ The longitudinal development of HPA dysregulation is suggested by a study of morning cortisol levels measured over the period from girlhood through young womanhood in persons experiencing childhood sexual abuse. Initially, there was cortisol hypersecretion, but over time cortisol hyposecretion ensued.⁴⁴ Progressive or cumulative dysregulation of the HPA axis over time as a consequence of early stress is further suggested by the findings of a cross-sectional study of physically and psychologically healthy adults. In this study the cortisol response to a stress challenge in those who reported childhood emotional abuse was more blunted (compared to controls) in the older than in the younger cohort (ie, 36–61 years vs 18–35 years).⁴⁵ Lower cortisol levels in response to stress have also been reported in depression, a common condition in abused populations, but data suggest that childhood maltreatment, a condition commonly associated with depression, determines a distinct HPA stress profile.⁴⁶ Dysfunction of the HPA axis has also been implicated in a variety of chronic pain conditions. Of note, lower cortisol levels have been reported in persons with fibromyalgia, chronic pelvic pain, endometriosis, and headache.^{47–49} Data specific to migraine showed normal HPA axis function in episodic migraine,⁵⁰ but abnormal HPA axis activity in chronic migraine (CM), including in the setting of medication overuse.^{51,52} The CM studies showed higher, rather than lower, cortisol levels. History of early life stress and depression was not factored into the analysis.

Childhood maltreatment is more common in girls than boys, but when abused, are girls more vulnerable to HPA stress axis dysregulation than boys? A 1987 meta-analysis of 12 psychophysiological studies examining the relationship between sex and stress responsiveness suggested that the sex-related response differences were limited,⁵³ but more recent studies using tests better able to generate adequate HPA axis responses are intriguing. These studies, summarized in a review by Kajantie, demonstrate that differences between age-matched men and women are minimal in the unstressed state, but between puberty and menopause women generally showed lower HPA axis and autonomic responses following a psychological stressor.⁵⁴ When the stress response is dissected, the male hypothalamus shows increase sensitivity and CRH leading to increased ACTH synthesis. The premenopausal female adrenal cortex is, however, more sensitive to ACTH, thus counterbalancing the lower ACTH concentrations, and minimizing differences in the production of cortisol. Cortisol bioavailability, however, is decreased in women because estrogen stimulates the synthesis corticosteroid binding globulin.⁵⁵ The complex effects of estrogen on HPA axis responsiveness are also reflected by estrogen receptor-beta inhibition of arginine vaso-pressin (AVP) gene transcription and synthesis.⁵⁶ AVP is produced in the hypothalamus and with potentiates ACTH release in the pituitary⁵⁷ in addition to directly stimulating cortisol secretion in the adrenal cortex.⁵⁸ In a CRH stimulation test combined with AVP administration, young women show greater plasma ACTH and total cortisol responses compared with men,⁵⁹ indicating an increased sensitivity of the female pituitary to AVP. Recently, an estrogen-responsive portion of the promoter region of the CRH gene has been identified, and the significance of this bears exploring.⁶⁰

Early stress also results in a number of other functional changes that may play a role in migraine. Preclinical studies demonstrate that stress increases dopamine levels and attenuates serotonin levels in the amygdala and nucleus accumbens.^{61–63} It also decreases serotonin 1B (5-HT1B) receptor expression⁶⁴ as well as reduces the density of both central

benzodiazepine receptors and high-affinity GABA-A receptors.⁶⁵ Other functional changes linked to early life stress include enhanced electrical irritability in limbic structures, and reduced activity of the cerebellar vermis,⁶⁶ which, with the highest density of glucocorticoid receptors during development, may be particularly vulnerable to the effects of stress hormones.^{67,68}

Studies in migraineurs demonstrate an ictal rise in inflammatory cytokines, as well as evidence of a baseline elevation in pro-inflammatory cytokines.^{69,70} Psychological stress also leads to the release of pro-inflammatory cytokines and this has been postulated as a link to the development of chronic pain.^{71–73} Given the growing epidemiological evidence of an association of early abuse and migraine, it is noteworthy that a recent biomarker study has demonstrated inflammatory changes in adults exposed to maltreatment in childhood.⁷⁴ Sex differences in these clinical studies have not been examined, but the preclinical finding that estradiol inhibits pro-inflammatory cytokine gene expression, nuclear factor kappa B (NFkB) activation, and pro-inflammatory cytokine production, suggests they may occur.^{75,76}

Structural Changes

Early stressful experiences have been associated with a number of structural neurobiological consequences including attenuated development of the left prefrontal cortex, amygdala, and hippocampus,⁶⁶ all structures which interact with each other and play important roles in the pain matrix, as well as in the stress response. The hippocampus, for instance, down-regulates the HPA stress response, and hippocampal atrophy may therefore result in a prolonged response to psychological stressors. The size of the corpus callosum is also reduced in persons who have early stressful experiences. The corpus callosum of boys appears to be particularly vulnerable to the effects of neglect, while that of girls appears to be more susceptible to the adverse effects of sexual abuse.⁷⁷ Animal studies indicate that early experience affects the number of corpus callosum axons in females, but only the diameter of corpus callosum axons in males.⁷⁸ Hence, there may be marked gender differences in the nature, and extent of corpus callosum vulnerability.

Age of the persons at the time of abuse may also be an important determinant of structural cerebral changes, with different regions showing unique sensitive periods to the effects of stress. In a recent volumetric analysis of brain magnetic resonance imaging scans from young women who had been victims of repeated childhood sexual abuse and healthy female controls, it was found that hippocampal volume was reduced in association with abuse at ages 3–5 years and ages 11–13 years. Corpus callosum was reduced with childhood sexual abuse at ages 9–10 years, and frontal cortex was attenuated in subjects with childhood sexual abuse at ages 14–16 years.⁷⁹

Genetics

There has been growing evidence that certain genotypes predict vulnerability to environment stressors, including early adverse experiences. This is referred to as a gene–environment (G × E) interaction. The serotonin transporter (5 serotonin transporter-linked polymorphic region [HTTLPR]) genotype, for instance, appears to moderate the effect of childhood maltreatment on adult psychiatric conditions, such as depression and post-traumatic stress disorder.^{80,81} With regards to sex-related differences in the G × E interaction, one study suggested that of those with the vulnerable short/short (SS) genotype, girls were more depressed, and boys less depressed than their peers with long/long (LL) and short/long (SL) genotypes.⁸² In another study of adolescents, evidence for G × E held only for girls.⁸³ The corticotropin releasing hormone receptor 1 (CRH-R1) gene has also been of considerable interest, because it has been associated with protection against adult depressive symptoms in

individuals, particularly men, who were maltreated as children.⁸⁴ A recent study showed that a CRH-R1 gene polymorphism interacts with male sex to decrease the cortisol response in the dexamethasone-corticotropin-releasing factor (CRF) test.⁸⁵

Epigenetics

Recent studies have highlighted the possibility that childhood abuse and early life stress may become hard-coded into the genome, creating an epigenetic memory of events that leads to impaired health at a later date. In a preclinical study,⁸⁶ early life stress in mice caused enduring hypersecretion of corticosterone and alterations in passive stress coping and memory accompanied by a persistent increase in AVP expression in neurons of the hypothalamic paraventricular nucleus, demonstrating that early life stress can lead to epigenetic changes that affect the neuroendocrine system as well as behavior. In a study of suicide victims stratified by childhood abuse history, post-mortum brain examination revealed an altered cytosine-methylation pattern in the promoter region of the hippocampal glucocorticoid receptor gene of the abused.⁸⁷

IMPLICATIONS FOR TREATMENT

No studies on the impact of childhood maltreatment on treatment response in migraine have been conducted, but the depression literature suggests the possibility of a lower rate of recovery in the abused^{88,89} and a need for tailoring therapy to address emotional, cognitive, behavioral issues as well as the neurobiological basis of disease.^{90,91} Preclinical studies suggest that treatment with serotonin-specific reuptake inhibitors may actually reverse some of the neurobiological effects of maltreatment, including decreasing the CRH response to stress.^{64,92} The emerging field of epigenetics presents the prospect of new therapies, including such strategies of methyl supplementation.⁹³ There are also a number of psychotherapeutic approaches to treat adults abuse in childhood, including emotion-focused therapy.⁹¹ Given the high prevalence of maltreatment in this population, determining whether knowledge of this history can guide differential treatment strategies in migraine and comorbid conditions is an exciting new avenue of research.

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Figure.

Prevalence of frequent headaches by Adverse Childhood Experiences (ACE) score and sex. Estimates adjusted for age, race, and educational attainment; trend in increasing prevalence by ACE score is significant for both men and women ($P < .001$).²⁶

Table

Association of Childhood Maltreatment and Headache

Reference Number and Year of Publication	Study Design	Population	Headache Diagnosis	Childhood Maltreatment History	Association of Headache and Maltreatment
18, 1991	Cross-sectional survey	231 adults, HMO sample	No specific headache diagnoses	Childhood sexual abuse	Chronic headache twice as common in abused
19, 1997	Cross-sectional survey	1931 women, multicenter primary care sample	No specific headache diagnoses	Childhood abuse	Headache more common in abused, prevalence ratio = 2.2, 95% CI 1.7–2.8
20, 1999	Meta-analysis	7502 pooled community-based sample of youth and adults	No specific headache diagnoses	Childhood sexual abuse	Headache more common in abused, OR = 1.9, 95% CI 1.2–3.0
21, 1999	Cross-sectional survey	1225 women, HMO random sample	No specific headache diagnoses	Sexual maltreatment	Headache more common in maltreated, OR = 1.3, 95% CI 1.1–1.6
22, 2003	Cross-sectional survey	3032 adults, community sample	Self-reported migraine	Childhood physical abuse	Migraine more common in frequently abused, OR = 2.7, 95% CI 1.2–5.8
23, 2004	Cross-sectional survey	4645 students, aged 13–15 years in Taiwan	Diagnosed by neurologists, CDH defined as a headache frequency of at least 15 days with headache per month for at least 3 months	Childhood physical abuse	Physical abuse more common in students with CDH, 10% vs 0%, $P = .012$
24, 2010	Cross-sectional survey	3955 students, aged 13–15 years in Taiwan	Diagnosed by neurologists, Migraine or probable migraine, by ICHD 2 criteria	Childhood physical maltreatment	Migraine and probable migraine more common in abused, OR = 1.6, 95% CI 1.4–1.9
25, 2010	Cross-sectional survey	2005 Canadian Community Health Survey was undertaken using a regional sample of 13,089 men and women	Migraine, self-reported, physician-diagnosed	Childhood physical abuse	Migraine was more common in abuse, OR = 1.77, 99% CI 1.39–2.25, adjusted for age, race, sex
26, 2011	Cross-sectional survey	17,337 adults in HMO in San Diego, CA, USA	Frequent headaches, self-reported	Childhood abuse, including emotional, physical, sexual, and emotional	Frequent headaches were more common in emotional abuse (OR = 1.6, 95% CI 1.4–1.7), physical abuse (OR = 1.4, 95% CI 1.3–1.5), and sexual abuse (OR = 1.3, 95% CI 1.1–1.4)

CDH = chronic daily headache; CI = confidence interval; HMO = health maintenance organization; ICHD = International Classification of Headache Disorders; OR = odds ratio.