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REVIEW

Struggling Can Also Show on the Inside: Current Knowledge of the Impact of Childhood Maltreatment on Biomarkers in Mood Disorders

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Abstract: The link between childhood maltreatment and mood disorders is complex and involves multiple bio-psycho-social factors that affect multiple molecular pathways. The present narrative review aims to clarify the current understanding of the impact of childhood maltreatment on biomarkers in patients with mood disorders and their first-degree relatives. Neurotransmitters, such as serotonin, dopamine, norepinephrine, and hormones (eg the stress hormone cortisol), play a crucial role in regulating mood and emotion. Childhood maltreatment can alter and affect the levels and functioning of these neurotransmitters in the brain; further, childhood maltreatment can lead to structural and connectivity changes in the brain, hence contributing to the development of mood disorders and moderating illness presentation and modifying response to treatments. Childhood maltreatment information, therefore, appears mandatory in treatment planning and is a critical factor in therapeutic algorithms. Further research is needed to fully understand these pathways and develop new treatment modalities for individuals with mood disorders who have experienced childhood maltreatment and effective preventive interventions for individuals at risk of developing mood disorders.

Keywords: biomarkers, childhood maltreatment, mood disorders, biosignatures, biotype

Introduction

Childhood maltreatment is an established risk factor for incident psychiatric disorders, including mood disorders (unipolar depressive disorder (UD) and bipolar disorder (BD)).[1] Childhood maltreatment is defined as exposure to actual or potential harm to a child including physical, sexual, or psychological abuse, neglect, or negligent treatment.[2] More than 10% of children are affected by maltreatment in high-income countries,[3,4] and the prevalence is even higher in low-income countries.[5] Among individuals with UD and BD, the figures are even higher, with approximately 25%,[6] and 40%[7] reporting severe childhood maltreatment, respectively. Further evidence supports that childhood maltreatment increases the risk of mood disorders substantially.[8,9] In addition, childhood maltreatment is associated with an earlier age at onset of mood disorder, a more severe illness course, impaired social functioning[10] including cognitive difficulties,[11] more perceived stress, lower quality of life,[12] sexual health problems,[13,14] and physical diseases.[15,16]

The landmark study by Caspi et al[17,18] showed that the impact of severe life events seems mediated through genetic variation, variations that contributed to an increased vulnerability in maltreated children. Caspi et al found that individuals with two copies of the short allele of the serotonin transporter gene (5-HTTLPR) were more likely to develop depression in response to stressful life events than individuals with one or two copies of the long allele, and this vulnerability was most pronounced in individuals who had experienced severe life events.[19] The study suggested that genetic variations interact with environmental factors, such as childhood maltreatment, to increase the risk of developing mental health problems. Since this

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gene–environment interaction model has been studied extensively, gene-environmental actions initiated in childhood may lead to changes in biological substrates with a long-lasting impact at the individual level.[20,21]

Increasing insight into proteomics, transcriptomics, genomics, and brain imaging has advanced the pathophysiological understanding of mood disorders.[22] However, there is a translational gap in clarifying to what extent such approaches can prove helpful in the clinic and help diagnostics to support a targeted treatment choice and optimize treatment overall.[23] One plausible explanation is that the distinct trajectory from early adverse events to clinical end-points is largely shaped by epigenetic or other modifications regulating the expression of genes.[24] Given that individuals differ in their genetic makeup, they will also vary in their transcriptional response to environmental influences.[24] Thus, at the individual level, an enhanced familial risk for mood disorders may act synergistically with exposure to childhood maltreatment capable of leaving long-lasting biological imprints. This is a pattern previously observed in a longitudinal high-risk study, where the risk of onset of psychiatric illness was higher in individuals carrying the short allele of the 5-HTTPLR who had also experienced more severe life events. The risk was further increased in individuals at familial risk carrying the short allele of the 5-HTTPLR.[25]

The hidden heritability or the heritability gap in severe mental illness, including mood disorders, is a phenomenon in which a significant proportion of the risk of the disorders cannot be accounted for by known genetic variants.[26] This gap may be elucidated by including early life stress in the models acknowledging stress, especially perceived stress, during critical periods in an individual's life (prenatal, postnatal puberty and adolescence). Childhood maltreatment can potentially alter levels of peripheral biomarkers such as markers of inflammation, metabolomics, and oxidative stress, which seems to be mediated by several molecular pathways involving dysregulation of neurotransmitters and hormones. This narrative review aims to clarify the current understanding of the impact of childhood maltreatment on peripheral biomarkers in patients with mood disorders and their first-degree relatives.

Pathophysiology

Homeostasis

Homeostasis is the body's process of maintaining a stable internal environment despite changes in the external environment.[27,28] The brain and body's stress system activates as an adaptive response to environmental stimuli. The initial active response to stressors promotes adaptation "allostasis", and the cumulative change from chronic stress and resulting unhealthy behaviors -"the allostatic load" can lead to disease, eg, diabetes, cardiovascular disease,[29] and also mood disorders ("allostatic overload") (Illustration, please see Figure 1). In the context of childhood maltreatment and mood disorders, homeostasis can be disrupted due to the impact of trauma on the human body's primary stress systems: the immune-inflammatory system, the hypothalamic–pituitary–adrenal (HPA) axis, and the autonomic nervous system.[30] Childhood maltreatment and socioeconomic disadvantage[31,32] may cause changes in these systems, potentially persisting into adulthood, leading to chronic stress and subsequent low-grade inflammation, changes that may trigger early risk factors, eg discrete sleep disturbances as observed in individuals at familial risk for BD.[33] Further, sleep disturbances seem to act as transdiagnostic mediators between childhood maltreatment and psychopathology in children and adolescents.[34] Hence, childhood maltreatment potentially disrupts homeostasis with the risk of inducing long-lasting scar effects even after the trauma has ended (Figure 1).

Childhood maltreatment can lead to changes in peripheral biomarkers and thereby disturb homeostasis, which are mediated by several molecular pathways involving neurotransmitters, inflammatory factors, and hormonal mechanisms. Below is a description of biological pathways of importance for the homeostasis and the current knowledge of possible changes related to childhood maltreatment and mood disorders (for an overview, please see Table 1).

Clinical Studies Including Childhood Maltreatment and Peripheral Biomarkers

Epigenetics

Childhood maltreatment can lead to changes in gene expression through epigenetic mechanisms such as DNA methylation and histone modification. Hence, early life stress can lead to epigenetic modifications, which can alter gene expression and increase the risk for mood disorders.[24] These changes can result in alterations in neurotransmitter systems, the HPA axis, and the immune system, which can contribute to the development of mood disorders in line with findings from a systematic review exploring the

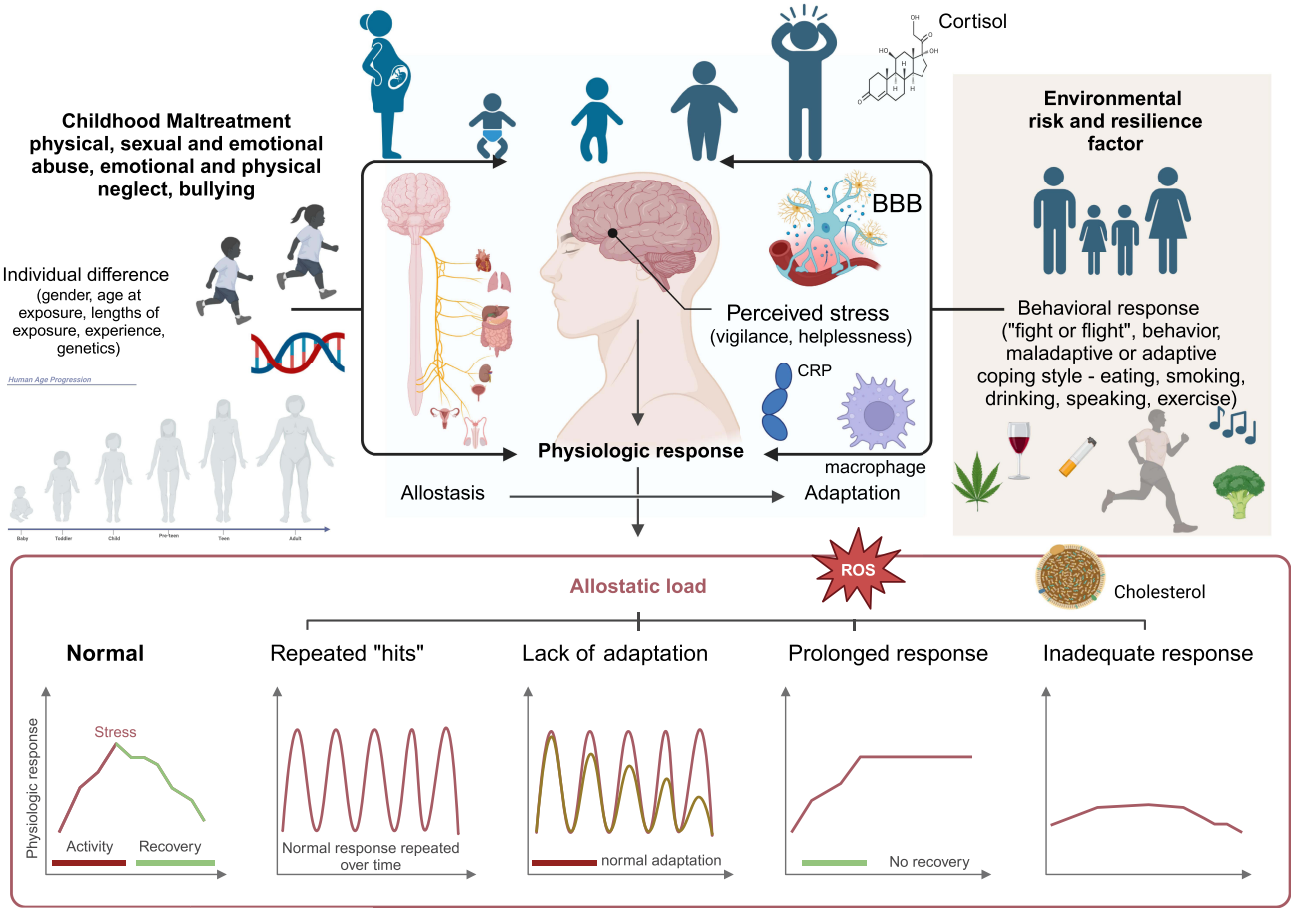

Figure 1 Childhood Maltreatment, Biomarkers, Homeostasis and Mood Disorders. Created with BioRender.com.
Abbreviations: BBB, Blood–brain barrier leakage and neuroinflammation; ROS, Reactive Oxidative Species.

association between epigenetic alterations and childhood maltreatment.[35] Childhood maltreatment further seems capable of accelerating epigenetic ageing long after the adversity occurs in proportion to the total number of experiences.[36] In addition, recent research has suggested that the impact of early life stress may be transmitted across generations through epigenetic

Table 1 An Overview of the Described Biomarkers Linking the Impact of Childhood Maltreatment

Mechanism	Biomarker	Proposed impact of Childhood Maltreatment
Genetic vulnerability	Gene expression and genetic polymorphisms	Changes in the gene expression regulating stress response and emotional regulation. Variations in genes encoding neurotransmitters eg serotonin and dopamine, neurotrophic factors, and inflammatory markers.
Epigenetic Modifications	DNA methylation Histone modifications MicroRNA expression	Altered DNA methylation patterns, particularly in genes associated with stress regulation and emotional processing. Changes in histone acetylation and methylation, influencing gene expression and neurobiological functioning. Changes in microRNA expression, affecting post-transcriptional gene regulation and cellular processes.
Neurotransmitters	Serotonin Dopamine	Changes in the regulation of the serotonergic and dopaminergic systems.

(*Continued*)

Table 1 (Continued).

Mechanism	Biomarker	Proposed impact of Childhood Maltreatment
Immune dysregulation and inflammation	Cytokine levels	Elevated levels of pro-inflammatory cytokines (eg, interleukin-6, tumor necrosis factor-alpha) because of chronic stress and immune dysregulation.
	C-reactive protein (CRP)	Increased CRP levels indicative of systemic inflammation and heightened immune response.
Neuroendocrine changes	Cortisol	Elevated cortisol levels due to chronic stress and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis.
Metabolomics	Lipids Glucose Insulin Ghrelin Leptin	Induce changes in the metabolic pathways involved in energy production, metabolism, and cellular signaling. Effects on insulin sensitivity and glucose metabolism, which can increase the risk of insulin resistance, type 2 diabetes, and metabolic syndrome later in life. Limited data, however, both hormones play a key role in regulating energy balance, appetite, and metabolism.
CNS markers	Brain Derived Neurotrophic Factor (BDNF) S100B	Can lead to changes in BDNF levels and impairments in neuroplasticity. Can elevate S100B levels that are associated astroglia activation and neuroinflammation.
Oxidative stress	Malondialdehyde (MDA): 8-hydroxy-2'-deoxyguanosine (8-OHdG):	Increased production of reactive oxygen species and oxidative damage to cellular structures, including DNA, proteins, and lipids. Impaired antioxidant defenses and reduced capacity to mitigate oxidative stress.
Neurodevelopmental Changes	Brain structure, Brain function Connectivity Network architecture	Alterations in brain regions involved in stress response (eg, amygdala, hippocampus, prefrontal cortex, and hippocampus, impacting cognitive and emotional processing). Changes in neuroplasticity and synaptic connectivity.

modifications.[37] For example, childhood maltreatment has been associated with increased methylation of the glucocorticoid receptor gene, which can lead to dysregulation of the HPA axis and an increased risk for depression.[38]

Hence, as described, studies found disturbances in neuro-immunological pathways and related peripheral markers linking childhood maltreatment and severe mental disorders. The findings of chromatin and histone modifications in patients with severe mental illness and childhood maltreatment support the idea that those epigenetic changes can play a pivotal role in mediating the effects of childhood maltreatment. However, these findings are biased by numerous methodological issues, selection bias, heterogeneity of measurement instruments, and lack of control over the use of psychotropic agents that have an established effect on DNA methylation.[39]

Neurotransmitter Systems

Childhood maltreatment can lead to dysregulation of neurotransmitter systems, particularly the serotonergic and dopaminergic systems, which are known as essential transmitters in the regulation of mood, reward, and motivation. Serotonin engages in regulating mood, and changes in its availability are linked to the development of mood disorders.[40,41] Dopamine, on the other hand, engages in reward processing and motivation, and changes in its availability have been linked to the development of addiction and other psychiatric disorders. However, dopamine receptor agonist also seems to have antidepressant effects in studies of major depressive disorder (MDD) and bipolar depression.[42]

Immune Dysregulation and Inflammation

Inflammation is associated with a range of physical and mental health problems, including cardiovascular disease, type 2 diabetes, and depression. It is hypothesized that inflammatory markers have a direct effect on neural–glial integrity and function and indirectly on neurotransmitter systems and neurocircuits.[43] Childhood maltreatment seems to be associated

with various changes in peripheral inflammatory markers in adulthood, which can have implications for both physical and mental health.[44] Childhood maltreatment has been linked to increased levels of C-reactive protein (CRP) and interleukin-6 (IL-6) in adulthood.[45] These changes can lead and contribute to a pro-inflammatory state in early adulthood, presumably driven or induced by childhood maltreatment,[46] and may contribute to nonspecific markers of inflammation and early metabolic and immune dysfunctions in young adults at or with emerging mood disorder.[47,48] A study including more than 2000 participants identified that childhood maltreatment had a significant positive relationship with inflammation as well as depressive symptoms.[49] Further, a study of 164 patients with MDD and 301 healthy control persons[50] investigated the associations between childhood maltreatment and levels of 41 inflammatory markers in the two groups. It revealed that childhood maltreatment did not exert any effect on levels of inflammatory markers. Nevertheless, a systematic review of the association between child maltreatment and systemic inflammation in adulthood concluded that there was evidence from prospective studies that childhood maltreatment is associated with elevated CRP in adulthood.[51]

The Hypothalamic-Pituitary-Adrenal (HPA) Axis

The HPA axis regulates the stress response and is a crucial mediator of the effects of childhood maltreatment on peripheral biomarkers including inflammatory markers. Childhood maltreatment can lead to dysregulation of the HPA axis, with prolonged increased cortisol levels and decreased cortisol responses to stress, both seen in patients with MDD[52] and BD.[53] Anyhow, these findings were not observed consistently, and cortisol levels were not a risk factor for onset in healthy high-risk relatives.[25,54,55] However, HPA dysregulation can lead to disturbances in the diurnal cortisol regulation[56] and persistent higher baseline levels measured as higher hair cortisol levels in individuals with schizophrenia and BD exposed to childhood trauma.[57] In another study, hair cortisol levels were higher in patients newly diagnosed with BD but not in their unaffected relatives, compared with healthy control individuals; however, childhood trauma was not associated with hair cortisol levels within patients with BD.[54] Clinically, the HPA axis regulates the diurnal rhythm. Accordingly, changes in the stress response system may result in sleep problems, which are well-known forerunners for new mood episodes and observed in individuals at risk of mood disorders.[33] Additionally, as previously described, childhood trauma is associated with long-term sleep problems,[58] which are a predictor of later onset of mood disorders.[59,60]

Metabolomics

Childhood maltreatment is weakly to moderately associated with physical inactivity, overweight, and obesity.[61] Studies of MDD and anxiety, as well as BD, found that participants with a history of childhood maltreatment more often have physical health problems, including a higher prevalence of aberrant metabolic syndrome components (waist circumference, triglycerides, high-density lipoprotein, cholesterol, blood pressure, and glucose).[62,63] Notably, these associations seem driven by childhood maltreatment and unaffected by lifestyle factors.[62] Another study showed that patients with MDD and childhood trauma had higher triglyceride levels and lower high-density lipoprotein levels compared with patients with MDD without childhood trauma.[64] Finally, looking at the appetite-regulating hormones ghrelin and leptin, a recent study, including 200 young adults, found that childhood trauma was statistically significantly associated with lower ghrelin levels when adjusted for body mass index (BMI).[65] In contrast, leptin levels were significantly higher in the group exposed to childhood trauma but no longer significant when accounting for BMI.[65]

Brain Derived Neurotrophic Factor

Another biomarker of interest is brain-derived neurotrophic factor BDNF, which promotes neuronal differentiation, synaptic connectivity, neural repair, and survival. Changes in BDNF levels seem closely associated with current mood episodes.[66] However, BDNF levels do not act as a predictor of the onset of mood disorders,[67] though lower levels were found to be associated with childhood maltreatment and a number of depressive episodes in one study.[68] Another study, including children with and without trauma, found that childhood trauma was associated with increased BDNF levels.[69] Nevertheless, a review of studies of the effect of childhood maltreatment on BDNF levels found no differences comparing the group exposed to childhood maltreatment to the non-exposed group.[70]

Oxidative Stress

In addition to inducing changes in the regulation of inflammatory and cortisol levels, childhood maltreatment may induce changes in other peripheral markers such as measures of telomere length and oxidative stress. Telomeres are protective caps at the end of chromosomes that shorten with age, and childhood maltreatment has already been linked to accelerated telomere shortening in childhood.[35] Oxidative stress markers function as a proxy for this process. It is linked to various diseases, including cardiovascular diseases,[71] type 2 diabetes,[72] and severe mental illness.[73] One study[74] found an association between childhood maltreatment and oxidative stress markers in adulthood both in patients with mood disorders, their first-degree relatives, and healthy control persons, suggesting that childhood maltreatment overall, notably emotional abuse and emotional neglect, seems associated with enhanced systemic damage to DNA and RNA in adulthood.[74] Further, individuals with mood disorders reported a higher prevalence of childhood maltreatment. Thus, childhood maltreatment may possibly have induced higher levels of nucleoside damage by oxidation in adulthood, possibly leading to an increased risk of developing mood disorders.[74] Another study, including patients with mood disorders and healthy control persons, found that childhood maltreatment and oxidative stress had a cumulative effect on the severity of depression, suggesting that childhood maltreatment could influence oxidative stress pathways, thereby causing a long-term adverse impact on the severity of depression.[75]

S100B

S100 is a calcium binding protein located in glial cells and a potential biomarker in mood disorders. S100B has been found to be elevated in acute mood episodes[76] and seems positively correlated with the severity of MDD.[77] S100B is an indicator of blood–brain barrier disruption, and childhood maltreatment can potentially affect the integrity of the blood–brain barrier indicated by the associated increase in s100B levels in young patients exposed to childhood trauma compared with young patients without trauma.[78] These findings suggest that there may be a link between childhood maltreatment and alterations in S100B levels. However, this intriguing association requires thorough investigation and further studies.

Structural Brain Changes

Childhood maltreatment is associated with changes in brain structure, function and connectivity and network architecture. Childhood maltreatment is associated with shifted developmental timing of regions with high gray matter density, particularly in the front limbic region's hippocampus, amygdala, and prefrontal cortex.[79] In concordance with the latter, altered functional connectivity in relation to adversities was also observed in a three-wave longitudinal study (9–19 years), alteration that seems to influence cognitive and emotion processing networks.[80] To study the course and potential changes in neurodevelopment, eg, the impact of severe stress exposure due to childhood maltreatment may change the synaptic plasticity, leading to changes in the consolidation of the trajectories that may hinder a solid mature structural plasticity,[60] it is informative to combine measures of peripheral biomarker with brain imaging prospectively. The described changes will impact the overall network functioning. Changes that may finally lead to changes in behaviors, for example, binge drinking, eating disorders, self-harm, or cannabis use, at an early age trigger a vicious cycle where new environmental factors add to changes in biological substrates.

Discussion

Childhood maltreatment is a significant risk factor in the development and progression of mood disorders. Childhood maltreatment may mediate this effect by direct epigenetic modifications (eg, methylation) or indirectly by changing the individual's behaviour, causing a higher epigenetic load. Emphasizing neurodevelopment as a sensitive temporal window in which individuals experience intensely influences the development of a specific phenotype.[81] Advances in understanding the pathophysiology of mood disorders, including understanding of the potential overruling pathological impact of severe life events and childhood maltreatment pathological effects, can expand the overall research scope when studying risk and resilience factors in individuals with mood disorders. However, few longitudinal studies have analyzed the possible biological changes in peripheral biomarkers that may occur after the experience of childhood maltreatment. This review emphasizes several biological pathways and circuits as potential mediators of long-lasting brain changes that could be associated with emotional and behavioral changes and, in the long run, capable of inducing psychopathology.

A comparison of the impact of childhood maltreatment across diagnoses shows that findings from mood disorders align with findings from transdiagnostic samples, including inpatients with psychotic, mood, and personality disorders.[82] A recent meta-analysis of childhood trauma in psychosis emphasized that unidirectional biological mechanisms linking trauma to clinical presentations are still lacking and suggest an affective pathway between childhood maltreatment and psychosis.[83]

Hen and Egg

The hen and egg problem refers to the difficulty in determining whether childhood maltreatment causes mood disorders or whether individuals with a predisposition to mood disorders are more likely to experience childhood maltreatment. Both factors likely play a role, as childhood maltreatment can impact biological systems that contribute to the development of mood disorders. In contrast, individuals with a genetic or other predisposition to mood disorders may be more vulnerable to the effects of childhood maltreatment. Further, they may change behavior after trauma, eg, react by self-harming, smoking, drinking, or substance abuse. These changes in behavior can include an increased risk for the experience of new adversities and trauma, a pattern also observed in individuals at familial risk for mood disorders with a risk of intergenerational transmission of trauma.[84] Individuals who have experienced childhood maltreatment may further have difficulties forming healthy relationships, experiencing pleasure, or regulating their emotions, even years after the trauma has occurred, leading to a vicious cycle where adverse childhood experiences trigger health-harming behavior in young adulthood.[85,86] For example, individuals who have experienced more childhood maltreatment more often drink and smoke,[87] habits that can also induce epigenetic changes. These changes may further influence the hypothalamic–pituitary–adrenal (HPA) axis and, thereby, the stress response.[88] In line with these observations, a recent study of mothers with a history of anxiety or depression and their infants found that maternal childhood trauma seemed prominent in altering maternal and infants' long-term cortisol levels.[89]

The Impact of Sex

There is evidence that points towards the fact that the impact of childhood maltreatment on peripheral biomarkers may differ between sexes.[90] Females seem more susceptible to alterations in both the neurotransmitter and the immune system compared to males.[91] One study found that childhood maltreatment was associated with increased IL-6 levels in females but not in males. However, another study found that males may be more susceptible to dysregulation of HPA Axis in response to childhood maltreatment than females. Nevertheless, the described sex differences in the potential biological effects of childhood maltreatment suggest that interventions targeting the involved biological systems may vary between male and female sex and need to be more sex specific.[92] Sex differences in the epigenetic response to childhood maltreatment are not widely studied[93] but may play a role in mediating sex differences in the biological effects of childhood maltreatment. So, in conclusion, prospective studies on differences between sexes and the impact of childhood maltreatment on biomarkers are highly warranted.

Factors Due to Trauma Nature, the Type of Trauma, Intensity, and Duration

The impact of childhood maltreatment on mood disorders is influenced by several factors related to the nature, intensity, and duration of the trauma. One factor is the type of trauma experienced. Childhood maltreatment can take various forms, including physical, sexual, and emotional abuse, as well as emotional neglect[94] and bullying.[95] Not all forms exert the same impact or trigger the same response.[96] Studies have found that all forms of childhood maltreatment increase the risk of mood disorders, but specific types of traumas may have a more substantial impact than others. For example, emotional neglect and sexual abuse seem linked to a higher risk of depression.[97]

Another factor is the intensity of the trauma. The severity and frequency of childhood maltreatment can influence the risk of developing mood disorders later in life. Studies have found that individuals who have experienced more severe, frequent, or chronic trauma are more likely to develop mood disorders.[98] The duration of the trauma is also a key factor. Childhood maltreatment that is chronic or long-lasting can have a more significant impact on the development of mood disorders than trauma that is short-lived. Further, there is evidence of a dose–response relationship with those exposed to multiple forms of maltreatment having more than three times increased risk of developing severe mental illness.[9]

Furthermore, the age of exposure to trauma can also impact the risk of mood disorders. Childhood maltreatment that occurs during sensitive periods of brain development, such as early childhood or adolescence, may have a more profound and long-lasting impact on the brain and increase the risk of mood disorders, as seen from a review including 58 studies that found that age of exposure in middle childhood (6–13 years) had the highest risk of depression, followed by late childhood (12–19 years) and early childhood (0–6 years).[99]

Limitations

Current evidence supporting a link between childhood maltreatment and changes in biological substrates leading to more reactive biological circuits is based on studies of adult patients with mood disorders that retrospectively report a history of childhood maltreatment rather than longitudinal studies of children. Therefore, other factors, especially environmental factors arising as a response to trauma, cannot be discounted. A topic analyzed in a systematic review and meta-analysis[100] that included 16 studies, with data on the agreement between retrospective and prospective measures on childhood maltreatment, showed substantial discrepancies. However, the study also suggested that it would be better if retrospective measures included interviews rather than questionnaires. Further, the authors noted that retrospective and prospective measures of childhood maltreatment might identify different groups, which could mean that children who experience childhood maltreatment and are observed prospectively may express a different risk pattern than retrospective adult reports.[100]

As mentioned before, a history of childhood maltreatment is associated with an earlier age of onset and an increased number of episodes after illness onset, also after adjusting for the current mood at the time of the assessment.[101] It is plausible that expression levels of genes associated with mood disorder and exposure to early life trauma[102] are determinants of clinical outcomes. Identifying these changes as peripheral biomarkers that could support or determine the optimal pharmacological and psychotherapeutic modalities at an individualized level[91] and could provide more personalized targeted treatment. This aspect emphasizes the importance of including a structured clinical assessment of childhood maltreatment, eg, in the clinical interview and using patient-reported outcomes in everyday clinics to guide treatment choices and prevent an overall poor treatment response.[103] Nevertheless, the field still needs to fill the gap between research data and routine practice[104] as there is a lack of evidence-based recommendations for treating individuals with mood disorders exposed to childhood maltreatment.

The present studies investigating childhood maltreatment and biological markers are limited by methodological issues, including a low degree of methodological standardization (eg, lack of consistency concerning the time of day when the biological samples were collected, variations in storage time, and use of different assays), and variations in study quality (eg, poorly characterized samples, small sample sizes, and unexplained between-study heterogeneity[105]). Potential bias in individual studies, heterogeneity of measurement instruments, and lack of standard operating procedures for personal assessment, including psychotropic agents, can lead to non-replication and failed studies.[66] Furthermore, most studies examining biomarkers and childhood maltreatment are cross-sectional, hindering causal inference between childhood maltreatment and biomarker changes. Along this line, most studies only investigated biomarkers of one biological system, eg, the immune system biomarkers or genetic biomarkers.[106] However, these systems are integrated. For example, changes in the HPA axis may also lead to changes in the immune system, oxidative stress generated tissue damage, and connectivity changes in the brain. Additionally, biological circuits may express different responses according to the duration and intensity of the stressor: a single acute event, repeated events, or chronic stressors.

Biomarkers encompass a range of biological measures, including neuroimaging findings, genetic markers, hormonal levels, and inflammatory markers. Childhood maltreatment also encompasses various forms, such as physical abuse, emotional neglect, sexual abuse, witnessing violence, and bullying. All forms may impact biomarkers. However, the specific nature and severity of the effect on biomarkers may vary due to the type of maltreatment.[107] Thus, different types of maltreatment may be associated with varying trajectories of both biological changes and psychopathology. Future research should, therefore, link a broad range of biomarkers with specific types of maltreatment and psychopathology to understand their unique biological correlations. Longitudinal studies that include repeated biomarker measures and follow individuals, eg, high-risk individuals, as done in VIA studies[108] over time from childhood through adulthood, are essential to observing the long-term effects of childhood maltreatment on biological processes and identifying critical periods of vulnerability or resilience. Including high-risk individuals offers a way of studying a relatively rare outcome

and can provide insight into potential risk factors and causal pathways without confounding effects of changes due to illness and treatment, including psychotropics.[109,110]

Finally, in this narrative review, we aimed to give a relevant overview of childhood maltreatment and biomarkers in patients with mood disorders. Thus, we did not apply rigorous research guidelines; consequently, we may have overseen relevant aspects of the topic.

Implications

Clinically, clinicians need to know and recognize that patients with mood disorders and a history of childhood maltreatment often fail to respond to treatment adequately[22] and are at markedly increased risk of relapse and difficult-to-treat depression.[111] The perspectives due to research in these biomarkers are to include and combine treatments that target both mental and physical diseases, eg using physical exercise in the prevention intervention as it is evident that physical activity has a protective effect on developing mood disorders[112] and also seems to have a moderating impact on the relationship between childhood maltreatment and health outcomes.[113]

Notably, of clinical relevance, patients with depression and childhood maltreatment still have significant improvement after pharmacological and psychotherapeutic treatments.[114] However, these patients present with higher severity of depressive symptoms and seem overall more difficult to treat, which has led to a recent consensus paper on treatment-resistant depression suggesting adding childhood maltreatment to be included in the standard assessment of patients with treatment-resistant depression.[115]

Conclusions

Childhood maltreatment has a substantial impact on both the onset and course of mood disorder and can have long-lasting detrimental effects on physical, sexual, and mental health and can translate into changes in peripheral biomarkers in adulthood. Thus, struggling with the impact of childhood maltreatment can lead to chronic stress and mental health problems that may further contribute to changes in markers of metabolomics, inflammation, oxidative stress, and cortisol. Notably, not all individuals who have experienced childhood maltreatment will express changes in these peripheral markers, and not all changes in peripheral markers will have negative health consequences. Nevertheless, early trauma combined with genetic vulnerability and epigenetic modifications have a long-lasting impact on the developing brain and its regulatory systems that can lead to a change in the developmental programming of mental and physical health. Accordingly, as suggested by Teicher et al, it should be mandatory to assess early adversity and recommended as a specifier "With Maltreatment History" to the primary diagnosis.[22] Further insight into the pathophysiological mechanisms that mediate exposure to childhood maltreatment and to changes in neurocircuits seems crucial to enable new treatments targeting neuroplasticity aiming to counteract the potential neurobiological toxicity that early adversity induces in a proportion of exposed individuals. It is highly warranted to include a clinical assessment of childhood maltreatment and to recognize childhood maltreatment as a critical prognostic and potential treatment target both in research and in clinical work.

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