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Review Article

Adverse Childhood Experiences and their Impact on Neurological Functioning in the Context of Traumatic Toxic Stress

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Abstract

Children that are exposed to multiple and chronic adversities undergo alterations to their stress response systems that have a significant impact on their long-term health. The response to adversity can lead to hormonal irregularities that in time will alter the brain's structure and functioning. In this review article we first highlight the importance of the Eco-bio-developmental model of disease, a model that takes into account many determinants of health. We will then review the effect of adverse events on the physiologic stress response and the subsequent neurological changes that occur when these systems are over activated. Lastly, we will consider the ways in which healthcare providers can respond to risk factors and help prevent the outcomes of chronic adversity.

Keywords: Adverse Childhood Events (ACEs); Toxic Stress; Trauma Informed Care (TIC)

Introduction

Pediatric medicine has continually emphasized the importance of the environmental context in which a child's development occurs. As we gain a better understanding of how biologic functions are affected by environmental factors, providers are armed with a new set of interventions that can impact the health of their patients. It is well established that multitude of environmental factors impact health outcomes. This review focuses specifically on how Adverse Childhood Experiences (ACEs) transform the physiologic stress response system. Chronic adversity leads to Traumatic Toxic Stress (TTS) and converts the stress response systems to a reactionary or "always-on" mode. We will summarize the current understanding of how TTS impacts the development of the neuroendocrine system, how these biological changes affect the medical and mental health trajectory of Pediatric patients, and what healthcare providers can do to intervene.

Eco-bio-developmental model of health

Genetics (biology) and its interplay with early childhood experiences (ecology) have significant impacts on development. Advances in the understanding of this concept have led to the development of the Eco-bio-developmental (EBD) model of health and disease: "The American Academy of Pediatrics: Early Brain and Child Development. Eco-Bio-Developmental model of human health and disease". This framework nicely emphasizes the importance of preventative health care in Pediatric medicine [1].

Adversity that occurs in childhood is especially detrimental to long-term health, and it comes in many forms. The original ACEs study by Felitti et al reported on the most common ACEs that are encountered in the US. These include child abuse (emotional, physical, or sexual), child neglect (emotional or physical), and household dysfunction (mother treated violently, household substance abuse, household mental illness, parental separation/absence, or criminal activity in the family) [2,3].

These experiences are not rare. In a national survey studying the rates of ACEs, children were found to have an even higher rate of violent exposures than adults. In a targeted sample of over 4500 children, almost half (46.3%) had been the victim of or witness to a physical assault and 6.1% had witnessed or been a victim of sexual assault [4].

Traumatic toxic stress and its deviation from the physiologic stress responses

The human body relies on the hypothalamic-pituitary-adrenal (HPA) axis for management of the stress response, in both acute and chronic settings [5]. The hormonal end product of this system, cortisol - triggers a host of responses that prepare the body for an impending insult. The body's regulation of this system contains this stress response within constructive boundaries and allows the body to return to baseline once the insult is eliminated. This is accomplished by a negative feedback loop in which cortisol, after its release, binds upstream in the hypothalamus and pituitary to prevent further activation [6].

In the case of TTS, the HPA axis becomes deregulated secondary to chronic over activation and cannot regulate itself by this negative feedback loop [5]. Thus in the short term, there will be an excess of blood cortisol, while in the long term a relative lack of cortisol. Studies in adults exposed to maltreatment as children have shown a blunted

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cortisol response, even in the absence of confounding psychiatric diagnoses [7]. Researchers have shown that the downstream effects of this deregulation can have disastrous outcomes. In a study of suicide completers that were victims of childhood abuse, there was a significantly decreased expression of glucocorticoid receptors in the brain when compared to controls (also suicide completers) that had no reports of childhood abuse [8].

Traumatic toxic stress remodels the brain

It is logical then, that the deregulated HPA axis impacts the structures of the brain that contain a high density of glucocorticoid receptors. These are the amygdala, the hippocampus, and the prefrontal cortex [9].

The amygdala is the region that is responsible for emotional and impulsive behaviors. In response to chronic stress, several studies have demonstrated significant growth and proliferation of the dendrites and over activity of the amygdala. These alterations then lead to an increase in impulsive behavior and anxiety [9,10].

In the hippocampus, comparable levels of stress can lead to loss of neurons and neural connections. The hippocampus functions by undergoing proliferation throughout childhood and into early adulthood, forming new memories and providing the ability to learn. Thus, this decrease in neurons can lead to impairment of learning and memory formation [11-13]. Most of the data on this subject initially came from animal models, showing a reduced concentration of glucocorticoid receptors in the hippocampi of mice with low levels of maternal care [14]. Newer data has demonstrated these results following volumetric analysis of MRI findings. Carrion et al (2007) reported that a predicted reduction in hippocampal volume could be seen in children with a history of traumatic stress [15].

Conversely, a study by Luby et highlights the impact of stress on hippocampal size in a study showing an increased volume of the hippocampus in middle childhood in children with supportive parents [11,16].

The prefrontal cortex, the part of the brain involved in impulse control and planning, is also underdeveloped in the context of TTS [17,18]. These brain adaptations can ultimately alter how a person responds to insults and even non-stressful insults by falsely activating the system to respond as if the insult were life threatening [9].

The mechanism of these alterations involves epigenetic programming of glucocorticoid receptor expression. Changes occur via DNA methylation, histone acetylation, and alterations to the telomeres. These changes highlight that traumatic toxic stress can lead to permanent changes in the brain,showing that adversity in childhood has the potential to actually influence the genetic makeup of a child [19].

Telomeres, the DNA sequences at the end of chromosomes, shorten with each cell division until they reach a certain length, at which point the cell undergoes apoptosis. Exposures to cytotoxins are known to have an effect on telomere length, however recent research has demonstrated that psychosocial stressors have an effect as well [20] Tyrka et al. published the first study that linked early life adversity with a reduced telomere length. The study reported a significant reduction in the length of telomeres in subjects that reported childhood adversity as compared to subjects that denied childhood adversity [21]. Many other studies have since confirmed these findings, and have subsequently found the relationship to be dose dependent, further supporting the association [22].

Epidemiology of toxic traumatic stress

This remodeling in various parts of the brain impacts the victims of TTS in a myriad of ways [3,23]. It is important to consider, however, that the neuronal changes are pieces of a much bigger puzzle. The individuals subjected to TTS may first develop maladaptive coping skills with downstream effects of high-risk health behaviors. Those exposed to four or more ACEs for instance, were reported to have a significantly higher risk of smoking, alcohol and/or illicit drug use/abuse, risky sexual behaviors, and suicide attempts [3,24,25]. Perception of poor health and the prevalence and odds of many diseases such as ischemic heart disease, asthma, gastrointestinal disorders, and mental health disorders were significantly higher in those who had been victims of multiple ACEs [24].

In addition to morbidity, the risk for premature death for those with multiple ACEs has also been well established. Studies have found that those with six or more ACEs died up to 20 years earlier than people with no ACEs [26]. This data is strengthened by a recent longitudinal study which describes a 66% increased risk of premature death in women who had experienced multiple adversities in childhood and a 57% increased risk in men as compared to those with no childhood adversity [27].

Equally as significant is the data that emphasizes the importance of protective effects that are fostered by healthy relationships in a child's life. These relationships can counter the negative impact of multiple adversities and produce resiliency factors that may disrupt the negative remodeling that occurs as a result of TTS [1,5].

Preventing and treating traumatic toxic stress

The primary goal in the prevention of TTS is the reduction of exposures to risk factors including childhood abuse, neglect, household dysfunction, and global conflict. To effectively identify and address the conditions that predispose an individual to TTS, clinicians should understand these risk factors and ask good questions to obtain a clear understanding of the environment, in which children and their family live. In addition, optimal medical practice should include educating parents on these risk factors and their potential health consequences.

Trauma Informed Care (TIC) is a thorough approach that is designed to respond to ACEs. It is defined by the Substance Abuse and Mental Health Services Administration as "a strengths-based service delivery approach that is grounded in an understanding of and responsiveness to the impact of trauma, that emphasizes physical, psychological, and emotional safety for both providers and survivors, and that creates opportunities for survivors to rebuild a sense of control and empowerment" [28]

Systems that serve children and their families, including the fields of education, healthcare, social welfare, and justice are often unaware of previous traumatic experiences of the clients they serve. This lack of awareness limits providers' understanding of the context of problems that bring the clients to the particular service system. Without this tool, providers may fail to recognize the root of the problems that

they are trying to manage. As a result, failure to provide the proper treatment and referrals may lead to re-traumatization [29,30]. Trauma Informed Care involves implementation of systems that both recognize and validate traumatic events as well as offer coping strategies and treatment options.

The very early phase of such implementation should involve setting policies that require staff to undergo training to understand ACEs and their impact on behavioral, social, physical, and mental health. Another important component of TIC is the implementation of screening methods to identify children and their parents who have experienced adversity in order to provide appropriate service and resources [30]. Screening for traumatic experiences should be coupled with the screening for protective factors such as resiliency, family functional capacity, and previous interventions. Implementation of these screening measures will result in a comprehensive understanding of a family's risk factors as well as their capacity for resilience and provide opportunities for both prevention and two-generational treatment to those that need them.

Many of these evidence based interventions focus on reduction of factors that trigger TTS by training either birth or adoptive caregivers in methods for successful behavioral management. This often includes trauma focused cognitive behavioral therapy (CBDT), which is the first line treatment for children and adolescents with PTSD secondary to abuse. This includes processing of the trauma as well as cognitive coping skills[31].

Other interventions, such asparent-child interaction therapy (PCIT), have focused on strengthening the relationship between caregiver and child by helping parents to more effectively respond to their child's needs. There is evidence that both CBT and PCIT of these techniques have positive effects in reversing the alterations made to the stress response system as a result of toxic stress [32].

There are some obvious limitations to objectively measuring an endpoint for the effectiveness of these methods. Due to the deregulation of the HPA axis as described above, cortisol levels have been proposed as a marker. Slopen et al published a systematic review of the evidence on the effectiveness of interventions on altering the cortisol regulation dysfunction of TTS [33]. Of the nineteen articles they identified in their study, eighteen had reported at least one difference in baseline cortisol, diurnal cortisol, or cortisol responsiveness between intervention and control participants. While there was a large amount of heterogeneity between interventions and their relative effect on cortisol levels, the conclusions of this review are important. Proving that the stress response systems are malleable suggests that it is possible to heal the deregulation of these systems even after significant experience with chronic adversity. By intervening, healthcare professionals will be able to promote lifelong in improvements on both physical and mental health. Furthermore, the findings of this review underscore the need for designing more effective strategies to identify and reduce the harmful effects of TTS [33,34].

Conclusion

The advances that have been made on the understanding of how TTS affects developing minds and bodies is summarized by the National Scientific Council on the Developing Child: "(1) early experiences are built into our bodies; (2) significant adversity can produce physiologic disruptions or biological memories that undermine the development of the body's stress response systems and affect the developing brain, cardiovascular system, immune system, and metabolic regulatory controls; and (3) these physiologic disruptions can persist far into adulthood and lead to lifelong impairments in both physical and mental health" [34].

The pediatric community has a duty to educate the public about TTS, to strive for meaningful interventions for children and their families experiencing adversity, and to advocate for community organization and institutional transformation to implement TIC [1]. By being informed about the risk factors for TTS and the immense effects that adversity can have on our patients' lifelong health, healthcare providers may play a pivotal role in transforming health care delivery systems. These efforts can alter the entire trajectory of childhood adversity and set the stage for lifelong physical and mental health.

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