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

Resmiye Oral, MD, Professor of Clinical Pediatrics, Carver College of Medicine, Department of Pediatrics, University of Iowa

Amy Walz, MD, Carver College of Medicine, Department of Pediatrics, University of Iowa

Emine O. Bayman, Assistant Professor of Statistics, Carver College of Medicine, Department of Anesthesiology, University of Iowa

Devin McCissic, MS, Carver College of Medicine, University of Iowa

Greta Dahlberg, MS, Carver College of Medicine, University of Iowa

Correspondence:

Resmiye Oral, MD

100 Hawkins Drive, 146A CDD

Iowa City, A 52242

319-356-7880 Tel

319-384-6295 Fax

Website: http://www.uihealthcare.com/childprotection/

Abstract

Adverse Childhood Experiences (ACEs) and childhood trauma are related to short- and long-term unhealthy social and behavioral adaptations and negative physical and mental health consequences for children, adolescents and specifically for adults. Studies of the last three decades on ACEs and traumatic stress have emphasized their impact on multiple domains of human existence consisting of: Social adjustment, behavioral adaptation, mental health, physical health, mortality and morbidity, health care costs to society, poor educational outcomes, subsequent reduced productivity while drawing excessive resources from the society, increased crime and legal problems, among other. Available data is impressive in stressing the need and the importance of preventing and addressing trauma across all service systems utilizing universal systemic approaches. However, at a global scale, all systems of care are organized via "crisis response" paradigm rather than with a long term preventive care focus. As a result, only symptomatic care is provided to those who need care at all domains of systems of care allowing underlying issues to be transferred in an intergenerational manner afflicting mankind generation after generation, sucking unreasonable amounts of resources. During the last decade, trauma informed care (TIC) has been identified as a tool to uncover and address both crisis issues that bring clients to any system of care and the underlying issues that necessitate the service in the first place. In implementing TIC institutions must survey their organizational structure first and foremost to make sure that the institutional environment is safe both for providers and clients. Secondly, communities must develop interagency collaboration so that both TIC is implemented in all relevant agencies and the needed

services in the community are made available. Current developments on the implementation of TIC in a variety of service systems call for the surveillance of trauma, resiliency, functional capacity and health impact of ACEs. When, clients are children under 18 years of age, it is important such surveillance to include the child's immediate caretakers, known as two-generational TIC approach. Many such efforts have been implemented in mental health agencies. However, other medical agencies, educational facilities, day care services, legal services, social services are among the agencies that must implement TIC as well so that the root causes of all social, behavioral, legal, educational, medical, and mental health issues can be unearthed as early as possible to address them with a new paradigm. Early identification of childhood trauma in children unfortunately has just recently gained some momentum in the USA, which still remains a significant public health need. The panelists on this presentation will review childhood adversity and traumatic toxic stress, present epidemiologic data on the prevalence of ACEs and their social, behavioral, legal, educational, financial, physical and mental health impacts, and discuss intervention modalities for prevention taking into account the crisis in Greece and how this might have affected children and adults alike in the country.

Introduction

Pediatric medicine has continually placed a great deal of significance on the environmental contexts in which a child's development occurs. As we continue to gain a better understanding of the biological functions that are affected by compounding environmental factors, it will help providers intervene in a meaningful way to prevent negative impacts as well as effectively treat the consequences. It is known that a multitude of environmental factors impact health in various ways. This paper focuses specifically on how adverse childhood experiences (ACEs) affect health by way of transforming the stress response systems. Chronic adversity leads to Traumatic Toxic Stress (TTS) and converts physiologic stress response systems to a reactionary "always-on" mode. We will summarize the current understanding of how TTS impacts the development of the neuroendocrine and immune systems, how these biological changes affect the medical and mental health trajectory, and what healthcare providers can do to help in the context of ecobiodevelopmental model for health services.

Ecobiodevelopmental 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 ecobiodevelopmental (EBD) model of health and disease (Figure 1). This framework emphasizes the importance of moving into a model of preventative health care in Pediatric medicine by stepping down from the clinical model in which we exclusively solve acute problems and handle crisis situations. [1]

Adversity that occurs in childhood is especially detrimental to long-term health, and it comes in many forms. [2]. The ACEs study by Felitti et al in collaboration with the Center for Disease Control reported on the most common ACEs 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 absence, or criminal activity in the family)[3, 4]. Other forms of potential adversity that have been described in the literature include parental death or loss of a loved one, serious accidents, life-threatening childhood illness or injury, natural disaster, extreme family economic adversity, sudden and frequent moves from home, pornography exposure or participation, prostitution, bullying, school violence, community violence, kidnapping, torture, war, refugee camps, and terrorism [3-8].

Using the EBD approach to ACEs we reveal how such adverse events may destabilize connections in the brain and lead to the adoption of unhealthy coping skills in order to survive the effects of trauma. The downstream effects of these maladaptive coping skills are manifested later in life in decreased self-esteem/self perception, unhealthy lifestyle behaviors, poor social networks, and high-risk health behaviors. Given the negative physical and mental health consequences of ACEs, it should not be surprising that people who reported more ACEs were more likely to report poor or fair health [9-11], poor access to medical and mental health services [4,11,12], less satisfaction with their lives

[13], and higher unemployment rates than people who had fewer ACEs. In addition, people with six or more ACEs tended to die 20 years earlier than people with no ACEs [4,14,15].

The EBD model also emphasizes the importance of protective effects that are fostered by healthy relationships in a child's life. These relationships can counter adversity and produce resiliency that may disrupt the negative remodeling that occurs as a result of TTS. Thus, healthy relationships can be protective against the downstream effects of adversity [2].

Traumatic Toxic Stress and its Deviation from the Physiologic Stress Responses

The human body has assigned two principle systems to be responsible for the stress response: the sympathetic nervous system, and the hypothalamic-pituitary-adrenal (HPA) axis [16]. The sympathetic nervous system is the network that responds to acutely stressful insults while the HPA axis is involved when the body is undergoing more chronic stress, hence HPA's significant role in TTS. Figure 2 shows that the involvement of the HPA axis begins in the hypothalamus by the release of corticotropin releasing hormone in response to a stressor. Corticotropin releasing hormone acts by promoting the release of adrenocorticotropic releasing hormone from the anterior pituitary [16]. Adrenocorticotropic releasing hormone then stimulates the release of hormones from the adrenal cortex that act throughout the body promoting the physiologic stress response: cortisol, norepinephrine, and epinephrine [17]. These hormones trigger a host of responses that prepare the body for the impending insult, for example: the cardiovascular system increases blood pressure and heart rate, the respiratory system dilates the bronchioles, and the liver increases gluconeogenesis and glucose production to provide fuel to the muscles [18]. Anti-inflammatory cytokines and the parasympathetic nervous system are charged with the task of keeping the stress response under control and allowing the body to return to baseline once the insult is eliminated [18]. Maintaining this homeostasis is crucial to conserving these responses within constructive boundaries and allowing the body to recover. In a system that has been chronically over activated, as in the pathophysiology of TTS, the individual will rarely have enough recovery time for de-escalation of these responses.

The HPA axis is regulated by structures of the brain that are high in glucocorticoid receptors: the amygdala, the prefrontal cortex, and the hippocampus. The hippocampus' effect is primarily inhibitory, with a network of interneurons that connect to the paraventricular nucleus of the hypothalamus. The hippocampus is also able to gauge the intensity of a stressful signal [19]. Like the hippocampus, the medial prefrontal cortex also inhibits the stress response through the periventricular nucleus of the hypothalamus. When these areas of the brain are overused, ACTH and glucocorticoid responses to stress are enhanced [19]. These brain regions are in contrast to the amygdala, which potentiates the HPA axis. All three brain regions have been shown to be stressor specific [19].

While temporary activation of the stress response is protective and necessary for survival, chronic overactivation of the system may cause the system to work against the best

interest of the individual. In the context of TTS, the HPA axis is chronically overactivated leading to the production of an excess of cortisol both in the body and the brain. Without healthy and stable relationships, which provide protection from the incessant stimulation of the response system, the increase in brain cortisol leads to the remodeling of these specific brain structures [16]. The chronic stimulation of the HPA axis may eventually lead to long term desensitization. Thus in the short term, there will be an excess of blood cortisol, while in the long term a relative lack of cortisol.

Research has demonstrated strong correlations between irregular cortisol levels and multiple pathologies. For example, subjects in animal studies with pituitary dysfunction or chronic stress leading to a poorly responsive HPA axis are at higher risk for autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome among others [20]. Correlations between suseptibility to viral infection, prolonged wound healing, and chronic fatigue syndrome have been linked to chronic high levels of cortisol as well [20].

Traumatic Toxic Stress Remodels the Brain

Perhaps the most striking feature of TTS is that it has been shown to lead to permanent alterations in brain architecture by inducing epigenetic changes via DNA methylation, histone acetylation, and telomeric changes [21,22,23]. Adverse childhood experiences leading to TTS are able to influence the genetic makeup of the child via the chronic elevation of stress hormones, namely glucorticoids in the brain tissue. Telomeres, the DNA sequences at the end of chromosomes are specifically involved in chromosomal stability. They shorten with each cell division until they reach a certain length, at which point the cell undergoes apoptosis. The shortening of telomeres, a marker of cellular aging, has been correlated to many disease processes including cardiovascular disease, diabetes, cancer, and major depressive disorder. 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 [23]. 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 between subjects that reported childhood adversity as compared to subjects that denied childhood adversity [24]. Many other studies have since confirmed these findings, which are also found to be dose dependent that support an association between early-life stressors and shortened telomere lengths. [25]

Young brains and the genes that are responsible for the regulation of the stress response systems are especially sensitive to these epigenetic modifications, which may lead to long-term alterations in physiology and behavior [22]. As such, the regions in the brain that are most prominently affected by the mediators via epigenetic modifications are the same regions of the brain that impact the regulation of the HPA axis: the hippocampus, the prefrontal cortex, and the amygdala [26].
The hippocampus functions by undergoing proliferation throughout childhood and even into adulthood, forming new memories and providing the ability to learn. In animal models exposed to TTS, this neuronal proliferation is suppressed and leads to significant

long-term impairment in the hippocampal functions of learning and memory formation [27,28]. The prefrontal cortex, the part of the brain involved in impulse control and planning, is underdeveloped with fewer neuronal connections when developed in the context of TTS. In the amygdala, which is the brain region responsible for emotional and impulsive behaviors, several studies have demonstrated growth and proliferation of the dendrites. These alterations increase impulsive behavior and decrease planned behaviors and impulse control [26,27]. These brain adaptations can ultimately alter how a person responds to stressful and even non-stressful insults by falsely activating the system to respond as if the insult were life threatening [21].

Chugani et al demonstrate these findings in a neuroimaging study of Romanian orphans. The group used statistical parametric mapping which analyzes the pattern of brain glucose metabolism. These scans compare the brains of post-institutionalized Romanian children that had undergone early global deprivation to control groups that had not experienced significant childhood deprivation. The study showed evidence of reduced glucose metabolism in limbic regions including the hippocampus and amygdala as well as the prefrontal cortex along with many other brain regions. These results are illustrated in figure 3 [29].

A more recent study conducted by Mehta et al investigated children from a similar demographic, who had spent early years of life living in Romanian institutions and had been later adopted into families living in the UK. This study however, analyzed volumetric changes in brain structures by structural MRI, paying close attention to the brain regions previously evidenced to have sensitivity to early stressful experiences. Mehta et al describe significant differences in regional sizes of the brain between institutionalized children as compared to control groups as well. The relative amygdala volumes were increased in children who had experienced deprivation. This study was not able to identify a significant change in hippocampal volumes [30]. These studies report some contradictory findings which are most likely due to limitations in methodology, however they indicate one important point: childhood adversity and deprivation do have measurable and significant changes in the brain structure and function.

The individuals at risk for the effects of TTS may first develop maladaptive coping skills such as overeating, cigarette smoking, substance abuse, unsafe sexual behaviors, and resolving conflicts via violence. These coping skills lead to what is called the “trauma organized” lifestyle [31]. These behaviors may predispose the individual to both mental and physical illness throughout their lives [32]. Thus, it is important to consider that the changes in the brain architecture as a result of TTS are a piece of a much bigger puzzle. Increased risk for the development of diseases such as liver cirrhosis, cardiovascular and pulmonary diseases, mental health problems including depression and suicidal behavior have all been linked to TTS by multiple studies [2,21,22,27,32] The neuronal changes in the context of TTS, the “trauma organized lifestyle”, and limitations in access to healthcare are all important mechanisms that fit together and greatly impact human morbidity and mortality [27].

Preventing ACE’s 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 as listed above. To effectively identify and address the conditions that predispose an individual to TTS, clinicians should understand these risk factors and their presentations and ask good questions to obtain a clear understanding of their patients' environments. In addition, optimal medical practice should also include educating parents on these risk factors and their potential health consequences.

Trauma Informed Care (TIC) is one of the most thorough approaches that are designed to respond to ACEs. 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 empowering tool, the very providers may fail to recognize the root of the problems that they are trying to manage/eliminate. As a result, failure to provide the proper treatment and referrals may lead to re-traumatization [33,34,35]. Trauma Informed Care involves implementation of systems that both recognize and validate traumatic events and offers coping strategies and treatment options. Transforming organizations that serve communities into trauma-informed systems requires huge organizational strides by implementation of policies and protocols that assure that TIC is enacted and enforced [35].

The very early phase of such implementation should involve setting policies that require staff to undergo training to understand ACEs and their impacts on physical and mental health. Another important component of TIC is the implementation of screening methods to identify children who have experienced adversity in order to provide appropriate service and resources [35]. 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 treatment to those that need them.

Many of the evidence based interventions focus on reducing the risk factors of TTS by training either birth or adoptive caregivers in methods for successful behavioral management. Other interventions 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 of these techniques have positive effects in altering the stress response system [36].

There are some obvious limitations to objectively measuring an endpoint for the effectiveness of these methods. Due to the dysregulation of the HPA axis as described above, cortisol levels have been proposed as this marker. Slopen et al published a systematic review of the evidence on the effectiveness of interventions on altering the cortisol regulation dysfunction of TTS [37]. They identified nineteen articles in their study, and eighteen of the nineteen articles had reported at least one difference in baseline

cortisol, diurnal cortisol, or cortisol responsivity 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 improvements on both physical and mental health. Furthermore, the findings of this review underscore the need for designing even more effective strategies to reduce the harmful effects of TTS [37].

Conclusions

The advances that have been made on the understanding of how TTS affects young 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*."[26]

The pediatric community has a duty to educate the public about TTS, to strive for meaningful interventions for children experiencing adversity, and to advocate for community organization and institutional transformation to implement TIC. Institutional transformation could include providing coordinated trauma specific evidence based services to those that have been affected by TTS [2]. By being informed about the risk factors for TTS and the immense effects that adversity can have on patients' lifelong health, healthcare providers may play a pivotal role in transforming health care delivery systems. These efforts will not only target the tip of the iceberg but also transform the entire pyramid of adversity and diminish its downstream effects making way for long lasting positive outcomes.

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Figures

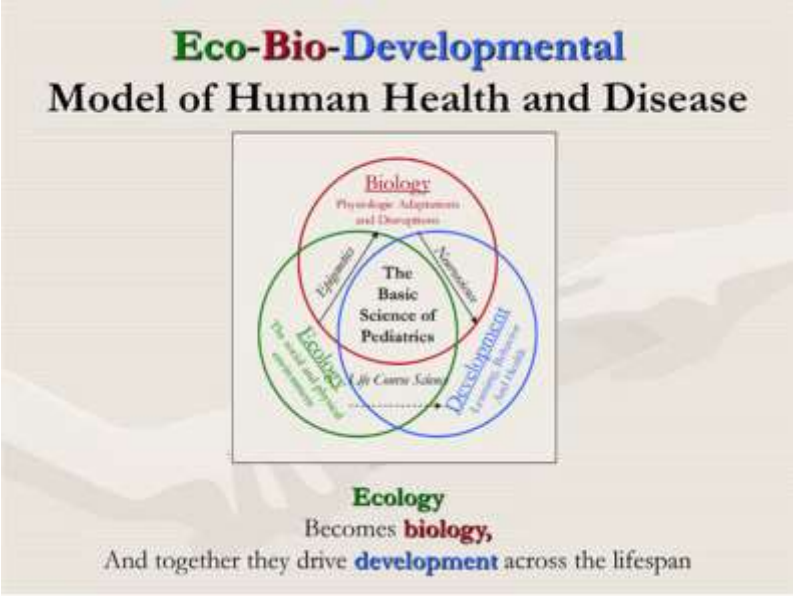

Figure 1: Ecobiodevelopmental model of human health and disease [1]

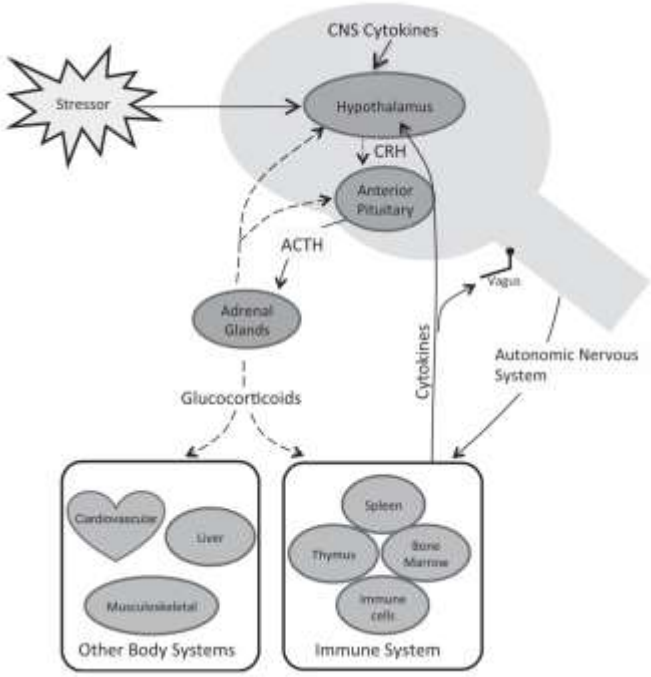

Figure 2. Relationship between the Hypothalamic- Pituitary- Adrenal axis, immune systems, and other body systems [16]

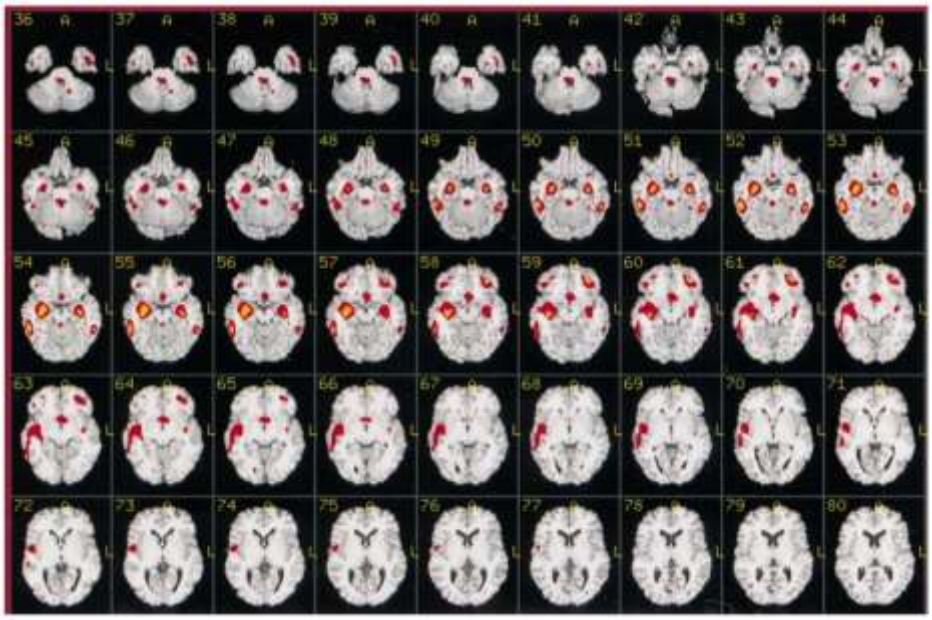

Figure 3. Statistical parametric mapping exhibiting regions with lower glucose metabolism in the Romanian orphan group as compared to an adult control group. The images were superimposed onto a representative MRI scan. Regions highlighted in red and yellow demonstrate areas of the brain that are statistically significantly decreased in glucose metabolism as compared to the control group. The amygdala, hippocampus, and prefrontal cortex are all included in this image. [29]