

Genetics and epigenetics of the war child (Review)

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Received March 22, 2024; Accepted April 26, 2024

DOI: 10.3892/ije.2024.21

Abstract. Conflicts and wars, particularly prevalent in regions such as Africa, the Middle East and Asia, have profound and multifaceted effects on individuals, spanning socioeconomic, medical and psychological realms. The present review delves into the intricate interplay between genetics, epigenetics and the experiences of individuals, particularly children, in conflict zones. Genetics, the study of inherited traits, and epigenetics, the study of how environmental factors influence gene expression, jointly shape the development and response to trauma of an individual. While traditionally, genes were considered the sole determinants of traits, epigenetic modifications reveal the significant role of environmental factors. Children in war zones are particularly vulnerable, suffering from a myriad of physical and psychological traumas, including post-traumatic stress disorder and depression. Moreover, exposure to violence during critical developmental periods can have transgenerational effects, affecting the mental and physical health of subsequent generations. Recent research highlights epigenetic changes in individuals affected by historical traumas, such as the Holocaust, demonstrating how parental trauma can influence offspring. Interventions targeting epigenetic mechanisms show promise in mitigating the effects of trauma. Narrative exposure therapy and other psychological interventions have been shown to induce epigenetic changes associated with

memory and trauma processing, offering hope for affected individuals. Additionally, environmental influences during critical periods, such as famine during adolescence, have been linked to long-term health outcomes, including the risk of developing colorectal cancer. Herein, the intricate interplay between genetics, epigenetics and environmental factors in shaping individual responses to trauma is underscored. Further research on a larger scale is warranted to validate and expand upon these findings, offering insight into potential avenues for intervention and support for individuals affected by conflict-related trauma.

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1. Introduction

Conflicts or wars, over the past 20 years, have taken place in numerous countries, with the majority of them occurring in Africa, the Middle East and Asia (1). Over the past decade, there were 30 armed state conflicts, 26 conflicts between states and 18 armed groups involved in civil war (1). The majority of modern wars occurred in a short time period, although there were also some conflicts that lasted for decades. The conflicts and wars have numerous effects on the lives of individuals; in addition, there a plethora of socioeconomic, medical and other effects (2,3).

Genetics is the scientific field which studies how genes and traits are passed on from one generation to the next. The genes that a child inherits from its biological parents provide information that guides its development, for example, how tall it could eventually become, what color eyes it could have etc. Epigenetics is an area of scientific research that reveals how environmental influences and factors and in particular children's experiences, actually affect the expression of their genes (4). During the development of an individual, the DNA that comprise the genes of an individual accumulates chemical marks that determines the levels of the genes that is expressed; this gathering of chemical marks is defined as the 'epigenome' (5). The different experiences

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Key words: conflict-related trauma, war child, genetics, epigenetics, transgenerational effects, psychological interventions

occurring in every child have rearranged these chemical marks. When the experiences of a child during development modify the epigenetic marks which are responsible for gene expression, they can determine whether and how genes release the information they carry. Consequently, the epigenome can be affected by positive influences, such as supportive maternal care and opportunities for education, or can be affected by negative experiences, such as stressful life circumstances. These marks can be temporary or permanent. This explains why genetically identical twins can exhibit different health, skills, behaviors and achievements (6). This indicates that the old notion that genes are 'the only player' has been disproven. Both nature and nurture play a crucial role in the lives of individuals (7).

Previous studies have demonstrated that there may be strategies with which to reverse the impact of certain negative influences and restore healthy functioning (8,9). Nonetheless, the optimal strategy with which to achieve healthy functioning is supportive relationships from the early life of babies, when the brain is developing most rapidly. Supportive experiences early in life cause epigenetic adaptations that influence whether, when and how genes release their instructions for building future capacity for health, skills and resilience.

2. Genetics and epigenetics of the war child

Violent or traumatic events in every war that occurred over the past 100 years have led to trauma survivors, who have developed disorders of the trauma spectrum, defined as post-traumatic stress disorder (PTSD) or even depression (10).

In particular, wars have detrimental effects on children, who also suffer from PTSD, high-energy tissue damage, massive burns and injuries; blasts leave children without feet or lower limbs, with genital injuries, blindness and deafness (11). Moreover, the wars of the past century have been transformed from being conventional to low intensity. The effects of the strategy used in such wars and conflicts of the new era involve the disruption of the medical, social, educational and public services of a country, and the terrorization of children (12). Notably, due to the war, their lives have markedly changed, as their houses have been destroyed, as well as their daily routines and children have also missed their chance of becoming mature productive members of society later in their lives (12).

Apart from these consequences of the war in children's lives, scientists have not yet studied extensively how exposure to violence can propagate effects across generations. For example, a study published several years ago, concluded that girls, following prenatal exposure to the Dutch Hunger Winter of 1944-1945 (acute food deprivation due to a Nazi blockade in 1944 to 1945), had an above-average risk of developing schizophrenia (13). Following the same reasoning, Swedish studies have revealed an association between the food supply of paternal ancestors in mid-childhood and longevity and deaths from diabetes in their grandchildren (14). Generally speaking, studies such as these have revealed the importance of lifestyle habits which could be inherited by other generations. For example, another study demonstrated that males who smoked before puberty had sons with a higher body mass index than those who smoked after puberty (15).

Specifically, as regards the condition of mental health during a war, it is well known that a population suffers from diseases referential to mental health, not only due to the breakdown of

mental health services, but also due to the increase in stress, and drug and alcohol use (16). PTSD is common among child soldiers who suffer from a higher rate of this disorder, and psychological disturbances and mental illnesses than the average civilian population (17). On the other hand, PTSD is also observed in civilian populations among children and women (18). Specifically in the Afghanistan war, a study revealed that mothers who had children <5 years of age had an increased rate (10 to 53%) of developing PTSD if they experienced at least one armed conflict event (19). PTSD also associated with a poor quality of life (bad conditions in camps) with increased odds (20). Mental disorders are also frequent in children; a previous systematic review demonstrated that children suffered from mental disorders and PTSD, as well as depression, anxiety, behavioral issues and attention deficit hyperactivity disorder (21). In addition, a study referring to the war in Somalia demonstrated that the rates of severe disability due to mental disorders were 8.4% among males and adolescents (≥ 12 years) and varied according to war experiences (no war experience, 3.2%; civilian war survivors, 8.0%; ex-combatants, 15.9%) (22).

Parental trauma exposure has been shown to be associated with trauma in descendants, particularly with childhood emotional abuse (23). Unfortunately, it has been difficult to separate the effects of parental exposure from those potentially conferred by the early-life influences of descendants (24). This is difficult to investigate as parents and children have not been studied at the same time, making it a demanding task to elucidate the origin of changes in parental exposure.

In order to overcome this issue, a previous study examined the epigenetic changes in FKBP prolyl isomerase 5 (FKBP5) methylation among Holocaust survivors, offspring and demographically matched Jewish parent offspring pairs from peripheral blood samples (25). The aim of that study was to determine whether Holocaust exposure and/or PTSD symptoms were associated with changes in FKBP5 methylation among the offspring of Holocaust survivors. FKBP5 has been found to be associated with PTSD and intergenerational effects, and it decreases glucocorticoid binding to glucocorticoid receptor, impeding glucocorticoid receptor translocation to the nucleus (26,27). The aforementioned study demonstrated that Holocaust exposure had an impact on FKBP5 methylation that was observed in exposed parents and in their offspring (25). More specifically, among Holocaust survivors, methylation was higher in comparison with the control group, while in Holocaust offspring, methylation was lower, with an association between survivors and offspring. In another cytosine-phosphate-guanine site, offspring methylation was linked to childhood physical and sexual abuse in interaction with an FKBP5 risk allele. These results suggest an association between parental trauma and the childhood trauma of offspring.

In a recent study on the effects of maternal PTSD on offspring epigenetic patterns, it was demonstrated that 72% of pregnant women had PTSD symptoms (28). Their babies were found to have higher cortisol levels and differential methylation at the nuclear receptor subfamily 3 group C member 1, 5-hydroxytryptamine receptor 3A and brain-derived neurotrophic factor genes. Moreover, no methylation differences were found, as revealed from epigenome-wide corrected significance levels. That study again reveals the outcome that the negative effects of trauma from a war are passed across generations (28).

In another study on the impact of paternal trauma on the children of survivors of the US Civil War (1861-1865) in their longevity at older ages, similar and interesting results were revealed (29). The authors of that study compared children born after the war, children whose fathers were not war veterans, children whose fathers were war veterans imprisoned in very different camp conditions, and also children born before and after the war within the same family by father veteran. The sons of veterans who were imprisoned with the worst camp conditions were more likely to die than the sons of non-veterans and again more likely to die than the sons of veterans imprisoned with better camp conditions. This outcome was found only for sons and no impact was found on daughters. Furthermore, an association was revealed in the quarter of birth; in sons born in the last quarter, there was no paternal veteran status due to maternal nutrition, in contrast to sons born in the second quarter (29). Even if scientists cannot exclude any psychological or cultural effects, these outcomes have an epigenetic explanation.

As regards children war soldiers, a recent trial examined 84 female former child soldiers from the war in Congo, as well as 53 female former child soldiers from Northern Uganda for any methylome-wide before and 6 months after narrative exposure therapy (30). Treatment had a significant impact on differentially methylated positions related to activated leukocyte cell adhesion molecule, RHO family interacting cell polarization regulator 2, actin filament associated protein 1 and molybdenum cofactor sulfurase. In addition, treatment associations overlapped at the gene level with baseline clinical and social outcomes. Treatment associated with differentially methylated positions was involved in memory, which is a key factor in trauma and enriched for molecular pathways that are usually affected by disorders associated with trauma (30). These outcomes suggest that psychological treatment in women with war-related childhood trauma could be efficient.

Another study investigated the famine and calorie restriction during childhood and adolescence with the risk of developing colorectal cancer in three circumstances; the Dutch Hunger Winter (1944-1945), World War II (1940-1944), and the employment status of fathers during the Economic Depression (1932-1940) (31). The outcomes revealed that subjects who experienced famine during the Dutch Hunger Winter had a decreased risk of developing a tumor compared to those who had not experienced the same circumstances. By contrast, there were non-significant differences compared with the other two periods (Economic Depression and World War II years) (31). This outcome suggests that environmental factors during adolescence have an impact on conditions in later life, and more specifically, on the development of colorectal cancer. In summary, the aftermath of a trauma can cause neural and epigenetic effects, as well as DNA methylation alterations. These results need to be investigated and validated on a larger scale.

On the whole, it is evident that the effects of wars on children can be profound and multifaceted. They involve both genetic and epigenetic influences that can be direct or indirect in action. Directly, exposure to certain agents during war, such as radiation, chemicals, toxins and DNA damaging factors can lead to mutations. This can affect both children and adults alike; however, the rapidly dividing cells of children are more prone to genetic mistakes (some of which can be passed down to

future generations). Moreover, war exposes individuals to stress, malnutrition and other adverse conditions that can increase the mutational load in germ cells (sperm and eggs). This can potentially contribute to heritable genetic changes in offspring.

On the other hand, epigenetic alterations experienced by pregnant women can influence the developing fetus. Stress hormones (such as cortisol) can alter gene expression patterns and these changes may persist across generations. Indeed, exposure to maternal stress during pregnancy has been linked to changes in DNA methylation patterns in offspring. Children are also affected by the disruption of food supplies and malnutrition. Food deficits during critical periods of development can cause epigenetic changes that affect metabolism, growth and immune function in children. In addition, toxins, such as heavy metals, pesticides, or pollution resulting from war, can also alter epigenetic markers. Finally, war-related trauma by witnessing violence or losing family members can have profound effects on the mental health of children. Chronic stress can lead to epigenetic changes that affect brain development and emotional regulation.

3. Conclusion

In examining the nexus between conflict-related trauma and genetics/epigenetics, it becomes evident that the effects extend far beyond the immediate individuals affected. The intricate interplay between genetic predispositions and environmental influences, particularly in childhood, shapes not only individual outcomes, but also potentially transgenerational effects. The findings underscore the importance of considering both genetic and environmental factors in understanding and addressing the consequences of trauma. Even if an individual survives a war conflict, that individual is genetically modified. Moreover, interventions targeting epigenetic mechanisms provide promising avenues for mitigating the long-term effects of trauma, providing hope for affected individuals and future generations. By recognizing the role of epigenetic modifications in response to trauma, therapeutic approaches can be tailored to address not only the immediate symptoms, but also the underlying molecular mechanisms. However, further research on a larger scale is warranted in order to validate and expand upon these findings, particularly in diverse populations and contexts. By elucidating the complex interplay between genetics, epigenetics and trauma, researchers can contribute to the development of more effective interventions and support systems for individuals affected by conflict-related trauma, ultimately fostering resilience and recovery.

Acknowledgments

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

EP, VE, GPC and DV wrote, drafted, revised, edited and reviewed the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

GPC is the Editor in Chief of the journal, and DV is an Editor of the journal. However, they had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The authors declare that they have no competing interests.

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