EDITORIAL

Early origins of neuropsychiatric disorders

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Advances in medicine mean that we are living longer and more economically productive lives. However, research in these past decades has highlighted increase in the prevalence of neuropsychiatric disorders linked to the changes in the physical and environmental stressors of our communities. These epidemiological studies have informed the development of novel neurodevelopmental models to study these psychiatric disorders. These have included models of prenatal, perinatal, and early life stressors that interact with a genetic susceptibility to ‘prime’ the brain and lead to subtle pre-clinical phenotypes. Then additional stressors during childhood/adolescent equivalent or later in life convert this susceptibility into psychiatric and neurological disorders.^{1,2} This priming concept is an extension of the Barker hypothesis of developmental origin of chronic adult diseases^{3,4} or the so-called Developmental Origin of Health and Disease (DOHaD).

This now well recognized and validated notion that toxic stress will have long-term adverse effects, is especially pertinent in the complex world that we live in that is placing pregnant mothers, children, and families under stress during critical periods of development.^{5,6} Political conflicts around the world have resulted in the social displacement and often forced migration of families from their homelands fleeing war, leading to incredible psychological and physical stress. This has included 2017 conflicts in Iraq, Syria and Yemen, Nigeria, South Sudan, and Myanmar. In Yemen alone in 2017 at least 5000 children were left dead or injured, and more than 11 million children needed humanitarian assistance.⁷ Further to this, government sanctioned separation of children from their parents or forced long-term internment of refugees in stable democratic countries⁸ including the USA and Australia (United 8) are also of concern. Long-term adverse effects on children are deemed highly likely by psychiatrists due to these policies, like the recent United States government-sponsored separation of children from their parents who entered the United States illegally,⁹ a policy which is now abandoned. Moving globally once more, there have been massive strides in reducing the levels of extreme poverty. However, although extreme poverty has reduced by 30% since the 1980s, there are still 10% of the world’s population, some 760 million people, living in extreme poverty (World 10)¹⁰, people for whom life stressors are constant and highly damaging. A further major health problem that contributes to poor neuropsychological outcomes for women and their babies is violence. One in three women experience intimate partner violence in their lifetime,¹¹ and this has impacts on their physical, mental, sexual, and reproductive health. Violence and poor socio-economic factors particularly impact negatively on the immediately quantifiable indices of infant birth weight and preterm birth.¹²

Preterm birth is a leading examples of an early life event that raises the risk for the development of neuropsychiatric disorder, specifically an autism spectrum disorder. Infants born before 28 weeks of gestation have a 10-fold increase risk to exhibit later

in life signs of ASD.¹³ This risk is further increased to 17-fold for preterm born infants if there was also presence of chorioamnionitis at birth,¹⁴ suggesting an important role of neuroinflammation, as reviewed in refs.^{15–17} In this neuroinflammation-driven risk hypothesis, long-term alterations to microglial biology, potentially through epigenetic mechanisms, might be a key mechanism mediating the genes–environment interaction leading to neuropsychiatric disorders. Indeed, microglia have key roles in the formation and maintenance of white matter and synaptic pruning with striking effects on brain connectivity.^{18–20}

Recent clinical research has also illustrated that the risk of bipolar disorders (BD) is also strikingly increased by negative early-life events. People with BP have frequently been subjected to childhood maltreatment, in particular emotional abuse.²¹ Childhood maltreatment also markedly increases the severity of the expression of BD, leading to earlier, more suicidal and recurrent forms of the disorder²², and lower response to conventional mood stabilizers.²³ Childhood maltreatment also interacts with cannabis use during adolescence to increase the severity of the clinical expression of BD.^{24,25} Childhood trauma might lead to BD by modifying amygdala volume and prefronto-limbic functional connectivity.²⁶

This Special Issue of *Pediatric Research* further expands on this work on early life events and neuropsychiatric outcomes, with a set state-of-the-art papers on some of the hottest topics in this rapidly moving field. Although this Special Issue is not exhaustive, it will cover several aspects and provide the reader a large overview of the recent progress in that field.

The first two articles (Constantino; Lahti) reviews the evidence of the impact of prenatal and perinatal factors, including maternal depression, intra-uterine growth retardation, and prematurity on the development of childhood psychiatric disorders, anchoring the concept of early origin of neuropsychiatric diseases.

The potential mechanisms linking prenatal and perinatal events to the development of psychiatric disorders are covered across articles by Bokobza; Bendix; Misolczi; Demaster; Warner; and Mulkey. Altogether the authors review the potential role of neuroinflammation and hyperoxia and their impact on myelination and synaptogenesis, the potential role of BDNF and impaired plasticity, the potential role of the gut microbiome, and very originally, the potential role of dysmaturity of the autonomic nervous system. The authors summarize the rapidly growing literature and propose hypotheses that could be tested in preclinical and clinical settings in the near future.

One article (Cayabyab) revisits the concepts of bilirubinemia and its effects on the developing brain and subsequent development of neuropsychiatric disorders. The final article (Chaffer) explores the original hypothesis that oxidative stress might play in an important role in the development of neurocognitive impairment in children with dietary-restricted phenylketonuria.

The present Special Issue brings together outstanding reviews that highlight the remarkable progress in the field during the last 10 years and offer a large overview of the state-of-the art of the field as well as on new avenues for research on mechanism, treatments and prevention.

ADDITIONAL INFORMATION

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