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The Myth of Autism Spectrum Disorder Etiology; An Endless Debate

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Short communication

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Abstract

In this commentary, the author summarizes the results of some of our studies that we have conducted on Egyptian children suffering from autism spectrum disorder aimed at exploring some important controversial issues regarding the development of such a distressing neurodevelopmental disorder with a multifactorial origin and no definitive cure.

Keywords: Autism Spectrum Disorder; Heavy Metal Intoxication; Mechanical Ventilation; Vitamin D; Mitochondrial and Immune Dysfunction; Oxidant; Antioxidant Imbalance

Abbreviations: ASD: Autism Spectrum Disorder; CARS: Childhood Autism Rating Scale; NADPH: Nicotineamide Adenine Dinucleotide Phosphate; HBOT: Hyperbaric Oxygen Therapy; ROS: Reactive Oxygen Species.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that manifests early in life by persistent deficits in social communication and interaction across multiple contexts with restricted, repetitive patterns of behavior, interests, or activities [1,2]. Delayed diagnosis of ASD hinders the implementation of early intervention for those in need with worsening of its long term prognosis. The perfect delicate balance between sensitivity and specificity of ASD screening tools is essential to avoid missing its early detection and subsequent poor prognosis or its overdiagnosis with subsequent abuse of the limited healthcare resources especially in developing countries [3].

The etiology of ASD remains elusive and controversial but there is a universal agreement that it is a multifactorial disorder that results from interaction between genetic susceptibility and exposure to a wide spectrum of hazardous environmental factors with the recognition of the genetic susceptibility as the main predisposing factor for its development [2,4]. In this commentary, the author has summarized the results of some of our studies that we have conducted on Egyptian children suffering from autism spectrum disorder aimed at exploring some important controversial issues regarding its development.

Heavy Metal Intoxication and ASD

The potential role of heavy metal intoxication in the development of ASD represents a hot issue for all researchers interested in exploring the etiology of such a buzzling disorder. To investigate the role of this environmental risk factor in the pathogenesis of ASD, Mohamed, et al, [5] assessed the levels of hair aluminum, lead, and mercury in a

sample of Egyptian autistic children. The results showed that the measured levels of these heavy metals were significantly higher in autistics compared to controls with significant positive associations with maternal fish consumption (for mercury), living nearby gasoline stations (for lead), and the usage of aluminum pans (for aluminum). It had been concluded that environmental exposure to such toxic heavy metals at crucial times in development may play a causal role in autism [5].

Neonatal Mechanical Ventilation and ASD

Mechanical ventilation is a crucial therapeutic modality in handling extremely preterm infants that is associated with increased risk of subsequent development of chronic lung disease, neonatal brain damage, and neurodevelopmental disorders including ASD. Zaky, et al., [6] evaluated the initial and follow up neurodevelopmental status of an Egyptian sample of newly (6 months follow up duration) and previously discharged mechanically ventilated infants (12 months follow up duration). We reported that the prolonged duration of mechanical ventilation during the neonatal period increased the risk of development of ASD and neurodevelopmental delay.

Also, we recorded significant negative correlations between CARS (Childhood Autism Rating Scale) and Composite Bayley Scale scores (cognitive, language, and motor) on both the initial and follow up assessments of the newly discharged group but similar correlations were not found in the previously discharged group. Such results meant that the severer the autistic manifestations, the lower the Composite Bayley Scale score as a predictor of neurodevelopmental delay in neonates with prolonged NICU stay especially preterms with low birth weights highlighting the negative morbid impact of prolonged neonatal mechanical ventilation [6].

Vitamin D and ASD

Vitamin D is an important neurosteroid hormone which can affect brain development and function. Nakhla, et al. [7] assessed the level of 25 OH vit D (cholecalceferol) in a group of Egyptian autistics compared to normally developing controls correlating it with disease severity. In addition, we evaluated the role of intake of therapeutic doses of vitamin D on the severity of manifestations in vitamin D deficient autistics. Our results showed significant reduction of serum levels of 25 OH vit D in autistics compared to controls with significant negative correlations with CARS and ATEC scores as measures of disease severity and response to therapeutic intervention respectively. Such scores improved significantly after the intake of therapeutic doses of vitamin D supporting its role in improving the prognosis of this distressing neurodevelopmental disorder [7].

Mitochondrial and Immune Dysfunctions and ASD

Mitochondrial and immune dysfunctions are often claimed to be implicated in the development of ASD. Abdel-Rahman, et al. [8] studied for the first time the relationship between autistic severity and mitochondrial respiratory rates in freshly isolated platelets of autistics as well as the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) in their isolated neutrophils. Also, we tested the impact of hyperbaric oxygen therapy (HBOT) on mitochondrial and immune functions and autistic severity. We found that routine basal respiration, complex I and complex complex I +II dependent oxidative phosphorylation rate were significantly impaired in autistic platelets with similar deficits in their neutrophil immune response as evidenced by lower rates of oxygen consumption and reactive oxygen species (ROS) production by phagocytic NOX.

Autistic behavioral manifestations were found to be moderately correlated with platelets' mitochondrial bioenergetic parameters and NOX mediated activity in neutrophils. On the other hand, HBOT did not improve mitochondrial dysfunctions or autistic severity but improved only one measure of immune response namely, NOX mediated superoxide burst which was not associated with significant change in the rate of concomitant recurrent infections [8].

Dna Damage and ASD

The imbalance of oxidants and antioxidants has a role in the pathogenesis of ASD. Zaky, et al. [9] tested autistic children for the presence of 8-hydroxy-2-deoxyguanosine (8-OH-dG) as a biomarker of oxidative DNA damage and its association with disease severity and omega 3 supplementation. We reported significantly higher levels of urinary 8-OH-dG/creatinine level in autistic children compared to normally developing controls with positive significant association with disease duration, severity, and relevant family history.

Furthermore, omega 3 supplementation resulted in significantly lower levels of the tested biomarker in autistics received it compared to those who did not. Using the cut off value of > 1.7 of urinary 8-OH-dG/creatinine ratio revealed sensitivity of 80.39% and specificity of 74.51% that was indicative of its discriminating power between autistics and normally developing counterparts. Such results of our study showed the potential role of oxidative DNA damage in ASD development and the value of urinary 8-OH-dG/creatinine ratio as a valuable non-invasive biomarker of disease severity [9].

Conclusion

In conclusion, finding the exact etiology of ASD is still the main concern of researchers interested in such a distressing neurodevelopmental disorder including our team aiming at better understanding of it's pathogenesis and hence, introducing more effective therapeutic modalities with the well established rehabilitation measures. Improvement of ASD prognosis and health related quality of life of it's sufferers and their caregivers is our ultimate goal in dealing with this disabling puzzling disorder.

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