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Perinatal Anxiety, Microbiome Alterations, and Implications for Research in the Development of Autism and Schizophrenia

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Abstract

Autism Spectrum Disorder (ASD) and Schizophrenia have appeared similar in recent years with respect to genetic consistencies, phenotypic overlap, and overall neurodevelopmental course. Both disorders present with heterogeneous groups of positive and negative symptoms in the context of varying cognitive and adaptive clusters. Not surprisingly, both disorders have similar maternal correlates such as anxiety and stress, which have been linked to microbiome alterations in both mother and child. This commentary provides a brief overview of this overlap with respect to maternal microbiome alterations seen in these disorders and its implications for future research. Issues surrounding equity and social differences are also addressed. Implication for future research and clinical implications from these formulated hypotheses are discussed.

Keywords: Autism, Schizophrenia, Microbiome alternations, Maternal anxiety

Background

While ASD and schizophrenia are notably separate disorders, they share a vast amount in common that may be useful in understanding the developmental pathogenesis of both disorders. In particular, maternal anxiety and subsequent microbiome alternations in utero may function as a casual mechanism in the development of both disorders in their offspring. Therefore, the purpose of the present paper is threefold: 1) to review the genetic and biological similarities between ASD and Schizophrenia, 2) review the relevant reach related to perinatal anxiety and microbiome alternations that may contribute to both disorders, and 3) to establish a relevant research trajectory related to mother-child psychological and behavioral treatments that may increase our understanding of these disorders across time. The present paper will also discuss both the research and clinical implications for mother-child psychological and behavioral treatment.

The Relationship between Autism Spectrum Disorder & Schizophrenia

Autism Spectrum Disorders (ASD), the fastest growing set of neurodevelopmental disorders, is characterized by deficits in reciprocal interaction and social communication, alongside the presence of restrictive and repetitive behaviors. Both children and adults with ASD present symptoms in heterogeneous clusters that are comprised of variations in both cognitive and neuropsychological functioning as well as adaptive skills. Much like ASD, Schizophrenia is a heterogeneous clinical syndrome that is marked by a wide range of characteristics and

functioning [1]. Schizophrenia spectrum disorder is a mental health condition characterized by thoughts that are out of touch with realty alongside disorganized speech and behavior. Other negative symptoms, such as flat affect or decreased emotional expression are also seen.

ASD and Schizophrenia share a long history; at one time ASD was even viewed as a subtype of Schizophrenia [2]. Although the two diagnoses are recognized as separate and distinct today, there are vast similarities between ASD and Schizophrenia, and the two are appearing more alike than they are dissimilar in recent research with respect to both genotypic similarities and phenotypic expression, despite difference in their diagnostic conceptualization [3]. Studies suggest correlations in both copy number variants [4] and genetic risk associated with impairments in social cognition in both disorders [5]. Phenotypic similarities include adaptive impairments in socialization alongside maladaptive behaviors (e.g. restrictive and repetitive behaviors in ASD and disorganized speech or behavior in Schizophrenia).

According to the neurodevelopment hypothesis purported by Owen et al. [6] Schizophrenia is a pathological neurodevelopmental process that begins as early as the first trimester, resulting in structuring and chemical wiring of neuronal systems that are primed to generate psychotic symptoms. In this vein, Schizophrenia takes a similar neurodevelopmental trajectory to that of ASD, which is exemplified in the overlap in symptoms, outcomes, and responses to treatment [4]. In light of this information, the potential benefit of studying ASD through the lens of Schizophrenia research is starting to be explored. Foss-Feig et al. [3] suggests that classifying ASD in the context of positive (e.g. intense interests, restrictive and repetitive behaviors), negative (e.g. poor social reciprocity, impaired adaptive and daily living skills), and cognitive dimensions (i.e., very higher or very low IQ or neuropsychological impairments) in the same way that symptom clusters are defined for Schizophrenia may have strong clinical utility for both assessment and treatment.

Autism, Schizophrenia, and the Maternal Microbiome

Beyond their genotypic and phenotypic similarities associated with the early developmental pathogenesis of ASD and Schizophrenia, biological and medical overlap in presentation has been noted. Recent genome-wide association studies as well as related epidemiological data have indicated both shared genetic and environmental triggers across both disorders, including glutamatergic, GABAergic, neurotransmission, inflammatory and oxidative stress related systems, gut microbiome, and early environmental risk factors [7]. Alternation in gut microbiota in both ASD and Schizophrenia has been found [8] as well as inflammatory state alternation, and alternations in both microbiota and the gastrointestinal systems. These findings were consistent across both ASD and neuropsychiatric disorders [9]. Hoffman et al. [10] suggested the critical role of the microbiome in the conceptualization of stress-related neurodevelopmental trajectories associated with Schizophrenia. In addition to alternations in microbiota of children with these disorders, a growing body of research to suggest that mothers of children with ASD also have altered gut microbiome [11].

Maternal anxiety and stress have been found to be correlated with both ASD [12,13] and Schizophrenia [14,15]. Foster et al. [16] suggested that gut microbiota has been implicated in a variety of stress-related conditions including anxiety. A wide array of studies has demonstrated the links between both pre- and post-natal maternal anxiety/stress and cognitive, behavioral, and emotional difficulties in offspring. Cortisol has been shown to cross the placenta and thus may affect neurodevelopment processes in the fetus; specifically, the development of the HPA-axis, limbic system, and the prefrontal cortex [17]. A major risk factor for prolonged intrauterine exposure to stress is poverty and related difficulties (i.e., malnutrition, lack of pre-natal care), and has been found to be more prevalent in low- and middle-income countries [18].

Beyond the known effects of stress on the mother and family, prolonged stress can impact offspring development by altering the temporal and spatial dynamics of the maternal microbiome during pregnancy, as well as offspring microbiota [19]. Early prenatal stress has been noted to influence bacterial community assembly in offspring through both gut microbial composition during pregnancy and transmission of dysbiotic vaginal microbiome at birth [19]. Researchers also noted these alternations in a sex-specific manner, which could account for the known gender gap in ASD (higher prevalence in males), and the higher prevalence of Schizophrenia in females. Finally, significantly higher rates of conditions such as obesity and diabetes have been noted in those with both ASD and schizophrenia [20,21] which have been found to be correlated with

changes in microbiota.

Similarities such as perinatal anxiety, for which there is evidence to suggest may exacerbate gut alterations, may play a role in the gene-environment interaction associated with both disorders. It is, in effect, hypothesized that maternal microbiome alterations may present as a casual mechanism for the early neurodevelopmental pathogenesis of ASD and Schizophrenia in their offspring. It is further hypothesized that mothers who experience perinatal anxiety may be at increased risk for microbiome alterations, and subsequently is at increased risk for the altered neurodevelopment of their children.

Conclusion

Based on this review and subsequent hypothesis, there are several important implications for researches to be noted and that should help drive subsequent research trajectories. First, fields of basic sciences, medicine and behavioral genetics would benefit from greater exploration in each of these areas. Many recent studies have shown that treatments that regulate gut microbiota can lead to improvement in symptoms of neurodevelopmental disorders [22,23]. Psychosocial and public health interventions also need to emphasize secondary and tertiary interventions including awareness, as well as screening and treatment for at-risk populations. This review also highlights the needs to monitor and develop accessible interventions for maternal stress and anxiety and related mental health conditions, in an effort to reduce the potential environmental contribution to debilitating neurodevelopmental disorders.

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