Dysbiosis, Maternal Immune Activation and Autism

Subjects: Nutrition & Dietetics

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Autism spectrum disorder (ASD) is a neuropsychiatric condition characterized by impaired social interactions and repetitive stereotyped behaviors. Growing evidence highlights an important role of the gut–brain–microbiome axis in the pathogenesis of ASD. Research indicates an abnormal composition of the gut microbiome and the potential involvement of bacterial molecules in neuroinflammation and brain development disruptions.

Keywords: autism spectrum disorders ; gut microbiota ; brain–gut axis ; maternal immune activation (MIA)

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition defined by early deficits in social interaction/communication and repetitive stereotyped behaviors [1]. The multifactorial etiology of ASD includes both genetics and environmental factors. Genetic mutations, maternal immune activation, and environmental triggers such as toxicants, insecticides, infections, and medications are involved [2]. ASD consists of frequent gastrointestinal (GI) symptoms with variable prevalence, including chronic diarrhea, constipation, abdominal bloating, and discomfort [3].

Correlations between GI dysfunction and worsened behavioral symptoms have become evidence of brain–gut axis pathophysiology in ASD patients and suggest the intestinal microbiome as a significant factor. Researchers observed changes in the ASD gut microbiome compared to typically developed children; however, they can result from differences in diet, medical comorbidities, and geographic location [4]. Thus, further work is needed to better understand the concept of the microbiota–gut–brain axis. The gut microbiome is shaped from the earliest years of life and regulates important processes such as digestion and immune response [5].

The number of intestinal bacteria exceeds the number of human cells and genes [6]. Therefore, there is no doubt that its role is crucial in the proper functioning of the human body. Changes in the mother's microbiome influence offspring gut microbial structure and composition [7]. Many data confirm the interaction of microbiota in pregnancy and the prenatal and newborn period [8].

Infections or injuries during pregnancy can induce inflammation, subsequently impacting fetal brain development [9]. Maternal immune activation (MIA) is considered to be a disease primer, making offspring more susceptible to other risk factors, like genetic and environmental ones [10]. Pregnant women exposed to MIA have been shown to have pathological activation of specific interleukins, which promotes abnormal cortical development and ASD-like phenotypes in the offspring [11].

2. The Mode of Delivery and Microbiota Transfer

Proper human development is an intricate process involving numerous genetic and environmental factors [12]. The gut microbiome has emerged as one of the crucial components due to its undoubted influence on health throughout the entire life [13].

The impaired balance of the gut flora in infancy is linked to an increased risk of numerous diseases, especially of immunological origins, like asthma [14] and allergies [15]. Moreover, disruptions in this balance have been associated with a range of mental and neurological disorders, such as depression [16][17], anxiety [18], schizophrenia [19][20], Parkinson's disease [21], Alzheimer's disease [22], and autism [23].

According to the well-established doctrine, microbiota acquisition begins at birth, as a result of exposition to the maternal birth canal environment [23]. However, this statement has recently been reassessed by a limited number of studies confirming the presence of microorganisms in the placenta [24][25][26]. These results are still the subject of debate in the scientific community, and there is no clear conclusion [27].

Kennedy et al. conducted a multidisciplinary evaluation of similar studies supporting the evidence of microbial presence in prenatal intrauterine locations. Based on their findings, it is more likely that the observed microbial signals were the effect of contamination during the collection and processing of samples and data, rather than genuine microbial colonization. Analyzed studies frequently indicate the presence of microorganisms, widely known as common contaminants such as *Bradyrhizobium* and *Micrococcus.* The researchers emphasize the challenge of distinguishing relevant microbial signals from contaminating noise in low-biomass samples, which can lead to misconceptions about tissue sterility. Therefore, they highlight the importance of following a trans-disciplinary approach, considering biological, ecological, and mechanistic explanations, when studying low-biomass samples. This approach should facilitate the proper interpretation of findings and address the challenges posed by contamination [28].

A characteristic microbiome has been identified in the placenta, the amniotic fluid, and the fetus in healthy pregnancies [24]. Nonetheless, it is unclear when the first fetal exposition to bacteria is and where they come from [8]. Modification in placental microbiota may be related to infections, including urinary tract infections resulting in placental enrichment of *Streptococcus*, *Arthrobacter*, *Klebsiella*, and *Acinetobacter* [24].

2.1. The Mode of Delivery and Microbiota Transmission

After birth, the diversity of microbiota changes due to the contribution of multiple factors such as skin-to-skin contact [29], breastfeeding [30], diet [31], antibiotic administration [32], and other environmental exposures [33][34][35]. Nevertheless, the mode of delivery is considered one of the most significant determinants influencing the heterogeneity of gut microorganisms in early life [36].

The majority of the studies show numerous differences between vaginal (VD) and cesarean section (CS) babies in terms of composition, amount, and maturation onset of gut microbiota [23][36][37][38][39][40][41]. CS children are more likely to be inhabited by bacterial species similar to the mother's skin surface (e.g., *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* spp.) [23]. Their microbiota is more abundant in potentially pathogenic species like *Enterococcus*, *Enterobacter*, and *Klebsiella*, usually associated with hospital units [37][38].

On the other hand, VD children inherit microbiota closely resembling the mother's vaginal environment [23]. Such neonates have more prevalent and diverse communities of Lactobacillus and Bifidobacterium taxa [36][39], known for their positive impact on infant's health (29). Moreover, the microbiota composition (at the genus and phylum levels) remains stable during VD children's development as opposed to CS [40]. Over time, those differences diminish and become less noticeable in 6–8 weeks after birth [39][42]. This brief period is crucial for proper neurodevelopment. It overlaps with the initiation of the most significant elongation of axons and dendrite branching, alongside the beginning of accelerated synaptogenesis [43].

2.2. Changes in Gut Microflora in Autism

Gut dysbiosis is a health complication with greater prevalence in ASD patients compared to neurotypical individuals [44]. ASD-diagnosed individuals have less diverse gut microbiota, with the main components consisting of *Bacteroidetes*, *Parabacteroides*, *Faecalibacterium*, *Phascolarctobacterium*, *Lactobacillus*, *Clostridioides*, *Desulfovibrio*, *Caloramator*, and *Sarcina* compared to the control group [45][46][47]. Additionally, decreased levels of *Coprococcus* and *Bifidobacterium* were discovered [46]. Another data analysis revealed a reduction in *Prevotella*, *Coprococcus*, *Enterococcus*, *Lactobacillus*, *Streptococcus*, *Lactococcus*, *Staphylococcus*, *Ruminococcus*, and *Bifidobacterium* species and higher levels of *Clostridia* and *Desulfovibrio* [48]. Nonetheless, not all studies confirm this relationship, i.e., research on ASD patients and their neurotypical siblings indicated no significant differences in gut microbiota diversity [49].

However, microbiota disturbances are still frequently linked to ASD. For example, intensive antibiotic therapy, repeatedly used in ASD-diagnosed children might result in the overgrowth of *Desulfovibrio* bacteria [50]. The involvement of *Desulfovibrio* in ASD pathogenesis is underscored through its production of Lipopolysaccharide (LPS) and its known role in promoting inflammation [50]. Tomova et al. in a study involving a small group of ASD-diagnosed children demonstrated a significant association between autism severity and the abundance of *Desulfovibrio* spp. [51].

Moreover, ASD patients typically exhibit decreased levels of *Lactobacillus* spp. [52]. It is worth noticing that attempts at recolonization with *Lactobacillus reuteri* have shown partial alleviation of intestine inflammation caused by LPS. Additionally, supplementation with *Bacteroides fragilis* has been found to reduce gut permeability [53].

The gut microbiota not only encompasses bacteria but also includes fungi. A good example is *Candida* spp., which has been proclaimed to take part in ASD pathogenesis [54]. Elevated concentrations of *Candida* yeasts have been observed in

fecal samples from individuals with ASD [55]. Maintaining an appropriate concentration of *Lactobacillus* spp. prevents the overgrowth of *Candida*; however, autistic individuals exhibit reduced numbers of *Lactobacillus* spp. [56]. Additionally, an excessive *Candida* population impedes re-establishment with commensal microorganisms [57]. The proliferation of *Candida* yeasts results in an increased production of ammonia and toxins, which studies have linked to the exacerbation of autistic behaviors [58]. Furthermore, Candida overgrowth may lead to the malabsorption of minerals and carbohydrates [57]. Therefore, addressing the balance of gut microbiota, particularly managing *Candida levels* and promoting the presence of beneficial bacteria, becomes essential research interest in the context of ASD.

Research on microbiome changes in autism is inconclusive. Differences may be influenced by individual variation in microflora composition, different ages and genders of subjects, severe eating restriction, food selectivity, disparities in the diet used or unknown factors.

3. Mode of Delivery and Autism Correlation

As the mode of delivery influences microbiota composition in early life, researchers focused on verifying its impact on the risk of autism.

Yip et al. analyzed records from the International Collaboration for Autism Registry Epidemiology (iCARE) database. Their study cohort consisted of 4,987,390 children born in 5 different countries (Norway, Sweden, Denmark, Finland, and Western Australia) and comprised 71,646 *C*-section deliveries. They ascertained that both—elective and emergency CS are associated with a higher risk of ASD in comparison to vaginal delivery [59]. Those findings were confirmed by more recent studies [60][61].

Furthermore, works by Chien et al., Huberman Samuel et al., and Yang et al. indicate that only CS performed under general anesthesia (GA) noticeably increases the risk of ASD. CS under regional anesthesia (RA) brought only an insignificantly higher risk than VD [62][63][64]. This might suggest that GA is a major factor contributing to the link between the mode of delivery and autism. However, those findings should be taken with caution due to several limitations of evaluated studies such as the omission of confounding factors, limited statistical power, and lack of sibling analysis. Moreover, the reason responsible for this phenomenon remains indistinct. Research based on human and animal models suggests that the administration of GA in early life might be the cause of neurotoxicity, which disturbs postpartum neurodevelopment [65]. These toxic effects might impact regions of synaptogenesis, which is especially accelerated in the first 6 months of life [43] and can be the cause of disruptions and delays in the subsequent development of other areas of the brain [66].

In addition, studies show that the general correlation between delivery mode and ASD might be related to confounding variables such as unknown genetic and environmental conditions. Curran et al. analyzed a large cohort of 2,697,315 children. Even though the general analysis proved that CS children are approximately 20% more likely to develop ASD after adjusting for sibling controls the association disappeared. Weaknesses of this study include the inability to verify the authenticity of the analyzed cases and determine whether the origin of confounding is a genetic or external factor. Furthermore, the sample size of the sibling control was significantly lower than the general study population [67].

In conclusion, most of the studies confirm that children delivered by cesarean section are more prone to the development of ASD. Additionally, the use of GA turned out to be one of the most feasible risk factors. Nevertheless, those findings must be taken cautiously as all confounders connected with CS should be considered.

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