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Gut Microbiota Alterations in Autism Spectrum Disorder

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The fascinating hypothesis of a gut–brain axis influencing cognition, emotions, and behavior has gradually developed in recent years, supported by increasingly relevant data.[1] Closely related to it, there is the theory according to which an alteration of the gut microbiota (GM) could play a key role in the pathogenesis of brain diseases, including psychiatric disorders such as schizophrenia, anxiety, and depression, as well as neurodevelopmental disorders, in particular autism spectrum disorder (ASD).[2] The etiopathogenesis of ASD[3] is multifactorial, characterized by a complex interaction involving genetic and environmental factors,[4] many of which may cause neuroinflammation.[2,4] In recent years, the epidemiological increase in ASD[5] has stimulated research into possible environmental pathogenetic factors.[4,6] Gut microbiota usually lives in symbiosis with the human host contributing to his/her lifelong health.[7] Development of GM begins at birth and its composition remains relatively stable after the age of approximately 3 years.[2] Among the functions of GM are intestinal barrier integrity preservation, energy intake, vitamin production, non-digestible fiber fermentation, defense against pathogens, and immunity control.[1,2,7] Therefore, it is not surprising that today a lot of data support the hypothesis of GM dysbiosis involvement in the etiopathogenesis of several internal diseases, such as metabolic syndrome, cardiovascular disease, inflammatory bowel disease, and celiac disease.[2] Several gut–brain axis pathways have been reported, represented by the autonomic nervous system, enteric nervous system, and hypothalamic-pituitary-adrenal axis, all using the vagus nerve for communication.[1,2] Also, hormonal, metabolic, and immunological pathways have been reported.[1,7] The production of serotonin, another gut–brain axis mediator that acts as a mood stabilizer, occurs mostly in the digestive tract and is largely influenced by microbiota.[7] But what could the link be between microbiota alterations and ASD? First of all, it should be underlined that gastrointestinal (GI) disorders are four times more frequent in ASD children than in neurotypical ones, and their severity seems to be correlated with the severity of behavioral symptoms' severity.[2] On the other hand, several pathogenetic mechanisms through which GM could influence brain development have been hypothesized. Gut microbiota seems to play a crucial role in brain synaptogenesis, glia cells' expansion, myelination, blood–brain barrier development, and immune system development.[8] A lot of heterogeneous early factors can modify GM composition, including human host genetic factors, as well as prenatal or perinatal events such as infections or inflammation during pregnancy, preterm birth, cesarean section, medications, nutritional intake, and environmental stressors.[2,7] The pathogenetic hypothesis relating to maternal immune activation has aroused particular interest. Maternal immune activation is a series of immune system alterations triggered by infections or environmental stressors leading to the production of high levels of proinflammatory cytokines that may cross the placental barrier and impair fetal brain development. Maternal immune activation has been considered a risk factor for ASD in newborns. Gut microbiota alterations detected in ASD children seem to reflect those found in their mothers, probably due to vertical transmission.[2] Also, epigenetics plays a role in ASD etiopathogenesis by combining the effects of genetic and environmental factors.[4] One of the epigenetic mechanisms hypothesized is related precisely to the production of short-chain fatty acids by intestinal microbes, which can control gene expression through histone deacetylase inhibition.[2] Furthermore, bacterial peptidoglycans produced by GM seem to be able to modulate gene expression involved in

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brain development and social behavior.[7] The data available so far do not allow us to identify a pattern of GM composition characteristic of children with ASD. However, according to the systematic review of Ho et al,[9] some GM changes turned out to be associated with ASD, concerning *Prevotella* (phylum Firmicutes), Clostridiales clusters (including *Clostridium perfringens*), and *Bifidobacterium* species.

Nevertheless, not everything has been clarified regarding the theory of GM alteration underlying ASD. In fact, we are not certain that the differences in GM composition precede the appearance of the ASD clinical picture and that they are not, instead, a direct or indirect consequence of autistic symptoms themselves. In this regard, we must not forget the tendency of ASD children to show persistent oral exploration of objects or even (in some cases) to ingest them. These behaviors could be the basis of GM alterations. At the same time, the food selectivity that is so frequent in these individuals, particularly in the youngest,[10] could lead to a less diversified diet which, in turn, could decrease microbiome diversity, altering the GM composition. Modulating food habits, instead, could raise microbiota diversity, improving GI symptoms and behavior.[2] Finally, in subjects with ASD, GM alterations could also be related to the frequent medical comorbidities (allergies, food intolerances, immune system alterations, etc.) found in these individuals or to the various medications (neuroleptics, antiseizure drugs, antidepressants, supplements) that they often take, and not to the autistic symptoms per se. For example, olanzapine and risperidone, both second-generation antipsychotics (SGA), have antimicrobial activity.[2] Metabolic disorders, including weight gain found during treatment with SGA, may be due to GM dysbiosis.[11]

Some considerations regarding treatment arise from the foregoing. Antibiotics may hypothetically modulate GM, but they can also eliminate beneficial bacteria and increase the risk of GI disorders in ASD children; therefore, they are not a good long-term therapy option. Probiotics are live microorganisms providing health benefits after their ingestion. In ASD children, they seem to improve GM dysbiosis, GI symptoms, and even autistic symptoms. Prebiotics are non-digestible fiber compounds acting as a substrate for the colon's beneficial bacteria; in ASD children they have been shown to improve behavior, sleep, and constipation.[2] However, the most effective types and doses of probiotics and prebiotics have yet to be precisely identified.[12] Fecal microbiota transplantation showed improvements in autistic behavior, GM diversity, and GI symptoms, but there are major concerns about its safety. Research on individualized microbiota characterization is necessary to study the effects of treatments targeting GM composition.[2] However, the time factor can play an important role because it is possible that once a hypothetical non-reversible brain damage causing autism has been established, treatments based on the GM, as well as other types of treatments, are not effective.[2]

Much remains to be discovered today regarding the role of microbiota in the ASD etiopathogenesis.

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