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Review Article

Faecal Microbiota Therapy: A Promising Therapeutic Tool for Autism Spectrum Disorder

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Abstract

Autism is a severe brain development disorder that is characterized by deficits in social communication, restricted, repetitive and stereotyped behaviours in children. There is currently almost no cure for autism, but early interventions and therapies can help individuals with autism to lead fulfilling and independent lives. The etiological factors suspected are in general, genetic and environmental. The literature survey provides legitimate reasons for the dysbiosis of the gut microbiota in these patients and an attempt to eubiotics gave promising results. Future focus on this modality in therapeutics will be beneficial to the patients with minimum side effects. In this review, we have discussed etiology, dysbiosis of the gut microbiota in the patients. More focus is given to the outcome of the faecal transplant therapy in human trials as well as in animal model.

Keywords: Prevalence; etiology; co-morbidities; clinic trials

Introduction

Autism spectrum disorder (ASD) is a developmental disorder appears in early childhood. While the cause is unknown, growing evidence has linked ASD to inflammation of brain tissue. In 2023, the CDC reported that around 1 in 36 children in the U.S. is diagnosed with autism. Autism prevalence has increased 178% since 2000. The country with the highest rate of diagnosed autism in the world is Qatar, and the country with the lowest rate is France.

The first cases of autism were described in the 1940s; it was also found that prevalence of this disorder is more in boys than girls. The exact reasons for the ratio remain unclear, however, It could be rooted in biological differences between the Men and boys are more frequently diagnosed with autism than women and girls. It is debated whether this is due to a sex difference in rates of autism spectrum disorders (ASD) or whether females are underdiagnosed. The prevalence ratio is often cited as about 4 males for every 1 female diagnosed. Some studies have found correlations between fetal testosterone levels and ASD. Other scientists believe that testosterone levels during pregnancy make the difference [1].

The exact cause of autism is still unknown; nevertheless, no doubt genetics play a significant role. Since autism is less prevalent in females, autism was always thought to be passed down from the mother. However, research suggests that autism genes are usually inherited from the father. Other reports also indicate that high levels of stress during pregnancy may also be connected to autism in children. This connection appears to have the most impact when the parent experiences stress between weeks 25 and 28 of pregnancy.

The rising rates of ASD can be attributed to multiple factors including increased access to care, awareness, and screening. ASD reflects the enormous complexity of the human brain displayed by our unique behaviours and the desire to understand the workings of the human brain is long-standing. 100 billion neurons in the human brain are connected to 10,000 other neurons. Although neuroscientists, psychologists, and linguistics have tried their best to decipher its codes for centuries, success is yet not in the hands of neuroscientists.

The most effective interventions available are behavioral therapies based on applied behavioral analysis (ABA). There are many different types of ABA to choose from based on the child's strengths and needs.

Many ASD patients have difficulties in social interactions, such as maintaining eye contact or understanding nonverbal cues, delayed speech and language development, and sensory sensitivities. The pathogenesis of

ASD is unclear and is currently thought to be related to genetic factors, immunomodulatory disorders, inflammation, and exposure to environmental toxins [2]. Evidences show that males are more susceptibe to the disease than females. In spite of research to decipher our understanding of potential etiologic mechanisms in ASD, currently, no unifying cause has been established [3]. Limited neuropathologic evidence has revealed those differences in cerebellar architecture and connectivity, limbic system abnormalities, frontal and temporal lobe cortical alterations, and other subtle malformations in ASD subjects. ASD patients often suffer from comorbidities, such as intellectual disability, gastrointestinal disorders as well as gastrointestinal dysfunctions, including altered bowel habits and chronic abdominal pain that accompany their neurological alterations. The incidences of constipation, diarrhoea, abdominal pain, vomiting, and flatulence occur in the range from 9% to 90% in these patients. Maladaptive behaviours sleep disorders, aggressive behaviour, irritability, and self-injury may result in ASD children suffering from gastrointestinal disorders.

Based on DSM-5-TR [4] expressions of mild ASD do exist with the following expression of characteristic features, framed in the manual, by the American Psychiatric Association for easy identification as well as for easy diagnosis by professionals such as paediatricians, psychiatrists, psychologists, and speech pathologists. Autistic subjects with mild ASD might approach conversations and social interactions in an abnormal way and find difficulty in expressing and interpreting nonverbal cues, facing difficulty in developing, maintaining, and understanding relationships. They may also adhere to specific routines and have specific and intense interests. This neurodivergence begins before birth though symptoms might not manifest until later in life [5].

Possible etiologies

Many of the genetic defects associated with ASD could be due to disparity in the encoding of proteins that are involved in the neuronal synapse or activity-dependent changes in neurons or regulatory proteins such as transcription factors. Sixteen newly identified genes associated with ASD suggesting new potential mechanisms including cellular cytoskeletal structure and ion transport [6]. Neocortical architecture from young children revealed the focal disruption of cortical laminar architecture in the majority of subjects, anticipating as a causal factor for problems associated with cortical layer formation and neuronal differentiation. Overgrowth both in cortical size and increased extra-axial fluid has been observed in children with ASD [7]. Susceptibility, to ASD is more for the siblings of disease-affected patients implying that genetic factors also may play a role, although not absolute, since, concordance of autism diagnosis in monozygotic twins is not been proved yet [8].

We know that certain environmental pollutants might also increase the risk of developing the disease. In Denmark, the researchers were able to identify 8842 children born between 2000 and 2013 with ASD and matched each one to five control kids of the same sex and age without autism. They could correlate the presence of groundwater lithium levels to autism rates [9]. Pregnant women drinking tap water with higher levels of lithium had a moderately higher risk of their offspring being diagnosed with ASD disorder. Earlier it was reported that ingestion of chronic and low-dose lithium from drinking can influence the occurrence of adult-onset neuropsychiatric disorders though scientific evidence is wanting [10].Young [11] suggested that serum levels of >2 mM may be associated with neurological symptoms, including cerebellar dysfunction. Prolonged lithium intoxication >2 mM can cause permanent brain damage. Ritz and her study group[12] suggested that some experimental research indicated that lithium, which is among several naturally occurring metals often found in water, could affect an important molecular pathway involved in neurodevelopment and ASD.This observation was in concurrence with world scenario because ASD is more prevalent arid climates, and arid climates tend to have more groundwater lithium [1]. Studies suggest that prenatal exposure to thalidomide and valproic acid have been reported to increase risk and prenatal supplements of folic acid in patients exposed to antiepileptic drugs may reduce risk. Advanced maternal and paternal age, maternal infection or immune activation during pregnancy, both shorter and longer inter-pregnancy intervals, premature babies have been demonstrated to carry a higher risk for ASD in addition to other neuro-developmental disorders. Obstetric factors including uterine bleeding, cesarean delivery, low birth weight, and preterm delivery were reported to be the few factors more consistently associated with this neuro-disorder [6].

An increasing body of evidence is showing that environmental factors can variably increase ASD risk through multiple mechanisms, namely deregulating gene expression, altering signal transduction or cytosolic calcium homeostasis, and inhibiting enzymatic activities critical to brain development and neural function, causing oxidative stress or neuroinflammation [13].

Some studies have found correlations between fetal testosterone levels and ASD. Other scientists believe that testosterone levels during pregnancy make the difference [14].Reports also indicate the impact of high levels of stress during pregnancy (between weeks 25 and 28 weeks of pregnancy) may be a causal factor for ASD in children [15].

Changes in gut microbiota composition

Changes in the composition of the gut microbiota and metabolites observed in both ASD patients and animal models give a clue for the dysbiosis of the gut microbiota to be a causal factor for the etiology of the disease[3]. Several studies have suggested a potential link between the microbiota and ASD because of great differences that exist in the gut microbiota between children with ASD and typically developing (TD) control group [16].Toxins produced by abnormal gut microbiota can increase intestinal permeability and aggravate ASD symptoms, for example, Fusobacterium produces some nerve factors and exerts systemic effects. Abnormal alterations in gut microbiota can lead to intestinal malfunction, thus resulting in increased intestinal permeability (also known as leaky gut), inflammation, and metabolism dysfunction [17], thus affecting distant organs or systems of the host. The leaky gut due to dysbiosis of the gut microbiota has been associated with many neural and non neural human diseases [18; 19; 20;21;22;23]. Increasing reports have indicated that the gut microbiota participates in a bidirectional signaling pathway between the gastrointestinal system and the brain, which is known as the microbiota-gut-brain (MGB) axis [24; 25]. An increasing number of studies have shown that deficy in the MGBA is one of the pathogenic mechanisms of ASD also. These findings suggest that gut microbiota disorders and metabolism may play an important role in gastrointestinal symptoms and neurodevelopmental dysfunction in ASD patients also [3].

Effect of faecal transplant therapy in ASD patients

Human trial-based evidence gives a clue that microecological therapies which have the ability to improve the gut microbiota can alleviate some gastrointestinal symptoms in ASD patients. So far, some reports have already proved that gut microbiota intervention therapy is helpful for ASD positive improvement [26; 27].

Li et al. [3] conducted an open-label clinical trial to investigate the safety and efficacy of FMT for gastrointestinal and behavioural symptoms in children with ASD as well as to explore the underlying mechanism of FMT-induced ASD improvement through the microbiome-gut-brain axis. The result of their study also supported that both oral and rectal routes of FMT could induce significant improvement in GI symptoms, and no significant difference was observed between oral or rectal FMT administration. They [3] also found that there was a large difference in baseline characteristics of behaviour, GI symptoms, and gut microbiota populations between children with ASD and TD control children. In addition, FMT significantly changed the serum levels of neurotransmitters. FMT could promote the colonization of donor microbes and shift the bacterial community of children with ASD toward that of TD controls. The decrease in Eubacterium coprostanoligenes abundance induced by FMT was associated with the FMT response in patients. Their study outcome suggests that this therapy might be a promising therapeutic strategy to improve the GI and behavioural symptoms of patients with ASD. A specific microbiota intervention that targets Eubacterium coprostanoligenes can enhance the FMT response. This trial was registered at the Chinese Clinical Trial Registry (www.chictr.org.cn) (trial registration number ChiCTR1800014745)[28].

In their study [3] though promising results were obtained, the beneficial effects were gradually lost within a few weeks of the end of therapy, suggesting that extended treatment with FMT is needed.

Neurotransmitters are important in neurological regulation and can affect mood, cognition, and behaviour in human beings in general. Alterations of several neurotransmitters were also found in the plasma samples of ASD children suggesting the probability of this abnormality leading to autistic behaviour [29]. After FMT, significantly changed the serum levels of neurotransmitters [3].

Gut microbiota changes after fmt.

There were no significant differences in alpha diversity between TD and ASD groups but found significant differences in beta diversity between the two groups. The study group also encountered a significant difference at both the phylum and genus levels between patients and controls. They identified significant differences of eight genera with significant differences in ASD children. Children in ASD group had a relatively higher abundance of Christensenellaceae, Akkermansiaceae at family level,and Christensenellaceae R 7 group, Akkermansia, Coprococcus, Eisenbergiella, and Tyzzerella in the genus level, while the control group had a higher abundance of Peptostreptococcaceae in family level, and Romboutsia, Fusicatenibacter, Eubacterium eligens group in genus level. FMT could promote the colonization of donor microbes and shift the bacterial population in ASD-affected subjects [3].

Based on the results of the clinical trial Li et al., [3] suggested that FMT might act partially to treat ASD by reducing the abundance of Eubacterium coprostanoligenes and that the genus Eubacterium coprostanoligenes is a potential regulator of FMT treatment response in children with ASD.

Conclusion:

FMT is generally safe therapy for ASD patients and induced minimal adverse effects. However, whether FMT has a therapeutic effect on ASD and how it works to improve neurological symptoms are not thoroughly understood. In the present scenario the knowledge we have gathered implied that FMT could improve GI symptoms and ASD symptoms without eliciting any severe complications. One drawback observed was that the beneficial effects were gradually lost within a few weeks after the end of therapy, suggesting that extended treatment with FMT is needed.

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