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Can oral microbiome dysbiosis affect the behavior of children with Autism Spectrum Disorders (ASD)? : Narrative review

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Abstract

Background: Autism spectrum disorders (ASD) are complex developmental disorders characterised by several levels of social interaction and communication difficulties. The prevalence of children with ASD worldwide is around 1:160, and the number of cases of autism has increased significantly. The oral microbiome is a diverse microbial biofilm with the second most complex microbiota in the human body after the gut. Several factors, such as lifestyle and health, can influence the oral microbiome's composition and metabolism. Children with ASD generally have poorer oral hygiene and suffer from periodontal disease and dental caries more than typical children; this is associated with behavioural disturbances, such as communication limitations, motoric limitations, eating habits and the side effects of drugs. Continued oral microbiome dysbiosis can lead to gut microbiome dysbiosis. There are two hypotheses for the transmission of oral bacteria to the gut, via the hematogenous route or via the enteral route. Gut microbiome dysbiosis may regulate social behaviour, such as emotional dissonance and anxiety, through blood-brain-barrier and gut-brain-axis pathways. When there is inflammation of the periodontal tissue in ASD children, it can cause lipopolysaccharide (LPS) leakage to the blood-brain barrier (BBB) that can cause an inflammatory response and disrupt metabolic activity in the central nervous system. Oral dysbiosis, which continues into gut dysbiosis, can affect behaviour through the gut-brain axis. This review aims to determine the impact of oral microbiome dysbiosis on the behaviour of children with ASD.

Keywords: Autism spectrum disorder (ASD); Oral microbiome; Dysbiosis; Behaviour; Children;

1. Introduction

Autism spectrum disorders (ASD) are complex developmental disorders classified as very diverse in exceptional children and characterised by some difficulty in social interaction and communication. Other characteristics include atypical behaviours and habits such as difficulty switching from one activity to another, attention to detail and unusual reactions to sensations. The three main symptoms of ASD according to the classification of mental illness in ICD-10 and DSM-IV (1), are:

- Impaired social relationships,
- Impaired speech and language, and
- Repetitive actions and interests (2–4).

Most children with ASD have poor oral hygiene and many suffer from gingivitis and dental caries. An imbalance in the commensal microbiota ecology can cause dental caries. These changes could be related to irregular tooth-brushing habits because caregivers and parents have difficulty brushing their children's teeth. The pooled prevalence of periodontal disease in ASD children was 69.4% (5–7).

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Children with ASD often experience problems in maintaining healthy teeth and mouths. Dental care is the most frequently unmet need to preserve the health of special needs children, especially children with ASD. This is a problem because dental and oral health is very important in the growth and development of children (8).

The oral microbiome can be described as a diverse group of microbial biofilms and has the second most complex microbiota in the human body after the gut. The microbiota can be considered more stable over time, for example, there may be only short-term disturbances in microbiota composition following external stress, such as the use of antibiotics. This stability is called resilience and can be divided into two explanations: resistance, namely the ability to deal with disturbances, and recovery, namely the capability to recover from the effects of disorders. Overall, resilience is the capacity of an ecosystem to deal with disruption without changing its symbiotic state (9).

Several factors can affect the oral microbiome's composition and metabolism, such as the host's lifestyle and health status. Each anatomic surface of the oral cavity has a specific microbiota organised as a biofilm. Even within the same tooth surface environment (either supragingival or subgingival), the composition of the bacterial community varies greatly. When the microbiota balance is broken, it will cause dysbiosis. When oral dysbiosis occurs, the microbiome will cause pathogens to develop and disease will occur (9).

Continued oral microbiome dysbiosis can lead to gut microbiome dysbiosis. There are two hypotheses for the transmission of oral bacteria to the gut. The first is via the hematogenous route, whereby oral bacteria enter the lesion and systemically circulate and colonise the gastrointestinal mucosa. The second is through the enteral route, in which oral bacteria move through the digestive tract to the intestine. The human body has several defence mechanisms against microbes, including neutralisation via gastric acid and resistance to colonisation by the enteral route. However, this defence mechanism may not work optimally. Some microbes, such as *P. gingivalis*, are known to be acid resistant, especially at higher inoculation doses. Regardless of the route, evidence suggests that more than half of the bacterial species in the gastrointestinal system undergo oral-gut translocation, even in the absence of pathology. Among the many oral bacteria found in the intestines of patients with gastrointestinal disease are members of the genera *Staphylococcus*, *Porphyromonas*, *Veillonella*, *Fusobacterium*, *Actinomyces* and *Parvimonas* (10).

Oral microbiome dysbiosis can influence complex behaviours such as emotional behaviour and anxiety in two ways. First, when there is inflammation of the periodontal tissue in ASD children, it can cause lipopolysaccharide (LPS) leakage to the blood-brain barrier (BBB) that can cause an inflammatory response and disrupt metabolic activity in the central nervous system. Second, oral dysbiosis, which continues into gut dysbiosis, can affect behaviour through the gut-brain axis. Therefore, oral health must be maintained because it can affect behaviour and emotions (11,12). This review aims to determine the effect of oral microbiome dysbiosis on the behaviour of children with ASD.

2. Literature review

2.1. Oral microbiome dysbiosis

Behaviours in children with ASD, such as communication limitations, motor limitations, eating habits, drug side effects and infrequent dental treatment, can cause oral microbiome dysbiosis. Alternative therapies that are carried out for children with ASD, such as a gluten/casein-free diet, can limit protein intake and indirectly cause an increase in carbohydrate content in saliva. Protein plays a role in increasing the buffer capacity of saliva. This can affect the condition of the oral microbiome (7).

There are significant differences in the bacterial content of ASD children and typical children. In children with ASD, significantly higher colonisation of *Proteobacteria*, *Actinobacteria* and *Bacteroidetes* was observed. At the genus level, increased colonisation by *Streptococcus* and *Haemophilus* and reduced colonisation by *Prevotella*, *Actinomyces*, *Porphyromonas* and *Fusobacterium* in tooth samples of children with ASD compared to typical children indicates dysbiosis of the oral microbiome of ASD children (5,9,13–15). Dysbiosis can be characterised by three different scenarios and can occur simultaneously, namely: a) loss of overall microbial diversity, b) loss of beneficial microbes, and c) increase in pathogenic microbes (16).

2.1.1. Loss of microbial diversity

The general ecological concept is the loss of biodiversity within a community, denoting a decrease in the number, genetic variability and variety of species of a biological community in a specified location. This loss of biodiversity can cause damage to the ecosystem. In the context of caries, several reports indicate a loss of diversity with increasing disease severity. This suggests that increased acidification of the oral microenvironment accompanied by loss of diversity and decreased level and metabolic activity of beneficial bacteria leads to the emergence of cariogenic bacteria (16–18).

2.1.2. Loss of beneficial microbes

One of the main features of dysbiosis is the loss of some of the benefits derived from a healthy oral microbiome. The oral microbiome is important for the maturation and development of an appropriate oral immune response; protects the host from oral pathogens and carcinogenic metabolites; and is part of the nitrate-nitrite-nitric oxide pathway, so there are several benefits. Loss of beneficial microbes can reduce the host's ability to fight pathogenic bacteria, responding to an exaggerated immune response against the host's tissues and exposing the host to carcinogenic metabolites and adverse vascular changes. This loss is especially important in periodontal disease, where excessive chronic inflammation leads to loss of supporting tissue around the teeth, including loss of alveolar bone, which can lead to tooth loss over time (16,19).

2.1.3. Increase in pathogenic microbes

In a healthy environment, the oral microbiome contains opportunistic pathogens at such low levels that they do not cause any problems to the host. However, increasing microbial pathogens can increase the risk of dental caries, periodontal disease and systemic disease (16,20).

2.2. Connection between oral microbiome dysbiosis and behaviour in children with ASD

The oral microbiome can influence the behaviour of children with ASD in two ways. First, changes in transcription results in microglia, leading to impaired microglia function, so the permeability of the BBB is higher (Figure 1). This causes the brain to be more easily exposed to bacterial metabolites. When inflammation of the periodontal tissue occurs in ASD children, it can cause leakage of LPS to the BBB. It can cause an inflammatory response and disrupt metabolic activity in the central nervous system. Prolonged disruption of energy metabolism in neurons, oligodendrocytes and glia can cause structural changes in the cortex, hippocampus, amygdala, or cerebellum, thus affecting behaviour disorders in ASD children. The increase in LPS in ASD children correlates with the increase in Interleukin 6 (IL-6) which acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. In addition, inflammation in the developing brain causes synapse malfunction. Synaptic malfunction resulting in vasopressin secretion can also affect social behaviour (21–23).

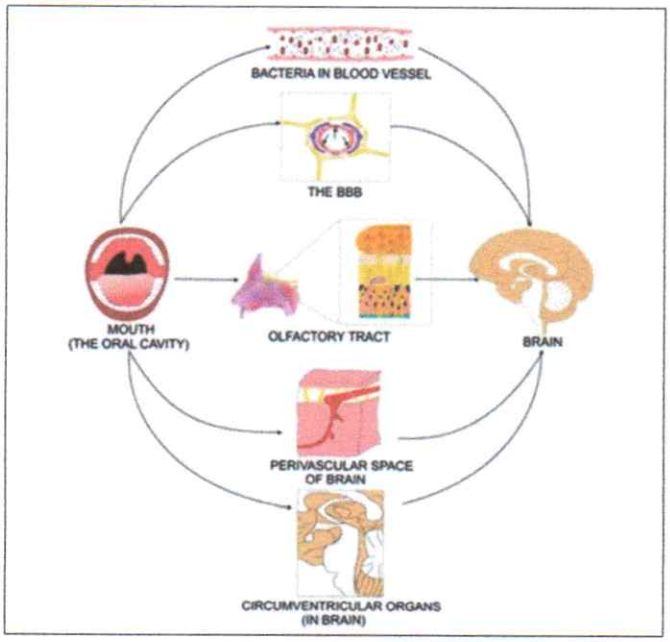

Figure 1 Direct and indirect mechanisms of bacteria infecting the brain (22).

In the direct mechanism, the oral cavity infects the olfactory tract and the olfactory nerves transfer the bacteria to the brain. In an indirect mechanism, bacteria in the mouth infect the blood and find their way through the blood, blood-brain barrier (BBB), perivascular space and circumventricular organs to the brain (22).

The second way is through the gut-brain axis, based on two-way physiological connections where information is exchanged between the host microbiome, the gut and the brain. This involves a link between the central nervous system and microbes in the gastrointestinal tract through direct neural activation. Prolonged oral microbiome dysbiosis can lead to microbiota dysbiosis in the gastrointestinal tract. Dysbiosis of the intestinal microbiota can affect several complex behaviours, such as emotional behaviour and anxiety (12,22,24,25). The microbiome is important for the immune system, brain and genome. A series of recent studies have demonstrated that the microbiome influences the central nervous system in multiple ways and influences the psychological state of individuals by mediating reactions to stress and anxiety (26–30).

The enteric nervous system (ENS), composed of two layers of approximately 100 million nerve cells that line the digestive tract from the oesophagus to the rectum, is an independent centre for neural processing and integration. The ENS can trigger nausea or malaise, build stress and evoke emotions. The microbiome, among other things, achieves both the recognition and synthesis of neuroendocrine hormones and produces neuroactive factors capable of communicating not only with the ENS but also with the central nervous system. The gut microbiome can influence synaptogenesis, regulation of neurotransmitters and neurotropic factors in the cerebral hemispheres. Administering probiotics (e.g. *Lactobacillus*) and faecal microbiome transplantation to treat conditions associated with depression and anxiety are no longer experimental but are good therapeutic avenues. The link between the microbiome and depression has been proven by research on bacterial abnormalities in depressed patients. It has also been shown that feeding multiple microbiome populations (*L. rhamnosus, B. infantis, B. longum*) can improve mood even in healthy subjects (26, 31–33).

In ASD children, compared to typical children, the adverse gut microbiome is more numerous than the beneficial microbiome. Behaviour, oral hygiene and the gut microbiome in ASD are interrelated factors. In general, gut microbiome dysbiosis often causes illnesses such as diarrhoea and abdominal pain, which can affect the psychology and behaviour of ASD children (11). The immune system is produced on the epithelial surface of the digestive system, which is inhabited by many bacteria, comprising both systemic and mucosal immune systems. Beneficial bacteria living in the intestinal wall epithelium play a major role in immunomodulation. When the healthy gut flora is disrupted, the number of cells that produce Immunoglobulin A (IgA) drops dramatically, reducing the immune system's ability and causing digestive disorders (14,27,34).

Digestive problems that children with ASD often experience include bloating, diarrhoea, constipation, difficulty eating and malnutrition in various degrees of severity. These digestive problems cause discomfort and pain. However, due to the inability of ASD children to communicate, most of them cannot tell their parents about it, so they express their feelings in other ways, such as self-harm, tantrums, refusing to eat, etc. (24,34,35).

The mainstay of therapy for ASD is based on behavioural therapy, applied behavioural analysis, and speech and occupational therapy. Given that ASD is so complex and diverse, additional treatments exist to improve cognitive, linguistic and adaptive abilities. Probiotic supplementation may improve ASD symptoms (25). Probiotics can intervene in the gut microbiome, thereby increasing the good bacteria in the intestines of children with ASD. The most effective probiotics are probiotics which include four lactobacilli strains, three bifidobacteria strains and one S. thermophiles strain. Such probiotics significantly reduce gastrointestinal distress, especially constipation, and substantially improve certain aspects of behaviour, such as repetitive and rebellious behaviour (36–38).

From this literature review, it can be seen that the condition of the oral microbiome needs more attention from dental practitioners because oral microbiome dysbiosis can progress to gut microbiome dysbiosis, which can affect emotional and anxiety behaviour in children with ASD through the blood-brain-barrier and gut-brain-axis pathways. It does not rule out the possibility that direct access from the oral microbiome to the brain can influence behaviour, which requires further research.

3. Conclusion

Oral microbiome dysbiosis may affect the behaviour of children with ASD. Oral microbiome dysbiosis can progress to gut microbiome dysbiosis, which may affect emotional and anxiety behaviour in children with ASD through the blood-brain-barrier and gut-brain-axis pathways.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this document.

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