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ALTERATIONS IN ORAL MICROBIOTA AS POTENTIAL BIOMARKERS FOR AUTISM SPECTRUM DISORDER: REVIEW AND PERSPECTIVES

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ABSTRACT

Objective: The objective of this narrative literature review article is to address the correlation between autism spectrum disorder and oral microbiota. Methodology: This article is a narrative literature review, and a specific methodology was developed for this type of review. To develop the article within the standards of a narrative review, Rother's (2007) study was used, which addresses systematic and narrative reviews, explaining how each type of review should be constructed, its characteristics, approach and structure, information that was useful to serve as a guide in this article. In addition, seeing the need to acquire articles with scientifically proven information that could compose the review, searches were carried out in the following online databases: COCHRANE; Scielo; PubMed; PROSPEROUS; Elsevier; The Cochrane Library in conjunction with Google Academy. In order to obtain only results that fit the topic addressed in the article, the following descriptors were used: Microbiota; Biomarkers; Autism Spectrum Disorder. Results: Recent studies have studied the bacteria present in the mouths of people with autism and people without autism, to identify differences in the microbiota. Other studies have studied oral bacteria of children with autism and neurotypical children, to identify bacteria that can be biomarkers in the diagnosis. Conclusion: Studies have obtained positive results for the scientific community, finding specific bacteria in children with ASD, which can be used as biomarkers contributing to early diagnosis. However, there is a need to expand studies on the subject to obtain more evidence so that these biomarkers become solid in the scientific community, enabling their use.

Keywords: Microbiota. Biomarkers. Autism Spectrum Disorder.

INTRODUCTION

Autism Spectrum Disorder (ASD) is characterized as a syndrome that affects people of different sexes, causing neurodevelopmental problems (Laluce et al., 2024). People with ASD have deficits in social interaction and communication together with stereotyped and repetitive patterns of behavior (Araújo & Schwartzman, 2019). This set of characteristics are the main forms of manifestation of the disorder, which can be varied or in increased or reduced degrees in each respective patient. In addition, other clinical conditions that are present in people with autism are symptoms of gastrointestinal problems, food allergies, constipation, malabsorption and maladjustment (Lefter et al., 2019). Autism Spectrum Disorder is related to changes in brain physiology, connectivity and morphology (Cadore et al., 2022). The behaviors associated with ASD are multifactorial, where environmental factors, mutations, epigenetic alterations and genetic factors influence. Studies carried out in recent years have identified that changes in the microbiota will also directly impact behavioral changes, which can reduce social sociability, interaction with unknown people and abnormalities in the expression of brain genes (Liu et al., 2019).

The human body is composed of a set of microorganisms, both pathogenic and commensal, which together form the microbiota. This community of microorganisms is formed shortly after a human being is born. When the baby leaves the mother's womb, the baby is exposed to a range of microorganisms, which increases even more as the years go by and the organism grows. After coming into contact with the human body, microorganisms begin to colonize various structures and organs such as the skin, intestine and oral cavity, establishing a symbiotic relationship, where the relationship between humans and microorganisms brings benefits to both. The oral microbiota is formed by viruses, archaea, bacteria, fungi and protozoa that are mostly commensals, causing no harm to oral balance, beings that help to keep other pathogenic microorganisms away from the oral cavity (Avila et al., 2009; Thomas et al., 2017; Chimenos-Küstner et al., 2017).

Recent studies have studied the oral microbiota of autistic patients in order to identify the microorganisms that are part of their microbiota, to compare with the microbiota of neurotypical people, seeking to identify whether there are differences or not, and whether there are potential biomarkers of autism in the oral environment. Thus, the objective of this narrative literature review article is to address the correlation between autism spectrum disorder and oral microbiota.

METHODOLOGY

This article is a narrative literature review, and a specific methodology was developed for this type of review. In order to develop the article within the standards of a narrative review, Rother's (2007) study was used, which addresses systematic and narrative reviews, explaining how each type of review should be constructed, its characteristics, approach and structure, information that was useful to serve as a guide in this article. In addition, seeing the need to acquire articles with scientifically proven information that could compose the review, searches were carried out in the following online databases: COCHRANE; Scielo; PubMed; PROSPERO; Elsevier; The Cochrane Library in conjunction with Google Academy. In order to obtain only results that fit the theme addressed in the article, the following descriptors were used: Microbiota; Biomarkers; Autism Spectrum Disorder. Grey literature was also used in this article, bringing richness and content to the literature review.

RESULTS

BIOMARKERS OF AUTISM SPECTRUM DISORDER

The identification of reliable biomarkers for Autism Spectrum Disorder (ASD) is a priority in contemporary neuroscience. ASD, being a multifactorial and heterogeneous condition, has been associated with genetic, epigenetic, immunological, metabolic and microbial alterations (Loth et al., 2016). Potential biomarkers already described include mutations in the SHANK3, MECP2, CHD8 and SCN2A genes, in addition to aberrant methylation patterns, alterations in the levels of inflammatory cytokines and disturbances in the metabolism of neurotransmitters, such as dopamine, serotonin and GABA (Geschwind & State, 2015; Coury et al., 2012). Metabolomic and proteomic studies have also revealed altered biochemical signatures in patients with ASD. In particular, elevated levels of propionic acid, butyric acid, and isobutyric acid—short-chain fatty acids (SCFAs) produced by gut bacteria—have been found in fecal samples from autistic children, suggesting an interface between the microbiome and brain metabolism (Kang et al., 2013; Adams et al., 2011).

In addition, functional and structural neuroimaging studies have demonstrated changes in the connectivity of brain networks involved in social cognition, language, and repetitive behavior, with studies pointing to the prefrontal cortex, amygdala, and corpus callosum as critical regions (Uddin et al., 2013). However, most of these biomarkers rely on expensive and invasive methods. Therefore, there is growing interest in accessible and noninvasive biomarkers such as those derived from the oral microbiota, which may represent a promising alternative for screening and early diagnosis of ASD.

ORAL BIOMARKERS

The oral cavity represents one of the most dynamic interfaces between the environment and the human organism, being colonized by a wide range of microorganisms, including bacteria, viruses, fungi and archaea. It is estimated that there are more than 700 distinct bacterial species in the human oral microbiota, whose composition and stability are modulated by factors such as diet, oral hygiene, medication use, systemic conditions and genetic factors (Dewhirst et al., 2010; Wade, 2013).

Recently, the role of the oral microbiota as a source of non-invasive biomarkers has aroused the interest of the scientific community. Saliva, as a diagnostic fluid, has significant advantages: its collection is simple, painless and low cost, and it can be performed repeatedly in children and individuals with cognitive limitations, such as those with Autism Spectrum Disorder (ASD) (Castagnola et al., 2011; Malamud & Rodriguez-Chavez, 2011).

Research suggests that there are significant differences in the composition of the oral microbiota between neurotypical individuals and individuals with ASD. Several bacterial species, such as Prevotella histicola, Selenomonas noxia, Haemophilus parainfluenzae, and Fusobacterium nucleatum, have been found in greater abundance in the saliva of autistic children, while commensal microorganisms such as Streptococcus sanguinis, Veillonella dispar, and Rothia mucilaginosa tend to be decreased (Qiao et al., 2022; Yang et al., 2022). These changes may reflect persistent proinflammatory states or altered immune barriers in patients with ASD. In addition to taxonomic profiling, there are also studies on salivary metabolomics in individuals with ASD. The concentration of metabolites such as lactate, citrate, glutamate, butyric acid, and succinic acid may be altered, directly impacting neurotransmission and synaptic plasticity (Hicks et al., 2018; Kong et al., 2021). These metabolites, often derived from microbial activity, are promising candidates as functional biomarkers.

In addition to bacteria, the analysis of non-coding RNA, including microRNAs present in saliva, has gained prominence. MicroRNAs such as miR-23a, miR-146a, and miR-155 have already been linked to neuroinflammatory and immune processes in ASD, and their detection in oral fluids opens new screening possibilities (Hicks et al., 2020).

In summary, the oral microbiota and its products represent a rich source of potential biomarkers for the early diagnosis of autism. The clinical applicability of these findings, however, will depend on multicenter validations, standardization of protocols and integration with other diagnostic approaches.

ORAL BIOMARKERS AND ASD

The oral microbiome of individuals with ASD presents relevant structural and functional differences when compared to neurotypical individuals. In a study conducted by Qiao et al. (2022), children with ASD showed lower alpha diversity (measured by Shannon index) and higher abundance of Haemophilus parainfluenzae, Fusobacterium nucleatum and Prevotella histicola, while Streptococcus mitis and Veillonella dispar were significantly reduced. Such alterations may indicate a local pro-inflammatory state, potentially related to systemic alterations in the microbiota-gut-brain axis.

The pathways through which the oral microbiota could impact neurodevelopment include the translocation of metabolites or bacterial fragments into the bloodstream, chronic immune activation and even signaling via the vagus nerve. Furthermore, locally produced cytokines, such as IL-6, IL-1β, and TNF-α, can exert distal effects by altering the blood-brain barrier or modulating neuronal gene expression (Hsiao et al., 2013; Diaz Heijtz et al., 2011).

Animal models also reinforce these associations. Mice with dysbiotic microbiota transferred from donors with autism developed ASD-like behaviors, in addition to alterations in synaptic gene expression (Sharon et al., 2019). These findings reinforce the possibility that the oral microbial composition, in addition to the intestinal one, is implicated in the genesis or maintenance of phenotypic aspects of the disorder.

DISCUSSION

The intersection between neurodevelopment and oral microbiota represents an emerging and highly promising frontier of translational research. The identification of oral microbial biomarkers in the context of ASD emerges as a practical, non-invasive and economically viable alternative to complement the traditional behavioral criteria used in diagnosis. The use of saliva as a diagnostic biofluid has several advantages: easy collection, safety, low cost and the possibility of frequent repetition without causing discomfort. In addition, saliva reflects both the oral microbiome and systemic immunological and neuroendocrine parameters, offering a comprehensive overview of the individual's physiological state (Castagnola et al., 2011; Hicks et al., 2018). Despite the promising initial evidence, important challenges remain. There is significant variability between studies, with methodological differences regarding the type of collection, sequencing techniques, 16S rRNA target regions analyzed, age ranges of participants and diagnostic criteria for ASD.

Furthermore, factors such as diet, medication use, oral hygiene habits, and systemic conditions can act as confounding variables (Sgritta et al., 2019). From a clinical perspective, the validation of a panel of microbial biomarkers requires multicenter, longitudinal studies with samples representative of the population diversity. Only with this basis will it be possible to consolidate an effective oral screening protocol and incorporate it into pediatric or multidisciplinary dental clinical practice. Finally, in addition to its diagnostic function, the study of the oral microbiota in ASD can pave the way for therapeutic interventions. Strategies such as the use of prebiotics, oral probiotics, oral microbiota transplantation, or immune signaling modulators may represent new adjuvant approaches in the management of neurobehavioral symptoms associated with ASD.

CONCLUSION

Studies have obtained positive results for the scientific community, finding specific bacteria in children with ASD, which can be used as biomarkers contributing to early diagnosis. However, there is a need to expand studies on the subject to obtain more evidence so that these biomarkers become solid in the scientific community, enabling their use.

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