Review

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Biomarkers for autism spectrum disorder: a short review

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Background: Autism spectrum disorder (ASD) is characterized by social disabilities and stereotyped behaviors. There is a relevant social impact on autistic people's lives and, therefore, biomarkers have become relevant for understanding neurobiological mechanisms.
Objective: This study aims to review current knowledge about the role of biomarkers and their main scientific evidence in autism.
Methods: The authors performed a non-systematic literature review through the PubMed database, using the keywords "biomarkers", "autism" and "autism spectrum disorder". The search was restricted to articles written in English, in the last 10 years.
Results: Analyzing the articles found, it is possible to delimit the biomarkers according to the development of ASD, from the prenatal period with exposure to diseases or association of autism with other genetic diseases, through the immune and nutritional factors exposed during pregnancy, and for end those associated with diagnoses phase in which there is the presence of symptoms in which these markers can be used to aid in the diagnosis.
Conclusion: Although preliminary, biomarkers may hold promise for prenatal and presymptomatic screening. It may also be used as predictors of treatment for autism spectrum disorder.

Keywords: 5-hydroxytryptamine, autism spectrum disorder, autism, biochemical, clinical research, dysmorphology, marker, melatonin

Introduction

Autism spectrum disorder (ASD) is characterized by neuropsychological and behavioral deficits. Cognitive impairment, social disability, repetitive and stereotyped behaviors are some of the symptoms that affect autistics early. Despite the social impact, we still seek to understand the neurobiological mechanisms that lead to this pathology[1].

Given the significant social and clinical impact of ASD, there is an urgent need to identify objective biomarkers that can aid in early diagnosis, monitor treatment response, and improve personalized care. Therefore, understanding neuroanatomy, neurochemistry, and identifying biomarker molecules in the brain can assist healthcare professionals in monitoring treatment response and predicting outcomes for children with these neurodevelopmental disorders[2].

The principal objective of this study is to examine the current evidence base for biomarkers associated with autism spectrum disorder (ASD), with a view to assessing their potential utility in clinical settings for early detection, diagnosis, and targeted therapeutic interventions.

HIGHLIGHTS

- Biomarkers have become relevant for understanding neurobiological mechanisms of autism spectrum disease
- This study aims to review current knowledge about the role of biomarkers and their main scientific evidence in autism
- it is possible to delimit the biomarkers according to the development of ASD, from the prenatal period with exposure to diseases or association of autism with other genetic diseases, through the immune and nutritional factors exposed during pregnancy, and for end those associated with diagnoses phase in which there is the presence of symptoms in which these markers can be used to aid in the diagnosis

Search strategy

A non-systematic literature review was carried out using the PubMed database, using the disease-specific keywords:

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"biomarkers", "autism" and "autism spectrum disorder". The search was restricted to articles written in English published in the last 10 years. All abstracts were selected by relevance and the most relevant articles were read and discussed.

The screening and selection of studies underwent a meticulous process that involved searching, identifying, and adapting the inclusion and exclusion criteria in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The PRISMA flowchart, which delineates the steps of identification, screening, eligibility, and inclusion of studies, is presented in Figure 1.

The inclusion criteria

The present review included only studies that met the following eligibility criteria: The following criteria were used to select articles for inclusion in this review: (1) articles published in English; (2) studies published within the last 10 years; (3) studies that explored the association between biomarkers and ASD with innovative approaches demonstrating potential clinical impact; and (4) only studies providing clinical data or measurable biomarkers were considered. Studies were excluded if they were (1) non-peer-reviewed, including those on preprint platforms; (2) primarily focused on topics unrelated to biomarkers for ASD; or (3) lacking robust empirical data or clear evidence on biomarkers.

Results

Study selection and characteristics

The selection of the final 19 articles was a systematic and careful process. Initially, a search of the PubMed database identified 78 potentially relevant articles. The first stage of selection was based on a review of article titles, excluding studies that did not meet the specific objectives of this review, such as those that focused on tangential topics or did not centrally address biomarkers.

Subsequently, the remaining articles abstracts were analyzed to ensure that they directly addressed the relationship between biomarkers and ASD. At this stage, studies presenting robust empirical data were considered, including randomized controlled trials, observational studies, case-control studies, cohort studies, and systematic reviews with meta-analyses.

Following the application of the stipulated criteria, 19 articles were selected as meeting the objectives of the review in the most optimal manner. The articles were then classified according to their methodological approach, which included one randomized controlled trial, one observational study, four case-control studies, five cohort studies, and six systematic reviews.

Outcomes

Biomarkers in ASD are of great importance for the delineation of the manifestations of the disorder, particularly with regard to

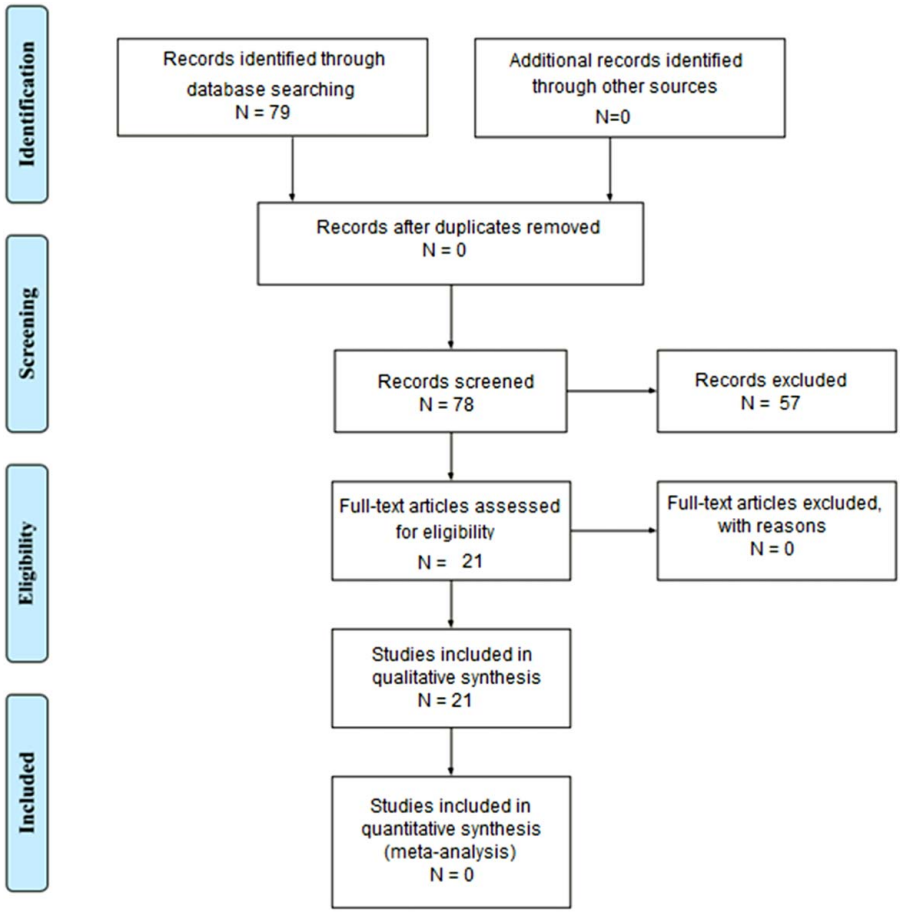

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of selected articles.

genetic and epigenetic profiles. The identification of these biomarkers enables the recognition of behaviors that respond more favorably to early biomarker profiles, thereby facilitating the identification of the most favorable manifestations for early intervention[3–5].

An understanding of the progression of ASD enables the tracking of a patient's development from the prenatal period through to the treatment phase. From the prenatal stage, it is possible to diagnose genetic diseases that are associated with the development of ASD, such as Down syndrome. Studies have identified a relationship between these two conditions, although prenatal tests remain nonspecific for the disease's follow-up[6,7].

A maternal inflammatory response during pregnancy has been linked to an elevated risk of conditions that contribute to the development of autism[8]. This maternal event may be explained by the ability of antibodies to target key proteins involved in development. Nevertheless, additional research is required to substantiate these findings, as they have yet to be replicated in human subjects[9]. Nutritional factors have also been linked to an increased risk of ASD, including deficiencies in folate and vitamin B12, excessive supplementation of these nutrients, elevated levels of folate receptor alpha autoantibodies, and alterations in vita min D levels[10–12].

Other biomarkers are associated with the diagnosis of ASD, particularly at the stage when symptoms are already present. Proteomics provides additional insight into the involvement of biomarkers at this phase, as evidenced by the literature[13,14]. It is also noteworthy that certain markers are associated with the intestinal and oral microbiota[3,4].

Discussion

Cord plasma acetaminophen metabolites

The potential adverse neurodevelopmental consequences of perinatal acetaminophen exposure. Positive associations between cord acetaminophen and ADHD and cord acetaminophen and ASD were observed in strata of relevant covariates, including maternal fever during pregnancy, which is an indicator for acetaminophen use. In addition, the liver is the main site for acetaminophen metabolism and, after being processed, a metabolite with a high toxic level, N-acetyl-p-benzoquinone imine, is generated, which is caused by the greater hepatotoxicity among the components of acetaminophen. In adults, this metabolism reaches about 10%, but in newborns, due to the immaturity of the hepatic system, the metabolite remains circulating for a longer time and still inhibits the synthesis of prostaglandins. Therefore, the most recent studies have concluded that perinatal umbilical cord biomarkers of acetaminophen increase or risk for ADHD and ASD in children[4].

Prenatal biomarkers genetics

Genetic markers in congenital disorders such as Down syndrome and other trisomies are directly related to the predisposition to develop ASD, with a prevalence of up to 42% observed in cohort studies using standard diagnostic tools. Furthermore, recent analyses have identified MID2 as a key genetic biomarker that differentiates control groups from ASD groups. Elevated expression of the MID2 gene, located on the X chromosome, has been associated with a potential predictor of ASD. However, randomized trials are still lacking to definitively prove the benefit of prenatal genetic testing for ASD[3,15].

Immune (antibodies, interleukin)

The most diverse studies show that immune activation during pregnancy increases the risk of developing ASD in newborns. In addition to the increased risk when associated with maternal viral and bacterial infections during pregnancy, particularly if hospitalization is required. Study with the mouse model identified specific immunological mediators, such as interleukin IL-6 and IL-17, no human biomarker was developed, therefore, only the medical history of such an event can be used as a biomarker to identify an increased risk. of ASD, increasing the relevance of a thorough follow-up during prenatal care[3].

Metabolic

The metabolic factor showed the relationship of TEA with alternations in one-carbon folate metabolism (FOCM) and related pathways, including methylation. Demonstrating that maternal methylation abnormalities, including DNA hypomethylation and abnormalities in metabolites integral to the methylation cycle, including plasma homocysteine, adenosine, and S-adenosylhomocysteine (SAM), were found in mothers who have children who have developed ASD[3].

Gut and oral microbiota

Further analysis revealed significant inter-individual differences in the gut and oral microbiomes of subjects with ASD compared to controls. It is noteworthy that children with ASD frequently exhibit altered microbiota profiles, including an overgrowth of Proteobacteria, which is associated with inflammatory bowel disease and metabolic syndrome. This may exacerbate ASD symptoms through the gut-brain signaling pathways. An unspecified genus of oral bacilli was identified, with a significantly different abundance between ASD and control subjects, thereby highlighting unique microbiota changes[5].

Notable strains include Butyricimonas, which has been linked to anti-inflammatory effects, and Parvimonas, which has been associated with systemic inflammation. The disrupted Firmicutes/Bacteroidetes ratio, which is often observed in ASD, provides further support for the potential role of the microbiota as diagnostic markers. These microbial signatures not only reflect underlying biological processes in ASD but also suggest potential therapeutic targets, thereby reinforcing the importance of microbiome research in ASD[16].

All this review discussion is scoped from the fact that the diagnosis of ASD is guided by the DSM-5 criteria, which are based only on clinical symptoms, without objective laboratory measures. Combining multiple biomarkers, such as genetic mutations, metabolic abnormalities, and distinct microbiome profiles, significantly enhances diagnostic accuracy in ASD. For instance, the presence of specific microbial signatures and metabolic pathway alterations provide valuable diagnostic clues and may guide early intervention strategies tailored to individual biomarker profiles.

Meta-analyses show convincing evidence (class 1) that advanced age, use of antidepressants, SSRIs and metabolic syndrome are important risk factors to autism 20–25. The metabolic syndrome causes low-grade inflammation and insulin resistance

that possibly can affect the fetal outcome cause maternal factors alter the gestational environment[17], it is elucidated by the fact that maternal autoantibodies, due to the breakdown of maternal immune tolerance, can recognize proteins in the fetal brain causing damage and by consequence the autism spectrum disorder[18,19]. Maternal autoimmune disease can also affect the fetus with the same mechanism.

Higher exposure to pollution, medication, mutations and complications in women above 35 years old is associated with an increased risk of autism spectrum disorder in comparison to younger maternal age[20].

SSRIs (selective serotonin reuptake inhibitors) use during pregnancy is also associated with the disorder, despite that meta-analysis shows that maternal psychiatric conditions can also increase the incidence of autism spectrum disorder. Notably both the use of SSRI and unexposed groups to these drugs but those that have a psychiatric condition are exposed to an increased risk[21].

At present, the diagnosis of ASD is primarily based on clinical criteria established by the DSM-5, which constrains the capacity to detect the disorder at an early stage and in an objective manner. Recent studies indicate that the global prevalence of ASD is ~1 in 68 births, with regional variations that may reflect differences in diagnostic criteria and the availability of health services. Notwithstanding advances in the identification of genetic, immunological, and metabolic biomarkers, there remains a significant gap in the utilization of these biomarkers in clinical practice for early diagnosis and prediction of treatment response. This review underscores the imperative for the incorporation of objective biomarkers into ASD assessment protocols, with the aim of overcoming current limitations and facilitating the delivery of more personalized care[1].

Limitations and future directions

This article identifies several limitations, including the observational nature of many studies, which restricts causal inference and the ability to isolate specific risk factors. A significant number of findings are based on observational data rather than randomized controlled trials, which has an impact on the robustness of the conclusions that can be drawn. Furthermore, there is a necessity for more comprehensive and controlled studies in domains such as acetaminophen exposure, genetic biomarkers, immune activation, metabolic pathways, and microbiome analysis.

Future research should seek to address these limitations by employing longitudinal and experimental designs, developing specific and standardized biomarkers, and integrating multiple factors in a comprehensive approach to ASD.

This article makes a significant contribution to the existing literature by identifying and summarising the key associations between perinatal exposure, genetic markers, immune factors, metabolic abnormalities and microbiome differences with ASD. It highlights the necessity for further research to elucidate the intricate interactions of these factors and enhance diagnostic and therapeutic strategies for ASD.

Conclusion

Although preliminary, biomarkers may hold promise for prenatal and presymptomatic screening. It may also be used as predictors of treatment for autism spectrum disorder.

Ethical approval

The local IRB waived the need for ethical approval due to the retrospective nature of the study.

Consent

Informed consent was not required for this review article.

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Author contribution

All authors have contributed equally in formation of all forms of manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflict of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Bipin chaurasia.

Data availability statement

None.

Provenance and peer review

None.

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