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Review Article

Neuroinflammation and Microglial Dysfunction Involved in the Neurobiology of Autism

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Abstract

Introduction: Autism spectrum disorder was first defined in the 1940s by Leo Kanner, although since 1911, Bleuler had referred to some similar behaviors. Important areas of development are affected, such as communication, social interaction, and the presence of restrictive, repetitive, and stereotypical behaviors. The study of the etiopathogenic factors involved helps to better understand it. Neuroinflammation and the leading role of glia have been addressed by the scientific community, which has allowed for the proposal of strategies and therapies that facilitate glial protection and enhance the neurotypical development of children.

Objectives: To deepen the understanding of glial dysfunction and its role in neuroinflammation, as well as to address strategies and therapies that promote glioprotection.

Methods: A review was conducted using databases such as Pubmed, Scielo, and Google Scholar, employing descriptors in both English and Spanish such as; glia, glial dysfunction, astrocytes, neurodevelopment, autism. During the period from June to September 2025. Files related to the topic of interest were included, specifically systematic reviews, meta-analyses, and case-control studies.

Conclusion: The role of glia has been evidenced and how its dysfunctions influence neuroinflammation. Progress has been made in studying protective factors by promoting glioprotection through natural therapies that combat oxidative stress and other harmful phenomena, highlighting omega-3 supplements, vitamin D, medicinal mushrooms, natural steroids, among others.

Keywords: *Glia; Dysfunction; Neuroinflammation; Astrocytes; Neurodevelopment; Autism*

Introduction

Autism spectrum disorder. Conceptualization

Autism spectrum disorder (ASD) was first defined in the 1940s by Leo Kanner, although Bleuler had referred to some similar behaviors as early as 1911. The impairment of important areas such as communication, social interaction, and the presence of restricted interest patterns in behavior grouped under the category of neurodevelopmental disorders in the diagnostic and statistical manual of mental disorders (DSM-5), Fifth Edition [1]. Any failure in the maturation and organizational processes of the nervous system can lead to neurodevelopmental disorders such as ASD [2].

It is a spectrum ranging from subtle symptoms to clear evidence of a mental disorder with severe impairments in social communication skills and extreme difficulty coping with change, requiring a significant level of support [1]. This definition has evolved through different classifications for mental illnesses and is now addressed more comprehensively thanks to its inclusion in the neurodevelopmental disorders section of the DSM-5.

Epidemiology

Until recently, it was an underdiagnosed disorder, and in the 1980s, the prevalence was estimated at approximately 4 cases per 10,000 births. However, changes in diagnostic criteria and increased awareness of this disorder have led to a current prevalence of 11.3 cases per 1,000 children [3].

It is estimated that worldwide, approximately 1 in 100 children have ASD. This estimate represents an average figure, and reported prevalence varies among studies. Some countries report higher figures, while others, particularly low-income countries, do not know the prevalence [4]. The autism and developmental disabilities monitoring network in the United States reported a prevalence of 16.8 per 1,000 (1 in 59) eight-year-olds in 2014 across 11 sites [5]. This same monitoring network highlights the higher prevalence of ASD at the beginning of the COVID-19 pandemic, reporting data of 1 in 36 eight-year-olds (2.8%) across eleven communities within the ASD and developmental disabilities monitoring network, showing higher numbers in 2020 compared to 2018 [6].

A recent systematic review of 71 studies estimated the average global prevalence of ASD between 2012 and 2022 to be 10 per 1,000 children and adults. Males are approximately 4.2 times more likely to be affected than females, with evident differences between the sexes in social communication, camouflage, and restrictive and repetitive behaviors [7].

In Cuba, there is a gradual increase in the number of cases, which, while not reaching the figures seen in many other countries, remains a significant health problem due to the disorder's impact on the individual, family, social, and academic functioning of these children. There are approximately 968 children and adolescents with autism; of these, more than 440 are in special education programs, and the rest attend mainstream schools [8].

In recent years, progress has been made in the diagnosis of these disorders; however, it remains a late diagnosis. Understanding the mechanisms involved in their etiopathogenesis, focusing on neuroinflammation as one of the most studied mechanisms, is of interest not only for making this diagnosis but also for the search for markers that can predict their presence from early stages. Furthermore, preventive medicine is based on the search for factors that can be addressed before disease progression. Thus, by understanding the functions of glial cells and their crucial role in neuroinflammation, strategies, therapies, and interventions can be studied to mitigate this damage and enhance neuroprotection and glioprotection.

This review is conducted with the aim of delving deeper into glial dysfunction and its role in neuroinflammation, as well as addressing strategies and therapies that promote glioprotection.

Development

Neurobiological factors involved in ASD

The etiology of ASD is multifactorial, shaped by inherited genetics and environmental contributions, particularly those related to pre-, peri-, and postnatal events that may occur around the child or the mother during gestation [9]. Epidemiological studies mention exposure to infections during pregnancy, obesity, gestational diabetes mellitus, the use of selective serotonin reuptake inhibitors, antibiotic use, and prenatal exposure to toxins as prenatal environmental factors that contribute to ASD [10,11]. These prenatal factors can alter various pathways during critical periods of development, particularly in genetically susceptible individuals [12].

Other studies address infection, obesity, gestational diabetes, the use of selective serotonin reuptake inhibitors, antibiotics, and exposure to toxins during pregnancy as factors that can influence inflammation, hormonal balance, mitochondrial function, and the gut microbiome to disrupt subsequent neurological development, leading to neurodevelopmental disorders. Evidence related to the potential pathways underlying the aforementioned prenatal factors is largely preclinical and involves immune dysregulation, mitochondrial dysfunction, oxidative stress, gut microbiome alterations, and hormonal imbalances [13].

In recent years, the role of neuroinflammation and its relationship to immune dysregulation has led to an investigation of phenomena occurring in the central nervous system that compromise its proper functioning. This has resulted in a deeper study of gliotoxicity as a key element in triggering these phenomena.

Maternal immune activation (MIA), triggered by infection or inflammation during pregnancy, has been associated with a range of developmental disorders in children, including an increased risk of language and motor delays. Disruptive behaviors, inappropriate emotional responses, and altered connectivity in brain regions related to working memory have also been described [14,15]. MIA elevates circulating and central proinflammatory cytokines in animal models, which could affect fetal immunity and neurodevelopment [16]. Maternal cytokines can cross the placenta, enter the fetal circulation, and activate the fetal immune system [17].

This has been demonstrated in the literature where pregnant rats administered streptozotocin, a diabetes-inducing agent, have been studied. This resulted in elevated levels of the inflammatory cytokines IL-1β and tumor necrosis factor (TNF)-α in the brain tissue of their offspring, accompanied by delays in neurological development in behavioral tasks [18].

It has also been shown that exposure to a high-fat diet during pregnancy in rodents increases local and systemic inflammation and, consequently, the production of proinflammatory cytokines, including IL-1β, IL-6, and TNF-α in the serum and brain of both mother and child. This increases atypical anxiety, cognitive, and social behaviors in offspring, symptoms present in autism spectrum disorder (ASD) [18].

IL-6, a key pro-inflammatory cytokine, has been shown to play a fundamental role in promoting MIA-induced ASD-like deficits in the control of inhibition and social interaction in mice. In addition to maternal IL-6 being able to cross the placenta and directly influence the fetus, there is evidence that placental IL-6 signaling in response to MIA leads to acute immune activation in the fetal brain and subsequent behavioral alterations [19,20]. With this evidence, concurrent risk factors or repeated infections are likely relevant for susceptibility to ASD [21].

Emerging research continues to shed light on the role of the immune system and neuroinflammation in ASD. Studies have identified potential links between immunological factors and ASD, demonstrating how atypical functional connectivity and alterations in neurotransmitter systems can contribute to the unique cognitive and behavioral characteristics of these disorders. This holistic exploration of ASD mechanisms has contributed to the evolving understanding of the disorder and has guided the development of more specific and personalized interventions for individuals living with ASD [22,23].

ASD arises from a complex interaction between genetic susceptibility and environmental influences. It is known to appear in early stages of development; however, its diagnosis is often made later [24,25]. It is important to recognize that all adverse events occurring from the prenatal period onward can disrupt the formation and organization of neural circuits, particularly in regions responsible for social cognition and communication, and may contribute to the characteristic features of ASD [26].

Synapses and the connections between neurons are vital for neuronal communication. Altered synaptic plasticity, the ability of synapses to strengthen or weaken in response to activity, may contribute to the learning and social interaction difficulties observed in ASD. Synaptic function is a fundamental neurobiological mechanism that plays a key role in the development, organization, and plasticity of neural

circuits within the brain. Evidence from murine models suggests that neuroligins are crucial for synaptic function, and mutations in these neuroligins have been identified in individuals with ASD, which can disrupt proper synaptic formation and function [27].

Individuals with ASD may exhibit atypical synaptic connectivity and organization in the brain. This can include excessive or deficient synaptic connections, irregular synaptic pruning (the removal of unnecessary synapses during development), and abnormalities in dendritic spines (small protrusions on neurons critical for synaptic connections) [28]. Microglia are considered essential cells for the proper functioning and integrity of the CNS, performing special functions, notably synaptic pruning [29].

Glial cell dysfunction: Implications in ASD

Glial cells (astrocytes, oligodendrocytes, and microglia) play a fundamental role in sculpting synaptic circuits and in instructing their remodeling and maturation during development [30]. Astrocytes are the most abundant glial cells and play an important role in brain homeostasis, regulating neurotransmitter systems and gliotransmission. Microglia, which represent between 5 and 20% of the total glial cells present in the adult brain and are considered the professional phagocytes of the CNS, are involved in several functions: maintenance of the neuronal environment, response to injury and repair, immunosurveillance, cytokine secretion, regulation of phagocytosis, synaptic pruning, and sculpting of postnatal neuronal circuits. Their dysfunction has been linked to neurodevelopmental disorders, most notably ASD. In this regard, the scientific community has addressed ways to protect glia through pharmacological intervention strategies applied in animal models [31].

These cells receive attention because they exhibit a wide spectrum of phenotypes at all stages of life, particularly in CNS diseases. Their prevalence in all neurological pathologies makes it pertinent to re-examine their various functions during steady-state and disease conditions. It is important in this field to determine whether the aggregation and phenotypic transformation of microglial cells are the main causes of pathogenesis or potentially neuroprotective responses to the onset of disease [32].

The study of glial cells enhances research, as changes in microglial functions have been demonstrated in the context of multiple neuropsychiatric and neurodegenerative diseases. Specific microglial markers and the availability of compounds that selectively target these cells *in vivo* have been identified, considering the possibility of disease intervention via the microglial pathway [33].

The ability to remodel synaptic networks during critical periods of development, also known as "plasticity," is necessary to form a high-functioning adult brain that is well-adapted to the individual's environment. However, the dynamic nature of neurodevelopment also makes the brain highly vulnerable to maladaptive changes, and this is where microglial function is affected [34].

A review was conducted addressing the accumulating evidence that astrocyte-neuron communication at the synapse is a shared mechanism underlying several neurodevelopmental disorders. It highlights that genetic mouse models have been indispensable for elucidating the underlying mechanisms and downstream effects of astrocyte function and dysfunction in neurodevelopmental disorders [35].

A well-characterized example is the Fmr1 KO mouse model of human fragile intellectual disability syndrome, which is caused by a trinucleotide repeat expansion in human FMR1 and the loss of its encoding protein, the RNA-binding protein of the fragile X chromosome mental retardation protein. In the Fmr1 KO mouse, synaptic and behavioral pathology has been strongly linked to astrocyte dysfunction [36]. It has also been associated with reduced expression of the astrocyte potassium channel, causing neuronal hyperactivity and changes in extracellular homeostasis [37].

Studies have shown that neuronal signaling to astrocytes influences the development of the synaptic circuit not only by regulating astrocyte maturation but also by recruiting other cell types in the CNS. For example, neuronal activity causes astrocyte crosstalk with

microglia, which in turn controls synaptic circuit remodeling [38,39]. Oxidative stress has been shown to be involved in the pathophysiology of ASD, particularly related to MIA, which has led to increased interest in prenatal factors associated with infections, chronic diseases, and medication use [40,41].

A meta-analysis reported that maternal infection during pregnancy was associated with a 12% increased risk of ASD in offspring [42]. Furthermore, coronavirus disease 2019 (COVID-19) infection during pregnancy is associated with MIA and may result in an increased risk of ASD due to altered maternal and fetal immune responses. These factors underscore the importance of a thorough understanding of the role of inflammation and oxidative stress in ASD pathogenesis [43].

Knowing the factors involved in neuroinflammation and, consequently, in glial dysfunction, necessitates reviews that promote pathways, strategies, and interventions to strengthen glioprotection.

Protection of glial cells

Glial protection is necessary to guarantee brain homeostasis. In this process, glia protect not only themselves but also neurons, ensuring the proper functioning of the central nervous system (CNS). This process is known as glioprotection [44]. Studies have indicated the need to redirect efforts to guarantee this protection through therapeutic strategies, studies in animal models, and other options that open doors in this line of research.

Once the physiological and molecular mechanisms involved in neurotoxicity have been identified, it becomes possible to approach strategies that allow for timely intervention to promote glioprotection. Glioprotective molecules can promote protection by improving glial functions and preventing toxicity in different pathological conditions, including neurodevelopmental disorders. Understanding the mechanisms associated with gliotoxicity-such as astrocyte metabolism, redox homeostasis/mitochondrial activity, inflammation, and glial signaling pathways-makes it possible to propose strategies [45].

Omega-3 and vitamin D supplementation

A systematic review was conducted to provide an updated understanding of the relationship between omega-3 and/or vitamin D supplementation in ASD. The review found that the effects of omega-3 supplementation on ASD were too weak to conclude that core symptoms were alleviated. Vitamin D supplementation improved core symptoms, particularly behavioral functioning. However, the results from the literature included in this study were slightly mixed. This allows for the consideration that vitamin D supplementation has a positive effect on behavioral functioning in ASD. Some studies indicate that, although omega-3 does not have direct effects on behavior, its combination with vitamin D has a beneficial combined effect on social and behavioral outcomes in patients with ASD [46].

Another study sought to estimate the efficacy of vitamin D supplementation in children with ASD. This meta-analysis included randomized controlled trials. Three of these trials found that vitamin D supplementation resulted in a small but significant improvement in hyperactivity scores (pooled MD: -3.20; 95% CI: [-6.06, -0.34]) with low heterogeneity (Y2 = 10%, p = 0.33), but there were no other statistically significant differences in ASD symptoms between the groups as measured by validated scales. The researchers concluded that vitamin D supplementation appears to be beneficial for hyperactivity, but not for core symptoms or other coexisting behaviors and conditions of ASD [47].

A systematic review and meta-analysis aimed to explore whether vitamin D supplementation can improve core symptoms and co-occurring conditions in children with ASD. Six randomized trials found that children receiving vitamin D supplementation showed a significant improvement in stereotyped behavior scores (pooled mean difference [MD]: -1.39; 95% CI: -2.7, -0.07; P = 0.04) with low heterogeneity (I^2 = 34%) [48].

They also found a trend toward decreased total scores on the social response scale (SRS) and the childhood autism rating scale (CARS, P = 0.05); however, there were no other significant differences in core ASD symptoms and co-occurring conditions between the groups, as measured by the aberrant behavior checklist (ABC) [49]. These studies concluded that vitamin D supplementation appears to improve stereotyped behaviors, but does not improve other core symptoms and coexisting conditions.

One study highlights the modulation of cellular resilience mechanisms induced by low levels of stressors, representing a novel approach for the development of therapeutic strategies. In this context, the neuroprotective effects of a wide range of polyphenolic compounds have been demonstrated in several *in vitro* and *in vivo* studies [50].

Medicinal mushrooms

The presence of polyphenols in nutritive mushrooms has been evidenced, and their protective effects have been demonstrated in different models of neurodegenerative disorders in humans and rats, based on their immunomodulatory, antioxidant, and antiviral properties, which leads to focusing attention on their ability to induce endogenous systems [50]. Mushrooms are emerging as strong nutritional supplements for human health; they are a food component of interest in different cultures with a millennia-old use in natural and traditional medicine [51].

These contain bioactive substances such as carbohydrates (chitosans, β-glucans/lentinans, trehalose), proteins (ribosome-inactivating proteins, antifungal proteins, ubiquitin-like proteins, protease inhibitors, lectins), fatty acids (linoleic, oleic, and palmitic acids), vitamins, terpenoids (carotenoids such as β-carotene and lycopene), phenolic compounds (caffeic acid, gallic acid, cinnamic acid, melatonin, p-hydroxybenzoic acid, p-coumaric acid, and protocatechuic acid), and other molecules (such as ergothioneine and glutathione) that confer the aforementioned properties [52].

Among these fungi, *Hericium erinaceus* (HE) stands out, having been studied for its beneficial effects on human health. In particular, HE induced several antioxidant and anti-inflammatory effects in neurodegenerative disorders. Erinacines, constituents of HE mycelium, can cross the blood-brain barrier and exert neuroprotective functions [53]. In a mouse model, HE utilization induced a reduction in Aβ deposition and reduced levels of reactive astrocytes and microglia [54].

Coriolus versicolor is another well-known edible and medicinal mushroom whose antioxidant and neuroprotective properties have been demonstrated in various animal models. Its use in a mouse model of Alzheimer's disease has been shown to increase levels of antioxidant enzymes and reduce pro-inflammatory cytokines such as TNF-α and IL-1β [55]; in other models, it induced an increase in the levels of redox-sensitive proteins involved in the cellular stress response, such as Hsp72, heme oxygenase-1, and thioredoxin, suggesting a significant impact of this nutritional intervention on the cellular stress response mechanism operating in the central nervous system [56].

One study evaluated the ability of *Coriolus versicolor* supplementation to stimulate neurogenesis in the hippocampus of mice. In particular, the biomass of this substance induced a significant increase in dendritic volume, length, and branching of immature hippocampal neurons associated with higher levels of β-catenin in the nucleus and cytoplasm of these cells. Increased hippocampal dendritic arborization is relevant to cognitive reserve and brain plasticity [57]. These results suggest that its use in ASD could be of interest due to the glioprotective effects described in other disorders.

N-acetylcysteine

N-acetylcysteine (NAC) is a derivative of the amino acid L-cysteine used in the production of glutathione, one of the body's main antioxidants. Its role in protecting cells against oxidative damage caused by free radicals supports its use in situations of glutamatergic dysfunction and oxidative stress.

A pilot study was conducted to evaluate the feasibility of oral NAC for behavioral disorders in children with autism spectrum disorder (ASD). The study was a 12-week, double-blind, randomized, controlled trial. Treatment began with 900 mg daily, which was increased every four weeks to three doses daily. Oral NAC was well tolerated with limited side effects. Compared to placebo, NAC resulted in significant improvements on the ABC irritability subscale ($F = 6.80$; $p < .001$; $d = .96$), supporting its usefulness [58].

It is a compound of growing interest in the treatment of psychiatric disorders. Primarily through its antioxidant, anti-inflammatory, and glutamate-modulating activity, NAC has been investigated in the treatment of neurodevelopmental disorders, schizophrenia spectrum disorders, bipolar disorder-related disorders, depressive disorders, anxiety disorders, obsessive-compulsive disorders, substance use disorders, neurocognitive disorders, and chronic pain [59].

Animal studies of NAC in ASD have yielded mixed results. Male rats prenatally exposed to valproate to phenotypically mimic ASD were treated with NAC (150 mg/kg/day). On dissection, the glutamatergic system in the amygdala of NAC-treated rats normalized, and their social interactions improved [59]. Other reviews have described improvement in symptoms and neuropathologies associated with various psychiatric disorders, including attention deficit hyperactivity disorder, anxiety, bipolar disorder, depression, obsessive-compulsive disorder, obesity-related compulsive disorder, post-traumatic stress disorder, and schizophrenia [60].

Corticosteroids

Corticosteroids such as prednisolone are steroid hormones secreted by the adrenal gland in response to stress. Since their discovery in the 1940s, they have been used to treat various immune and/or inflammatory diseases based on their immunosuppressive and/or anti-inflammatory effects [61].

Studies have suggested that they can suppress pro-inflammatory microglial/monocytic activation and restore various immune cell imbalances (e.g. regulatory T cell/T helper-17 imbalances) by decreasing levels of pro-inflammatory cytokines, such as interleukin (IL)-6 and/or IL-17A, in both the blood and brain of individuals with ASD [62]. In a randomized, placebo-controlled trial of 26 patients receiving prednisone, prednisolone, as an adjunct to risperidone, was found to significantly improve central features in children with regressing ASD [63].

Studies have shown that exposure of animals to acute stress immediately induced microglial activation, and the administration of corticosteroids regulated this activation, suggesting that they may serve as an important endogenous suppressive signal that limits neuroinflammation that might otherwise occur during stress and other neuropsychiatric illnesses [64].

A prospective, double-blind, randomized, placebo-controlled clinical trial conducted at a federal university hospital highlighted the benefit of prednisolone on language scores in participants under five years of age with a history of developmental regression, but the authors noted limitations, stating that the low dose in the trial may have limited this benefit [65].

Pregnenolone is a naturally occurring neurosteroid metabolized from cholesterol. Beneficial effects of pregnenolone have been confirmed in a variety of neuropsychiatric conditions, including depression, anxiety, and schizophrenia [66]. It has modulatory effects on γ-aminobutyric acid neurotransmission. This was used in a group of adolescents with ASD in association with risperidone, and a greater improvement was observed for the pregnenolone group in the patients' irritability, stereotypy, and hyperactivity subscales [67].

Conclusion

Autism spectrum disorder (ASD) is a disorder that affects typical child development, impacting important developmental areas. Glial cells (astrocytes, oligodendrocytes, and microglia) play a fundamental role in sculpting synaptic circuits and in instructing their remodeling and maturation during development. Numerous studies have highlighted the role of the immune system and its relationship with the

central nervous system, which has facilitated the study of inflammatory cytokines released once the inflammatory cascade is triggered. The need to redirect efforts to ensure glial protection through therapeutic strategies, studies in animal models, and other options that open doors in this line of research has been defined. Supplements such as Omega-3, vitamin D, medicinal mushrooms, corticosteroids, and N-acetylcysteine, among others, have been used in children with ASD, showing favorable effects on the core symptoms of the disorder.

Conflict of Interest

The authors declare no conflict of interest.

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