Review Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry 2023; 15(4):577-588
doi: 10.18863/pgy.1189139

Role of Glia Cells in Autism Spectrum Disorders

Otizm Spektrum Bozukluklarında Glia Hücrelerinin Rolü

Melis Elif Elçi[1], Miraç Barış Usta[1], Koray Karabekiroğlu[1]

[1]Ondokuz Mayıs University, Samsun

ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with an increasing frequency, manifested by functional disorders in social communication and social interaction, limited interests, and repetitive behaviors. The etiology of autism spectrum disorder has not yet been fully elucidated and there are many areas that need further study. Increasing studies have shown that disruptions in synaptic functions are critical in the onset of ASD. Glial cells have a role in the regulation of synaptic functions. In ASD, changes are seen in the number of neurons and glia cells in the affected cerebral cortex, and these changes cause dysregulation in synaptic functions and affect behaviors. Studies provide information about the role of glia cells in the pathophysiology of ASD, but more data is needed on the relationship between ASD and glia cells. In this review, the importance of glial cells in the etiopathogenesis of ASD and studies will be discussed.
Keywords: Glia cells, astroglia, neurons, autism spectrum disorder

ÖZ

Otizm spektrum bozukluğu (OSB), sıklığı giderek artmakta olan, sosyal iletişim ve sosyal etkileşimde işlevsel bozukluklar, sınırlı ilgi alanları, tekrarlayan davranışlar ile kendini gösteren nörogelişimsel bir bozukluktur. Otizm spektrum bozukluğu etiyolojisi henüz tam olarak aydınlatılamamıştır ve daha fazla çalışmaya ihtiyaç olan birçok alan vardır. Artan çalışmalar sinaptik fonksiyonlardaki bozulmaların OSB başlangıcında kritik öneme sahip olduğunu göstermiştir. Sinaptik fonksiyonların düzenlenmesinde glial hücrelerin rolü bulunmaktadır. OSB' de etkilenen serebral kortekste nöron ve glia hücre sayılarında değişiklikler görülmekte, bu değişiklikler sinaptik fonksiyonlarda düzensizliğe yol açmakta ve davranışları etkilemektedir. Yapılan çalışmalar glia hücrelerinin OSB patofizyolojisinde ki rolü ile ilgili bilgiler sunmakta ancak OSB ile glia hücreleri arasında ki ilişki ile ilgili daha çok veriye ihtiyaç duyulmaktadır. Bu derlemede glial hücrelerin OSB etiyopatogenezindeki önemine ve yapılan çalışmalara değinilecektir.
Anahtar sözcükler: Glia hücreleri, astrogilia, nöron, otizm spektrum bozukluğu

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by repetitive behaviors and inability in social communication, affecting 1% of children in the USA (Falcone et al. 2021). In DSM 5, the term autism spectrum disorders is used to include Asperger syndrome, Rett syndrome, pervasive developmental disorders not otherwise specified, and rare genetic disorders with behavioral symptoms related to ASD (APA 2013). ASD symptoms are often accompanied by language delay, epilepsy and mental retardation (Waterhouse et al. 1996). Over the last 50 years, advances in the diagnosis of ASD and the expansion of symptoms within the spectrum have led to a 30-fold increase in the prevalence rate of ASD (Mottron 2021). In a recent systematic review, the prevalence of ASD in 4-year-old children in the USA was reported as 1.70%, and the prevalence of ASD in 8-year-old children was reported as 1.85%, indicating an increase in the prevalence of ASD (Bougeard et al. 2021). In a study conducted in Egypt, 2.8% of preschool children were at high risk for ASD. Congenital anomalies, drug treatments in children in the first year of life, maternal drug treatment during pregnancy and family history of psychiatric illness were identified as risk factors in these children (Yousef et al. 2021).

Symptoms of ASD appear in early childhood and while the diagnosis is made during this period, the symptoms persist into adulthood and have negative effects on daily life (Schmitz et al. 2008). Although environmental and genetic factors are known to play a role in the etiology of ASD, the main mechanism is still unknown; therefore, there is still no specific treatment option for ASD symptoms (Aronson et al. 1997). Most ASD cases are idiopathic, and the interaction of genetic and environmental factors leads to the development of ASD (Gzielo et al. 2021). Maternal infections play an important role in the development of ASD along with environmental factors; studies have indicated that maternal immune activation leads to ASD-like behaviors by increasing the neuroinflammatory response in the placenta (Jones et al. 2017). Studies have associated increasing parental age

Address for Correspondence: Miraç Barış Usta, Ondokuz Mayıs University Faculty of Medicine Department of Child and Adolescent Mental Health, Samsun, Türkiye **E-mail:** dr.miracbarisusta@gmail.com
Received: 14.10.2022 | **Accepted:** 17.01.2023

with ASD, one study found that men older than 40 years were 5.75 times more likely to have a child with ASD than those younger than 30 years, while advancing maternal age was not associated with ASD (Reichenberg et al. 2006). In a meta-analysis of 27 studies, a 10-year increase in maternal age was reported to create an 18% higher risk for ASD, whereas a 10-year increase in paternal age posed a 21% higher risk for ASD (Wu et al. 2017).

Clinical heterogeneity and variability in ASD cause challenges in diagnosis, treatment and neurobiology studies (Jeste et al. 2014). Meanwhile, neuroanatomical and functional abnormalities have been noted in studies on autism (Amaral et al. 2008). Studies examining the neuropathology of autism have revealed mild abnormalities in the development of the cerebellum, hippocampus, amygdala, brainstem and cerebral cortex, and these abnormalities have been correlated with the development of neuropsychiatric disorders (Palmen et al. 2004). Children diagnosed with ASD generally have increased brain weight, head circumference and cortical thickness in the first years of life (Carper et al. 2002). These macroscopic changes may be related to changes in the cellular content of specific brain areas (Varghese et al. 2017). In some children with ASD, the dorsolateral prefrontal cortex contains more neurons than neurotypical children without ASD (Courchesne et al. 2011). Since the dorsolateral prefrontal cortex is involved in emotion, attention, working memory, and interaction with social stimuli, abnormal neuronal development in this area may be associated with ASD behaviors (Bedford et al. 2020). While the number of neurons in the dorsolateral prefrontal cortex and other cortical areas increases in ASD, the number of cortical inhibitory interneurons in the prefrontal cortex decreases (Amina et al. 2021). Glial cell numbers in the prefrontal cortex, including the dorsolateral prefrontal cortex, have been found to be reduced in ASD (Falcone et al. 2021). There are also studies indicating that the number of neurons in the amygdala is lower in ASD (Schumann et al. 2006). There are studies showing that the number of neurons differs within the layers in the cortex, neuron density decreased in layer 3 in the fusiform gyrus, the number of neurons decreased in layers 3, 5 and 6, and the decrease in pericardial volume was in layers 5 and 6 (van Kooten et al. 2008).

Neuroimmune changes and glial cell activations have been the subject of research on the neurobiology of ASD (Vargas et al. 2005). Glial cells play a role in the formation and termination of synapses, supporting the neuronal network, and inflammatory processes (Gzielo et al. 2021). Glia cells function in protecting neurons from excitotoxicity, myelinization, clearing cellular debris, buffering ions and proper functioning of the brain (Verkhratsky et al. 2018). Changes in the number and morphology of astrocytes are closely related to processes such as inflammation and injury (Gzielo et al. 2019). Other data suggest that glia cells are associated with pathological processes that can cause autism, including changes in the amount of astroglia markers (GFAP) and glial cell number (Edmonson et al. 2014). Impaired expression of glial markers in ASD is consistent with pathological changes in neurons in brain structures (prefrontal cortex, hippocampus, striatum, amygdala, cerebellum) related to social adaptation, reward, attention and cognitive processes (Chrobak et al. 2017). Disruption of the appropriate support provided by glia cells may play a role in the emergence of neuropsychiatric disorders such as autism by causing alterations in neuronal and synaptic connections (Gzielo et al. 2021).

Neuroglia in the Nervous System:

In the neural circuit within the nervous system, intercellular connections are regulated by synapses that operate chemically and gap-junctionally between neurons or electrically connecting astrocytes (Kettenmann et al. 2011). The formation, reorganization, modeling and development of complex neural networks require precise homeostatic control which is carried out by neuroglia (Zeidán-Chuliá et al. 2014). Initially, glia cells were categorized by Virchow as cells of macroglia (neural) origin and microglia (myeloid) origin (Virchow 2020). Cells of macroglia (neuronal) origin are astroglia, oligodentroglia and NF2 cells (Nishiyama et al. 2005). The common task of these different cell types is to maintain the balance of the central nervous system, therefore neuroglia can be defined as the homeostatic cell of the central nervous system (Zeidán-Chuliá et al. 2014). Glial cells are involved in neuronal repair in case of damage, neuroinflammation and neurodegeneration (Franklin et al. 2015). Table 1 summarizes glia cells and their functions.

Astrocytes are diverse neuroglial cells, found in different forms in different tissues, such as fibrous astrocytes of the white matter, protoplasmic astrocytes of the gray matter, Müller cells in the retina, Bergman glia cells in the cerebellum. Astrocytes have many functions; they participate in the blood brain barrier, control neurogenesis, regulate ion homestasis, play a role in synaptic transmission by providing glutamine, a precursor for glutamate and GABA, help provide energy substrate to neurons, and scavenge reactive oxygen species (Verkhratsky et al. 2013).

Oligodentrocytes, another constituent of neuroglia cells, are involved in axon myelination (Hartline et al. 2007). Myelin increases the speed of impulse transmission of neurons and the capacitance of the neuron cell membrane (Gzielo et al. 2021). The second type of oligodentroglia-like cells are the precursors of oligodentrocytes or

polydentrocytes, which are also called NG2 cells because they express the NG2 protein and NG2 is a transmembrane proteoglycan containing chondrotin sulfate and is required for the differentiation of glia and nerve cells (Stallcup 1981).

Table 1. Glia cells and their functions

Macroglia (Neural) origin	**Microglia (Myeloides) origin**
Astroglia - Maintaining the Blood Brain Barrier - Regulating neurotransmitter levels around the synapse - Regulating ion levels and supporting metabolism	Microglia -Providing immunity of the brain, removing dead cells and pathogens by phagocytosis
Ependymal cells -Participate in the structure of the inner ventricles -Production of cerebrospinal fluid	
Oligodentroglia -Providing neuron myelinization -Protecting the structural framework	

Microglial cells develop from the exraembryonic yolk sac (Ginhoux et al. 2010). Microglia cells, which play the main role in the immune system in the brain, continuously monitor the environment for any signs of harm or damage in a normal state. Pathological conditions may occur in the central nervous system as a result of microglia cells becoming macrophages capable of phagocytosis and microglial processes retreating (Kettenmann et al. 2013). Microglia cells appear on the 8th day of the embryonic period and are mainly clustered around the hippocampus and corpus callosum, at the same time, microglia are ameboid (immature) when first formed, branch (mature) on the 30th day after birth and gain the ability to monitor the immediate environment, and factors that disrupt neuron development, infections disrupt the maturation of microglia (Gzielo et al. 2021). Microglia play a role in synaptogenesis by providing growth factors and thrombospondins, eliminating unnecessary synapses, regulating synaptic transmission by secreting factors such as BDNF or TNF, providing trophic support to neurons, and regulating neurogenesis (Tremblay et al. 2010).

Astrocytes in ASD

Astrocytes play an important role in maintaining brain homeostasis, maintaining metabolism and signaling between cells in the central nervous system. For these functions, they have different molecules, receptors, transporters and various pumps, and since they are not electrically stimulated, they communicate using ions such as calcium, sodium and potassium. Astrocytes use potassium and water channels (aquaporin4) to clear cellular debris (Iliff et al. 2012). Alterations in the homeostasis of astrocytic water channels and potassium ions in the brain can alter the balance between neuronal excitation and inhibition. Small changes in extracellular potassium ion concentration cause hyperexcitability in neurons. Reduced potassium channel activity increases extracellular potassium ion (Gzielo et al. 2021). Knockout of potassium channels causes depolarization of the glial membrane and inhibits glutamate uptake (Djukic et al. 2007). At the same time, loss or disruption of water channels such as aquaporin 4 in astrocytes impairs potassium buffering and leads to over-excitation of neurons, which is implicated in many neuropsychiatric disorders, including autism. Astrocytes, together with the glutamate transport proteins GLT-1 and GLAST on the astrocytic membrane, are involved in the transport and clearance of glutamate (Gzielo et al. 2021). Disorders related to glutamate metabolism in glial cells can lead to behavioral disorders in animals. GLT-1 deficiency was found to increase excitation in neurons and cause self-harm and excessive repetitive behaviors in mice (Aida et al. 2015). These findings were also replicated in later studies (Jia et al. 2020, Jia et al. 2021). Excitatory neurotransmitter signals through glutamate receptors play an important role in cognitive functions such as impaired memory and learning in ASD (Choudhury et al. 2012). In a study with autistic patients, significant abnormalities were found in glutamate transporters in the cerebellum (Smith et al. 2011). Inflammatory processes during neurogenesis and gliogenesis can have harmful consequences in the developmental period of the brain. During this inflammatory process, microglia begin to proliferate and change shape depending on the cytokine flow, and depending on the amount of gliosis, glia collect leukocytes and cause tissue damage (Sofroniew 2015). With the increase in gliosis, the main function of glia cells may change, resulting in malfunctions and disturbances in neuronal connectivity, especially the impaired permeability of the blood-brain barrier formed by astroglia is important for the onset of ASD (Meyer 2014).. Blood-brain barrier integrity prevents abnormal neuroinflammation in the central nervous system (Gzielo et al. 2021). Astrocytes may increase proinflammatory signaling, leading to an increase in brain damage, while the scar formed by glia protects the brain from strong inflammation (Cregg et al. 2014).

In case of impaired postnatal glia proliferation, changes in social interaction and hyperactive behaviors may

occur in rats (Mony et al. 2016). Inhibition of the GABA B-Gi pathway in striatum enhances attention and reduces behavioral hyperactivity in mice (Nagai et al. 2021). There is evidence that astrocytes are also involved in the formation of memory, which is possible as a result of the activation of astroglia and the release of D-serine and ATP from astrocytes (Adamsky et al. 2018). Astroglia also contribute to cognition and memory processes by supplying neurons with lactate, and a deficiency in lactate transport has been implicated in amnesia in rodents (Park et al. 2020).

Excitation and inhibition balance abnormalities in the brain and problems in synaptogenesis are presumed to be important in ASD (Gzielo et al. 2021). One study demonstrated that glial fibrillary acid protein (GFAP) immunostaining levels increased in the medial prefrontal cortex and hippocampus of rats exposed to valproic acid on day 35 (Codagnone et al. 2015). GFAP+ astroglial cells are involved in neurogenesis in the adult mammalian central nervous system and are assumed to positively control neurogenesis in the dentrate gyrus of the hippocampus and subventricular region during adulthood (Pekny et al. 2007). Increased GFAP levels in areas with impaired neuronal structure in ASD suggest astrogliotic response (Laurence et al. 2005). In a human study, autistic individuals of the same age had increased GFAP levels in the frontal and parietal cortex, anterior cingulate gyrus and cerebellum, suggesting reactive astrogliosis (Vargas et al. 2005).

Mitochondrial metabolism in astrocytes influences the metabolism, secretion and transport of neurotransmitters required for neurons through ATP-dependent processes (Verkhratsky et al. 2013). Astrocytes use gap junction channels called connexins to take part in coordination and metabolic coupling within the astroglial syncytium (Escartin et al. 2013). CX43 (connexin43) expression was reported to be increased in astrocytes in ASD, and the increased amount of gap junction channels may affect astroglial syncytium in ASD. In a preclinical study, influenza viral infection during pregnancy was linked to changes in connexin 43, causing abnormal aquaporin-4 expression in astrocytes and abnormal glial-neural interaction (Fatemi et al. 2008).

The development of ASD is often accompanied by gastrointestinal problems (Eshraghi et al. 2020). Clinical and preclinical studies over the last 20 years have demonstrated the relationship between the gut microbiota and the brain, commonly referred to as the microbiota-gut-brain axis (Yu et al. 2021). Up to 25% of ASD patients have different gut microbiota and metabolic composition compared to healthy individuals. This difference is likely to be correlated with the severity of gastrointestinal disorders and ASD symptoms (Williamson et al. 2012).

The gut microbiota regulates BDNF and serotonin levels by releasing GABA and plays a role in the activity of the enteric nervous system (Morais et al. 2021). Metabolites of Lactobacillus reuteri have been shown to reduce behavioral symptoms of ASD by increasing oxytocin levels (Sgritta et al. 2019). In another study, the intestinal microbiota was revealed to be involved in regulating microglia function in mice (Erny et al. 2015).

As a result of altered composition of the gut microbiota, intestinal epithelial permeability increases, inflammatory factors enter the bloodstream, resulting in systematic inflammation. Continued inflammatory processes modify the integrity of the blood-brain-barrier, which can lead to neuroinflammation (De Punder et al. 2015). The microbiome, if its composition is not impaired, can impact the course of inflammation by reducing the amount of pro-inflammatory cytokines by releasing butyrate, altering glutamate release and spontaneous neuron firing, and facilitating GABA release (Noh et al. 2005). Therefore, the microbiome has an significant effect on the stimulation/inhibition of homeostasis, which is often impaired in ASD. In addition, a decrease in the amount of butyrate may cause disruption of blood-brain-barrier integrity (Gzielo et al. 2021).

A previous study has indicated that with normal recolonization of the gut microbiota, microglia characteristics improved and ASD symptoms decreased (Matta et al. 2019). Short-chain fatty acids, phenolic compounds, free amino acids in the gut microbiota have been associated with the behavior of ASD patients (Cryan et al. 2019). Propionic acid, a short-chain fatty acid, can cross the blood-brain barrier by altering neurotransmitter transmission, intracellular calcium signaling pathway and gap junction, accumulate in nerve cells and increase the risk of ASD (Aabed et al. 2019).

Astrocytes are activated by Ca2+ increase mediated by type 2 1,4,5-trisphosphate receptors (IP 3 R2) (Gzielo et al. 2021). IP 3 R2 gene was detected to be affected in ASD patients in one study (A Rahn et al. 2012). In another study, astrocyte-specific IP3R2 conditional knockout mice were shown to have repetitive behaviors and atypical social skills. The study also analyzed the levels of gliotransmitters in the medial prefrontal cortex involved in social behavior in rodents using in vivo microdialysis to find the neurobiological mechanisms underlying the autistic features found in IP3R2 mutant mice and astrocyte-specific knockout mice. ATP levels were found to be low in both knockout mice, whereas ATP treatment mediated by astrocytic P2X2 receptors improved social behavior in mice and appeared to facilitate GABA-dependent transmission (Wang et al. 2021).

Microglia Cells in ASD

Microglial cells are the primary immune cells of the central nervous system and are involved in physiological processes such as neural development and synaptic plasticity (Perry et al. 2013). In normal conditions, microglia monitor their surroundings for signs of damage by continuous restructuring of fine branched processes. The withdrawal of microglial processes, which become macrophages capable of phagocytosis, is a sign of pathological conditions in the central nervous system (Kettenmann et al. 2013). When activated, microglial cells increase the release of neurotrophins, nerve growth factor, intraleukins, glial-derived neurotrophic factor and neurotrophic factors that affect neuronal survival. While microglia-derived factors include proinflammatory cytokines such as IL-6, tumor necrosis factor (TNF) or nitric oxide (NO), which are associated with neurotoxicity, the types of these factors released by microglia mostly depend on the type of pathological condition (Hanisch et al. 2007). One of the important functions of microglia cells is the synapse removal process called synaptic pruning, which enables the controlled elimination of abnormal or unnecessary synapses (Weinhard et al. 2018).

In studies, the effect of maternal immune activation on ASD was found to be higher in boys than in girls, and this gender difference in response to maternal inflammation suggests that the sensitivity of microglial activation in boys may be higher than in girls (Patel et al. 2020). Moreover, increased expression of microglial genes has been reported in the maturation, development and function of microglia in the brains of boys compared to girls (Block et al. 2022). Infection with microorganisms such as Herpes simplex virus during pregnancy has been linked to increased maternal immune activation, activation of microglia in the fetal brain and ASD-like behaviors in offspring in a study with mice (Malkova et al. 2012).

The involvement of microglia cells in inflammatory processes and synaptic pruning plays an integral role in ASD formation (Matta et al. 2020). Inflammation and impaired synaptogenesis can lead to the emergence of ASD symptoms (Haida et al. 2019). In neuroimaging studies utilizing MRI or PET, inflammation has been observed in the brains of subjects with ASD (Suzuki et al. 2013). In postmortem studies, microglia density in the gray matter increased and neuronal interactions changed in subjects with ASD (Morgan et al. 2010). An active neuroinflammatory process was noted in the cerebral and cerebellar cortex and white matter of people with ASD (Wei et al. 2011). In a postmortem study, microglia density in the visual cortex and frontoinsular cortex was elevated in individuals with autism, and elevated microglia density in the visual cortex may be associated with the phenotype related to perceptual integration in autism (Tetreault et al. 2012).

There is a gender difference in microglia maturation during brain development, this difference is due to the fact that the microglial development index (MDI), which is based on the global gene expression pattern, is higher in women than in men during early development and early adulthood. Therefore, a greater proportion of autism in men may develop due to a difference in microglia maturation during brain development. As a result, the response of the immune system of men and women to proinflammatory factors may vary, which may increase or decrease the risk of developing autism symptoms (Bolton et al. 2017). In an animal study, reduced chemokine receptor Cx3cr1 (microglial-specific chemokine receptor) led to decreased synaptic pruning, deficits in social behavior, and increased repetitive movements in mice. Reduced Cx3cr1 receptor number was observed only in male mice (Zhan et al. 2014).

If microglial cells are activated, the release of reactive oxidative stress (ROS) and proinflammatory cytokines from these cells may inhibit mitochondrial energy metabolism (Rodriguez et al. 2011). Although ROS produced as a result of microglial activation and subsequent oxidative stress play an important role in the pathogenesis of neurodevelopmental disorders, oxidative stress is recognized as a common feature in autism (Derecki et al. 2013).

The amount of saturated and unsaturated very long chain fatty acids is increased in people with autism, suggesting that mitochondrial oxidation of fatty acids is impaired, cytosolic fatty acid elongation and fatty acid desaturation are increased (Pastural et al. 2009). Glutaminergic pathways expressed by neurons and astrocytes may cause changes in fatty acid metabolism by increasing microglial activation and neurodegeneration (Innis et al. 2002).

Oligodentroglia in ASD

Oligodentrocytes are glial cells that form the myelin sheath to electrically isolate neuron axons and provide metabolic and trophic support to neurons (Bradl et al. 2010). The second type of oligodentroglia-like cells are precursors of polydendrocytes or oligodendrocytes, but these cells express a chondrotin sulfate-containing transmembrane proteoglycan called NG2, and NG2 is essential for the differentiation of glia cells (Stallcup 1981). A subpopulation of NG2-expressing cells establish synaptic connections with neurons, release glutamate

and regulate axonal transmission by stimulating α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (Bergles et al. 2000).

Abnormal white matter development in patients with ASD and impaired protein levels in oligodendrocytes in ASD mouse models suggest impaired maturation of oligodendrocytes which can transmit changes in the white matter (Hughes 2007). Some studies suggest an association of ASD with altered white matter integrity and myelin sheath thickness, especially in the corpus callosum (Ameis et al. 2016). In a study, adult mice prenatally exposed to valproic acid (VPA) showing the main symptoms of ASD were found to have reduced myelin content in the basolateral amygdala and priform cortex, which are linked to social behavior (Graciarena et al. 2019). These mice with lack of myelination were reported to have lower levels of sociability. Another study reported a decrease in the myelin thickness of the orbitofrontal cortex, a subregion of the prefrontal cortex, in the postmortem brain tissue of ASD patients (Zikopoulos et al. 2010). While these studies indicate that decreased myelin content may be associated with social symptoms in ASD due to the involvement of white matter, more studies are still highly needed in this area..

The Effect of Environmental and Genetic Factors on Glial Pathology in ASD

Although a genetic predisposition is widely accepted as being involved in the etiology of ASD, the genes responsible are mostly unknown (Mefford et al. 2012). Family studies have revealed that the prevalence of autism may be 100 times higher in families with at least one diagnosis and that higher incidence may be observed in monozygotic and dizygotic twins (Bolton et al. 1994). Although genetic factors constitute an important risk in the development of ASD, they alone are not sufficient to explain the varying clinic and epidemiology of ASD. Environmental factors in the development of ASD may explain the rising prevalence of ASD (Block et al. 2009). A higher incidence of ASD has been reported in children exposed to ethanol prenatally (Nanson 1992). Ethanol increases microglial activation through Toll like receptor 4 (TLR4) response, which is associated with ASD (Guizzetti et al. 2010). Prenatal exposure to anticonvulsant drugs such as valproic acid has been associated with ASD development (Moore et al. 2000). Valproic acid induces apoptosis in hippocampal neurons differentiated by TNF α release from astrocytes (Christianson et al. 1994). Another study suggested that the CNS may be affected, damage to the prefrontal cortex and cognitive dysfunction may develop in children exposed to polluted air, especially in early childhood (Block et al. 2009).

Autistic symptoms may be observed in patients exposed to rubella virus, one of the viral pathogens, prenatally; rubella virus targets astrocytes in the brain tissue to proliferate and causes neurological damage by disrupting astroglial function, which may exacerbate ASD findings (Chantler et al. 1995).

Neuroinflammation in ASD

Glia cells are sensitive to injury and inflammation in the CNS (Depino 2013). Microglia are resident macrophages of the CNS and when activated, produce proinflammatory cytokines, proliferate, migrate and present antigens to T cells (Harry et al. 2012). The release of proinflammatory cytokines such as TNF α and IL-1 β by microglia enables to initiate the activation of astrocytes (Carniglia et al. 2017). At the same time, microglia can reduce inflammation by releasing anti-inflammatory cytokines such as IL-10 and TGF- β (Franco et al. 2015). Astrocytes form the blood brain barrier in the CNS and are involved in proinflammatory cytokine secretion and induction of inflammatory cascades (Li et al. 2019). When there is a change in the homeostasis of the CNS, activation of microglia and astrocytes occurs, resulting in a prolonged inflammatory response and damaging neuronal cells (Kinney et al. 2018). Oligodentrocytes are responsible for myelinating axons in the CNS, and in case of impaired myelination, neuronal cells face proinflammatory damage (Schmitz et al. 2008).

Although neuroinflammation in ASD has become more prominent in studies, it is not yet clear whether neuroinflammation causes ASD or is a consequence of ASD (Wong 2022). One study showed that individuals with ASD had active neuroinflammation in the cortex, white matter and cerebellum, with simultaneous activation of astrocytes and microglia (Vargas et al. 2005). In another study, changes such as decreased branching and increased retention were detected in microglia in the prefrontal cortex of men with ASD (Morgan et al. 2010). Studies suggest that conditions such as the morphology, number and activation of astroglia cells may play a role in the pathophysiology of ASD. Prolonged duration of glial activation negatively affects cognitive function in ASD (Kinney et al. 2018).

Based on a study using magnetic resonance-positron emission tomography (MR-PET) scanning, young adult males with ASD were reported to have lower expression of translocator protein (TSPO), a mitochondrial protein expressed by microglia and astrocytes and involved in mitochondrial homeostasis and immune regulation,

compared to the control group. The sites of low expression of translocator protein (TSPO) were angular gyrus, bilateral insular cortex, lateral occipital cortex, left postcentral gyrus, orbitofrontal cortex, precuneus, posterior cingulate cortex, putamen, superior temporal gyrus and supramarginal gyrus. The translocator protein (TSPO) was found to be inversely correlated with the severity of the symptoms (Zürcher et al. 2021).

Several studies reported an increase in synapses and a decrease in synaptic pruning in the brains of children with ASD (Tang et al. 2014). Synaptic pruning, which is necessary for neurons to maintain significant functionality, appears to be carried out by microglia-derived cytokines such as TNF α (Onore et al. 2012). Synaptic pruning is mostly activated from the age of 2 and is vital for ASD (Hansel 2019). The activation of ASD-related behaviors around the age of 3 is likely to be in parallel with this situation (TSAI 2014). Previous studies demonstrated that synaptic pruning increases as a result of the increase in TNF α produced by microglia (Li et al. 2009). Although synaptic pruning is considered important for ASD, contradictory results have emerged in studies and thus more studies and research are needed.

Neurotranmitter Changes in ASD

Neurotransmitters play an important role in memory, behavior and brain development, and their role in the pathophysiology of ASD is crucial. The neurotransmitters most frequently associated with the pathophysiology of ASD are gamma aminobutyric acid (GABA), glutamate, serotonin and dopamine (Marotta et al. 2020). As the main inhibitory neurotransmitter in the brain, GABA is responsible for maturation in the development of the CNS and, together with glutamate, for the appropriate inhibition/excitation balance (Gzielo et al. 2021). Although GAD is the enzyme that enables the conversion of glutamate to GABA, decreased GAD release leads to decreased inhibition. GABA-related pathophysiology in ASD has been associated with decreased expression of glutamic acid decarboxylase (GAD) (Fatemi et al. 2002).

Glutamate, one of the important neurotansmitters in the brain, accompanies excitatory signals in the nervous system, regulates synaptogenesis, and is involved in learning and memory (Zhou et al. 2014). Studies on individuals with ASD and rodents have shown that glutamate and GABA levels exhibit regional differences. A proton magnetic resonance spectroscopy study found that the level of the main excitatory neurotransmitter in the brain with ASD varies in the strial structures of the brain (Horder et al. 2018). Although the homeostasis of the excitation/inhibition balance in the brain is provided by astrocytes, impaired function of astroglia facilitates excitatory events in the brain (Mahmoud et al. 2019). There are reports of changes in dopaminergic and serotonergic systems in the pathophysiology of ASD (Pavăl 2017). Alterations in the expression of dopaminergic receptors, dopamine transporters and dopamine levels have been noted in ASD (DiCarlo et al. 2020).

Conclusion

In the development of autism spectrum disorder, functional changes occur in glia cells with the influence of genetic and environmental factors. Since glia cells have many significant roles in the nervous system such as supporting neurons, maintaining homeostasis, playing a role in inflammation, synaptogenesis and neurogenesis, impairment in their functions due to various reasons causes various symptoms of ASD, a neurodevelopmental disorder. Astrocyte, microglia, oligodentroglia pathologies have been detected in individuals with ASD, but more studies are needed to reach a consensus on whether these pathologies develop as a result of ASD or whether ASD symptoms develop due to these pathologies. The fact that glia cells play roles on neurotransmitters glutamate, GABA and ATP may enable the development of new drugs for the use of various drugs for specific symptoms of ASD in the future. Studies have mostly emphasized that glia pathologies develop due to various conditions, and that this leads to ASD. Further studies in this area will also play a role in the development of new treatment strategies for ASD.

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Authors Contributions: The author(s) have declared that they have made a significant scientific contribution to the study and have assisted in the preparation or revision of the manuscript
Peer-review: Externally peer-reviewed.
Conflict of Interest: No conflict of interest was declared.
Financial Disclosure: No financial support was declared for this study.