

Autism Spectrum Disorder and Iron Deficiency

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by difficulties in social communication and interaction, along with restrictive and repetitive patterns of behavior. Its etiology involves a combination of genetic and environmental factors. Children with ASD have been shown to frequently prefer consuming the same foods and to have limited food choices. This situation may lead to inadequate intake of certain nutrients due to reduced dietary variety. One of the nutrients commonly found to be deficient in this population is iron. This review aims to evaluate the relationship between ASD and iron deficiency in children. In addition to limited food preferences, difficulties in chewing and swallowing harder foods—such as red meat, which is a rich source of iron—may further reduce iron intake. While some studies have indicated that children with ASD have a lower dietary iron intake compared to their typically developing peers and exhibit a higher prevalence of iron deficiency, others have found no significant differences. To better understand this relationship, there is a need for large-scale studies that utilize multiple types of biological samples and objective assessment methods. Additionally, since ASD is more commonly observed in boys, studies assessing iron intake and status should consider gender- and age-stratified analyses.

Keywords: Autism spectrum disorder, iron deficiency, nutrition

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INTRODUCTION

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders that includes autism, Asperger syndrome (AS), and pervasive developmental disorders not otherwise specified (PDD-NOS). It is characterized by restrictive and repetitive behavior patterns as well as difficulties with social communication and interaction (1-3). The etiology and clinical course of ASD are affected by both genetical and environmental factors, with latter have drawn more attention in recent years. One of these factors is iron deficiency, which can lead to cognitive, developmental, and behavioral delays, as iron is involved in various neurodevelopmental mechanisms such as synaptogenesis and myelination (4-6). Iron deficiency is frequently observed among children with ASD, and may be exacerbated by food selectivity, food allergy, food intolerance, and gastrointestinal problems such as diarrhea, steatorrhea, and, indirectly, constipation —through impaired nutrient absorption. Nevertheless, low iron status, especially in early childhood, can have permanent effects on neurodevelopment and affect the severity of ASD symptoms (4). Considering that iron is necessary for normal cognitive functions, iron deficiency can make it difficult for children to acquire new skills and abilities and may further exacerbate ASD symptoms (6). This suggests that there may be a bidirectional link between ASD and iron deficiency. While iron deficiency may play a role in the onset of ASD, symptoms of ASD may also negatively affect iron status by leading to decreased dietary iron intake (5). The aim of this narrative review is to discuss the possible mechanisms of this bidirectional relationship between ASD and iron deficiency in the light of current data in the literature.

Epidemiology and Etiology

Autism spectrum disorder affects approximately 1% of the global population, with the disorder being 2.5 times more common among boys (5). In the United States, ASD affects about one in every 54 and is reported to be 4 times more prevalent among boys. Similarly, ASD affects approximately one in every 45 children in Türkiye (7, 8). Lower ASD prevalence has historically been reported among individuals of non-white race, Hispanic ethnicity, and lower socioeconomic status, likely due to disparities in access to diagnostic services in the United States. In contrast, in Scandinavian countries, where healthcare systems offer more equitable access, lower socioeconomic status has been associated with higher ASD prevalence (9).

Advanced parental age, short interval between pregnancies (<12 months), gene mutations, birth complications such as hypoxia, ischemia and trauma, prenatal exposure to drugs such as anticonvulsants and β 2-adrenergic receptor agonists, premature birth, cesarean delivery, maternal obesity, diabetes, metabolic syndrome and hypertension are risk factors for ASD (2,

10, 11). Genetic factors are estimated to account for >50% of ASD risk, with first-degree relatives showing a significantly higher likelihood of being affected (12). The risk of developing ASD is estimated to be 2-8% among siblings of affected children, while in identical twins, the risk ranges from 36% to 95% if the condition is present in one twin. A history of psychiatric disorders or autoimmune diseases in parents is also correlated with a higher risk of ASD in their children (1, 2).

Environmental risk factors may determine 40-50% of the variance in ASD susceptibility (11). Among the environmental risk factors for ASD, advanced parental age is one of the most consistently supported, as every 10-year increase in paternal and maternal age has been linked to an 21% and 18% higher risk, respectively. The increased risk of ASD associated with advanced parental age is thought to result from pregnancy complications and epigenetic modifications linked to older maternal age, as well as a higher number of de novo mutations observed in older fathers (11). Given the well-established link between advanced parental age and chromosomal abnormalities, prenatal genetic screening is routinely advised for older parents (2, 10).

Although maternal history of psychiatric disorder could be a confounding factor, use of selective serotonin reuptake inhibitor antidepressants while pregnant has been linked to a higher incidence of ASD (2). Premature birth, even at 37 weeks' gestation, is a prominent risk factor for ASD. The preterm brain is vulnerable to brain damage affecting subcortical and cortical connectivity. The prematurity-related consequences of hypoxia and hypoglycemia exacerbate the increased risk of ASD (10). A possible association between ASD and certain heavy metals such as inorganic mercury and lead, has been reported. While the exact biological basis explaining the link between environmental factors and ASD remains unclear, potential pathways are believed to involve genetic interactions, inflammation, oxidative stress, endocrine disruption, hypoxia or ischemia, alterations in neurotransmitter systems, and disruptions in cellular signaling pathways. Furthermore, several environmental factors such as maternal smoking, vaccination, and the use of assisted reproductive technologies, have been found to be associated with an increased risk of ASD (11).

Diagnosis and Symptoms

Since there are no reliable biomarkers that can be used in the diagnosis of ASD, the diagnosis relies on behavioral observations. The Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria published by the American Psychiatric Association in 2013 made the diagnosis of ASD much easier (13). Parents are often the initial identifiers of autism-related

behaviors, long before diagnosis. Tools used to diagnose autism early are based on parental observations. The most common parent-reported concerns are related to language development and communication, with motor/sensory delay, atypicality, and problems with sleep or feeding (12).

Autism spectrum disorder is frequently comorbid with a wide range of conditions, including attention deficit hyperactivity disorder (ADHD), anxiety, bipolar disorder, obsessive-compulsive disorder (OCD), intellectual disability, nonverbal learning disorder, schizophrenia, epilepsy, neuroinflammation and immune-related disorders, gender dysphoria, fragile X syndrome, sensory processing issues, sleep disturbances, inflammatory bowel disease, tuberous sclerosis, as well as Tourette syndrome and other tic disorders. About 75% of ASD patients have been shown to have comorbid diseases such as ADHD, anxiety, depression, bipolar disorder, and Tourette syndrome. Among these comorbid conditions, the relationship between ADHD and ASD is particularly strong, with 30-50% of individuals with ASD exhibiting ADHD symptoms and approximately 66% of those with ADHD displaying ASD symptoms (1).

Screening for ASD is typically recommended during routine developmental checks at 18 and 24 months of age. When diagnosed early (<18 months), symptoms can be improved. For early diagnosis, primary healthcare professionals should be equipped with the knowledge of etiological evaluations aligned with ASD diagnostic criteria, as well as the medical and behavioral symptoms such as sleep and eating disturbances, gastrointestinal problems, obesity, seizures, ADHD, and anxiety that can adversely impact a child's overall health and health-related life quality (3). This group is of particular importance for screening given the elevated risk of ASD development among later-born siblings (12).

Autism Spectrum Disorder and Neurodevelopment

The impact of autism on neurodevelopment has begun to be explored, as evidenced by findings that the average head circumference of patients with ASD falls between the 60th and 70th percentiles compared to their neurotypical peers (14). While the precise timing and underlying mechanisms remain unclear, it is believed that neurodevelopmental alterations in ASD initiate during the prenatal stage, coinciding with the peak expressions of numerous ASD risk genes. During this stage, it is proposed that neural apoptosis and/or abnormal synaptic pruning may contribute to brain development abnormalities in ASD, as the failure of these processes—particularly during the onset of myelination—can lead to abnormal brain volume growth and atypical neural connectivity (10).

Autism Spectrum Disorder and Iron Deficiency

Trace elements including calcium, magnesium, zinc, and iron are known for their protective effects on neurodevelopment (15). Among these, iron is essential for early neurodevelopmental processes—such as myelination, neurotransmitter synthesis, and immune regulation—all of which are often disrupted in individuals with ASD, highlighting its potential role in the pathophysiology of ASD. (16). The World Health Organization identifies iron deficiency as the most prevalent micronutrient deficiency globally, impacting over 30% of the global population and representing a significant public health issue in both high- and low-income countries (17). Iron deficiency is a common comorbidity as a result of food selectivity triggered by stereotyped behaviors, which is one of the distinguishing features of ASD. Feeding difficulties have been reported to be 46-89% among children with ASD (18).

Food selectivity, characterized by the avoidance of specific foods or food groups, is quite common in patients with ASD. It has been reported that 62% of children with ASD exhibit food selectivity, 72% have limited dietary variety, and 57% show food refusal (19). In a study conducted in Türkiye involving 37 children with autism and 19 typically developing children, it was found that children with autism transitioned to solid foods later than their healthy peers and exhibited poorer chewing function. Compared to typically developing children, impaired chewing function in children with ASD may reduce the consumption of iron-rich foods such as red meat, as these foods require more chewing effort (18). Further evidence from a Turkish study indicates that among 164 children with ASD aged 4 to 18 years, 30% exhibited food selectivity, 17% experienced gagging or coughing when consuming textured foods, and 16% demonstrated food refusal. Additional issues reported include pica, resistance to swallowing or prolonged oral retention of food, dysphagia, loss of appetite, eating slowly, requesting to be spoon-fed by a parent or caregiver, consuming limited volumes of food or not eating enough, and vomiting. However, dietary iron intake was found to be low in girls with ASD aged 9-18 years, based on the average of 3-day food records (20). Problems affecting the gastrointestinal system, such as constipation, diarrhea and steatorrhea, food allergies and food intolerance also negatively affect nutrient intake and use in children with ASD (21). A study comparing 22 children with autism and 22 age-matched typically developing children, both with a mean age of 8 years, reported that the typically developing children consumed an average of 54.5, while children with autism consumed only 33.5 different food items per month. Those with food selectivity were found to be at higher risk of having at least one severe nutrient deficiency (22). Children with ASD often prefer starchy and processed foods instead of fruits and vegetables.

Food selectivity leads to inadequate intake of nutrients essential for both physical growth and cognitive development, such as protein, iron, calcium, vitamins B12, D, A and C (18). In a study involving 53 children with ASD (2-13 years of age), it was shown that their consumption of vegetables and fruits and their dietary intake of B complex vitamins, calcium and iron were low (23). In a study involving 40 children with ASD and 113 typically developing children aged between 6 and 10 years, nutrient intake was assessed using a 3-day food record. The results showed that, compared to typically developing children, children with ASD had a higher risk of not meeting their nutritional requirements —5.55 times higher for calcium, 5.24 times for iron, and 3.28 times for both protein and vitamin C (24).

A study conducted in Türkiye including 116 children with ASD (3-16 years of age), 24.1% were reported to have iron deficiency and 15.5% to have anemia (25). Another study comparing 100 children with ASD aged 2-18 years in Türkiye with 100 typically developing children, it was shown that hemoglobin, hematocrit and iron levels of children with ASD were significantly lower than healthy children, but iron deficiency anemia was not reported (26). In the United States, a study involving 222 children with ASD aged 2 to 11 years, despite less than 2% having inadequate dietary iron intake based on 3-day food records, 8% were found to have iron deficiency and 1% had anemia (27). In a case-control study comparing children with ASD and typically developing children aged 2 to 8 years, children with ASD were found to have higher serum levels of calcium, potassium, and magnesium, lower levels of copper and zinc, while no significant difference was observed in iron levels (28). A meta-analysis by Tseng et al., reported no notable disparities in serum ferritin levels, hair iron concentrations, or dietary iron intake between children with ASD and their typically developing peers. However, the bidirectional comorbidity between ASD and iron deficiency was found to be significantly higher compared to typically developing children (29). A study involving 40 children with autism and 40 typically developing children aged 2 to 6 years found that hemoglobin levels were significantly lower in children with autism aged 4 to 6 age compared to their typically developing counterparts. Moreover, when the iron content in various brain regions was evaluated using the quantitative susceptibility mapping (QSM) method, children with autism were found to have significantly lower brain iron levels compared to typically developing children (30). Similarly, Zhou et al., applied the APART (iterAtive magnetic suscepTibility sources sepARaTion) QSM imaging technique to compare school-aged 65 children with ASD with 60 typically developing children, and revealed that children with ASD exhibit significantly reduced brain iron and myelin content —particularly in the globus pallidum and substantia nigra— with these

reductions correlating negatively with symptom severity, highlighting novel insights into ASD pathology and potential biomarkers (31). In conclusion, although the relationship between ASD and iron status is complex, iron deficiency and decreased brain iron content may influence the severity of ASD symptoms. Therefore, monitoring dietary iron intake and assessing iron status in children with ASD is of great importance.

Autism Spectrum Disorder and Iron Supplementation

Iron deficiency during early life has been associated with delays in cognitive functions, motor skills, social, and language development, while iron supplementation has been shown to improve these outcomes (10, 16). Iron deficiency affects approximately 40-50% of pregnancies. Since the fetus relies solely on maternal iron as its source, maternal iron deficiency can lead to fetal/neonatal iron deficiency. When maternal iron supplementation starting from the three months prior to pregnancy through the breastfeeding period, as well as cereal consumption, were assessed, it was reported that low iron intake (<30 mg/day), advanced maternal age (≥ 35 years), and the presence of metabolic disorders together increased the risk of ASD by fivefold (16). However, another study reported that prenatal iron or folic acid supplementation did not reduce the risk of autism, while multivitamin use may be protective (32). The meta-analysis by Fraguas et al. indicated that omega-3 and vitamin supplements outperformed placebo in enhancing functional abilities, and clinical outcomes, yet the relationship between iron supplementation and ASD was not addressed (33). The number of studies examining iron supplementation among individuals with ASD is limited, and those available have primarily focused on its effects on sleep disturbances, given the potential link between iron deficiency and sleep problems within the ASD pediatric group (34, 35).

In a study involving 33 children with ASD aged 2 to 10 years, participants received either 6 mg/kg/day of oral elemental iron supplementation for 8 weeks or 60 mg/day through home-based food fortification for those unable to tolerate oral supplementation. It was found that 69% of preschool-aged children and 35% of school-aged children had inadequate dietary iron intake. It was reported that 77% of the children initially had sleep problems, which showed significant improvement following supplementation. The low prevalence of ferritin deficiency among school-aged children indicates that patients with ASD require continuous screening for iron deficiency (34). In a placebo-controlled trial designed to treat insomnia in children with ASD who had low or normal ferritin levels, 20 children with ASD aged 2 to 10 years received 3 mg/kg/day of iron sulfate supplementation for 3 months. In individuals receiving iron supplementation, significant increases were observed in ferritin levels and scores on the Clinical

Global Impressions of Sleep Scale, which is used to assess sleep history. However, no significant differences were reported in sleep onset latency and awakening time after sleep onset (35).

CONCLUSION AND RECOMMENDATIONS

Feeding difficulties, including food selectivity, food refusal, swallowing difficulties, and chewing issues are common in children with ASD. These feeding problems appear to be one of the reasons for reduced dietary iron intake. Among children with ASD, some studies report lower iron status in comparison with typically developing children, while others have found no significant differences. This discrepancy is thought to stem from the use of different biological samples —such as hair, nails, or plasma—as sources for comparing iron concentrations. Comprehensive studies incorporating multiple iron sources should be designed to minimize this confounding factor. Considering the significant gender and age differences within the ASD population, there remains a critical need to stratify iron intake and/or status by gender and age. In conclusion, the dietary intake of iron and other essential nutrients should regularly be assessed in children with ASD, and routine screening for iron deficiency is recommend as part of clinical monitoring.

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