International Journal Multidisciplinary
Homepage : https://journal.antispublisher.com/index.php/IJMI
Email : admin@antispublisher.com

e-ISSN : 3031-9870
IJMI, Vol. 3, No. 3, August 2026
Page 144-157
© 2026 IJMI :
International Journal Multidisciplinary

The Relationship Between Glutathione and Folate Status in Children with Autism Spectrum Disorder: A Narrative Review

Heleen S. Agab[1], Baidaa R. Ali[2]
[1,2]Department of Pathology Analysis, College of Science, University of Thi-Qar, Iraq

Check for updates OPEN ACCESS

DOI : https://doi.org/10.61796/ijmi.v3i3.568

Sections Info

Article history:
Submitted: June 15, 2026
Final Revised: July 05, 2026
Accepted: July 30, 2026
Published: August 21, 2026

Keywords:
Autism spectrum disorder
Oxidative stress
Folate receptor alpha
Autoantibodies
Glutathione

ABSTRACT

Objective: *This narrative review discusses the possible relationship between folate status, glutathione metabolism, and behavior in children with autism spectrum disorder (ASD), utilizing evidence from early Moriarty et al. studies exploring biochemical links of redox homeostasis, oxidative stress, and neurodevelopment through the FOLATE -dependent one-carbon metabolism pathway.* ***Method:*** *A review of the literature was performed from relevant publications related to glutathione depletion, folate receptor autoantibodies, and their interaction in pathogenesis of ASD.* ***Results:*** *Evidence reveals the prevalence of decreased glutathione (GSH) levels and oxidative stress imbalance in children with ASD, correlated with anti-FOLR1 IgG autoantibodies blocking folate transport across blood brain barrier.* ***Novelty:*** *This is the review combining the integrated metabolic pathways of GSH and folate; thus, it proposes that improving both oxidative stress and at least folate deficiency diagnosis via these two biomarker systems may provide novel diagnostic predictive or therapeutic biomarkers for ASD.*

INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by restricted interests, stereotyped behaviors, communication deficits and impaired social interaction that impacts the social and cognitive functioning of children [1][2]. The etiology of ASDs is unclear, although there is growing evidence that it may be caused by a combination of ascertainable genetic susceptibility and as yet unidentified environmental factors. Over 1,000 genes have been implicated in ASD. Concurrent to this, lifestyle and environmental factors like maternal disease, endocrine or hazardous chemical exposures, diet, and stress have also been explored as risk factors for its emergence [3][4]. These complex interactions are behind the growing interest in ASD and its clinical heterogeneity, prompting increasing research into their molecular and biochemical mechanisms [5].

Folate is an essential water-soluble B vitamin that is important for the generation of DNA, nucleotide production, methylation reactions and development of proper brain function. Experimental and genetic approaches have shown that adequate availability of folate during fetal–embryonic brain development is essential for proper neurodevelopment while disruption in folate transport or decreased concentrations of this vitamin can have a negative impact on these processes [6][7]. The cerebral folate receptor α (FRα or FOLR1) is a high-affinity transporter that mediates the uptake of folate across the blood-brain barrier. Involvement of FOLR1-mediated folate transport (also disrupted by folate receptor autoantibodies) can decrease brain bioavailability of folate, also observed in subsets of children with ASD [8][9].

Glutathione (GSH) is the main antioxidant in cells and a key player in cellular redox balance. As we have pointed out, there is increasing evidence that disturbances in glutathione metabolism and oxidative balance may play a role in asd. A systematic review found that children with ASD had lower blood levels of reduced glutathione (GSH), total glutathione, and the GSH/GSSG ratio compared to healthy controls in a meta-analysis, with higher molar proportions of oxidized glutathione (GSSG). This analysis simultaneously found changes in some metabolites related to transmethylation and transsulfuration pathways, such as cysteine, homocysteine acid and methionine acid [10]. and vitamin B9. These observations corroborate the involvement of glutathione metabolism and redox imbalance in biological pathways implicated in ASD.

Significantly, both folate and glutathione metabolism are biochemically coupled through one-carbon metabolism, methionine cycle, and the transsulfuration pathway. Reactive species derived from folate-dependent reactions allow for the formation and regeneration of methyl donors, while cystathionine-dependent transsulfuration provides a route to connect homocysteine metabolism with cysteine concentrations, the precursor required for glutathione synthesis. Accordingly, changes in these related processes can modulate methylation potential and cellular antioxidant protection. Studies in child ASD populations have found disturbed transmethylation and transsulfuration metabolites, and some studies show improved glutathione redox status with combined methylcobalamin and folinic acid administration in certain children with ASD [11].

While studies have previously explored the independent roles of folate status, folate transport, oxidative stress and abnormalities in glutathione homeostasis in ASD etiology it remains important to establish how insufficient folate availability might globally affect levels of reduced GSH while inducing an imbalance in redox homeostasis. Thus, this narrative review intends to elucidate the association between folate status and glutathione metabolism in children with ASD, focusing on possible biochemical pathways linking folate-dependent one-carbon metabolism, redox homeostasis, oxidative stress, and neurodevelopment.

RESEARCH METHOD

A thorough search of the literature was carried out utilizing databases including Google Scholar, PubMed, and Scopus. Articles published up until 2024 were included in the search using the phrase combinations including 'ASD', 'Glutathione', 'Folate Receptor Alpha', 'Oxidative Stress', and 'Biomarkers'. Both preclinical and clinical studies were reviewed to synthesize the current understanding of the relationship between folate status and redox metabolism in ASD.

RESULTS AND DISCUSSION

ASD Epidemiology

Leo Kanner, an American physician, initially described ASD as "early infantile autism" in 1943 [12]. Although ASD was formerly thot to be a rare condition, its frequency has significantly increased over the past several decades in a number of different nations

[13]. As per the globe Health Organization, ASD is one of the severe disorders that is spreading the fastest in the globe. It is a significant public issue that has a negative impact on children's health [14]. Based on data collected by the U.S. Centers for Disease Control and Prevention, 1 in 54 8-year-old children in the country had autism in 2016, with a 4.3:1 male to female ratio [15]. According to surveys conducted in other nations, the prevalence of ASD has risen over time [16]. ASD is more common in urban than rural areas, and urban areas.

The Etiology and Pathogenesis of ASD

As of right now, it is unknown what causes ASD. Since the 1980s, research on autism has entered a new phase, and scientists have started to reject the theory that "improper parental care" is the root cause. Medical professionals first attempted to determine the biological origin of ASD [17]. However, as research on ASD has progressed, we now understand that autism is a complex neurodevelopmental condition brought on by a combination of environmental and genetic factors [3]. Studies have shown that > 1,000 genes are related to ASD.

Identical twins have a much higher comorbidity rate of ASD than fraternal twins, and some close relatives of ASD patients exhibit clinical symptoms like social and communication disorders, stereotyped behaviors, etc., even tho they have not received an ASD diagnosis. All of these results point to a significant involvement for genetic variables in the pathophysiology of ASD [4][18]. Numerous studies have examined the possible link between ASD and lifestyle and environmental variables, including stress, drugs, hazardous chemicals, maternal illnesses during pregnancy, and diet [19][20].

Serotonin (5-hydroxytryptamine [5-HT]) levels in peripheral blood are markedly elevated in around one-third of children with ASD, and 5-HT reuptake medications help alleviate the emotional symptoms and repetitive, stereotyped behaviors of ASD patients [21]. Dopamine-blocking medications can lessen the stereotyping of ASD, however an increase in dopamine levels in the hypothalamus can cause stereotyped behaviors in children with ASD [22]. In the meanwhile, children with ASD have aberrant brain function, anatomy, and electroencephalograms [23]. Research has shown that people with ASD have narrower frontal, parietal, and occipital cortexes. The functional connections between the frontal and temporal cortexes of the brain and other brain areas are diminished in ASD individuals, leading to decreased information transmission [24].

White blood cells (WBC), CD38+ B-cells, and HLA-DR (the cell-activation marker of CD8+ and CD4+ T-cells) are all higher in children with ASD, according to immunological research, indicating an immunological imbalance [25]. One kind of ASD model that is now in use is the maternal immune-activation (MIA) model, which stimulates the immune system during pregnancy and causes illness in the fetus. When double-stranded polyinosine: cytosine was injected into pregnant rats at 9.5 days of gestation, the offspring displayed characteristics similar to ASD [26].

Clinical Characteristics and Symptoms

The severity of autism spectrum disorder (ASD), a common neurodevelopmental disease, varies widely. Distinctive symptoms usually start to appear as early as 18–24

months of age, causing parents to identify developmental disparities compared to typically growing children, even tho a formal diagnosis is often established at three years of age [27]. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria-based behavioral observations are the only means of diagnosis because there are presently no reliable molecular indicators.

The core clinical criteria of ASD consists of the two main domains of restricted or repetitive behavior and difficulties in social communication [28]. This can also result in difficulties with non-verbal communication, maintaining relationships, having reciprocal socioemotional behaviours and understanding others' mental states [29][30]. Patients often exhibit atypical sensory responses, stereotypic behaviours, and strict adherence to a routine with repetition of motor actions or words (echolalia).

Besides the core symptoms, ASD is often associated with other comorbid and systemic diseases. These are mental health conditions such as anxiety, OCD and sleep difficulties [31]. In other words, people with ASD frequently also suffered from neurological problems like seizures and cognitive dysfunction as well as functional systemic issues [32], such as constipation or GI pathologies.

Risk factors

Some of these factors are operating in a multifactorial milieu across multiple developmental stages and have been summarized into three broad classes including genetic susceptibility, neurological pathways, and maternal health for the development of ASD [33][34]. While the timescale separating any prenatal environmental/genetic risk factors and the diagnosis precludes direct prospective assessment, identifying these risk indicators is a critical first step in either performing early clinical screening or elucidating disease pathogenesis [35].

Redox metabolism

An imbalance in GSH-dependent redox metabolism has been connected to autism spectrum disorder (ASD). Metabolic mechanisms that have been shown to be abnormal in ASD include folate and methylation metabolism are connected to GSH production and intracellular redox equilibrium. These metabolic anomalies collectively characterize a unique endophenotype of ASD that is strongly linked to environmental variables associated with ASD as well as genetic, epigenetic, and mitochondrial problems. In order to Biomarkers that reflect these metabolic anomalies will be investigated in the context of an ASD metabolic endophenotype in order to get a better understanding of the pathophysiological processes behind core along with ASD symptoms [36]. The pathophysiology of ASD, a complicated and multifaceted neurodevelopmental disorder, is still largely unknown. The reductive paradigm of an imbalance between oxidants and antioxidants was frequently used in earlier descriptions of oxidative stress in ASD.

Glutathione

Glutathione is the primary non-protein thiol antioxidant identified in the tissue of mammals, making it one of the most researched antioxidants. A naturally occurring cysteine-glutamate-glycine tripeptide with strong antioxidative properties, GSH is mostly produced in the liver. Apart from its pivotal function in redox signaling, which is

essential for the detoxification of xenobiotics, GSH plays a significant role in regulating cell division, apoptosis, immunological responses, and fibrogenesis. GSH peroxidase, which produces GSSG by reducing Reactive Oxygen Species (ROS) like hydrogen peroxide and lipid peroxide, mediates the antioxidant action of GSH. GSSG reductase and NADPH regenerate GSH for further antioxidant activity. Cysteine is the main rate-limiting factor that restricts GSH production. Numerous processes, such as the transsulfuration of methionine, protein breakdown, recycling in the liver, and nutrition, can produce cysteine [37].

Its antioxidant properties can lead to the redox balance in ASD [38]. Through several methods, this GSH depletion may play a crucial role in the pathophysiology of ASD. First, it might result in more damage from oxidative stress. Second, excessive stimulation of excitatory glutamatergic neurotransmission might result in excitotoxicity [39].

It is thot that GSH is vital for the emergence and course of neurodegenerative illnesses. These brain illnesses are thot to be primarily due by GSH redox imbalance, which can be employed as a biomarker for diagnosis. One of the key regulators of the oxidant-antioxidant balance in many cells, such as immunological and neural cells, is GSH. By scavenging various oxidants or indirectly by supplying reducing equivalents to the enzymatic antioxidant network, it aids in the detoxification of oxidants [40]. GSH is an endogenous antioxidant with various kinds of uses, including the detoxification of xenobiotics and the preservation of intracellular redox equilibrium.

Children with ASDs could impose odd GSH metabolism, which may be a major factor in the disorder, per to several studies. In order to guard against the effects of both endogenous and exogenous toxins, cellular detoxification processes are crucial. One such system is GSH redox and the GSH S-transferases discussed below [41]. In mammalian cells, diminished GSH is a crucial non-enzymatic antioxidant. In addition to acting directly as an antioxidant to protect cells against pro-oxidants and free radicals, GSH can also act as a cofactor for antioxidant and detoxification enzymes such GSH peroxidases, GSH S-transferases, and glyoxalases. GSH peroxidases detoxify peroxides via a mechanism connected to GSH oxidation to glutathione disulfide (GSSG) [42].

Folic Acid

A water-soluble B vitamin, folate is vital for multiple physiological processes, namely neurodevelopment [43]. A set of structurally similar compounds with a pteridine ring, p-aminobenzoic acid, and glutamate or polyglutamate make up folate (vitamin B9). These compounds are essential cofactors in many physiological processes, such as methylation, amino acid metabolism, DNA synthesis, and repair [44]. Several systems, in particular the FRα, are implemented to transport folate across cellular membranes [45]. Numerous studies demonstrate the significance of FA in enhancing childhood behavioral outcomes and underpinning Its function as an adjustable risk factor for ASDs.

Supplementing children with ASD with FA and/or folinic acid has improved the concentration of one-carbon metabolites as well as several neurologic and behavioral symptoms. Serum auto-antibodies against folate receptor alpha (FRAA) are more common in children with ASD, according to several investigators (Hoxha). When

compared to other moms who did not take the supplement, FA intake is associated with a lower incidence of ASD [46]. In this category, FA can be regarded as an autism protector, particularly when administered during preconception and the early stages of pregnancy, as studies have demonstrated that it lowers the offspring's risk of autism. If ingested throughout the remainder of pregnancy, this positive impact cannot be verified [47].

It should be mentioned that eight out of the fifteen research that were examined indicate that FA supplementation has a positive impact on ASD [48]. Children with ASD may benefit from oral folinic acid in terms of their symptoms. Nevertheless, there are not many randomized controlled trials (RCTs). This double-blind, placebo-controlled RCT aimed to compare the Childhood Autism Rating Scale scores at 24 weeks between the folinic acid (2 mg/kg/day, up to 50 mg/day) and placebo groups in children with ASD between the ages of 2 and 10. Both groups received ABA and sensory integration therapy as standard treatments. Blood levels of FA and anti-folate receptor autoantibodies were connected with variations in the intensity of autistic symptoms, and the Child Behavior Checklist was used to measure behavioral problems [49].

Folate and Fetal Brain Development

The critical nature of folate throughout embryonic and fetal brain development has been demonstrated by genetic animal models and dietary changes related to folate deficiency [6][7]. If either the transit of folate or the concentration of folate in the blood is adversely affected, the development of the embryo and fetus is significantly altered. Mouse knockout models of genes like FOLR1 that encode for FRα cause mortality in litters, along with orbito-facial abnormalities, congenital heart malformations, and/or neural tube diseases [50]. In FOLR1 knockout mice, enough folinic acid supplementation (N5-formyltetrahydrofolate, a reduced form of folate) can prevent these fatalities. These striking outcomes originate from the KO mouse's deficiency in folate transport in areas where abnormalities develop and throughout the early phases of neurulation [51].

Folate deprivation reduces progenitor cells and increases apoptosis in mouse models, which may result in infertility, embryo resorption, or fetal abnormalities [52]. Rat pups born to moms that consume a diet lacking in methyl donors during pregnancy exhibit behavioral abnormalities [53]. Resorption of embryos and abnormalities of the brain and craniofacial area were documented in a rat model of exposure to rat folate receptor antibodies during pregnancy. Lower dosages of the antibodies allowed embryos to develop to term and produce pups that looked normal. These puppies did, however, exhibit serious behavioral problems. Treatment with folinic acid and dexamethasone before antibody exposure can recover the behavioral phenotype [54].

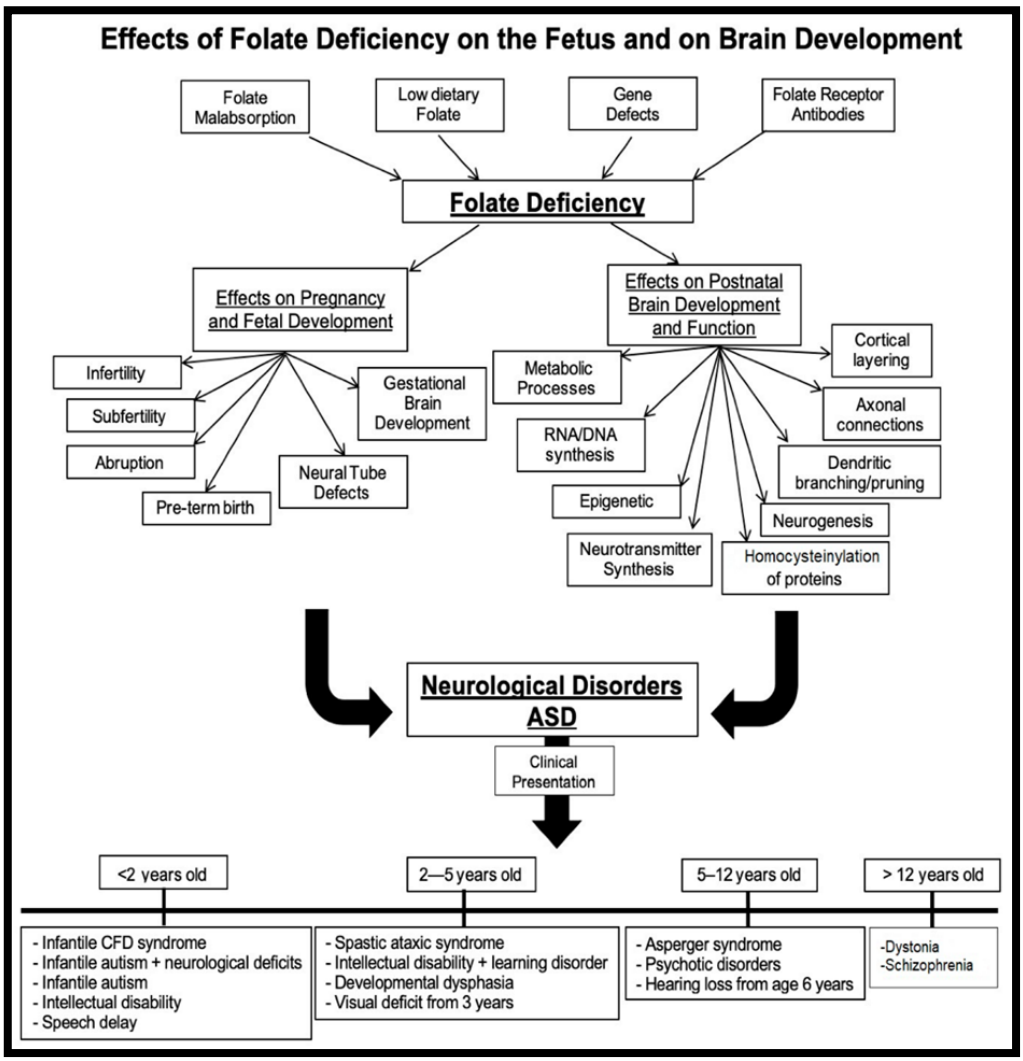

Figure 1. Effects of folate deficiency on the fetus and on brain development [55].

The cerebral folate receptor alpha (FRα)

Cerebral folate deficiency (CFD) is caused by low levels of 5-methyltetrahydrofolate (5-MTHF), which is transported into the brain via the cerebral FRα. By mediating high-affinity absorption and endocytosis primarily in the choroid plexus, FRα plays a crucial role in controlling folate entrance into the central nervous system. Functional or structural disruption of FRα can reduce the availability of folate in the central nervous system and cause anomalies in development or neurological dysfunction [56].

Anti-Folate Receptor Autoantibodies

The production and presence of anti-FOLR1 IgG (antibodies to the FRα) are among the most frequently identified autoimmune components in children diagnosed with ASD. The presence of anti-FOLR1 IgG inhibits the binding of FOLR1 to folate, thus preventing the transport of folate from the blood to the brain throughout BBB [57]. Locally altering levels of folates in a person's central nervous system (CNS) creates disruption to key biological functions associated with DNA methylation, de novo nucleotides, and the formation of cortical areas of development, which will lead to an increased severity of that individual's ASD. Pursuant to a comprehensive study and meta-analysis, children

with autism had a 71% prevalence rate of these antibodies, and their likelihood of being positive was 19 times higher than that of children with normal development [58].

Cerebral folate deficiency syndrome (CFDS)

Any neuropsychiatric or developmental condition marked by reduced CSF folate levels in the context of adequate folate status outside the nervous system is known as cerebral folate deficiency syndrome (CFDS). Serum folate receptor-alpha (FRα) autoantibodies have been found to be the main cause of CFDS, since they hinder the delivery of folate to the brain via the choroid plexus. Treatment involves oral leucovorin (folinic acid), and the earlier appropriate treatment is initiated, the greater the likelihood of preventing or mitigating neurocognitive deficits [9].

The Interplay between Glutathione and Folate in ASD

The hepatic and central nervous system one-carbon metabolic network intrinsically couples folate metabolism and glutathione synthesis [59]. This pathway connects with the donation of its methyl group from 5-methyltetrahydrofolate (5-MTHF) that is required to remethylate homocysteine into methionine by cobalamin dependent enzyme methionine synthase [60]. Methionine is then activated to S-adenosylmethionine (SAM) and all methods of methylation, DNA methylation, phospholipid synthesis and neurotransmitters metabolism in developing brain are mainly dependent on SAM supply [61]. The transfer of a methyl to substrate from SAM occurs, which is then donated, resulting in the formation of S-adenosylhomocysteine (SAH) and later on returning it back to homocysteine. This biochemical cascade illustrates the direct requirement of sufficient folate bio-availability in sustaining constant methylation flux and regulating cellular homocysteine pools [62].

Under normal physiological conditions a large proportion of homocysteine is shunted away from the methylation cycle into the transsulfuration pathway through cystathionine beta-synthase (CBS) [63]. The transsulfuration route which converthomocystine to cystathionine that subsequentlycatabolised into L-cysteine. L-cysteine is the main and rate-limiting amino acid substrate for de novo GSH (reduced glutathione) biosynthesis [64]. It is the principal endogenous intracellular anti-oxidant protecting neuroglial cells from free radicals, lipid peroxidation and xenobiotic toxicity. Moreover, this illustrates the absolute dependency of homeostatic balance between upstream folate-driven one-carbon metabolism and transsulfuration in regulating glutathione synthesis [65].

Autoantibodies against Folate Receptor Alpha (FOLR1), MTHFR gene polymorphisms, or transport impairment cause severe downstream metabolic consequences in children with ASD via disruption of folate bioavailability. The impaired folate transport decreases the status of conversion from homocysteine to methionine, and changes SAM/SAH methylation ratio [55]. At the same time, one-carbon throughput reduction results in reduced cellular (but not plasma) homocysteine flux through the transsulfuration pathway and, ultimately, cysteine depletion. GSH is synthesized from cysteine, but in the absence of sufficient cysteine the cellular GSH content becomes severely depleted, while oxidized glutathione (GSSG) accumulates leading to a

pathological GSH/GSSG redox baseline. This complete GSH depletion renders the central nervous system greatly susceptible to unregulated reactive oxygen species (ROS) and cellular oxidative stress [66].

Moreover, this interaction incorporates a vicious pathogenic feedback loop because ASD is implicated in glutathione deficiency and the inverse correlation between folate status and glutathione deficiency. Lack of GSH leads to chronic oxidative stress, which not only oxidizes cobalamin (vitamin B12), but also directly inactivates methionine synthase, thereby blocking the folate cycle even further. In addition, excessive reactive oxygen species impair the integrity of Folate Receptor Alpha (FOLR1) structure in blood-brain barrier [8] , which worsens cerebral folate deficiency. This bidirectional inhibition shows that folate deficiency leads directly to the depletion of glutathione and vice versa, so that the central transport of folate and methyl utilization are reduced due to the depletion of gluthatione in response to folate deficiency. Restoring this balance with lower molecular weight derivatives of folate (e.g., folinic acid) in conjunction with GSH precursor support, we believe, is an important metabolic targeted therapeutic approach to ultimately reduce neuroinflammation and oxidative stress in ASD [67].

CONCLUSION

Fundamental Finding : ASD is a complex neurodevelopmental disorder influenced by genetic and environmental factors, with oxidative stress, neuroinflammation, and immune dysregulation playing important roles. The review identifies a persistent reduction in glutathione (GSH), the brain's primary endogenous antioxidant, alongside elevated circulating anti-FRα autoantibodies that disrupt folate transport across the blood-brain barrier and contribute to cerebral folate deficiency syndrome (CFDS). **Implication :** The interdependence between GSH depletion and folate deficiency suggests that redox and folate-related pathways may have potential as diagnostic biomarkers for ASD. These findings also support the possibility of targeted interventions, including folinic acid supplementation, to reduce the severity of ASD symptoms. **Limitation :** The review highlights the biological relationship between glutathione-dependent redox metabolism and folate status, but it does not establish a definitive causal relationship between these abnormalities and ASD pathogenesis. **Future Research :** Future studies should further investigate the relationship between GSH depletion, folate deficiency, and ASD development, particularly their potential application as diagnostic biomarkers and therapeutic targets. Research should also evaluate the effectiveness of folinic acid supplementation in improving ASD symptom severity.

REFERENCES

[1] M. S. Farooq, R. Tehseen, M. Sabir, and Z. Atal, "Detection of autism spectrum disorder (ASD) in children and adults using machine learning," *Sci. Rep.*, vol. 13, no. 1, p. 9605, 2023, doi: 10.1038/s41598-023-35910-1.

[2] A. H. Issa, "Gut Flora in Autistic Children as Biomarker for Autism in Thi-Qar Province/Iraq," *Univ. Thi-Qar J. Sci.*, 2020.

[3] G. Steinman, "The putative etiology and prevention of autism.," *Prog. Mol. Biol. Transl. Sci.*, vol. 173, pp. 1–34, 2020, doi: 10.1016/bs.pmbts.2020.04.013.

[4] S. Bölte, S. Girdler, and P. B. Marschik, "The contribution of environmental exposure to the etiology of autism spectrum disorder.," *Cell. Mol. Life Sci.*, vol. 76, no. 7, pp. 1275–1297, Apr. 2019, doi: 10.1007/s00018-018-2988-4.

[5] C. L. Arberas, "Genetic and Epigenetic Aspects Linked to The Etiology of Autism," *J. Hum. Clin. Genet.*, vol. 4, no. 1, pp. 7–19, 2025.

[6] C. Kappen, "Folate supplementation in three genetic models: implications for understanding folate-dependent developmental pathways.," *Am. J. Med. Genet. C. Semin. Med. Genet.*, vol. 135C, no. 1, pp. 24–30, May 2005, doi: 10.1002/ajmg.c.30050.

[7] L. Peng, N. Dreumont, D. Coelho, J.-L. Guéant, and C. Arnold, "Genetic animal models to decipher the pathogenic effects of vitamin B12 and folate deficiency.," *Biochimie*, vol. 126, pp. 43–51, Jul. 2016, doi: 10.1016/j.biochi.2016.05.007.

[8] D. A. Rossignol and R. E. Frye, "Cerebral Folate Deficiency, Folate Receptor Alpha Autoantibodies and Leucovorin (Folinic Acid) Treatment in Autism Spectrum Disorders: A Systematic Review and Meta-Analysis.," *J. Pers. Med.*, vol. 11, no. 11, Nov. 2021, doi: 10.3390/jpm11111141.

[9] V. T. Ramaekers and E. V Quadros, "Cerebral Folate Deficiency Syndrome: Early Diagnosis, Intervention and Treatment Strategies.," *Nutrients*, vol. 14, no. 15, Jul. 2022, doi: 10.3390/nu14153096.

[10] L. Chen *et al.*, "Oxidative stress marker aberrations in children with autism spectrum disorder: a systematic review and meta-analysis of 87 studies (N = 9109).," *Transl. Psychiatry*, vol. 11, no. 1, p. 15, Jan. 2021, doi: 10.1038/s41398-020-01135-3.

[11] R. E. Frye, J. M. Sequeira, E. V Quadros, S. J. James, and D. A. Rossignol, "Cerebral folate receptor autoantibodies in autism spectrum disorder.," *Mol. Psychiatry*, vol. 18, no. 3, pp. 369–381, Mar. 2013, doi: 10.1038/mp.2011.175.

[12] J. Harris, "Leo Kanner and autism: a 75-year perspective.," *Int. Rev. Psychiatry*, vol. 30, no. 1, pp. 3–17, Feb. 2018, doi: 10.1080/09540261.2018.1455646.

[13] B. Zablotsky, L. I. Black, M. J. Maenner, L. A. Schieve, and S. J. Blumberg, "Estimated prevalence of autism and other developmental disabilities following questionnaire changes in the 2014 National Health Interview Survey," 2015.

[14] M.-C. Lai *et al.*, "Biological sex affects the neurobiology of autism.," *Brain*, vol. 136, no. Pt 9, pp. 2799–2815, Sep. 2013, doi: 10.1093/brain/awt216.

[15] M. J. Maenner, "Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2016," *MMWR. Surveill. Summ.*, vol. 69, 2020.

[16] M.-C. Lai *et al.*, "Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis.," *The lancet. Psychiatry*, vol. 6, no. 10, pp. 819–829, Oct. 2019, doi: 10.1016/S2215-0366(19)30289-5.

[17] L. Campisi, N. Imran, A. Nazeer, N. Skokauskas, and M. W. Azeem, "Autism spectrum disorder.," *Br. Med. Bull.*, vol. 127, no. 1, pp. 91–100, Sep. 2018, doi: 10.1093/bmb/ldy026.

[18] H. Famitafreshi and M. Karimian, "Overview of the Recent Advances in Pathophysiology and Treatment for Autism.," *CNS Neurol. Disord. Drug Targets*, vol. 17, no. 8, pp. 590–594, 2018, doi: 10.2174/1871527317666180706141654.

[19] K. A. Bala, M. Doğan, S. Kaba, T. Mutluer, O. Aslan, and S. Z. Doğan, "Hormone disorder and vitamin deficiency in attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASDs).," *J. Pediatr. Endocrinol. Metab.*, vol. 29, no. 9, pp. 1077–1082, Sep. 2016, doi: 10.1515/jpem-2015-0473.

[20] Y. C. Kaplan, E. Keskin-Arslan, S. Acar, and K. Sozmen, "Prenatal selective serotonin reuptake inhibitor use and the risk of autism spectrum disorder in children: A systematic review and meta-analysis.," *Reprod. Toxicol.*, vol. 66, pp. 31–43, Dec. 2016, doi: 10.1016/j.reprotox.2016.09.013.

[21] H. A. Abdulamir, O. F. Abdul-Rasheed, and E. A. Abdulghani, "Serotonin and serotonin transporter levels in autistic children.," *Saudi Med. J.*, vol. 39, no. 5, pp. 487–494, May 2018, doi: 10.15537/smj.2018.5.21751.

[22] T. B. Kirsten and M. M. Bernardi, "Prenatal lipopolysaccharide induces hypothalamic dopaminergic hypoactivity and autistic-like behaviors: Repetitive self-grooming and stereotypies.," *Behav. Brain Res.*, vol. 331, pp. 25–29, Jul. 2017, doi: 10.1016/j.bbr.2017.05.013.

[23] C. R. Gibbard, J. Ren, D. H. Skuse, J. D. Clayden, and C. A. Clark, "Structural connectivity of the amygdala in young adults with autism spectrum disorder.," *Hum. Brain Mapp.*, vol. 39, no. 3, pp. 1270–1282, Mar. 2018, doi: 10.1002/hbm.23915.

[24] J. Naaijen *et al.*, "Striatal structure and its association with N-Acetylaspartate and glutamate in autism spectrum disorder and obsessive compulsive disorder.," *Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol.*, vol. 28, no. 1, pp. 118–129, Jan. 2018, doi: 10.1016/j.euroneuro.2017.11.010.

[25] S. Kim *et al.*, "Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring.," *Nature*, vol. 549, no. 7673, pp. 528–532, Sep. 2017, doi: 10.1038/nature23910.

[26] A. Meltzer and J. Van de Water, "The Role of the Immune System in Autism Spectrum Disorder.," *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.*, vol. 42, no. 1, pp. 284–298, Jan. 2017, doi: 10.1038/npp.2016.158.

[27] M. Hashemipour, M. Sheikh-Hosseini, and H. Mabudi, "Association of Autism Spectrum Disorder in an Iranian Pedigree with a Novel Hereditary Mutation in SETD5," *Int. J. Biomed.*, vol. 14, pp. 170–174, Mar. 2024, doi: 10.21103/Article6(1)_CR4.

[28] Y. Chen *et al.*, "Research trends of inflammation in autism spectrum disorders: a bibliometric analysis," *Front. Immunol.*, vol. Volume 16-2025, 2025, doi: 10.3389/fimmu.2025.1534660.

[29] M. P. Pereira and G. Conti-Ramsden, *Language development and social interaction in blind children*. Routledge, 2019.

[30] K. Bottema-Beutel, S. K. Kapp, J. N. Lester, N. J. Sasson, and B. N. Hand, "Avoiding ableist language: Suggestions for autism researchers," *Autism in adulthood*, vol. 3, no. 1, pp. 18–29, 2021.

[31] M. J. Hollocks, T. Charman, G. Baird, C. Lord, A. Pickles, and E. Simonoff, "Exploring the impact of adolescent cognitive inflexibility on emotional and behavioural problems experienced by autistic adults," *Autism*, vol. 26, no. 5, pp. 1229–1241, 2022.

[32] N. E. Mathew *et al.*, "The search for gastrointestinal inflammation in autism: a systematic review and meta-analysis of non-invasive gastrointestinal markers.," *Mol. Autism*, vol. 15, no. 1, p. 4, Jan. 2024, doi: 10.1186/s13229-023-00575-0.

[33] M. Elsabbagh, "Linking risk factors and outcomes in autism spectrum disorder: is there evidence for resilience?," *BMJ*, vol. 368, p. l6880, Jan. 2020, doi: 10.1136/bmj.l6880.

[34] A. Modabbernia, E. Velthorst, and A. Reichenberg, "Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses," *Mol. Autism*, vol. 8, no. 1, p. 13, 2017.

[35] C. Mahony and C. O'Ryan, "A molecular framework for autistic experiences: Mitochondrial allostatic load as a mediator between autism and psychopathology.," *Front. psychiatry*, vol. 13, p. 985713, 2022, doi: 10.3389/fpsyt.2022.985713.

[36] R. E. Frye and S. J. James, "Metabolic pathology of autism in relation to redox metabolism.," *Biomark. Med.*, vol. 8, no. 3, pp. 321–330, 2014, doi: 10.2217/bmm.13.158.

[37] Y. Lu, K. F. Tonissen, and G. Di Trapani, "Modulating skin colour: role of the thioredoxin and glutathione systems in regulating melanogenesis.," *Biosci. Rep.*, vol. 41, no. 5, May 2021, doi: 10.1042/BSR20210427.

[38] K. Radwan, G. Wu, K. Banks-Word, and R. Rosenberger, "An Open-Label Case Series of Glutathione Use for Symptomatic Management in Children with Autism Spectrum Disorder.," *Med. Sci. (Basel, Switzerland)*, vol. 11, no. 4, Nov. 2023, doi: 10.3390/medsci11040073.

[39] M. M. Essa, N. Braidy, K. R. Vijayan, S. Subash, and G. J. Guillemin, "Excitotoxicity in the pathogenesis of autism.," *Neurotox. Res.*, vol. 23, no. 4, pp. 393–400, May 2013, doi: 10.1007/s12640-012-9354-3.

[40] G. Bjørklund *et al.*, "The role of glutathione redox imbalance in autism spectrum disorder: A review.," *Free Radic. Biol. Med.*, vol. 160, pp. 149–162, Nov. 2020, doi: 10.1016/j.freeradbiomed.2020.07.017.

[41] P. A. Main, M. T. Angley, C. E. O'Doherty, P. Thomas, and M. Fenech, "The potential role of the antioxidant and detoxification properties of glutathione in autism spectrum disorders: a systematic review and meta-analysis.," *Nutr. Metab. (Lond).*, vol. 9, p. 35, Apr. 2012, doi: 10.1186/1743-7075-9-35.

[42] D. A. Averill-Bates, "The antioxidant glutathione," in *Vitamins and hormones*, vol. 121, Elsevier, 2023, pp. 109–141.

[43] M. M. Black, "Effects of vitamin B12 and folate deficiency on brain development in children.," *Food Nutr. Bull.*, vol. 29, no. 2 Suppl, pp. S126-31, Jun. 2008, doi: 10.1177/15648265080292S117.

[44] H. Saitsu, "Folate receptors and neural tube closure.," *Congenit. Anom. (Kyoto).*, vol. 57, no. 5, pp. 130–133, Sep. 2017, doi: 10.1111/cga.12218.

[45] X. Song, P. Huang, T. Wang, S. Zhang, L. Chen, and J. Qin, "Association of periconceptional folate supplements and FOLR1 and FOLR2 gene polymorphisms with risk of congenital heart disease in offspring: A hospital-based case-control study.," *Zhong nan da xue xue bao. Yi xue ban = J. Cent. South Univ. Med. Sci.*, vol. 47, no. 1, pp. 52–62, Jan. 2022, doi: 10.11817/j.issn.1672-7347.2022.200992.

[46] H. Chen *et al.*, "Neurodevelopmental effects of maternal folic acid supplementation: a systematic review and meta-analysis.," *Crit. Rev. Food Sci. Nutr.*, vol. 63, no. 19, pp. 3771–3787, 2023, doi: 10.1080/10408398.2021.1993781.

[47] M. Ressel *et al.*, "Systematic review of risk and protective factors associated with substance use and abuse in individuals with autism spectrum disorders.," *Autism*, vol. 24, no. 4, pp. 899–918, May 2020, doi: 10.1177/1362361320910963.

[48] A. C. Sampaio *et al.*, "Association of the Maternal Folic Acid Supplementation with the Autism Spectrum Disorder: A Systematic Review.," *Rev. Bras. Ginecol. e Obstet. Rev. da Fed. Bras. das Soc. Ginecol. e Obstet.*, vol. 43, no. 10, pp. 775–781, Oct. 2021, doi: 10.1055/s-0041-1736298.

[49] P. K. Panda, I. K. Sharawat, S. Saha, D. Gupta, A. Palayullakandi, and K. Meena, "Efficacy of oral folinic acid supplementation in children with autism spectrum disorder: a randomized double-blind, placebo-controlled trial.," *Eur. J. Pediatr.*, vol. 183, no. 11, pp. 4827–4835, Nov. 2024, doi: 10.1007/s00431-024-05762-6.

[50] Y. Shulpekova *et al.*, "The Concept of Folic Acid in Health and Disease.," *Molecules*, vol. 26, no. 12, Jun. 2021, doi: 10.3390/molecules26123731.

[51] L. S. Tang, D. R. Santillano, B. J. Wlodarczyk, R. C. Miranda, and R. H. Finnell, "Role of Folbp1 in the regional regulation of apoptosis and cell proliferation in the developing neural tube and craniofacies.," *Am. J. Med. Genet. C. Semin. Med. Genet.*, vol. 135C, no. 1, pp. 48–58, May 2005, doi: 10.1002/ajmg.c.30053.

[52] A. Harlan De Crescenzo *et al.*, "Deficient or Excess Folic Acid Supply During Pregnancy Alter Cortical Neurodevelopment in Mouse Offspring.," *Cereb. Cortex*, vol. 31, no. 1, pp. 635–649, Jan. 2021, doi: 10.1093/cercor/bhaa248.

[53] A. Michel *et al.*, "Folate and Cobalamin Deficiencies during Pregnancy Disrupt the Glucocorticoid Response in Hypothalamus through N-Homocysteinilation of the Glucocorticoid Receptor.," *Int. J. Mol. Sci.*, vol. 24, no. 12, Jun. 2023, doi: 10.3390/ijms24129847.

[54] K. Ahmavaara and G. Ayoub, "Cerebral folate deficiency in autism spectrum disorder," *Lancet Neurol*, vol. 5, no. 11, pp. 949–960, 2022.

[55] N. Bobrowski-Khoury, V. T. Ramaekers, J. M. Sequeira, and E. V Quadros, "Folate Receptor Alpha Autoantibodies in Autism Spectrum Disorders: Diagnosis, Treatment and Prevention.," *J. Pers. Med.*, vol. 11, no. 8, Jul. 2021, doi: 10.3390/jpm11080710.

[56] C. E. Clare, A. H. Brassington, W. Y. Kwong, and K. D. Sinclair, "One-Carbon Metabolism: Linking Nutritional Biochemistry to Epigenetic Programming of Long-Term Development.," *Annu. Rev. Anim. Biosci.*, vol. 7, pp. 263–287, Feb. 2019, doi: 10.1146/annurev-animal-020518-115206.

[57] P. Phunsawat *et al.*, "Folate receptor alpha autoantibodies in children with autism spectrum disorder," *Biomarkers*, vol. 27, no. 8, pp. 715–719, Nov. 2022, doi: 10.1080/1354750X.2022.2125579.

[58] A. M. Molloy *et al.*, "Lack of association between folate-receptor autoantibodies and neural-tube defects.," *N. Engl. J. Med.*, vol. 361, no. 2, pp. 152–160, Jul. 2009, doi: 10.1056/NEJMoa0803783.

[59] S. J. James *et al.*, "Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism.," *Am. J. Clin. Nutr.*, vol. 80, no. 6, pp. 1611–1617, Dec. 2004, doi: 10.1093/ajcn/80.6.1611.

[60] A. Frustaci *et al.*, "Oxidative stress-related biomarkers in autism: systematic review and meta-analyses.," *Free Radic. Biol. Med.*, vol. 52, no. 10, pp. 2128–2141, May 2012, doi: 10.1016/j.freeradbiomed.2012.03.011.

[61] R. Deth, C. Muratore, J. Benzecry, V.-A. Power-Charnitsky, and M. Waly, "How environmental and genetic factors combine to cause autism: A redox/methylation hypothesis.," *Neurotoxicology*, vol. 29, no. 1, pp. 190–201, Jan. 2008, doi: 10.1016/j.neuro.2007.09.010.

[62] S. Melnyk *et al.*, "Metabolic imbalance associated with methylation dysregulation and oxidative damage in children with autism.," *J. Autism Dev. Disord.*, vol. 42, no. 3, pp. 367–377, Mar. 2012, doi: 10.1007/s10803-011-1260-7.

[63] V. Vitvitsky, M. Thomas, A. Ghorpade, H. E. Gendelman, and R. Banerjee, "A functional transsulfuration pathway in the brain links to glutathione homeostasis.," *J. Biol. Chem.*, vol. 281, no. 47, pp. 35785–35793, Nov. 2006, doi: 10.1074/jbc.M602799200.

[64] S. C. Lu, "Glutathione synthesis.," *Biochim. Biophys. Acta*, vol. 1830, no. 5, pp. 3143–3153, May 2013, doi: 10.1016/j.bbagen.2012.09.008.

[65] J. H. Suh *et al.*, "Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid.," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 101, no. 10, pp. 3381–3386, Mar. 2004, doi: 10.1073/pnas.0400282101.

[66] A. Ghanizadeh, S. Akhondzadeh, M. Hormozi, A. Makarem, M. Abotorabi-Zarchi, and A. Firoozabadi, "Glutathione-related factors and oxidative stress in autism, a review.," *Curr. Med. Chem.*, vol. 19, no. 23, pp. 4000–4005, 2012, doi: 10.2174/092986712802002572.

[67] R. E. Frye *et al.*, "Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial.," *Mol. Psychiatry*, vol. 23, no. 2, pp. 247–256, Feb. 2018, doi: 10.1038/mp.2016.168.

***Heleen S. Agab (Corresponding Author)**
Department of Pathology Analysis, College of Science, University of Thi-Qar, Iraq
Email: helen.salih@utq.edu.iq

Baidaa R. Ali
Department of Pathology Analysis, College of Science, University of Thi-Qar, Iraq
Email: baida77-path@sci.utq.edu.iq