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Folic Acid in Neuropsychiatric Disorders

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Abstract

It is known that Folic Acid (FA) plays an important role in normal brain development and functions. Interest is growing about the implications of folic acid employment in neuropsychiatric disorders. This work reviews the literature available from 2018 to 2022 on the biochemical and clinical correlates of FA administration in cognitive diseases such as Autism Spectrum Disorders (ASD), Attention Deficit-Hyperactivity Disorder (ADHD), and Obsessive-Compulsive Disorder (OCD). It was found that FA supplementation is a safe and promising therapeutic strategy to mitigate the symptoms of these diseases.

Keywords: Folic acid; Cognitive disorders; ASD; ADHD; OCD.

Introduction

Folate is a member of the vitamin B family, essential for production and mainteinance of homocysyeine at non-toxic levels in new cells, as well as for nucleotide and neurotransmitter synthesis, DNA and histone methylation reactions, myelin synthesis [1]. From a biochemical point of view, dietary folic acid is metabolized to tetrahydrofolate that is activated in one-carbon unit to 10-formyltetrahydrofolate, 5,10-methylenetetrahydrofolate, and 5-methyltetrahydrofolate that, in turn, supports a biosynthetic pathway for the synthesis of purines and thymidylate and the remethylation of Homocysteine (HC) to methionine. Synthesis of methionine requires 5-Methyltetrahydrofolate (MTHF) and vitamin B12. Folic acid is converted to dihydrofolate and then tetrahydrofolate by dihydrofolate reductase, that is dependent on NADPH [2].

The potential of folic acid in psychiatric disorders is largely known and folate has been found that to be safe, with no risks for adverse effects [2]. In addiction, blood folate levels can be easily assessed. A correct maternal folate status is essential for brain development and functioning of offspring. Particularly, animal models show morphological, physiological, and genetic alterations in offspring as a consequence of prenatal or postnatal exposure to irregular levels of folate. Human studies indicate a positive correlation between sufficient maternal folate status and offspring cognitive function [3].

The importance of a regular folate intake during pregnancy even for mother's mental health emerged from a recent work. The authors reported a possible link between Methyltetrahydrofolate Reductase (MTHFR) C677T mutation C677T mutation and post-partum psychopathology including psychosis, bipolar and unipolar disorders, thus suggesting that that these variants may influence. Interestingly, this mutation is known to be implicated in psicotic disturbances, bipolar and unipolar disorders, folate level and symptoms of postpartum psychopathology, and suggesting that these variants may influence folate metabolism and be implicated in depression during pregnancy [4].

Cerebral Folate Deficiency (CFD) in adults is relatively common. A study examining clinical and radiological aspects of patients with CFD before and after folinic acid supplementation highlighted the importance of CSF 5MTHF dosage in patients with mitochondrial diseases, primary brain calcifications and unexplained complex neurological disorders [5].

Folate deficiency is reported in different neuropsychitric diseases [6,7]. A meta-analysis of randomized controlled trials examined the efficacy and safety of adjunctive folate for schizofrenia, bipolar disorder and major depressive disorder. It has emerged that for schizophrenia adjunctive folate is not superior to placebo in terms of total psychopatology, while for bipolar and unipolar depression it is superior to placebo in the acute phase of mania but not in improving depressive symptoms [6].

In line with the relevance of folate in neuropsychiatric disorders, the role of levomefolic acid or 5-methylfolate acid supplementation has been analysed, especially as an adjunct pharmacotherapy, in improving some clinical variables. The authors pointed out significant effect of this supplementation not only for schizophrenia and mood disoders, but also for autism

spectrum disorder and attention-deficit hyperactivity disorder (ADHD), with minimal side effects [7]. Moreover, the importance of folic acid for the prevention of Alzheimer Disease (AD) is largely reported. Polymorphisms in MTHFR [8,9] as well as folic acid deficiency [10,11] and subsequent alterations in folate pathways [12,16,17] can be associated with cognitive disturbances. Meantime, folic acid supplementation has been proven beneficial in people with cognitive impairment [10,18], even in haemodialysis [16]. Therefore, given the frequent assessment of blood folate levels, the aim of the present review is to analyse literature on the possible relationships between folic acid blood levels and some neuropsychiatric disorders and to comment on the possible therapeutic role of this vitamin supplementation.

Materials and methods

Search strategy: According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we manually searched eligible literature for this systematic review. We carried out this work through PubMed from 2018 to 2022 with the following search items: 1) folic acid and neuropsychiatric disorders; 2) folic acid and autism spectrum disorders; 3) folic acid and obsessive-compulsive disorder. Furthermore, we manually added other articles to the selection by screening the bibliographies of the eligible articles.

Selection criteria

Inclusion criteria: Articles were included if written in english and they satisfied one of the following study designs: clinical study, clinical trial, comparative study, controlled clinical trial, multicenter study, observational study, randomized controlled trial, systematic review, and meta- analysis. We also decided to include studies carried out in animal models.

Data extraction: Data were abstracted using a predefined data extraction form: first author, publication year, study design, sample size, basic information of participants (gender, age), diagnosis, criteria for the assessment of the mood disorders, specific biomarker alterations.

Results

Folic acid and cognitive disorders: Three studies have investigated MTHFR genes polymorphisms in animal models. One of them showed that polymorphisms in the 5,10 MethyleneTetrahydrofolate Reductase (MTHFR) genes are associated with high risk for developing late-onset AD by affecting the Amyloid-β Protein Precursor (AβPP), a protein with a crucial role in neurodegenerative disease [7]. Particularly, MTHFR knockout mice present increased cortical and hippocampal AβPP phosphorylation at the regulatory Thr668 site, that, in turn, enhances accumulation of demethylated protein phosphatase 2 (PP2A) and glycogen synthase kinase 3β(GSK-3β). All these mechanisms contribute to alter neuronal homeostasis, thus highlighting a possible linking between dietary folate deficiency and risk of sporadic AD [7]. A MTHFR polymorphism thought to be implicated in the late onset AD is the MTHFR 667 C>T polymorphism.Two groups of mice, wild type and Mthfr (a model for the MTHFR 667C>T polymorphism) were fed control or folate-deficient diets from weaning until 8 and 10 months of age. Those with Mthfr $^{+/-}$genotype presented altered transcriptional levels of synaptic markers and epigenetic enzymes, reduced levels of S-adenosylmethionine and acetylcholine, thus suggesting how genetic and dietary folate metabolic disturbances increase risk for cognitive decline [8].

Folate seems to play a role in preventing senescence through alleviation of telomere attrition. Senescente-Accelerated Mice Prone 8 (SAMP8) were divided into 4 experimental groups: FA-deficient diet group (FA-D group), FA-normal diet group (FA-N group), low FA-supplemented diet (FA-L) and high FA-supplemented diet (FA-H) group. There was also a Senescent-Accelerated Mouse Resistant (SAMR1) control group (Con-R) and a young SAMP8 control group (Con-Y). It was found that FA supplementation delayed age-related cognitive decline and neurodegeneration in SAMP8 mice thanks to alleviated telomere attrition and in turn, to lower levels of reactive oxygen species [15].

Moreover, chronic folate deficiency has been shown to induce lipid and glucose metabolism disorders in murine models. The authors enrolled seven-week-old mice which were fed with either a Chronic Folate Deficiency (CFD) and a control diet for 25 days. Except from glucose intolerance and increased triglyceride levels, after 24-week diet treatment, CFD induced anxiety-related activities and impairment of spatial learning and memory performance, thus highlighting the relationship between CFD and cognitive deficits [10].

Five studies examined effects of folate on neurocognitive problems in humans. Another biochemical mechanism implicated in folate good effects in cognitive functions is the increase of Hcy. A recent review [14] showed that folic acid could improve cognitive functions by decreasing Hcy, vascular care, attenuating inflammatory status, modificating folic acid deficiency and facilitating antioxidant responses. The authors's conclusion was that peolple with high levels of Hcy have a better response to folic acid supplementation in terms of improvement of cognitive functions [14]. Starting from the known relevance of Aβ deregulation in cognitive impairment, the combination of folic acid and Docosahexaenoic Acid (DHA) was proved useful in mild cognitive impaired patients. Infact, DHA and folic acid supplementation effect in improving cognitive functions has recently been related to reduction of blood Aβ-related biomarkers in patients with Mild Cognitive Impairment (MCI) [17].

A study, analysing relationship between folate levels and cognitive impairment among individuals with vitamin B12 deficiency, found that the association between low intake of vitamin B12 and folate and cognitive diseases could be mediated by elevation of homocystein and homocysteic acid. Infact, these molcecules have a neurotoxic effect and the consequence of their increase may be irreversible cognitive impairment [13]. Another molecular mechanism implicated in cognitive effects of folate deficiency is the deregulation of mitochondrial function. A case-controlled studied investigated serum folate metabolites and mitochondrial function function in peripheral blood cells of 82 AD cases and the same number of controls, matched by age, gender, and education. AD patients presented lower reduced mitochondrial DNA (mtDNA) copy number, higher mtDNA deletions and increased 8-hydroxy-2-deoxyguanosine(8-OHdG) content in mtDNA. From the other side, the authors found that the highest level of mtDNA copy number was associated with a reduction in AD risk, independently of serum folate and Hcy levels. Overall, these results pointed out lower mitochondrial function in peripheral blood cells of AD patients with a folate deficiency [12]. Intriguingly, usefulness of folate supplementation has been proved even in haemodialysised patients with congitive problems [16].

FA in Autism Spectrum Disease (ASD) and Attention-Deficit Hyperactivity Disorder (ADHD): Nine studies included in our work reported a positive correlation between prenatal maternal folate levels and ASD risk in the offspring [18-26] three of them a negative correlation [27,36,37] and five ones failed to report a significant correlation [28-30,33-35].

Two studies reported significant correlation in animal models [19,25]. The first one focused on periconceptional folate deficiency in murine model of Wistar rat's offspring. Female rats were divided in two groups: control (with a basal diet) or exposed during one month before breeding until gestational day 15 to a modified diet with no added folic acid, reduced choline and added 1% SST (a non-absorbable antibiotic used to inhibit folate synthesis by gut bacteria). It was found out that offsprings with periconceptional deficit in folate presented congenital body malformations, reduced social interactions, increased anxiety, repetitive behaviors compared to controls. These results support the linking between maternal periconceptional deficit in folate and autistic-like phenotype [19].

A study carried out in rat moldels highligthed that maternal FA supplementation at high doses can prevent growth and development delay as well as deficits in social communication and repetitive behaviors probably thanks to an increase in dendritic spine density and a downregulation of inhibitory ones. The author's conclusion was that this vitam supplementation may play a key role in preventing ASD [25]. Six studies made on human models reported interesting findings on the role of maternal folic acid supplementation in the pre-conception period and beginning of pregnancy as a protective effect in ASD. [18,20,26,31,24,31]. A work carried out in mothers who used FA in the 6 weeks before and after conception showed protective effect of folic acid supplementation in these mothers compared to those who hadn't used it. From the other side, it was seen that an excess of FA may result in an increased risk of ASD [18]. Some authors focused on the effects of vitamins in general in reducing ASD risk in siblings of children with ASD in high-risk families and found that maternal prenatal vitamin intake during the first month of pregnancy can reduce ASD recurrence [20].

In line with these findings, 416 ASD children and 201 typically developed controls were analysed for laboratory measures, such as vitamin A(VA), D(VD), B12(VB12), folate and ferritine. ASD children's mothers presented lower levels of maternal folic acid or micronutrient supplementation during pregnancy. Moreover, these children had more social cognition and communication impairment, autism behavioural mannerisms as well as more severe gastrointestinal symptoms than children whose mothers received regular supplements [26]. A recent systematic review examined the correlation between maternal prenatal folic acid supplementation and ASD in the offspring. Globally, it was pointed out that the consumption of a daily amount of at least 400 micrograms of folic acid from dietary sources and supplements was associated with a reduced risk of ASD in the offspring compared to a control group that didn't receive this supplementation [24]. Overall, a review and meta-analysis found that even though previous literature suggests that periconceptional use of folic acid is associated with reduced ASD risk [21-23], the global reduction in ASD risk was about the 58%, whereas no effect was registered on mental and motor development [31].

However, five studies failed to find an association between folic acid prenatal levels and ASD risk [28-30,32,34]. From the other side, three works reported negative association between maternal folate levels and ASD risk. In the first one, a group of 1257 mother-child pairs were enrolled and had their maternal plasma folate and B12 levels measured 2-3 days after child birth. It was seen that very high levels of maternal plasma folate at birth (>60, 3 nmol/L) were associated with 2,5 times increased risk of ASD [27]. Similar findings were highlighted by the second study. The authors collected samples from 100 women with ASD offspring and from 100 control women with typically developing children. Concentrations of metabolic biomarkers were determined, including amino-acids, vitamins, biomarkers related to folate, lifestyle factors and PCR. Weak evidence emerged for a positive association between higher maternal serum concentrations of folate and occurrence of ASD. Internal biochemical relations between the biomarkers were confirmed. It was concluded that high maternal serum folate status during early pregnancy could be associated with occurrence of ASD in the offspring [35]. It was proposed a particular interpretation of this eventual increased risk of ASD in case of high-dose gestational folic acid. Starting from the hypothesis that ASD children are more likely to be the first or second born, and that women tend to consume higher levels of folate during their first or second pregnancy, the linking between higher doses of folic acid and ASD could be influenced by this bith order bias[36].

Impairmeint of folate patways in ASD and ADHD may be due to genetic causes [24,38,40,43,57], and autoimmunitary aspects [41,42]. Moreover, a folic acid deficiency was associated with neural [5] and oro-facial defects [39]. Starting from the consideration that ASD is characterized by abnormalities in methionine patways, plasma levels of metabolites in methionine trans-methylation and trans-sulfuration patways were measured in 80 ASD and 73 control children. Moreover, common polymorphic variants known to modulate these patways were evalued in 360 children and 205 controls. Plasma methionine and indicators of methylation capacity, such as S-Adenosylmethionine (SAM) to S-Adenosylhomocystein (SAH) ratio, as well as plasma levels of cysteine, glutathione, and the ratio of reduced to oxidized glutathione resulted decresed in ASD children compared to controls. These findings suggest that clinical manifestations of ASD could be related to increased vulnerability to oxidative stress [37]. A study was carried out in two groups of respectively 89 ASD people and 89 matched controls. Participants were examined for 13 serological metabolites and two genetic variants related to folate metabolism. It was found that folate-related metabolism contributed to ASD and differences between ASD and healthy controls could be found to detect folate-related metabolism biomarkers [39]. A work made in Han Chinese population failed to find an association between genetic causes and ASD. The population was studied for the association between a single-Nucleotide Polymorphism (SNP) in genes involved in vitamin B12 and folate and childhood AS; no significant association was found between all these genotypes and ASD risk [38]. Similarly, a review explored genetic causes of ASD and ADHD by investigating the possible role of folate and folate-related patways in neurodevelopmental disorder, such as ASD and Attention Deficit-Hyperactivity Disorder (ADHD) [40]. Folate deficiency during pregnancy has been associated with both ADHD [41] and ASD [42]. Some studies reported the MTHFR C677T mutation in ASD as well as the presence of T allele or TT/CT genotypes more commons in mothers of ASD subjects compared to typically developed people [37,43,44,45,21,46,47]. The authors also reported some studies which failed to find an association between MTHFR variant and autism risk [48-

50,38]. Moreover, they presented a single work supporting the role of MTHFR C677T polymorphism in ADHD [51]. Another polymorphism found in ASD is the RFC1 A80G [52]. MTRR A66G genotype has been considered an important risk factor for ADHD [53]. The 19bp deletion DHFR was found associated with ASD in an Australian cohort of 17 patients and 16 controls [48,40]. Some works carried out in children with autism spectrum disorders provided an autoimmune explanation of lower levels of folic acid in ASD individuals [54,55]. Infact, the authors found a high prevalence of serum Folate Receptor Autoantibodies (FRAA) in ASD patients, and this may reduce the effect of this vitamin supplementation in pregnacy.

From a therapeutical point of view, four studies-one of them made on murine models [60] - documented the importance of folate supplementation for psychomotor [58], behavioral [59] and social aspects of ASD [61]. A study carried out in BTBR + Itpr3tf/J (BTBR) mice receiving FA (0,2 mg/kg/) orally from postnatal day 14-35 pointed out that FA supplementation could reduce repetitive and stereotyped behaviors, improve social communications, enhanced memory and spatial learning via the downregulation of cell loss in hippocampal CA1 region of the brain and modulated oxydative stress and inflammatory responses by altering the ferropotosis signaling pathways [60]. A study analysing Mexican children for effects of dietary intake of folate and viatamin B12 in mental and psychomotor development showed that dietary folate intake in early childhood may be beneficial for the mental development of children [58]. Another work carried out in 19 ASD children, was made to evaluate the efficacy of folinic acid at a lower dose of 5 mg twice daily in improving Autism score. It was seen that Autism Diagnostic Observation Schedule (ADOS) score, social interaction, communication sub scores were improved at week 12 compared to baseline only in the folinic acid group. The greater change of ADOS global score was noted in the folinic acid group, thus suggesting a possible therapeutic role of folate in ASD [59]. Moreover, beneficial effects of folinic acid as an adjuvant to risperidone for the treatment of inappropriate speech and other behavioral symptoms in children with autism have recently been highlighted [61].

Regarding folate role in treatment of ADHD, it has been questioned if L-methylfolate could augment methylphenidate in the treatment of ADHD. A clinical trial of 15 mg of L-methylfolate in combination with osmotic-release oral system methylfenidate showed that L-methylfolate was well tolerated with an improvement in the ASR scale. Methylphenidate level was higher in individuals treated with L-methylfolate probably due to a variation in a guanosine triphosphate cyclohydrolase gene. All these findings could suggest a possible beneficial effect of L-methylfolate in ADHD [62].

Folic acid in Obsessive-Compulsive Disorder (OCD): The role of folate supplementation in OCD is still quite limited.

A work examined serum folate and homocysteine concentrations in 23 OCD patients and in control subjects. The severity of the disease was assessed through Yale-Brown Obsession Compulsion Scale (Y-BOCS). It emerged that OCD patients presented lower levels of folate, whereas their homocysteine concentration resulted higher. Meantime, methylation and monoamine metabolism were impaired in OCD patients [63]. However, other three studies did not confirm previous findings [64-66].

FA and cognitive disturbances:

Authors and year	Study design	Sample				Diagnostic criteria	Results	Limits
		Patients		Control group				
		N (M/F)	Age±SD	N (M/F)	Age			
Lv et al.2019 [16]	Case-control	82 Alzheimer Disease (AD)	-	82 controls	-	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA)	AD patients with folate deficiency or hyperhomocisteinemia had low mitochondrial function in peripheral blood	Small sample size, brain tissue and peripheral system are different
Lu et al. 2021 [15]	Prospective, randomized, placebo-controlled, double-blind	115 patients in Maintenance Haemodialysis (MHD) who had Montreal Cognitive Assessment (MoCA)score lower than 26 and receiving thiamine 90 mg/die combined with folic acid 30 mg/die followed for 96 weeks	-	115 controls receiving thiamine placebo 90 mg/die and folic acid placebo 30 mg/die followed for 96 weeks	-	MoCA	Thiamine and folic acid could reduces homocysteine levels, so as to relieve the oxidative stress and improve cognitive function in patients with MHD.	Cognitive score measurement by different researchers may differ in the evaluation of cognitive function of subjects in a multicentre study.
Li et al. 2021 [18]	Single-center, double-blind, randomized clinical trial (RCT) design	160(138 completed the trial) patients with Mild Cognitive mpairment (MCI), divided in 3 groups: Folic Acid (FA) (N=35), folic acid+ Docosahexaenoic Acid (DHA) (N=34), DHA(N=36)	Mean age of FA group= 67, 51±5, 07 years. FA+DHA group=66, 74±5, 79 years. DHA group=70, 17±6,54 years	Control group (N=33)	Mean age=68, 30±6, 38 years	Chinese version of the Wechsler Adult Intelligence Scale-Revised (WAISRC). At baseline, the Mini-Mental State Examination (MMSE)	6 months of supplementation with 0.8 mg/day folic acid combined with 800 mg/day DHAimproves cognitive function in older adults with MCI. In addition, intervention reduced homocysteine and A_-related biomarker levels, while increasing the SAM/SAH ratio, folate, DHA, and SAM levels relative to those in the placebo group	Blood biological indicators not tested at 6 months after stopping intervention. Treatment duration has been short.

Authors and year	Study design	Sample/Studies included for meta-analysis				Diagnostic criteria	Results	Limits
		Patients		Control group				
		N (M/F)	Age±SD	N (M/F)	Age			
Levine et al. 2018 [19]	Case-cohort	45300 children (M=23210; F=22090), 572 with ASD. 11917 children born by mother exposed to FA before pregnancy, 21884 children born to mothers exposed to FA after pregnancy	10±1,4 years			International Classification of Diseases, Eighth Revision, and the International Classification of Diseases, Ninth Revision)	Maternal exposure to folic acid/ multivitamin supplements before pregnancy was associated with a lower likelihood of ASD in the offspring compared to no exposure before pregnancy	Presence of confoundings.Small sample size. Lack of information on gestational age decreasing the accuracy of exposure classifications
Schmidt et al. 2018 [22]	Prospective cohort	Younger siblings of ASD children (N=241, M=140, F=101)	Mean age= 36, 5±1, 6 months	-	-	Autism Diagnostic Observation Schedule (ADOS), Mullen Scales of Early Learning (MSEL)	Maternal prenatal vitamin intake during the first month of pregnancy may reduce ASD recurrence in siblings of children with ASD in high-risk families	Small sample size. The possibility of residual confounding or confounding by unmeasured factors cannot be ruled out.
Raghavan et al. 2018 [23]	Prospective	86 ASD children	Mean age of children mothers= 30,9±6,5 years	1171 neurotypical children	Mean age of their mothers=28, 3±6,6 years	EMR (Electronic Medical Record)	Extremely high maternal plasma folate and B12 levels at birth were associated with ASD risk.	Diagnosis was made on the basis of EMR. Lack of information about maternal dietary intake data during preconception and pregnancy
Vàzquez et al. 2019 [29]	Systenatic review and meta-analysis	756365 children	Range=11 months to 15 years				Routine prenatal supplements of folic acid were associated with significantly lower levels of ASD.	
Guo et al. 2019 [33]	Systematic review and meta-analysis	Observational studies (a total of 13 reports; 840,776 children and 7127 cases)					This study doesn't provide support for the association between maternal FA intake during the prenatal period and the reduced risk of ASD in children	Small number of studies in literature
Raghavan et al. 2020 [20]	A prospective cohort	92 ASD children	Mean Mothers age=29, 8±6, 2 years	475 neurotypical controls	Mean mothers age=28, 3±6,4 years	EMR using ICD-9 and ICD-10	Higher concentrations of cord UMFA, but not 5-methyl THF or total folate, were associated with a greater risk of ASD in Black children.	Diagnosis of ASD made on the basis of EMR. Study limited to a subset of children. Presence of possible confounders. UMFA not measured in maternal circulation. DHFR polymorphism is the only analysed
Tan et al. 2020 [32]	Retrospective	ASD children (N=416, M=333, F=83)	Mean age= 4,68±1,94	Typically developing children (N=201)	Mean age= 4,47±1,06 years	DSM-5	Children born by mothers without folic acid and micronutrient supplementation during pregnancy had more severe cognition and communication impairment, autistic behavior mannerism, delays in adoptive gross and gastrointestinal than children born by mothers who didn't use FA and supplementation	Disproportion between males and females
Santos et al. 2020 [35]	Cohort	4571 Brazil participants	Range=35-74 years	-	-		Not found significant associations between serum folate and cognitive performance in this large sample, which is characterized by a context of food fortification policies and a consequent low frequency of folate deficiency.	Very few participants had serum folate levels below the WHO cutoffs for folate deficiency. Not included red cell folate and homocysteine. Single determination of folate for each participants.

Egorova et al. 2020 [36]	Case-control group	100 women with ASD diagnosed offspring with 76 male children and 24 females	Median age of mothers=31 years Range=28-34 years	100 women whose offspring were typically developed with 78 male children and 22 females	Median=30 years Range=26-33 years	DSM-IV	High maternal folate status during early pregnancy may be associated with the occurrence of ASD in the offspring	Disproportion between children M/F ratio
Liu et al. 2022 [30]	Systematic review and meta-analysis	9795 ASD cases (10 studies and 23 sub-studies included)	-	-	-	-	Folic acid supplementation during early pregnancy was associated with a lower risk of offspring's ASD. The consumption of a daily amount of at least 400 µg folic acid from dietary sources and supplements, was associated with a reduced risk of offspring ASD. Critical effective maternal folic acid supplementation strategies may aid the reduction in the risk of offspring ASD.	Detailed information was acquired through questionnaires. Residual or unmeasured confounding factors are possible.

Abnormalities in folate patways in ASD and ADHD:

Authors and year	Study design	Sample				Diagnostic criteria	Results	Limits
		Patients		Control group				
		N (M/F)	Age±SD	N (M/F)	Age			
James et al. 2006 [38]	Retrospective	80 autistic children (M=89%, F= 11%)	Range: 3-14 years, Mean age=7,3±3,2 years	73 controls	Mean age=10,8±4,1 years	DSM-IV	Plasma methionine and the ratio of S-Adenosylmethionine (SAM) to S-Adenosylhomocysteine (SAH), were significantly decreased in ASD children relative to age-matched controls. Plasma levels of cysteine, glutathione, and the ratio of reduced to oxidized glutathione were decreased. Differences in allele frequency and/or significant gene–gene interactions were found for relevant genes encoding the reduced folate carrier (RFC 80G>A), transcobalaminII (TCN2776G>C), catechol-O-methyltransferase (COMT 472G>A), methylenetetrahydrofolate reductase (MTHFR 677C>T and 1298A>C), and glutathione-S-transferase (GST M1).	Disproportioned M/F ratio
Ramaekers et al. 2008 [41]	Retrospective	ASD patients (N=25, M=18, F=7)	Median age=6,88 years Range=2,8-12,3 years	25 controls (M=14, F=11)	Median age=6,76 years Range=3,3-11,4 years	DSM-5, Autism Diagnostic Observation Schedule (ADOS) in conjunction with the Autism Diagnostic Interview (ADI)	CSF 5MTHF was low in 23 out of 25 patients. The reduced CSF folate in 19 out of these 23 patients could be explained by serum FR autoantibodies blocking the folate binding site of the membrane-attached FR on the choroid epithelial cells. Oral folinic acid supplements led to normal CSF 5MTHF and partial or complete clinical recovery after 12 months.	Small sample size. Disproportion in M/F ratio in the first group
Zhang et al. 2018 [40]	Cohort	Han ASD Chinese population (N=201)		Healthy children (N=200)		Childhood Autism Rating Scale (CARS), patients with scores of <36 were classified as mild-to-moderate and 36 as severe.	Lack of association of all examined SNPs with childhood ASD and its severity.	Small sample size. Absence of M/F stratification
Zhou et al. 2018 [42]	Retrospective	ASD Children (N=40, M=32, F=8)	Mean age=3,225±1,476 years. Range=2-6 years	Typical development (TD) children (N=40, M=32, F=10)	Mean age=4,309±1,506 years. Range=2-6 years	DSM-5	Serum FRAA are more prevalent in children with ASD than TD. Children with ASD may have defects in folic acid absorption.	Small sample size. Disproportioned M/F ratio in both ASD and controls.
Zou et al. 2019 [43]	Retrospective	ASD people (N=89, M=78, F=11)	Mean age=6,68±2,92 years	Controls (N=89, M=78, F=11)	Mean age=6,71±2,95 years	DSM-5	Folate-related metabolism contributes to predisposition of ASD. Folate-related metabolism biomarker could be useful both for detection of ASD individuals from controls both for early ASD diagnosis	Disproportion between males and females in ASD people group and in control one.

Therapeutic value of folate supplementation in ASD and ADHD:

Authors and year	Study design	Sample				Diagnostic criteria	Results	Limitations
		Patients		Control group				
		N (M/F)	Age±SD	N (M/F)	Age			
Gatica-Domínguez et al. 2018 [59]	Cross-sectional	229 children (55% male, 45% female) and their mothers	Children: 24 months and 32 months. Mothers: 22,2±4,3 years			Non autistic children	Dietary folate intake in early childhood may be beneficial for the mental development of children	Not significant results. It is possible that the reported associations are conservative estimate due to random measurement error inherent to the food frequency questionnaire used to estimate dietary folate and vitamin B12
Renard et al. 2020 [60]	Randomized, placebo-controlled	19 children receiving placebo or folinic acid	-	19 children receiving placebo or folinic acid	-	Autism Diagnostic Observation Schedule (ADOS)	The global ADOS score and social interaction and communication sub scores were significantly improved at week 12 compared to baseline in the folinic acid group but not in the placebo group. A greater change of ADOS global score was observed in the folinic acid group compared to the placebo group. No serious adverse events were observed.	Small sample size. Absence of stratification for M/F ratio and for age
Batebi et al. 2020 [61]	Double-blind, placebo-controlled, randomized	ASD children receiving folinic acid (N=28, M=16, F=12)	Mean age=8,36±1,81 years	ASD children receiving placebo (N=27, M=19, F=8)	Mean age= 7,82±1,84 years	DSM-5	Folinic acid dosage was 2 mg/kg up to 50 mg per day for the entire course of the study. The repeated measures analysis showed significant effect for time × treatment interaction on inappropriate speech, stereotypic behavior, and hyperactivity noncompliance subscale scores. In contrast, no significant effect for time × treatment interaction was found on lethargy/social withdrawal and irritability subscale scores. The study provided preliminary evidence suggesting that folinic acid could be recommended as a beneficial complementary supplement for alleviating speech and behavioral symptoms in children with ASD.	Small sample size, disproportioned M/F ratio in ASD group receiving placebo
Surman et al. 2019 [58]	Randomized, double-blind, placebo-controlled	ADHD adults receiving L-Methylfolate (N=22, M=8, F=14)	Mean age= 41,3±11,4 years	ADHD adults receiving placebo (N=19, M=7,F=12)	Mean age= 37,7±8,9 years	DSM-IV	Methylfolate was well tolerated, with no significant effect over placebo except improvement from abnormal measures on the mean adaptive dimension of the Adult Self Report (ASR) scale. Methylphenidate dosing was significantly higher in individuals on L-methylfolate over time.	Limited ability to predict value of biomarkers. Small sample size.

FA and OCD:

Authors and year	Study design	Sample				Diagnostic criteria	Results	Limitations
		Patients		Control group				
		N (M/F)	Age±SD	N (M/F)	Age			
Atmaca et al.2005 [63]	Placebo controlled study	OCD patients (N=23, M=8, F=15)	Mean age= 29, 1±6, 3 years Range = 18-44 years.	Healthy individuals (N=23, M=10, F=13)	Mean age= 27, 2±5, 4 years. Range= 21-44 yeras	OCD was diagnosed through DSM-IV criteria. severity was determined through Y-BOCS scale	A group of patients with OCD might have folate deficiency, higher homocysteine levels and probable impaired metylation and monoamine metabolism	Small sample size, disproportioned M/F ratio in the patient group.
Dar et al. 2021 [64]	The study consisted of two phases: a 2-week open-label prospective phase to confirm resistance to SRIs and the second 6-week open-label addition phase for non- responders of the first phase	Patients (N=115, 60 of them were considered resistant and entered in the second phase of the study. At the baseline F=60, M=55)	Mean age of females=29,2±10,4 years	-	-	DSM-5 criteria were used for OCD diagnosis. Y-BOCS and CGI scales were used for disease severity assessment	Methylfolate wasn't effective in treatment of resistant OCD people	Long-term tolerability of adding antipsychotics to SRIs in patients with resistant OCD cannot be commented upon while the need of giving antipsychotics for longer a duration is there since high chances of relapse are present on discontinuation after a response is seen. None of patients had poor insight of OCD, so it wasn't possible to comment the effect of antipsychotics for insight.

Tural et al. 2018 [65]	Double blind, placebo-controlled	Patients receiving fluoxetine and folic acid (N=18, M=8, F=10)	Mean age= 31,06±10,18 years	Patients receiving fluoxetine and placebo (N=18, M=6, F=12)	Mean age= 33,44±11,62 years	OCD diagnosis was assessed through DSM-IV criteria. (Yale Brown Obsession Compulsion Scale) Y-BOCS was used to detect severity of symptoms. The Hamilton Anxiety Rating Scale (HAM-A) for anxiety. Hamilton Depression Rating Scale for depression. The Clinical Global Impression (CGI) for general improvement or deterioration	It may be assumed that there is no beneficial effect of folic acid addition to fluoxetine in the treatment of OCD	The study has a relative small sample, not implemented a dietary restriction, and not used methylfolate the active metabolite of folate
Yan et al. 2022 [66]	Systematic reviews and meta-analysis of case-controls studies	Experimental group (N=172 cases)	'	Control group (N=137 cases)	'	Eight databases were used (e., PubMed, Embase, Web of Science, the Cochrane Library, China Biology Medicine disc, China National Knowledge Infrastructure, Wanfang Database, China Science and Technology Journal Database), and the retrieval time was up to March 2021)	The content of folate in the OCD group was not significantly different from that in the control group	Some articles' measures data aren't distributed normally and weren't reported in the form of median and quartile. Only English and Chinese language reports have been searched. Small sample size. The results were based on unadjusted estimates, more accurate outcomes would be achieved due to adjustments for other confounding factors. Some factors hadn't been taken consider into study (e.g., renal function) of participants. One set of trails from the last century hasn't mentioned the details about the diagnosis and detection methods. Most of the participants in 1 study were women. There are also some differences in the laboratory examination methods for each index in each group due to time.

Discussion

The present review showed a potential benefit of folates supplementation in neuropsychiatric diseases. Globally, a certain number of studies reported a protective role of folate prenatal regular intake from ASD risk in the offspring [18-26]. Intriguingly, by analysing receptorial profile of some ASD children, endogenous factors of resistence to folate supplementation were detected [54,55], whereas in other ASD individuals beneficial effects of folate supplementation on different aspect of autistic disease, such as stereotyped behaviors and social communication, are largely supported [58,59,61]. We also decided to include in our work the role of folate supplementation in cognitive disturbances [9,17]. Studies made on animal models reported how genetic and dietary folate metabolic disorders increase risk for cognitive decline [9,11]. Meanwhile, a beneficial role of folic acid in alleviating telomere attrition in cells and in lowering levels of reactive oxygen species [15] was higlighted, while works carried out in humans pointed out that folate deficiency may induce a cognitive impairment via decrease of Hcy [68] and blood Aβ-related biomarkers [17]. Indeed, some limitations of the published studies should be acknowledged. Some of the significant findings of folic acid benefits on neuropsychitric diseases were carried out in animal models. Moreover, a great number of studies focused on specific genotypes or polymorphism, thus limiting the extension of these findings to general population, who is not routinely screened for these variants. Sometimes, other intermediate molecules, such as homocysteine, mediated the effects of folate. As a result, that of folic acid was often an indirect effect.

Conclusion

Taken together, the findings derived from the present review suggest into that folic acid supplementation may be a safe and advantageous for the prevention and improvement of different neuropsychiatric disorder. However, the exact role of folic supplementation for prevention of these diseases is still rather unclear and needs to be deeply investigated

Declaration of interest: None

References

1. Reynolds E. Vitamin B12, folic acid, and the nervous system. Lancet Neurol. 2006; 5(11): 949-60. doi: 10.1016/S1474-4422(06)70598-1. PMID: 17052662.

2. MS Field and PJ Stover, 'Safety of folic acid', Ann. NY Acad. Sci. 2018; 1414(1): 59-71. doi: 10.1111/nyas.13499.

3. EFG Naninck, PC Stijger, and EM Brouwer-Brolsma, 'The Importance of Maternal Folate Status for Brain Development and Function of Offspring', Adv. Nutr. 2019; 10(3): 502-519. doi: 10.1093/advances/nmy120.

4. E Morris et al., 'A prospective study to explore the relationship between MTHFR C677T genotype, physiological folate levels, and postpartum psychopathology in at-risk women', PLoS One. 2020; 15(12): 1-16. doi: 10.1371/journal.pone.0243936.

5. M Masingue et al., 'Cerebral folate deficiency in adults: A heterogeneous potentially treatable condition', J. Neurol. 2019; 396(2018): 112-118. doi: 10.1016/j.jns.2018.11.014.

6. W Zheng et al., 'Adjunctive folate for major mental disorders: A systematic review', J. Affect. Disord. 2020; 267(2019): 123-130.

doi: 10.1016/j.jad.2020.01.096.

7. NSK Lam et al., 'The potential use of folate and its derivatives in treating psychiatric disorders: A systematic review', Biomed. Pharmacother. 2022; 146: 112541. doi: 10.1016/j.biopha.2021.112541.

8. A Hoffman et al., 'Methylenetetrahydrofolate Reductase Deficiency Deregulates Regional Brain Amyloid-β Protein Precursor Expression and Phosphorylation Levels', J. Alzheimer's Dis. 2018; 64(1): 223-237. doi: 10.3233/JAD-180032.

9. RH Bahous et al., 'Early Manifestations of Brain Aging in Mice Due to Low Dietary Folate and Mild MTHFR Deficiency', Mol. Neurobiol. 2019; 56(6): 4175-4191. doi: 10.1007/s12035-018-1375-3.

10. DMA O'Connor et al., 'Plasma concentrations of vitamin B 12 and folate and global cognitive function in an older population: Cross-sectional findings from the Irish Longitudinal Study on Ageing (TILDA)', Br. J. Nutr. 2020; 124(6): 602-610. doi: 10.1017/S0007114520001427.

11. M Zhao et al., 'Chronic folate deficiency induces glucose and lipid metabolism disorders and subsequent cognitive dysfunction in mice', PLoS One. 2018; 13(8): 1-16. doi: 10.1371/journal.pone.0202910.

12. X Lv et al., 'Association of Folate Metabolites and Mitochondrial Function in Peripheral Blood Cells in Alzheimer's Disease: A Matched Case-Control Study', J. Alzheimer's Dis. 2019; 70(4): 1133-1142. doi: 10.3233/JAD-190477.

13. B Wang, NR Sahyoun, K Shao, E Dutta, and J Clarke, 'Assessment of the Dose–Response Relationship Between Folate Exposure and Cognitive Impairment: Synthesizing Data from Documented Studies', Risk Anal. 2020; 40(2): 276-293. doi: 10.1111/risa.13404.

14. A. Enderami, M. Zarghami, and H. Darvishi-Khezri, 'The effects and potential mechanisms of folic acid on cognitive function: a comprehensive review', Neurol. 2018; 39(10): 1667-1675. doi: 10.1007/s10072-018-3473-4.

15. X. Lv et al., 'Folic acid delays age-related cognitive decline in senescence-accelerated mouse prone 8: Alleviating telomere attrition as a potential mechanism', Aging (Albany. NY). 2019; 11(22): 10356-10373. doi: 10.18632/aging.102461.

16. R Lu et al., 'Protocol for thiamine and folic acid in the treatment of cognitive impairment in maintenance haemodialysis patients: A prospective, randomised, placebo-controlled, double-blind, multicentre study', BMJ Open. 2021; 11(12): 1-7. doi: 10.1136/bmjopen-2021-050605.

17. M Li et al. 'Effect of folic acid combined with docosahexaenoic acid intervention on mild cognitive impairment in elderly: a randomized double-blind, placebo-controlled trial', Eur. J. Nutr. 2021; 60(4): 1795-1808. doi: 10.1007/s00394-020-02373-3.

18. S. Z. Levine et al., 'Association of maternal use of folic acid and multivitamin supplements in the periods before and during pregnancy with the risk of autism spectrum disorder in offspring', JAMA Psychiatry. 2018; 75(2): 176-184. doi: 10.1001/jamapsychiatry.2017.4050.

19. S Degroote, D Hunting, and L Takser, 'Periconceptional folate deficiency leads to autism-like traits in Wistar rat offspring', Neurotoxicol. 2018; 66: 132-138. doi: 10.1016/j.ntt.2017.12.008.

20. RJ Schmidt, AM Iosif, E Guerrero Angel, and S Ozonoff, 'Association of Maternal Prenatal Vitamin Use with Risk for Autism Spectrum Disorder Recurrence in Young Siblings', JAMA Psychiatry. 2019; 8638. doi: 10.1001/jamapsychiatry.2018.3901.

21. RJ Schmidt et al., 'Prenatal vitamins, one-carbon metabolism gene variants, and risk for Autism', Epidemiology. 2011; 22(4): 476-485. doi: 10.1097/EDE.0b013e31821d0e30.

22. M Wang, K Li, D Zhao, and L Li, 'The association between maternal use of folic acid supplements during pregnancy and risk of autism spectrum disorders in children: A meta-analysis', Mol. 2017; 8(1): 4-7. doi: 10.1186/s13229-017-0170-8.

23. RJ Schmidt et al., 'Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study', Am. J. Clin. 2012; 96(1): 80-89. doi: 10.3945/ajcn.110.004416.

24. X Liu, M Zou, C Sun, L Wu, and WX Chen, 'Prenatal Folic Acid Supplements and Offspring's Autism Spectrum Disorder: A Meta-analysis and Meta-regression', J. Autism Dev. 2022; 52(2): 522-539. doi: 10.1007/s10803-021-04951-8.

25. Y Di et al., 'Maternal folic acid supplementation prevents autistic behaviors in a rat model induced by prenatal exposure to valproic acid', Food Funct. 2021; 12(10): 4544-4555. doi: 10.1039/d0fo02926b.

26. M Tan et al., 'Maternal folic acid and micronutrient supplementation is associated with vitamin levels and symptoms in children with autism spectrum disorders', Reprod. 2020; 91(2019): 109-115. doi: 10.1016/j.reprotox.2019.11.009.

27. R Raghavan et al., 'Maternal Multivitamin Intake, Plasma Folate and Vitamin B12 Levels and Autism Spectrum Disorder Risk in Offspring', Paediatr. Perinat. 2018; 32(1): 100-111. doi: 10.1111/ppe.12414.

28. R Raghavan et al., 'A prospective birth cohort study on cord blood folate subtypes and risk of autism spectrum disorder', Am. J Clin. Nutr. 2020; 112(5): 1304-1317. doi: 10.1093/ajcn/nqaa208.

29. J Virk, Z Liew, J Olsen, EA Nohr, JM Catov, and B Ritz, 'Preconceptional and prenatal supplementary folic acid and multivitamin intake and autism spectrum disorders', Autism. 2016; 20(6): 710-718. doi: 10.1177/1362361315604076.

30. EA Devilbiss et al., 'Antenatal nutritional supplementation and autism spectrum disorders in the Stockholm youth cohort: Population based cohort study', BMJ. 2017; 359: 1-9. doi: 10.1136/bmj. j4273.

31. L Iglesias Vázquez, J Canals, and V Arija, 'Review and meta-analysis found that prenatal folic acid was associated with a 58% reduction in autism but had no effect on mental and motor development', Acta Paediatr. Int. J. Paediatr. 2019; 108(4): 600-610. doi: 10.1111/apa.14657.

32. BQ Guo, H Bin Li, DS Zhai, and S Bin Ding, 'Association of maternal prenatal folic acid intake with subsequent risk of autism spectrum disorder in children: A systematic review and meta-analysis', Prog. Neuro-Psychopharmacology Biol. Psychiatry, 2019; 94: 109650. doi: 10.1016/j.pnpbp.2019.109650.

33. M Strøm, C Granström, K Lyall, A Ascherio, and SF.Olsen, 'Research Letter: Folic acid supplementation and intake of folate in pregnancy in relation to offspring risk of autism spectrum disorder', Psychol. 2018; 48(6): 1048-1054. doi: 10.1017/S0033291717002410.

34. I. de S. Santos et al., 'Serum folate levels and cognitive performance in the ELSA-Brasil baseline assessment', Arq. Neuropsiquiatr., vol. 78, no. 11, pp. 672–680, 2020, doi: 10.1590/0004-282X20200074.

35. O Egorova et al., 'Maternal blood folate status during early pregnancy and occurrence of autism spectrum disorder in offspring:

A study of 62 serum biomarkers', Mol. Autism. 2020; 11(1): 1-15. doi: 10.1186/s13229-020-0315-z.

36. G Koren, SS Moser, 'Does high-dose gestational folic acid increase the risk for autism? The birth order hypothesis', Med. Hypotheses. 2019; 132: 109350. doi: 10.1016/j.mehy.2019.109350.

37. SJ James et al., 'Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism', Am. J. Med. Genet. Part B Neuropsychiatr. Genet. 2006; 141(8): 947-956. doi: 10.1002/ajmg.b.30366.

38. Z Zhang, L Yu, S Li, and J Liu, 'Association study of polymorphisms in genes relevant to vitamin B12 and folate metabolism with childhood autism spectrum disorder in a han chinese population', Med. Sci. 2018; 24: 370-376. doi: 10.12659/MSM.905567.

39. M Zou et al., 'Fisher discriminant analysis for classification of autism spectrum disorders based on folate-related metabolism markers', J. Nutr. Biochem. 2019; 64: 25-31. doi: 10.1016/j.jnutbio.2018.09.023.

40. C Lintas, 'Linking genetics to epigenetics: The role of folate and folate-related pathways in neurodevelopmental disorders', Clin. Genet. 2019; 95(2): 241-252. doi: 10.1111/cge.13421.

41. W Schlotz, A Jones, DIW Phillips, CR Gale, SM Robinson, and KM Godfrey, 'Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring', J. Child Psychol. Psychiatry Allied Discip. 2010; 51(5): 594-602. doi: 10.1111/j.1469-7610.2009.02182.x.

42. EA Devilbiss, RM Gardner, CJ Newschaffer, and B. K. Lee, 'Maternal folate status as a risk factor for autism spectrum disorders: A review of existing evidence', BrJ Nutr. 2015; 114(5): 663-672. doi: 10.1017/S0007114515002470.

43. SP Paşca et al., 'One carbon metabolism disturbances and the C677T MTHFR gene polymorphism in children with autism spectrum disorders', J Cell. Mol. 2009; 13(10): 4229-4238. doi: 10.1111/j.1582-4934.2008.00463.x.

44. NS Mohammad, JMN Jain, KP Chintakindi, RP Singh, U Naik, and RRD Akella, 'Aberrations in folate metabolic pathway and altered susceptibility to autism', Psychiatr. 2009; 19(4): 171-176. doi: 10.1097/YPG.0b013e32832cebd2.

45. X Liu et al., 'Population- and family-based studies associate the MTHFR gene with idiopathic autism in simplex families', J. Autism Dev. 2011; 41(7): 938-944. doi: 10.1007/s10803-010-1120-x.

46. V Rai, 'Association of methylenetetrahydrofolate reductase (MTHFR) gene C677T polymorphism with autism: evidence of genetic susceptibility', Metab. Brain Dis. 2016; 31(4): 727-735. doi: 10.1007/s11011-016-9815-0.

47. F El-baz, M Abd El-Aal, T Moustafa Kamal, A Abdrabou Sadek, and AA Othman, 'Study of the C677T and 1298AC polymorphic genotypes of MTHFR Gene in autism spectrum disorder', Electron. Physician. 2017; 9(9): 528-5293. doi: 10.19082/5287.

48. M Adams, M Lucock, J Stuart, S Fardell, K Baker, and X Ng, 'Preliminary evidence for involvement of the folate gene polymorphism 19 bp deletion-DHFR in occurrence of autism', Neurosci. Lett. 2007; 422(1): 24-29. doi: 10.1016/j.neulet.2007.05.025.

49. PAC Dos Santos, D Longo, APC Brandalize, and L Schüler-Faccini, 'MTHFR C677T is not a risk factor for autism spectrum disorders in South Brazil', Psychiatr. Genet. 2010; 20(4): 187-189. doi: 10.1097/YPG.0b013e32833a2220.

50. EF Sener, DB Oztop, and Y Ozkul, 'MTHFR gene C677T polymorphism in autism spectrum disorders', Genet. Res. Int. 2014. doi: 10.1155/2014/698574.

51. T Saha, S Dutta, U Rajamma, S Sinha, and K Mukhopadhyay, 'A pilot study on the contribution of folate gene variants in the cognitive function of ADHD probands', Neurochem. Res. 2014; 39(11): 2058-2067. doi: 10.1007/s11064-014-1393-0.

52. N Al Mahmuda et al., 'A study of single nucleotide polymorphisms of the SLC19A1/RFC1 gene in subjects with autism spectrum disorder', Int. J. Mol. 2016; 17(5): 1-9. doi: 10.3390/ijms17050772.

53. T Saha et al., 'Genetic variants of the folate metabolic system and mild hyperhomocysteinemia may affect ADHD associated behavioral problems', Prog. Neuro-Psychopharmacology Biol. Psychiatry. 2018; 84: 1-10. doi: 10.1016/j.pnpbp.2018.01.016.

54. VT Ramaekers, N Blau, JM Sequeira, MC Nassogne, and EV Quadros, 'Folate receptor autoimmunity and cerebral folate deficiency in low-functioning autism with neurological deficits', Neuropediatrics. 2007; 38(6): 276-281. doi: 10.1055/s-2008-1065354.

55. J Zhou et al., 'High prevalence of serum folate receptor autoantibodies in children with autism spectrum disorders', Biomarkers. 2018; 23(7): 622-624. doi: 10.1080/1354750X.2018.1458152.

56. JL Roffman, 'Neuroprotective effects of prenatal folic acid supplementation: Why timing matters', JAMA Psychiatry. 2018; 75(7): 747-748. doi: 10.1001/jamapsychiatry.2018.0378.

57. SB Zablow, 'Folate Deficiency Based Autism as an Orofacial Clefts/Neural Tube Defect Spectrum Disorder', J Am. Acad. Child Adolesc. Psychiatry. 2019; 58(11): 1126-1127. doi: 10.1016/j.jaac.2019.02.023.

58. G Gatica-Domínguez, SJ Rothenberg, L Torres-Sánchez, M de L Schnaas, RJ Schmidt, and L. López-Carrillo, 'Child dietary intake of folate and vitamin B12 and their neurodevelopment at 24 and 30 months of age', Salud Publica Mex., vol. 60, no. 4, pp. 388–394, 2018, doi: 10.21149/8581.

59. E Renard, B Leheup, RM Guéant-Rodriguez, A Oussalah, EV Quadros, and JL Guéant, 'Folinic acid improves the score of Autism in the EFFET placebo-controlled randomized trial', 2020; 173: 57-61. doi: 10.1016/j.biochi.2020.04.019.

60. Q Zhang et al., 'Folic acid improves abnormal behavior via mitigation of oxidative stress, inflammation, and ferroptosis in the BTBR T+ tf/J mouse model of autism', J. Nutr. Biochem. 2019; 71: 98-109. doi: 10.1016/j.jnutbio.2019.05.002.

61. N. Batebi, H. S. Moghaddam, A. Hasanzadeh, Y. Fakour, M. R. Mohammadi, and S. Akhondzadeh, 'Folinic Acid as Adjunctive Therapy in Treatment of Inappropriate Speech in Children with Autism: A Double-Blind and Placebo-Controlled Randomized Trial', Child Psychiatry Hum. 2021; 52(5): 928-938. doi: 10.1007/s10578-020-01072-8.

62. C Surman et al., 'Does l-Methylfolate Supplement Methylphenidate Pharmacotherapy in Attention-Deficit/Hyperactivity Disorder? Evidence of Lack of Benefit from a Double-Blind, Placebo-Controlled, Randomized Clinical Trial', J. Clin. Psychopharmacol. 2019; 39(1): 28-38. doi: 10.1097/JCP.0000000000000990.

63. M Atmaca, E Tezcan, M Kuloglu, O Kirtas, and B Ustundag, 'Serum folate and homocysteine levels in patients with obsessive-compulsive disorder', Psychiatry Clin. Neurosci. 2005; 59(5): 616-620. doi: 10.1111/j.1440-1819.2005.01425.x.

64. SA Dar, RA Wani, and I Haq, 'A Comparative Study of Aripiprazole, Olanzapine, and L-Methylfolate Augmentation in Treatment Resistant Obsessive-Compulsive Disorder', Psychiatr. 2021; 92(4): 1413-1424. doi: 10.1007/s11126-021-09892-0.

65. Ü Tural et al., 'Double blind controlled study of adding folic acid to fluoxetine in the treatment of OCD', Psychiatr. Danub. 2019;

31(1): 69-77. doi: 10.24869/psyd.2019.69.

66. S Yan, H Liu, Y Yu, N Han, and W Du, 'Changes of Serum Homocysteine and Vitamin B12, but Not Folate Are Correlated With Obsessive-Compulsive Disorder: A Systematic Review and Meta-Analysis of Case-Control Studies', Front. Psychiatry. 2022; 13. doi: 10.3389/fpsyt.2022.754165.

67. Miller AL. The methionine-homocysteine cycle and its effects on cognitive diseases. Altern Med Rev. 2003; 8(1): 7-19. PMID: 12611557.

68. Kruman II, Culmsee C, Chan SL, Kruman Y, Guo Z, Penix L, Mattson MP. Homocysteine elicits a DNA damage response in neurons that promotes apoptosis and hypersensitivity to excitotoxicity. J Neurosci. 2000; 20(18): 6920-6. doi: 10.1523/JNEUROSCI.20-18-06920.2000. PMID: 10995836; PMCID: PMC6772815.