Homocysteine and Psychiatric Disorders

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Abstract
Psychiatric disorders are highly prevalent all over the world with a great impact on public health. Altered homocysteine metabolism is implicated in the pathogenesis of many of these disorders, as it can interfere in normal methylation of subcellular components, promote neuroexcitotoxicity, and induce oxidative stress and inflammation. There are cumulative data implicating these mechanisms in the development of autism, schizophrenia, depression, bipolar disorder, and Alzheimer disease. Altered homocysteine metabolism is multifactorial in its origin. On one hand, genetic factors act as predisposing factors through brain development and function, and on the other hand, environmental factors give the opportunity for nutritional interventions improving metabolic status and possibly also clinical parameters. This article provides a review on the association of 1-carbon metabolism and autism, schizophrenia, depression, bipolar disorder, and dementia and goes through studies on the role of different cofactors and metabolites involved in this pathway.

Keywords
homocysteine, autism, schizophrenia, depression, bipolar disorder, Alzheimer disease

Introduction
The importance of mental diseases in global health is unquestionable. A meta-analysis of 85 studies from 39 countries between 1983 and 2013 revealed a 29.2% prevalence of common mental disorders in the adult population across lifetime and 10% to 20% in children and adolescents suffering from mental disorders worldwide.1,2

Homocysteine (Hcy) and correlated folate metabolic pathways have received considerable attention in recent decades regarding its association with psychiatric disorders. Elevated level of Hcy is considered a well-established risk factor for Alzheimer disease (AD),3,4 and alterations in this pathway have been also associated with mental disorders such as autism, schizophrenia, depression, and bipolar disorder.5-8

Homocysteine is formed from the metabolic demethylation of dietary methionine. In this pathway, S-adenosylmethionine (SAM) is synthesized and can participate in a large number of methylation reactions, including DNA, RNA, phospholipids, and the synthesis of neurotransmitters.9 After transmethylation reactions, SAM is converted into S-adenosylhomocysteine (SAH) and then hydrolyzed to adenosine and Hcy. Homocysteine can follow 2 paths: to enter the transsulfuration route and produce cysteine, which may be further used in glutathione (GSH) synthesis, or to be remethylated to methionine by ubiquitously distributed methionine synthase (MS), a cobalamin-dependent enzyme. During remethylation dependent of MS, Hcy receives the methyl group from 5-methyltetrahydrofolate (5-MTHF), the product of methylenetetrahydrofolate reductase (MTHFR) reaction.10 In the liver and kidney of some species, betaine–homocysteine methyltransferase uses betaine as a methyl donor to convert Hcy to methionine.11

Environmental factors such as folate and cobalamin deficiencies are associated with high levels of Hcy, as well as mutations and polymorphisms in key enzymes in the metabolic pathway, such as MS, MTHFR, and cystathionine β-synthase (CBS).10,12 Furthermore, the reduced folate carrier 1, involved in the 5-MTHF cell influx, is associated with low folate level, changes in DNA methylation pattern, and DNA repair capacity.13

Beyond altered methylation of cellular components, Hcy and psychopathology may be connected by other

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mechanisms. Literature data strongly suggest that Hcy has neurotoxic properties such as activation of N-methyl-D-aspartate receptor subtype, which activation leads to neuronal cell death via Ca\(^{2+}\) cell influx and resultant phosphorylation of extracellular signal-regulated kinase and mammalian family of mitogen-activated protein kinase.\(^{14}\) Additionally, elevated level of Hcy increases oxidative stress and is closely related to accumulation of asymmetric dimethyl arginine, an endogenous nitric oxide synthase inhibitor.\(^{15}\) Nitric oxide is an important mediator of many physiological phenomena, such as blood vessel relaxation, neurotransmission, and pathogen suppression.\(^{16}\) Additionally, Hcy has potential mechanisms of protein modification, the N-homocysteinylation, that may induce protein and cell damage, activation of adaptive immune response, and synthesis of autoantibodies against N-Hcy-proteins.\(^{17}\)

**Autism**

Autism spectrum disorders are a heterogeneous group of neurodevelopmental disorders manifested before 3 years of age, compromising social and language skills, associated with repetitive behaviors, restricted interests, and gastrointestinal and immunologic comorbidities. Its actual incidence reaches 1 in every 68 children in the United States, with a 4:1 male to female prevalence.\(^{18,19}\)

Although autistic behavior can be present in many chromosomal, genomic (microdeletions, insertions, and imprinting), monogenic, dysmorphic, and metabolic syndromes, most of the cases are multifactorial in origin, with some susceptibility loci already described.\(^{20-22}\) In such scenario, brain dysfunction can be in some extent related to hypomethylation of subcellular components and to damage due to oxidative stress, both pathogenic mechanisms implicating altered Hcy metabolism as an associated factor, as mentioned before.

Indeed, altered remethylation of Hcy to methionine and transulfuration of Hcy to cysteine were described in children with autism by James et al in 2004.\(^{5}\) The metabolic phenotype denoted decreased plasma concentrations of methionine, SAM, Hcy, cysteine, and total GSH and increased concentrations of SAH, adenosine, and oxidized GSH as compared to control children.\(^{5}\)

Opposite results were reported by Tu et al\(^{23}\) in China and by Ali et al\(^{24}\) in Oman, where children with autism presented increased plasma Hcy levels when compared to an age- and gender-matched control group. In these studies, reduced plasma folate concentration has been demonstrated in children with autism, and in the study by James et al,\(^{5}\) the cases studied were receiving folinic acid and vitamin B\(_{12}\) supplementation, which may explain the different results. Ali et al\(^{24}\) also found reduced plasma vitamin B\(_{12}\) concentration in cases as compared to controls. Increased urine Hcy concentration was also described for nonsupplemented children with autism in Poland.\(^{25}\)

Studying Hcy metabolism in different autistic spectrum disorder subtypes, Pas¸ca et al demonstrated an impairment of this metabolic pathway across nonspecified pervasive disorders and prototypic autistic disorder with increased metabolic derangement in more severe cases. Mild cases presented only remethylation impairment (decreased methionine and z-aminobutyric acid plasma concentrations), and the most severe cases presented transulfuration disturbances (decreased methionine, z-aminobutyric acid, cysteine, and total GSH plasma concentrations). Interestingly, no metabolic changes were observed in Asperger syndrome,\(^{26}\) a specific autistic syndrome with a less severe impairment of intelligence and linguistic skills.\(^{27}\)

Nutritional factors may be implicated in altered Hcy metabolism in autism, as many children may experience food refusal and selectivity, with varied protein and vitamins intake,\(^{28-30}\) but genetic polymorphisms in genes involved in this metabolic pathway can also be important. James et al\(^{31}\) found a functional polymorphism (A80G) in reduced folate carrier able to increase 40% the risk of autism in the offspring of heterozygous (AG) and homozygous mothers (GG), independent of the child genotype.\(^{31}\) Methylene tetrahydrofolate C677T or A1298C, MS reductase A66G, and transcobalamin II C776G polymorphisms were also studied and inconsistently associated with autism risk.\(^{26,31-34}\)

Vitamin supplementation has been recommended for treating autistic spectrum disorders based both on the altered metabolic profile of these patients and also in studies that demonstrated attenuation of these metabolic alterations in vitamin supplemented patients. In a pilot study, James et al\(^{5}\) observed increased methionine and improved SAM:SAH ratio after a month of methyl cobalamin supplementation. The same group demonstrated improved antioxidant capacity in a 3-month folic acid and methyl cobalamin supplementation open-label trial.\(^{35}\) Urinary Hcy excretion was also reduced after 3-month pyridoxine and cobalamin supplementation and further reduced when folic acid was included in the protocol for the same period.

Furthermore, Hendren et al\(^{37}\) reported improved clinical status in children with autism after an 8-week randomized, placebo-controlled trial of methyl cobalamin supplementation, with improved Clinical Global Impressions–Improvement score and improved social motivation in Social Responsiveness Scale.

**Schizophrenia**

Schizophrenia is a chronic, frequently disabling multifactorial mental disorder that affects 1% of the global population.\(^{38}\) Clinically, it is recognized by the presence of positive symptoms (hallucinations, paranoia, and delusions), negative symptoms (reduced motivation, impoverished speech, blunted affect, and social withdrawal), and cognitive impairment.\(^{39,40}\)

Regland et al\(^{41}\) were the first to associate increased blood Hcy concentrations with schizophrenia in 1995. The association was latter subject of a meta-analysis in 2006 by Muntjewerff et al\(^{42}\) who collected data from 8 case–control studies and demonstrated a 70% increase in the risk of schizophrenia for every 5 mM increase in Hcy concentration and many other studies since then have corroborated this hypothesis,\(^{43-52}\) although negative results are also present in the literature.\(^{53}\)
Genetic factors associated with Hcy metabolism are also associated with schizophrenia risk. Muntjewerff meta-analysis implicated C677T MTHFR polymorphism as a genetic risk factor for the disease,42 as recently corroborated in another meta-analysis by Nishi et al47 according to gender analysis and by Yadav et al54 in African, Asian, and Caucasian subgroup population. MS A2756G, trifunctional folate enzyme 5,10-methylenetetrahydrofolate dehydrogenase, 5,10-methylenetetrahydrofolate cyclohydrolase, and 10-formyltetrahydrofolate synthetase G1958A, reduced folate carrier A80G, MTHFR A1298C, MS reductase A203G, and folate hydrolase T484C polymorphisms were also associated with increased schizophrenia risk.55-57 CBS 844ins68 polymorphism was evaluated in 1 study and demonstrated to be a protective factor.58

Nutritional factors can also play a role in this association. Low folate concentrations are associated with increased Hcy levels and schizophrenia.48,50 Low betaine plasma concentrations have also been demonstrated in patients with first-episode schizophrenia and can influence Hcy metabolism in these individuals.59

The link between Hcy metabolism and schizophrenia can be related to fetal hypoxia, altered DNA methylation, and partial antagonistic effect on N-Methyl-D-aspartate (NMDA) glutamatergic neurons.60 In fetal life, maternal hyperhomocysteinemia (hHcy) can be linked to schizophrenia risk by reducing placental blood supply and inducing fetal hypoxemia. Brown et al61 found increased third-trimester Hcy in case mothers as compared to controls, but no differences in first and second trimesters of pregnancy.

Kinoshita et al62 found hHcy to be correlated with altered DNA methylation in neutrophils of patients with chronic schizophrenia under multiple antipsychotic treatments: 15.8% of these changes were located in cytosine-phosphate-guanine (CpG) islands and 34.9% of which located in promoter regions, including promoter regions of genes already associated with schizophrenia, such as solute carrier family 18 member A2, G protein subunit alpha L, potassium voltage-gated channel subfamily, and netrin G2.

Few studies on Hcy-lowering strategies have been performed in patients with schizophrenia.50,63 Roffman et al64 reported a multicenter randomized controlled trial in which a 16-week folate and vitamin B12 supplementation in chronic patients resulted in improved negative symptoms, evaluated by the Scale for Assessment of Negative Symptoms and the Positive and Negative Syndrome Scale.

Bipolar Disorder

Bipolar disorder, also known as an idiopathic mood disorder, is characterized by episodes of depression and mania and affects approximately 2% to 4% of the global population.76,77 High levels of Hcy may potentially be toxic to dopaminergic systems, and dysfunction of dopamine neurons has been associated with bipolar disorder.78,79 Moreover, increased concentration of Hcy and decreased concentration of folate and vitamin B12 levels are observed in patients with bipolar depression in both acute episode and euthymic phase8,80; poor appetite observed in these patients could be associated with decreased intake of B vitamins and consequent hHcy. Despite this, the mechanisms underlying hHcy in bipolar disorder are not fully understood and seem to involve not only nutritional intake but also reduced glomerular filtration and mood-stabilizing medications use.72,81,82

Valproic acid and lamotrigine used for bipolar disorder treatment can interfere with folate and Hcy metabolism through methionine adenosyltransferase and dihydrofolate reductase inhibition.83,84 However, evaluations of Hcy levels in patients with epilepsy treated with mood stabilizers do not present consistent results. A study published by Gidal et al85 did not show increased Hcy levels in patients with epilepsy treated with sodium valproate and lamotrigine, but the meta-analysis published by Ni et al86 associated sodium valproate monotherapy with increased levels of Hcy in patients with epilepsy. Genetic background related to enzymes involved in 1-carbon metabolism could explain the increased Hcy in bipolar patients on mood stabilizers therapy or even indicate Hcy as an independent risk factor for the development of bipolar disorder. Indeed, studies show an association between 2 common polymorphisms in the MTHFR (C677T and A1298C) gene and a risk of developing bipolar disorder.87,88 However, other meta-analysis studies did not find an association to 2% of preadolescent children and 0.9% to 42% of elderly patients in Caucasian population.68,69

Evidence for the association between Hcy and depression comes from several studies that found elevated Hcy levels in patients with depression.7,70 Moreover, folate deficiency was observed in up to one-third of patients with severe depression.71 It is relevant to notice that evaluations addressing this topic have conflicting results, since most studies analyzing Hcy levels are performed in elderly patients and there is an increase in both Hcy levels and depression onset with aging.68,69

Folate deficiency in these patients is frequently attributed to poor diet. In addition, some medicines used for depression treatment can potentially interfere with folate and Hcy metabolism.72 However, whether the deficiency is primary or secondary to depression, low level of folate limits the response to antidepressants.73 Furthermore, previous studies consistently support the efficacy of folate replacement on enhancing recovery of the mental state and showed an antidepressant function of SAM, probably via the 1-carbon metabolism pathway that produces methyl groups required for the synthesis of serotonin, dopamine, and norepinephrine, neurotransmitters imbalanced in patients with depression.6,74,75

Major Depressive Disorder

Major depressive disorder (MDD) is a severe and complex psychiatric illness, characterized by loss of interest or pleasure (anhedonia) in all or nearly all activities, depressed mood, and significant distress.65 Alterations in the brain neuroanatomy, neurotransmitters, and neuroendocrine systems are related to the cause of MDD, along with strong evidence for genetic factors.66,67 According to World Health Organization, MDD is the third most disabling disorder worldwide, affecting 1%
between these polymorphisms and bipolar disorder. Considering that increased levels of Hcy are observed in bipolar patients, and folate is a cofactor involved in both Hcy metabolism and monoamine synthesis, Baek et al suggest that folate supplementation could normalize monoamine synthesis and correct mood stabilizer-associated functional folate deficiency.72

Alzheimer Disease

Alzheimer disease is a chronic neurodegenerative disorder characterized by the presence of brain extracellular amyloid plaques, intracellular neurofibrillary tangles (NFT) composed by hyperphosphorylated tau, and neuronal loss.97 Alzheimer disease is the most common cause of disability and dementia in the elderly population and currently affects between 30 and 45 million people worldwide.92,93

The sporadic form, or late-onset Alzheimer disease (LOAD), accounts for 90% of the cases and is favored by both genetic and environmental factors,98 such as higher age, female gender, and presence of the apolipoprotein E4 allele. In addition, a moderate elevation in plasma total Hcy is considered a potential risk factor for AD and the total Hcy level higher than 14 μmol/L almost doubles the risk of AD in people older than 60 years.4

Although several studies report that high levels of plasma Hcy are an independent risk factor for the development of dementia and AD, it is not clear whether increased Hcy is the cause or consequence.4,4,96 A study published by Nilsson et al96 showed that elevated plasma Hcy concentration did not seem to be a primary cause of the disease but rather a reflection of plasma total Hcy main determinant changes in patients with AD, such as cobalamin/folate deficiencies and renal impairment. On the other hand, an animal model of AD was more vulnerable to hHcy-inducing diet and therefore more vulnerable to the 5-MTHF depletion. Moreover, the folate reduction and hHcy seem to contribute to neurodegeneration and can also be triggered by neurodegenerative processes, being both a cause and consequence of neurodegeneration.97

The link between neuropsychiatric manifestations and hHcy seems to be related to impairments in 1-carbon metabolism and methylation process. In fact, the SAM/Hcy cycle alterations in AD animal model and cell culture modified DNA methylation status with consequent deregulation of genes involved in the amyloid metabolism.98 It is reported that hHcy and decreased SAM production might result in impaired tau protein phosphorylation and NFT formation and increased production and deposition of amyloid peptides.98-100 Besides, the brain of subjects with LOAD showed significant changes in the methylation patterns of MTHFR and DNMT1 promoters, highlighting the possible contribution of this pathway to LOAD predisposition.101 In a transgenic mouse model of AD, it was observed that hHcy-inducing diet worsened the memory and learning performances, increased amount and deposition of β amyloid (Aβ) peptides, and increased τ insoluble fraction, the 3 major pathological features linked to AD.102 The mechanisms involved in Aβ elevation and deposition were mediated by an activation of the γ-secretase pathway, and τ phosphorylation at specific epitopes was mediated by Cyclin-dependent kinase 5 (CDK5) pathway.102

Supplementation with folic acid and cobalamin may normalize Hcy levels in patients with hHcy; however, there is no clear evidence that this improves cognitive decline.103,104 Moreover, it seems that the positive response to intervention is only observed in patients with AD with mild cognitive decline.105,106

Conclusion

Despite advances in our understanding about psychiatric disorders, there are still many unanswered questions. However, Hcy and correlated 1-carbon metabolism pathway seem to give important clues to the multifactorial etiology of psychiatric disorders, since impaired gene methylation may be a critical pathological component in disorders such as autism, schizophrenia, depression, bipolar disorder, and AD. In fact, this association has also been observed in other psychiatric conditions such as posttraumatic stress disorder,107-109 obsessive–compulsive disorder,110,111 panic disorder,112 and anxiety113 but as there are still only a few publications concerning those conditions, they were not included in this review. Accumulating evidence suggests altered 1-carbon metabolism in the pathophysiology of these psychiatric disorders, since folate and vitamin B12—which are essential cofactors of enzymes involved in Hcy methylation to methionine—are found to be deficient in these patients. Methionine is the precursor of SAM, which is the most important methyl donor for numerous cellular reactions, including proteins, phospholipids, DNA, and neurotransmitters methylation. Nevertheless, caution is needed to address these associations because environmental factors such as diet disposition of precursors and pharmacological agents can challenge these pathways and act as confounding factors.

Cause or consequence, patients with low folate status and consequent hHcy presented poor response to antidepressants, and an improved clinical response is observed after combining antidepressant drug treatments with folic acid supplementation.114,116 Besides, improved clinical status in patients with schizophrenia and children with autism is observed after vitamin B12 and folate supplementation.37,64 Although some studies did not find improvement in the clinical condition of patients after vitamin supplementation,105 recommendations for the routine clinical setting for patients with psychiatric disorders, cognitive impairment, or dementia include an assessment of cobalamin and folate status and appropriate treatment when necessary.117 Folate levels below 7.5 nmol/L and vitamin B12 below 200 nmol/L are considered deficient. Upper reference limits for total Hcy is 10 μmol/L (children <15 years), 15 μmol/L (adults 15-65), and 20 μmol/L (elderly individuals >65 years).117 No specific recommendation for the determination of MTHFR or other 1-carbon-related genetic polymorphisms is available in the context of psychiatric disorders.

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