IλIAD Neurosciences

FOLIC ACID, THE BRAIN AND AUTISM RELATED DISORDERS

A Book of Abstracts

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Introduction

Iliad Neurosciences Inc. is a life sciences company dedicated to the development of products for the diagnosis and treatment of neuro-developmental disorders with emphasis on Autism and related conditions. Currently, Iliad has identified and licensed a late stage patented diagnostic technology related to **Folate Receptor A Autoantibodies (FRA-Ab)**. Iliad's assays, which are performed in a CLIA certified laboratory, are aimed at assessing the ability of folate (folic acid), a major vitamin essential for normal function of many tissues, to enter the brain.

Iliad continues its research endeavors in the study of Folate Receptor A Autoantibodies and their implications with regards to CFD, ASD, and other neurological and brain disorders on an on-going basis. We are driven to understand and potentially treat all conditions that are affected by Folate Receptor A Autoantibodies.

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Mol Psychiatry. 2016 Oct 18. doi: 10.1038/mp.2016.168. [Epub ahead of print]

FOLINIC ACID IMPROVES VERBAL COMMUNICATION IN CHILDREN WITH AUTISM AND LANGUAGE IMPAIRMENT: A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

Frye RE[1,2,3], Slattery J[2,3], Delhey L[2,3], Furgerson B[1], Strickland T[1], Tippett M[1,2], Sailey A[2,3], Wynne R[2,3], Rose S[2,3], Melnyk S[2,3], Jill James S[2,3], Sequeira JM[4], Quadros EV[4].

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ABSTRACT

We sought to determine whether high-dose folinic acid improves verbal communication in children with non-syndromic autism spectrum disorder (ASD) and language impairment in a double-blind placebo control setting. Forty-eight children (mean age 7 years 4 months; 82% male) with ASD and language impairment were randomized to receive 12 weeks of high-dose folinic acid (2 mg kg^{-1} per day, maximum 50 mg per day; n=23) or placebo (n=25). Children were subtyped by glutathione and folate receptor-α autoantibody (FRAA) status. Improvement in verbal communication, as measured by a ability-appropriate standardized instrument, was significantly greater in participants receiving folinic acid as compared with those receiving placebo, resulting in an effect of 5.7 (1.0,10.4) standardized points with a medium-to-large effect size (Cohen's d=0.70). FRAA status was predictive of response to treatment. For FRAA-positive participants, improvement in verbal communication was significantly greater in those receiving folinic acid as compared with those receiving placebo, resulting in an effect of 7.3 (1.4,13.2) standardized points with a large effect size (Cohen's d=0.91), indicating that folinic acid treatment may be more efficacious in children with ASD who are FRAA positive. Improvements in subscales of the Vineland Adaptive Behavior Scale, the Aberrant Behavior Checklist, the Autism Symptom Questionnaire and the Behavioral Assessment System for Children were significantly greater in the folinic acid group as compared with the placebo group. There was no significant difference in adverse effects between treatment groups. Thus, in this small trial of children with non-syndromic ASD and language impairment, treatment with high-dose folinic acid for 12 weeks resulted in improvement in verbal communication as compared with placebo, particularly in those participants who were positive for FRAAs.Molecular Psychiatry advance online publication, 18 October 2016; doi:10.1038/mp.2016.168.

Clin Chem Lab Med. 2013 Mar 1;51(3):545-54. doi: 10.1515/cclm-2012-0577.

THE DIAGNOSTIC UTILITY OF FOLATE RECEPTOR AUTOANTIBODIES IN BLOOD

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ABSTRACT

Folate supplementation reduces the risk of neural tube defect (NTD) pregnancy, and folinic acid has been used to correct cerebral folate deficiency (CFD) in children with developmental disorders. In the absence of systemic folate deficiency, the discovery of autoantibodies (AuAbs) to folate receptor α (FRα) that block the uptake of folate offers one mechanism to explain the response to folate in these disorders. The association of FRα AuAbs with pregnancy-related complications, CFD syndrome, and autism spectrum disorders and response to folate therapy is highly suggestive of the involvement of these AuAbs in the disruption of brain development and function via folate pathways. The two types of antibodies identified in the serum of patients are blocking antibody and binding antibody. The two antibodies can be measured by the specific assays described and exert their pathological effects either by functional blocking of folate transport as previously shown or hypothetically by disrupting the FR by an antigen-antibody-mediated inflammatory response. We have identified both IgG and IgM AuAbs in these conditions. The predominant antibodies in women with NTD pregnancy belong to the IgG1 and IgG2 isotype and in CFD children, the IgG1 and IgG4 isotype. This review describes the methods used to measure these AuAbs, their binding characteristics, affinity, cross-reactivity, and potential mechanisms by which folate therapy could work. Because these AuAbs are associated with various pathologies during fetal and neonatal development, early detection and intervention could prevent or reverse the consequences of exposure to these AuAbs.

Front Neurosci. 2016 Mar 9;10:80. doi: 10.3389/fnins.2016.00080. eCollection 2016.

BLOCKING AND BINDING FOLATE RECEPTOR ALPHA AUTOANTIBODIES IDENTIFY NOVEL AUTISM SPECTRUM DISORDER SUBGROUPS

Frye RE[1], Delhey L[1], Slattery J[1], Tippett M[1], Wynne R[1], Rose S[1], Kahler SG[1], Bennuri SC[1], Melnyk S[1], Sequeira JM[2], Quadros E[2].

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ABSTRACT

Folate receptor α (FRα) autoantibodies (FRAAs) are prevalent in autism spectrum disorder (ASD). They disrupt the transportation of folate across the blood-brain barrier by binding to the FRα. Children with ASD and FRAAs have been reported to respond well to treatment with a form of folate known as folinic acid, suggesting that they may be an important ASD subgroup to identify and treat. There has been no investigation of whether they manifest unique behavioral and physiological characteristics. Thus, in this study we measured both blocking and binding FRAAs, physiological measurements including indices of redox and methylation metabolism and inflammation as well as serum folate and B12 concentrations and measurements of development and behavior in 94 children with ASD. Children positive for the binding FRAA were found to have higher serum B12 levels as compared to those negative for binding FRAAs while children positive for the blocking FRAA were found to have relatively better redox metabolism and inflammation markers as compared to those negative for blocking FRAAs. In addition, ASD children positive for the blocking FRAA demonstrated better communication on the Vineland Adaptive Behavior Scale, stereotyped behavior on the Aberrant Behavioral Checklist and mannerisms on the Social Responsiveness Scale. This study suggests that FRAAs are associated with specific physiological and behavioral characteristics in children with ASD and provides support for the notion that these biomarkers may be useful for subgrouping children with ASD, especially with respect to targeted treatments.

Clin Chem Lab Med. 2013 Mar 1;51(3):497-511. doi: 10.1515/cclm-2012-0543.

CLINICAL RECOGNITION AND ASPECTS OF THE CEREBRAL FOLATE DEFICIENCY SYNDROMES

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ABSTRACT

We characterized cerebral folate deficiency (CFD) as any neuro-psychiatric condition associated with low spinal fluid (CSF) N5-methyltetrahydrofolate (MTHF) but normal folate status outside the central nervous system (CNS). The commonest cause underlying CFD syndromes is the presence of serum autoantibodies of the blocking type directed against folate receptor-α (FRα) attached to the plasma-side of choroid plexus epithelial cells. Blocking FR antibodies inhibit MTHF transport across the choroid plexus. Serum titers of FR antibodies may fluctuate significantly over time. Less frequent causes of CFD are FOLR-1 mutations, mitochondrial disorders and inborn errors affecting folate metabolism. Maternal FR antibodies have been associated with neural tube defects while the presence of FR antibodies in either one or both parents increases the risk of an offspring with infantile autism. Recognizable CFD syndromes attributed to FR-antibodies in childhood are infantile-onset CFD presenting 4-6 months after birth, infantile autism with neurological deficits, and a spastic ataxic syndrome from the age of 1 year, while progressive dystonic or schizophrenic syndromes develop during adolescence. FR autoantibodies are frequently found in autism spectrum disorders, in an Aicardi-Goutières variant and in Rett syndrome. The heterogeneous phenotype of CFD syndromes might be determined by different ages of onset and periods when FR autoantibodies are generated with consequent CNS folate deficiency. Folate deficiency during various critical stages of fetal and infantile development affects structural and functional refinement of the brain. Awareness of CFD syndromes should lead to early detection, diagnosis and improved prognosis of these potentially treatable group of autoimmune and genetically determined conditions.

Biochimie. 2016 Jul;126:31-42. doi: 10.1016/j.biochi.2016.02.012. Epub 2016 Feb 24.

THE METABOLIC BASIS FOR DEVELOPMENTAL DISORDERS DUE TO DEFECTIVE FOLATE TRANSPORT

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ABSTRACT

Folates are essential in the intermediary metabolism of amino acids, synthesis of nucleotides and for maintaining methylation reactions. They are also linked to the production of neurotransmitters through GTP needed for the synthesis of tetrahydrobiopterin. During pregnancy, folate is needed for fetal development. Folate deficiency during this period has been linked to increased risk of neural tube defects. Disturbances of folate metabolism due to genetic abnormalities or the presence of autoantibodies to folate receptor alpha (FRα) can impair physiologic processes dependent on folate, resulting in a variety of developmental disorders including cerebral folate deficiency syndrome and autism spectrum disorders. Overall, adequate folate status has proven to be important during pregnancy as well as neurological development and functioning in neonates and children. Treatment with pharmacologic doses of folinic acid has led to reversal of some symptoms in many children diagnosed with cerebral folate deficiency syndrome and autism, especially in those positive for autoantibodies to FRα. Thus, as the brain continues to develop throughout fetal and infant life, it can be affected and become dysfunctional due to a defective folate transport contributing to folate deficiency. Treatment and prevention of these disorders can be achieved by identification of those at risk and supplementation with folinic acid.

Mol Psychiatry. 2013 Mar;18(3):369-81. doi: 10.1038/mp.2011.175. Epub 2012 Jan 10.

CEREBRAL FOLATE RECEPTOR AUTOANTIBODIES IN AUTISM SPECTRUM DISORDER

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ABSTRACT

Cerebral folate deficiency (CFD) syndrome is a neurodevelopmental disorder typically caused by folate receptor autoantibodies (FRAs) that interfere with folate transport across the blood-brain barrier. Autism spectrum disorders (ASDs) and improvements in ASD symptoms with leucovorin (folinic acid) treatment have been reported in some children with CFD. In children with ASD, the prevalence of FRAs and the response to leucovorin in FRA-positive children has not been systematically investigated. In this study, serum FRA concentrations were measured in 93 children with ASD and a high prevalence (75.3%) of FRAs was found. In 16 children, the concentration of blocking FRA significantly correlated with cerebrospinal fluid 5-methyltetrahydrofolate concentrations, which were below the normative mean in every case. Children with FRAs were treated with oral leucovorin calcium (2 mg kg(-1) per day; maximum 50 mg per day). Treatment response was measured and compared with a wait-list control group. Compared with controls, significantly higher improvement ratings were observed in treated children over a mean period of 4 months in verbal communication, receptive and expressive language, attention and stereotypical behavior. Approximately one-third of treated children demonstrated moderate to much improvement. The incidence of adverse effects was low. This study suggests that FRAs may be important in ASD and that FRA-positive children with ASD may benefit from leucovorin calcium treatment. Given these results, empirical treatment with leucovorin calcium may be a reasonable and non-invasive approach in FRA-positive children with ASD. Additional studies of folate receptor autoimmunity and leucovorin calcium treatment in children with ASD are warranted.

Am J Clin Nutr. 2009 January; 89(1): 425–430.

EFFICACY OF METHYLCOBALAMIN AND FOLINIC ACID TREATMENT ON GLUTATHIONE REDOX STATUS IN CHILDREN WITH AUTISM

S Jill James, Stepan Melnyk, George Fuchs, Tyra Reid, Stefanie Jernigan, Oleksandra Pavliv, Amanda Hubanks, and David W Gaylor

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BACKGROUND: Metabolic abnormalities and targeted treatment trials have been reported for several neurobehavioral disorders but are relatively understudied in autism.

OBJECTIVE: The objective of this study was to determine whether or not treatment with the metabolic precursors, methylcobalamin and folinic acid, would improve plasma concentrations of transmethylation/transsulfuration metabolites and glutathione redox status in autistic children.

DESIGN: In an open-label trial, 40 autistic children were treated with 75 μg/kg methylcobalamin (2 times/wk) and 400 μg folinic acid (2 times/d) for 3 mo. Metabolites in the transmethylation/transsulfuration pathway were measured before and after treatment and compared with values measured in age-matched control children.

RESULTS: The results indicated that pretreatment metabolite concentrations in autistic children were significantly different from values in the control children. The 3-mo intervention resulted in significant increases in cysteine, cysteinylglycine, and glutathione concentrations ($P < 0.001$). The oxidized disulfide form of glutathione was decreased and the glutathione redox ratio increased after treatment ($P < 0.008$). Although mean metabolite concentrations were improved significantly after intervention, they remained below those in unaffected control children.

CONCLUSION: The significant improvements observed in transmethylation metabolites and glutathione redox status after treatment suggest that targeted nutritional intervention with methylcobalamin and folinic acid may be of clinical benefit in some children who have autism. This trial was registered at clinicaltrials.gov as NCT00692315.

Neuropediatrics. 2007 Dec;38(6):276-81. doi: 10.1055/s-2008-1065354.

FOLATE RECEPTOR AUTOIMMUNITY AND CEREBRAL FOLATE DEFICIENCY IN LOW-FUNCTIONING AUTISM WITH NEUROLOGICAL DEFICITS

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SOURCE

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ABSTRACT

Reduced folate transport to the CNS was identified in two autism spectrum disorders, i.e., Rett syndrome and infantile low-functioning autism with neurological abnormalities. Twenty-five patients with early-onset low-functioning autism with or without neurological deficits, were evaluated for serum folate, cerebrospinal fluid (CSF) 5-methyltetrahydrofolate (5MTHF), and serum FR autoantibodies of the blocking type to determine the significance of folate receptor (FR) autoantibodies with respect to folate transport across the blood-CSF barrier. In spite of normal serum folate, CSF 5MTHF was low in 23 of 25 patients. The reduced CSF folate in 19 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. Serum FR autoimmunity appears to represent an important factor in the pathogenesis of reduced folate transport to the nervous system among children with early-onset low-functioning autism associated with or without neurological deficits. Early detection of FR autoantibodies may be a key factor in the prevention and therapeutic intervention among this subgroup of patients with autism.

N Engl J Med. 2005 May 12;352(19):1985-91.

AUTOANTIBODIES TO FOLATE RECEPTORS IN THE CEREBRAL FOLATE DEFICIENCY SYNDROME

Ramaekers VT[1], Rothenberg SP, Sequeira JM, Opladen T, Blau N, Quadros EV, Selhub J.

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ABSTRACT

In infantile-onset cerebral folate deficiency, 5-methyltetrahydrofolate (5MTHF) levels in the cerebrospinal fluid are low, but folate levels in the serum and erythrocytes are normal. We examined serum specimens from 28 children with cerebral folate deficiency, 5 of their mothers, 28 age-matched control subjects, and 41 patients with an unrelated neurologic disorder. Serum from 25 of the 28 patients and 0 of 28 control subjects contained high-affinity blocking autoantibodies against membrane-bound folate receptors that are present on the choroid plexus. Oral folinic acid normalized 5MTHF levels in the cerebrospinal fluid and led to clinical improvement. Cerebral folate deficiency is a disorder in which autoantibodies can prevent the transfer of folate from the plasma to the cerebrospinal fluid.

Dev Med Child Neurol. 2004 Dec; 46(12):843-51.

CEREBRAL FOLATE DEFICIENCY

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ABSTRACT

Cerebral folate deficiency (CFD) can be defined as any neurological syndrome associated with low cerebrospinal fluid (CSF) 5-methyltetrahydrofolate (5MTHF), the active folate metabolite, in the presence of normal folate metabolism outside the nervous system. CFD could result from either disturbed folate transport or from increased folate turnover within the central nervous system (CNS). We report on a novel neurometabolic syndrome in 20 children, which we term 'idiopathic CFD'. Typical features became manifest from the age of 4 months, starting with marked unrest, irritability, and sleep disturbances followed by psychomotor retardation, cerebellar ataxia, spastic paraplegia, and dyskinesia; epilepsy developed in about one third of the children. Most children showed deceleration ofhead growth from the age of 4 to 6 months. Visual disturbances began to develop around the age of 3 years and progressive sensorineural hearing loss started from the age of 6 years. Neuroimaging showed atrophy of frontotemporal regions and periventricular demyelination in seven children, slowly progressive supra- and infratentorial atrophy in three children, and normal findings in the remainder. Because active folate transport to the CNS occurs through receptor-mediated folate receptor protein 1 (FR1) endocytosis, DNA sequencing of the FR1 gene was performed and found to be normal. However, CSF protein analysis revealed a non-functional FR1 protein, suspected to result from either post-translational defects of FR1 protein N-glycosylation, the presence of folate antagonists with irreversible binding, or autoantibodies blocking the folate binding site of FR1. Oral treatment with 5-formyltetrahydrofolate (folinic acid) should be started in low doses at 0.5-1mg/kg/day, but in some patients higher daily doses of folinic acid at 2-3 mg/kg/day are required to normalize CSF 5MTHF values. This proposed treatment protocol resulted in a favourable clinical response in patients identified before the age of six years while partial recovery with poorer outcome was found beyond the age of 6 years. Careful clinical and EEG monitoring should be performed 1, 3, and 6 months after the beginning of treatment. After four to six months of folinic acid treatment, CSF analysis should be repeated in order to prevent over- or under-dosage of folinic acid. Secondary forms of CFD have been recognized during chronic use of antifolate and anticonvulsant drugs and in various known conditions such as Rett syndrome, Aicardi-Goutières syndrome, 3-phosphoglycerate dehydrogenase deficiency, dihydropteridine reductase deficiency, aromatic amino acid decarboxylase deficiency, and Kearns-Sayre syndrome. The pathogenic link between these underlying specific disease entities and the observed secondary CFD has not been resolved.

Front Neurosci. 2016 May 10;10:192. doi: 10.3389/fnins.2016.00192. eCollection 2016.

NEUROPATHOLOGICAL MECHANISMS OF SEIZURES IN AUTISM SPECTRUM DISORDER

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ABSTRACT

This manuscript reviews biological abnormalities shared by autism spectrum disorder (ASD) and epilepsy. Two neuropathological findings are shared by ASD and epilepsy: abnormalities in minicolumn architecture and γ-aminobutyric acid (GABA) neurotransmission. The peripheral neuropil, which is the region that contains the inhibition circuits of the minicolumns, has been found to be decreased in the post-mortem ASD brain. ASD and epilepsy are associated with inhibitory GABA neurotransmission abnormalities including reduced GABAA and GABAB subunit expression. These abnormalities can elevate the excitation-to-inhibition balance, resulting in hyperexcitablity of the cortex and, in turn, increase the risk of seizures. Medical abnormalities associated with both epilepsy and ASD are discussed. These include specific genetic syndromes, specific metabolic disorders including disorders of energy metabolism and GABA and glutamate neurotransmission, mineral and vitamin deficiencies, heavy metal exposures and immune dysfunction. Many of these medical abnormalities can result in an elevation of the excitatory-to-inhibitory balance. Fragile X is linked to dysfunction of the mGluR5 receptor and Fragile X, Angelman and Rett syndromes are linked to a reduction in GABAA receptor expression. Defects in energy metabolism can reduce GABA interneuron function. Both pyridoxine dependent seizures and succinic semialdehyde dehydrogenase deficiency cause GABA deficiencies while urea cycle defects and phenylketonuria cause abnormalities in glutamate neurotransmission. Mineral deficiencies can cause glutamate and GABA neurotransmission abnormalities and heavy metals can cause mitochondrial dysfunction which disrupts GABA metabolism. Thus, both ASD and epilepsy are associated with similar abnormalities that may alter the excitatory-to-inhibitory balance of the cortex. These parallels may explain the high prevalence of epilepsy in ASD and the elevated prevalence of ASD features in individuals with epilepsy.

Dev Med Child Neurol. 2008 May;50(5):346-52. doi: 10.1111/j.1469-8749.2008.02053.x. Epub 2008 Mar 19.

A MILK-FREE DIET DOWNREGULATES FOLATE RECEPTOR AUTOIMMUNITY IN CEREBRAL FOLATE DEFECIENCY SYNDROME

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SOURCE

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ABSTRACT

In cerebral folate deficiency syndrome, the presence of autoantibodies against the folate receptor (FR) explains decreased folate transport to the central nervous system and the clinical response to folinic acid. Autoantibody crossreactivity with milk FR from different species prompted us to test the effect of a milk-free diet. Intervention with a milkfree diet in 12 children (nine males, three females; mean age 6y [SD 4y 11mo], range 1-19y), decreased autoantibody titer significantly from 2.08pmol of FR blocked per ml of serum (SD 2.1; range 0.24-8.35) to 0.35pmol (SD 0.49; range 0-1.32; p=0.012) over 3 to 13 months, whereas FR autoantibody titer increased significantly to 6.53 (SD 6.08; range 0.54-14.07; p=0.013) in nine children who were reexposed to milk for 6 to 14 weeks. In 12 children on a normal diet (eight males, four females; mean age 5y 5mo [SD 4y 1mo], range 1y 6mo-16y 4mo), the antibody titer increased significantly from 0.84pmol of FR blocked per ml (SD 0.39; range 0.24-1.44) to 3.04pmol (SD 1.42; range 0.84-6.01; p=0.001) over 10 to 24 months. Decreasing the autoantibody titer with a milk-free diet in conjunction with folinic acid therapy may be advocated for these patients.

Clin Biochem. 2011 Jun; 44(8-9):719-21. doi: 10.1016/j.clinbiochem.2011.03.002. Epub 2011 Mar 22.

FOLATE ANALYSIS FOR THE DIFFERENTIAL DIAGNOSIS OF PROFOUND CEREBROSPINAL FLUID FOLATE DEFICIENCY

Ormazábal A, Perez-Dueñas B, Sierra C, Urreitzi R, Montoya J, Serrano M, Campistol J, García-Cazorla A, Pineda M, Artuch R.

SOURCE

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ABSTRACT

OBJECTIVE: To evaluate the automated determination of total cerebrospinal fluid (CSF) folates for the diagnosis of cerebral folate deficiency.

METHOD: CSF and serum samples were analyzed in 60 children with different neurological disorders.

RESULT: In all patients with genetic conditions leading to profound cerebral folate deficiency (impaired folate transport and metabolism), the automated folate determination showed altered values.

CONCLUSION: CSF folate quantification provided profound CSF folate deficiency diagnosis caused either by folate transport or metabolism deficiencies.

Neurology. 2005 Mar 22; 64(6):1088-90.

CEREBRAL FOLATE DEFICIENCY WITH DEVELOPMENTAL DELAY, AUTISM AND RESPONSE TO FOLINIC ACID

Moretti P, Sahoo T, Hyland K, Bottiglieri T, Peters S, del Gaudio D, Roa B, Curry S, Zhu H, Finnell RH, Neul JL, Ramaekers VT, Blau N, Bacino CA, Miller G, Scaglia F.

SOURCE

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ABSTRACT

The authors describe a 6-year-old girl with developmental delay, psychomotor regression, seizures, mental retardation, and autistic features associated with low CSF levels of 5-methyltetrahydrofolate, the biologically active form of folates in CSF and blood. Folate and B12 levels were normal in peripheral tissues, suggesting cerebral folate deficiency. Treatment with folinic acid corrected CSF abnormalities and improved motor skills.

[N A J Med Sci. 2014;7(2):53-56. DOI: 10.7156/najms.2014.0702053]

FOLATE RECEPTOR ALPHA AUTOANTIBODIES MODULATE THYROID FUNCTION IN AUTISM SPECTRUM DISORDER

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The folate receptor alpha (FRα) is essential for folate transportation across the blood-brain barrier and is closely associated with cerebral folate deficiency, a syndrome that commonly presents with autism spectrum disorder (ASD) features. FRα autoantibodies (FRAAs) interrupt FRα function and have a high prevalence in children with ASD. Since the FRα is also located on the thyroid, FRAAs could also interfere with thyroid function. Interestingly, ASD has been inconsistently associated with hypothyroidism. The aim of this study was to determine if thyroid dysfunction in ASD could be related to FRAAs. To this end we investigated the relationship between serum FRAA titers (both blocking and binding) and thyroid stimulating hormone (TSH) in 32 children with ASD. Blocking, but not binding, FRAAs were found to be related to TSH levels. Higher FRAAs were significantly correlated with higher TSH concentrations ($r = 0.36$, $p = 0.025$), while ASD children who were positive for blocking FRAAs demonstrated a significantly higher serum concentration of TSH than children who were negative for FRAAs ($t(31) = 2.07$, $p = 0.02$). These results are consistent with the notion that blocking FRAAs are associated with reduced thyroid function and suggest that thyroid function should be examined in children with ASD who are positive for the blocking FRAAs.

Am J Hum Genet. 2009 Sep; 85(3):354-63. doi: 10.1016/j.ajhg.2009.08.005.

FOLATE RECEPTOR ALPHA DEFECT CAUSES CEREBRAL FOLATE TRANSPORT DEFICIENCY: A TREATABLE NEURODEGENERATIVE DISORDER ASSOCIATED WITH DISTURBED MYELIN METABOLISM

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ABSTRACT

Sufficient folate supplementation is essential for a multitude of biological processes and diverse organ systems. At least five distinct inherited disorders of folate transport and metabolism are presently known, all of which cause systemic folate deficiency. We identified an inherited brain-specific folate transport defect that is caused by mutations in the folate receptor 1 (FOLR1) gene coding for folate receptor alpha (FRalpha). Three patients carrying FOLR1 mutations developed progressive movement disturbance, psychomotor decline, and epilepsy and showed severely reduced folate concentrations in the cerebrospinal fluid (CSF). Brain magnetic resonance imaging (MRI) demonstrated profound hypomyelination, and MR-based in vivo metabolite analysis indicated a combined depletion of white-matter choline and inositol. Retroviral transfection of patient cells with either FRalpha or FRbeta could rescue folate binding. Furthermore, CSF folate concentrations, as well as glial choline and inositol depletion, were restored by folinic acid therapy and preceded clinical improvements. Our studies not only characterize a previously unknown and treatable disorder of early childhood, but also provide new insights into the folate metabolic pathways involved in postnatal myelination and brain development.

Birth Defects Res A Clin Mol Teratol. 2016 Mar;106(3):201-7. doi: 10.1002/bdra.23483. Epub 2016 Feb 22.

AUTOANTIBODIES AGAINST HOMOCYSTEINYLATED PROTEINS IN A MOUSE MODEL OF FOLATE DEFICIENCY-INDUCED NEURAL TUBE DEFECTS

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ABSTRACT

BACKGROUND: Periconceptional supplementation with folic acid results in a significant reduction in the incidence of neural tube defects (NTDs). Nonetheless, NTDs remain a leading cause of perinatal morbidity and mortality worldwide, and the mechanism(s) by which folate exerts its protective effects are unknown. Homocysteine is an amino acid that accumulates under conditions of folate-deficiency, and is suggested as a risk factor for NTDs. One proposed mechanism of homocysteine toxicity is its accumulation into proteins in a process termed homocysteinylation.

METHODS & RESULTS: Herein, we used a folate-deficient diet in pregnant mice to demonstrate that there is: (i) a significant inverse correlation between maternal serum folate levels and serum homocysteine; (ii) a significant positive correlation between serum homocysteine levels and titers of autoantibodies against homocysteinylated protein; and (iii) a significant increase in congenital malformations and NTDs in mice deficient in serum folate. Furthermore, in mice administered the folate-deplete diet before conception, supplementation with folic acid during the gestational period completely rescued the embryos from congenital defects, and resulted in homocysteinylated protein titers at term that are comparable to that of mice administered a folate-replete diet throughout both the pre- and postconception period. These results demonstrate that a low-folate diet that induces NTDs also increases protein homocysteinylation and the subsequent generation of autoantibodies against homocysteinylated proteins.

CONCLUSION: These data support the hypotheses that homocysteinylation results in neo-self antigen formation under conditions of maternal folate deficiency, and that this process is reversible with folic acid supplementation.

Brain. 2012 Jul;135(Pt 7):2022-31. doi: 10.1093/brain/aws122. Epub 2012 May 13.

MOLECULAR CHARACTERIZATION OF FOLATE RECEPTOR 1 MUTATIONS DELINEATES CEREBRAL FOLATE TRANSPORT DEFICIENCY

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ABSTRACT

Cerebral folate transport deficiency is an inherited brain-specific folate transport defect that is caused by mutations in the folate receptor 1 gene coding for folate receptor alpha (FRα). This genetic defect gives rise to a progressive neurological disorder with late infantile onset. We screened 72 children with low 5-methyltetrahydrofolate concentrations in the cerebrospinal fluid and neurological symptoms that developed after infancy. We identified nucleotide alterations in the folate receptor 1 gene in 10 individuals who shared developmental regression, ataxia, profound cerebral hypomyelination and cerebellar atrophy. We found four novel pathogenic alleles, one splice mutation and three missense mutations. Heterologous expression of the missense mutations, including previously described mutants, revealed minor decrease in protein expression but loss of cell surface localization, mistargeting to intracellular compartments and thus absence of cellular binding of folic acid. These results explain the functional loss of folate receptor alpha for all detected folate receptor 1 mutations. Three individuals presenting a milder clinical phenotype revealed very similar biochemical and brain imaging data but partially shared pathogenic alleles with more severely affected patients. Thus, our studies suggest that different clinical severities do not necessarily correlate with residual function of folate receptor alpha mutants and indicate that additional factors contribute to the clinical phenotype in cerebral folate transport deficiency.

Mol Genet Metab. 2011 Nov;104(3):369-72. doi: 10.1016/j.ymgme.2011.06.004. Epub 2011 Jun 14.

CEREBRAL FOLATE DEFICIENCY: A NEUROMETABOLIC SYNDROME?

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BACKGROUND: Cerebral folate deficiency (CFD) is increasingly recognized in various neurological conditions, raising the question of whether it might represent a clear-cut clinical syndrome.

METHODS: Retrospective analysis of patients with low cerebral spinal fluid (CSF) 5-methyltetrahydrofolate (5MTHF) values was performed.

RESULTS: 58 pediatric patients with low (-2nd to -3rd standard deviation) and 45 patients with very low 5MTHF values (<3rd standard deviation) were identified, including 22 patients with defined underlying neurological conditions. The leading symptoms were mental retardation (n=84), motor retardation (n=75), epilepsy (n=53), ataxia (n=44) and pyramidal tract signs (n=37). There was no relationship between 5MTHF levels and the severity of clinical disease, the duration of clinical disease, distinct neurological symptoms and antiepileptic drug treatment, respectively. Genetical analysis for mutations in the folate receptor 1 gene proved normal in all 16 children studied.

CONCLUSIONS: For the majority of patients CFD is not a clear-cut neurometabolic syndrome but the common result of different genetic, metabolic or unknown processes. Nevertheless, CFD may represent a treatable disease-modifying factor which should therefore be addressed in prospective studies.

Arch Neurol. 2011 May; 68(5):615-21. doi: 10.1001/archneurol.2011.80.

CEREBRAL FOLATE DEFICIENCY SYNDROMES IN CHILDHOOD: CLINICAL, ANALYTICAL AND ETIOLOGICAL ASPECTS

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SOURCE

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BACKGROUND: Cerebral folate deficiency may be amenable to therapeutic supplementation. Diverse metabolic pathways and unrelated processes can lead to cerebrospinal fluid 5-methyltetrahydrofolate (5-MTHF) depletion, the hallmark of cerebral folate deficiency.

OBJECTIVE: To analyze cerebral folate abundance in a large prospective series of children diagnosed with any neurologic disorder for which a diagnostic lumbar puncture was indicated.

DESIGN: We studied the spectrum and frequency of disorders associated with cerebral folate deficiency by measuring cerebrospinal fluid 5-MTHF, biogenic amines, and pterins. Direct sequencing of the FOLR1 transporter gene was also performed in some patients.

SETTING: Academic pediatric medical center.

PARTICIPANTS: We studied 134 individuals free of neurometabolic disease and 584 patients with any of several diseases of the central nervous system.

RESULTS: Of 584 patients, 71 (12%) exhibited 5-MTHF deficiency. Mild to moderate deficiency (n = 63; range, 19-63 nmol/L) was associated with perinatal asphyxia, central nervous system infection, or diseases of probable genetic origin (inborn errors of metabolism, white matter disorders, Rett syndrome, or epileptic encephalopathies). Severe 5-MTHF depletion (n = 8; range, 0.6-13 nmol/L) was detected in severe MTHF reductase deficiency, Kearns-Sayre syndrome, biotin-responsive striatal necrosis, acute necrotizing encephalitis of Hurst, and FOLR1 defect. A strong correlation was observed between cerebrospinal fluid and plasma folate levels in cerebral folate deficiency.

CONCLUSIONS: Of the 2 main forms of cerebral folate deficiency identified, mild to moderate 5-MTHF deficiency was most commonly associated with disorders bearing no primary relation to folate metabolism, whereas profound 5-MTHF depletion was associated with specific mitochondrial disorders, metabolic and transporter defects, or cerebral degenerations. The results suggest that 5-MTHF can serve either as the hallmark of inborn disorders of folate transport and metabolism or, more frequently, as an indicator of neurologic dysfunction.

Autism Res. 2013 Oct;6(5):384-92. doi: 10.1002/aur.1300. Epub 2013 May 7.

ASSOCIATION BETWEEN MTHFR GENE POLYMORPHISM AND THE RISK OF AUTISM SPECTRUM DISORDERS

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ABSTRACT

Methylenetetrahydrofolate reductase (MTHFR) is essential for DNA biosynthesis and the epigenetic process of DNA methylation, and its gene polymorphisms have been implicated as risk factors for birth defects, neurological disorders, and cancers. However, reports on the association of MTHFR polymorphisms with autism spectrum disorders (ASD) are inconclusive. Therefore, we investigated the relationship of the MTHFR polymorphisms (C677T and A1298C) and the risk of ASD by meta-analysis. Up to December 2012, eight case-control studies involving 1672 patients with ASD and 6760 controls were included for meta-analysis. The results showed that the C677T polymorphism was associated with significantly increased ASD risk in all the comparison models [T vs. C allele (frequency of allele): odds ratio (OR) = 1.42, 95% confidence interval (CI): 1.09-1.85; CT vs. CC (heterozygote): OR = 1.48, 95% CI: 1.09-2.00; TT vs. CC (homozygote): OR = 1.86, 95% CI: 1.08-3.20; CT+TT vs. CC (dominant model): OR = 1.56, 95% CI: 1.12-2.18; and TT vs. CC+CT (recessive model): OR = 1.51, 95% CI: 1.02-2.22], whereas the A1298C polymorphism was found to be significantly associated with reduced ASD risk but only in a recessive model (CC vs. AA+AC: OR = 0.73, 95% CI: 0.56-0.97). In addition, we stratified the patient population based on whether they were from a country with food fortification of folic acid or not. The meta-analysis showed that the C677T polymorphism was found to be associated with ASD only in children from countries without food fortification. Our study indicated that the MTHFR C677T polymorphism contributes to increased ASD risk, and periconceptional folic acid may reduce ASD risk in those with MTHFR 677C>T polymorphism.

S C H I Z O P H R E N I A

Biochimie. 2016 Jul;126:79-90. doi: 10.1016/j.biochi.2016.04.005. Epub 2016 Apr 8.

THE BASIS FOR FOLINIC ACID TREATMENT IN NEUROPSYCHIATRIC DISORDERS.

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ABSTRACT

Multiple factors such as genetic and extraneous causes (drugs, toxins, adverse psychological events) contribute to neuro-psychiatric conditions. In a subgroup of these disorders, systemic folate deficiency has been associated with macrocytic anemia and neuropsychiatric phenotypes. In some of these, despite normal systemic levels, folate transport to the brain is impaired in the so-called cerebral folate deficiency (CFD) syndromes presenting as developmental and psychiatric disorders. These include infantile-onset CFD syndrome, infantile autism with or without neurologic deficits, a spastic-ataxic syndrome and intractable epilepsy in young children expanding to refractory schizophrenia in adolescents, and finally treatment-resistant major depression in adults. Folate receptor alpha (FRα) autoimmunity with low CSF N(5)-methyl-tetrahydrofolate (MTHF) underlies most CFD syndromes, whereas FRα gene abnormalities and mitochondrial gene defects are rarely found. The age at which FRα antibodies of the blocking type emerge, determines the clinical phenotype. Infantile CFD syndrome and autism with neurological deficits tend to be characterized by elevated FRα antibody titers and low CSF MTHF. In contrast, in infantile autism and intractable schizophrenia, abnormal behavioral signs and symptoms may wax and wane with fluctuating FRα antibody titers over time accompanied by cycling changes in CSF folate, tetrahydrobiopterin (BH4) and neurotransmitter metabolites ranging between low and normal levels. We propose a hypothetical model explaining the pathogenesis of schizophrenia. Based on findings from clinical, genetic, spinal fluid and MRI spectroscopic studies, we discuss the neurochemical changes associated with these disorders, metabolic and regulatory pathways, synthesis and catabolism of neurotransmitters, and the impact of oxidative stress on the pathogenesis of these conditions. A diagnostic algorithm and therapeutic regimens using high dose folinic acid, corticosteroids and milk-free diet is presented which has proven to be beneficial in providing adequate folate to the brain and decreasing the FRα autoantibody titer in those positive for the antibody.

Mol Genet Metab. 2014 Dec;113(4):307-14. doi: 10.1016/j.ymgme.2014.10.002. Epub 2014 Oct 12.

FOLINIC ACID TREATMENT FOR SCHIZOPHRENIA ASSOCIATED WITH FOLATE RECEPTOR AUTOANTIBODIES

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ABSTRACT

BACKGROUND: Auto-antibodies against folate receptor alpha (FRα) at the choroid plexus that block N(5)-methyltetrahydrofolate (MTHF) transfer to the brain were identified in catatonic schizophrenia. Acoustic hallucinations disappeared following folinic acid treatment. Folate transport to the CNS prevents homocysteine accumulation and delivers one-carbon units for methyl-transfer reactions and synthesis of purines. The guanosine derivative tetrahydrobiopterin acts as common co-factor for the enzymes producing dopamine, serotonin and nitric oxide.

METHODS: Our study selected patients with schizophrenia unresponsive to conventional treatment. Serum from these patients with normal plasma homocysteine, folate and vitamin B12 was tested for FR autoantibodies of the blocking type on serial samples each week. Spinal fluid was analyzed for MTHF and the metabolites of pterins, dopamine and serotonin. The clinical response to folinic acid treatment was evaluated.

RESULTS: Fifteen of 18 patients (83.3%) had positive serum FR auto-antibodies compared to only 1 in 30 controls (3.3%) ($\chi(2)=21.6$; $p<0.0001$). FRα antibody titers in patients fluctuated over time varying between negative and high titers, modulating folate flux to the CNS, which explained low CSF folate values in 6 and normal values in 7 patients. The mean±SD for CSF MTHF was diminished compared to previously established controls (t-test: 3.90; $p=0.0002$). A positive linear correlation existed between CSF MTHF and biopterin levels. CSF dopamine and serotonin metabolites were low or in the lower normal range. Administration of folinic acid (0.3-1mg/kg/day) to 7 participating patients during at least six months resulted in clinical improvement.

CONCLUSION: Assessment of FR auto-antibodies in serum is recommended for schizophrenic patients. Clinical negative or positive symptoms are speculated to be influenced by the level and evolution of FRα antibody titers which determine folate flux to the brain with up- or down-regulation of brain folate intermediates linked to metabolic processes affecting homocysteine levels, synthesis of tetrahydrobiopterin and neurotransmitters. Folinic acid intervention appears to stabilize the disease process.

WOMEN'S HEALTH

N Engl J Med. 2004 Jan 8;350(2):134-42.

AUTOANTIBODIES AGAINST FOLATE RECEPTORS IN WOMEN WITH PREGNANCY COMPLICATED BY A NEURAL TUBE DEFECT

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ABSTRACT

BACKGROUND: In the absence of clinical folate deficiency, periconceptional supplementation with folic acid reduces a woman's risk of having an infant with a neural-tube defect. Since antiserum to folate receptors induces embryo resorption and malformations in rats, we hypothesized that autoantibodies against folate receptors in women may be associated with pregnancy complicated by a neural-tube defect.

METHODS: Serum from 12 women who were or had been pregnant with a fetus with a neural-tube defect and from 24 control women (20 with current or prior normal pregnancies and 4 who were nulligravid) was analyzed for autoantibodies by incubation with human placental folate receptors radiolabeled with [3H]folic acid. The properties of these autoantibodies were characterized by incubating serum and the autoantibodies isolated from serum with placental membranes, ED27 cells, and KB cells, which express the folate receptors.

RESULTS: Serum from 9 of 12 women with a current or previous affected pregnancy (index subjects) and 2 of 20 control subjects contained autoantibodies against folate receptors ($P<0.001$). The autoantibodies blocked the binding of [3H]folic acid to folate receptors on placental membranes and on ED27 and KB cells incubated at 4 degrees C and blocked the uptake of [3H]folic acid by KB cells when incubated at 37 degrees C.

CONCLUSIONS: Serum from women with a pregnancy complicated by a neural-tube defect contains autoantibodies that bind to folate receptors and can block the cellular uptake of folate. Further study is warranted to assess whether the observed association between maternal autoantibodies against folate receptors and neural-tube defects reflects a causal relation.

Mol Psychiatry. 2016 Sep 20. doi: 10.1038/mp.2016.153. [Epub ahead of print]

PREVENTION OF BEHAVIORAL DEFICITS IN RATS EXPOSED TO FOLATE RECEPTOR ANTIBODIES: IMPLICATION IN AUTISM

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ABSTRACT

Folate receptor alpha (FRα) autoantibodies have been associated with fetal abnormalities and cerebral folate deficiency-related developmental disorders. Over 70% of the children with autism spectrum disorders (ASD) are positive for these autoantibodies and high-dose folinic acid is beneficial in treating these children. Here we show that antibodies (Abs) to the rat FRα administered during gestation produce communication, learning and cognitive deficits in a rat model that can be prevented by folinic acid and dexamethasone. FRα Ab can trigger inflammation as well as block folate transport to the fetus and to the developing brain to produce the functional deficits. In humans, exposure to FRα autoantibodies during fetal development and infancy could contribute to brain dysfunction such as that seen in ASD and other developmental disorders. Identifying women positive for the autoantibody and treating them with high-dose folinic acid along with other interventions to lower the autoantibody titer are effective strategies that may be considered to reduce the risk of having a child with developmental deficits. Molecular Psychiatry advance online publication, 20 September 2016; doi:10.1038/mp.2016.153.

Hum Reprod. 2011 Aug;26(8):2232-8. doi: 10.1093/humrep/der144.

ASSOCIATION BETWEEN INHBITED BINDING OF FOLIC ACID TO FOLATE RECEPTOR ALPHA IN MATERNAL SERUM AND FOLATE-RELATED BIRTH DEFECTS IN NORWAY

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ABSTRACT

BACKGROUND: Folic acid intake during pregnancy can reduce the risk of neural tube defects (NTDs) and perhaps also oral facial clefts. Maternal autoantibodies to folate receptors can impair folic acid binding. We explored the relationship of these birth defects to inhibition of folic acid binding to folate receptor α (FRα), as well as possible effects of parental demographics or prenatal exposures.

METHODS: We conducted a nested case-control study within the Norwegian Mother and Child Cohort Study. The study included mothers of children with an NTD (n = 11), cleft lip with or without cleft palate (CL/P, n= 72), or cleft palate only (CPO, n= 27), and randomly selected mothers of controls (n = 221). The inhibition of folic acid binding to FRα was measured in maternal plasma collected around 17 weeks of gestation. On the basis of prior literature, the maternal age, gravidity, education, smoking, periconception folic acid supplement use and milk consumption were considered as potential confounding factors.

RESULTS: There was an increased risk of NTDs with increased binding inhibition [adjusted odds ratio (aOR) = 1.4, 95% confidence interval (CI) 1.0-1.8]. There was no increased risk of oral facial clefts from inhibited folic acid binding to FRα (CL/P aOR = 0.7, 95% CI 0.6-1.0; CPO aOR = 1.1, 95% CI 0.8-1.4). No association was seen between smoking, folate supplementation or other cofactors and inhibition of folic acid binding to FRα.

CONCLUSIONS: Inhibition of folic acid binding to FRα in maternal plasma collected during pregnancy was associated with increased risk of NTDs but not oral facial clefts.

Birth Defects Res A Clin Mol Teratol. 2016 Aug;106(8):685-95. doi: 10.1002/bdra.23517. Epub 2016 May 11.

LEVELS OF FOLATE RECEPTOR AUTOANTIBODIES IN MATERNAL AND CORD BLOOD AND RISK OF NEURAL TUBE DEFECTS IN CHINESE POPULATION

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BACKGROUND: After years of periconceptional folic acid supplementation, the prevalence of neural tube defects (NTDs) remains stable following the remarkable reduction observed immediately after the fortification practice. There is accumulating evidence that folate receptor (FR) autoimmunity may play a role in the etiology of folate-sensitive NTDs.

METHODS: From 2011 to 2013, 118 NTD cases and 242 healthy controls were recruited from a population-based birth defects surveillance system in Northern China. Enzyme-linked immunosorbent assay was used to measure FR autoantibodies in maternal and cord blood. Logistic regression models were used to estimate the odds ratios (OR) and 95% confidence intervals (95% CI).

RESULTS: Plasma FR autoantibodies levels were significantly elevated in mothers of infants with NTDs compared with mothers of healthy controls. Using the lowest tertile as the referent group, 2.20-fold (95% CI, 0.71-6.80) and 5.53-fold increased odds (95% CI, 1.90-16.08) of NTDs were observed for the second and third tertile of immunoglobulin G (IgG), respectively, and the odds of NTDs for each successive tertile of IgM was 0.98 (95% CI, 0.35-2.75) and 3.49 (95% CI, 1.45-8.39), respectively. A dose-response relationship was found between FR autoantibodies levels and risk of NTDs ($P < 0.001$ for IgG, $P = 0.002$ for IgM). The same pattern was observed in both subtypes of spina bifida and anencephaly. No significant difference in levels of cord blood FR autoantibodies was observed.

CONCLUSION: Higher levels of FR autoimmunity in maternal plasma are associated with elevated risk of NTDs in a dose-response manner. Birth Defects Research (Part A) 106:685-695, 2016.

Sci Rep. 2015 Nov 9;5:15548. doi: 10.1038/srep15548.

ROLE OF GENETIC MUTATIONS IN FOLATE-RELATED ENZYME GENES ON MALE INFERTILITY

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ABSTRACT

Several studies showed that the genetic mutations in the folate-related enzyme genes might be associated with male infertility; however, the results were still inconsistent. We performed a meta-analysis with trial sequential analysis to investigate the associations between the MTHFR C677T, MTHFR A1298C, MTR A2756G, MTRR A66G mutations and the MTHFR haplotype with the risk of male infertility. Overall, a total of 37 studies were selected. Our meta-analysis showed that the MTHFR C677T mutation was a risk factor for male infertility in both azoospermia and oligoasthenoteratozoospermia patients, especially in Asian population. Men carrying the MTHFR TC haplotype were most liable to suffer infertility while those with CC haplotype had lowest risk. On the other hand, the MTHFR A1298C mutation was not related to male infertility. MTR A2756G and MTRR A66G were potential candidates in the pathogenesis of male infertility, but more case-control studies were required to avoid false-positive outcomes. All of these results were confirmed by the trial sequential analysis. Finally, our meta-analysis with trial sequential analysis proved that the genetic mutations in the folate-related enzyme genes played a significant role in male infertility.

Fertil Steril. 2009 Apr;91(4 Suppl):1518-21. doi: 10.1016/j.fertnstert.2008.08.104. Epub 2008 Oct 23.

ASSOCIATION BETWEEN BLOCKING FOLATE RECEPTOR AUTOANTIBODIES AND SUBFERTILITY

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ABSTRACT

The association between blocking folate receptor (FR) autoantibodies and subfertility was investigated in a longitudinal study of women attempting to become pregnant. Seventeen women with subfertility (failure to conceive during 12 menstrual cycles) and 25 control women (women who conceived and went on to have normal pregnancy outcomes) were studied. Subfertility risk was 12 times higher in women with blocking FR autoantibodies compared with those without (odds ratio, 12; 95% confidence interval, 1.9-129.6).

PLoS One. 2016 Mar 24;11(3):e0152249. doi: 10.1371/journal.pone.0152249. eCollection 2016.

EXPOSURE TO FOLATE RECEPTOR ALPHA ANTIBODIES DURING GESTATION AND WEANING LEADS TO SEVERE BEHAVIORAL DEFICITS IN RATS: A PILOT STUDY

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ABSTRACT

The central nervous system continues to develop during gestation and after birth, and folate is an essential nutrient in this process. Folate deficiency and folate receptor alpha autoantibodies (FRα-AuAb) have been associated with pregnancy-related complications and neurodevelopmental disorders. In this pilot study, we investigated the effect of exposure to FRα antibodies (Ab) during gestation (GST), the pre-weaning (PRW), and the post weaning (POW) periods on learning and behavior in adulthood in a rat model. In the open field test and novel object recognition task, which examine locomotor activity and anxiety-like behavior, deficits in rats exposed to Ab during gestation and pre-weaning (GST+PRW) included more time spent in the periphery or corner areas, less time in the central area, frequent self-grooming akin to stereotypy, and longer time to explore a novel object compared to a control group; these are all indicative of increased levels of anxiety. In the place avoidance tasks that assess learning and spatial memory formation, only 30% of GST+PRW rats were able to learn the passive place avoidance task. None of these rats learned the active place avoidance task indicating severe learning deficits and cognitive impairment. Similar but less severe deficits were observed in rats exposed to Ab during GST alone or only during the PRW period, suggesting the extreme sensitivity of the fetal as well as the neonatal rat brain to the deleterious effects of exposure to Ab during this period. Behavioral deficits were not seen in rats exposed to antibody post weaning. These observations have implications in the pathology of FRα-AuAb associated with neural tube defect pregnancy, preterm birth and neurodevelopmental disorders including autism.

Birth Defects Res A Clin Mol Teratol. 2015 Dec;103(12):1028-30. doi: 10.1002/bdra.23436. Epub 2015 Sep 21.

FOLATE RECEPTOR AUTOANTIBODIES IN PREGNANCY RELATED COMPLICATIONS

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ABSTRACT

BACKGROUND: Folate receptor autoantibodies in women have been associated with neural tube pregnancy and in children with cerebral folate deficiency syndrome and autism. These autoantibodies have been implicated in blocking folate transport to the fetus and to the brain in infants.

METHODS: We report a woman with multiple pregnancy related complications who was diagnosed with autoantibodies to the folate receptor alpha.

RESULTS: A treatment strategy with folate supplementation and reducing the antibody titer proved effective in normal pregnancy outcome.

CONCLUSION: This long-term follow up of a subject with folate receptor autoantibodies is a first report of its kind and describes treatment strategy to prevent pregnancy related complications due to folate receptor autoantibodies.

Nutrition. 2015 Oct;31(10):1224-7. doi: 10.1016/j.nut.2015.04.008. Epub 2015 May 11.

THE ROLE OF FOLATE RECEPTOR AUTOANTIBODIES IN PRETERM BIRTH

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ABSTRACT

OBJECTIVE: Cellular uptake of folate is mediated by folate receptor (FR)α. Prior studies indicate that a FRα autoantibody (FRAb) is implicated in poor pregnancy outcomes. The aims of this study were to determine the prevalence of FRAbs in women with preterm and term pregnancies, and to investigate the role of maternal FRAbs in preterm birth.

METHODS: This prospective observational study included 23 mothers and 25 preterm infants (two twin births) born at gestational age (GA) ≤32 wk and/or birth weight ≤1500 g (group 1) and 25 mother-term infant pairs (infants born at GA ≥37 wk, group 2). Blocking and binding FRAbs in maternal and in cord blood were determined. The association between maternal FRAbs and pregnancy outcome was measured using multiple logistic regression, adjusted for maternal age and previous preterm birth.

RESULTS: The prevalence of FRAbs was 65.2% in women with preterm birth, which was twofold higher than in those with term pregnancy (28%; relative risk [RR], 2.3; 95% confidence interval [CI], 1.2-4.7). The prevalence of FRAbs in preterm infants (64%) was significantly higher than in term infants (24%; RR, 2.7; 95% CI, 1.3-5.7). Pregnant women with positive FRAbs had 4.9 times higher odds of having preterm birth (odds ratio, 4.9; 95% CI, 1.4-17.7), adjusted for maternal age and previous preterm birth.

CONCLUSIONS: These findings suggest that the presence of FRAbs might be a contributing factor to preterm birth, which could be prevented with appropriate testing and therapeutic interventions. Further studies are warranted to investigate the possible mechanisms of fetal sensitization resulting in FRAb production in utero and its possible clinical correlates.

Clin Chem Lab Med. 2007;45(12):1717-27.

IMPORTANCE OF FOLATE-HOMOCYSTEINE HOMEOSTASIS DURING EARLY EMBRYONIC DEVELOPMENT

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ABSTRACT

Although the beneficial effects of maternal folate supplementation in the periconceptional period have been shown to prevent neural tube defects, congenital heart defects and orofacial clefts, the exact protective mechanism of folates remains unknown. Folates affect DNA synthesis, amino acid metabolism and methylation of genes, proteins and lipids via S-adenosylmethionine-mediated one-carbon transfer reactions. Our laboratory has created several mouse knock out models of folate transport using gene targeting to inactivate folate receptor 1 (Folr1), folate receptor 2 (Folr2) and reduced folate carrier 1 (Slc19a1) genes. Gene ablation of both Folr1 and Slc19a1 leads to lethality, but with maternal folate supplementation, nullizygous embryos for both genes present with neural tube defects (NTDs) and congenital heart defects (CHDs). Folr1 nullizygous mice also exhibit orofacial clefts when the dams are provided with low folate supplementation during pregnancy. Finally, women with NTD-affected pregnancies have been reported to have high autoantibody titers against the folate receptor, potentially inhibiting the transport of folate to the developing embryo. This may be an explanation for some of the folate-responsive NTDs and perhaps other congenital malformations. Herein, we propose how homocysteinylation of the folate receptor may contribute to generation of these autoantibodies against the folate receptor.

FOLATE RECEPTOR

Nature. 2013 Aug 22;500(7463):486-9. doi: 10.1038/nature12327. Epub 2013 Jul 14.

STRUCTURAL BASIS FOR MOLECULAR RECOGNITION OF FOLIC ACID BY FOLATE RECEPTORS

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ABSTRACT

Folate receptors (FRα, FRβ and FRγ) are cysteine-rich cell-surface glycoproteins that bind folate with high affinity to mediate cellular uptake of folate. Although expressed at very low levels in most tissues, folate receptors, especially FRα, are expressed at high levels in numerous cancers to meet the folate demand of rapidly dividing cells under low folate conditions. The folate dependency of many tumours has been therapeutically and diagnostically exploited by administration of anti-FRα antibodies, high-affinity antifolates, folate-based imaging agents and folate-conjugated drugs and toxins. To understand how folate binds its receptors, we determined the crystal structure of human FRα in complex with folic acid at 2.8 Å resolution. FRα has a globular structure stabilized by eight disulphide bonds and contains a deep open folate-binding pocket comprised of residues that are conserved in all receptor subtypes. The folate pteroate moiety is buried inside the receptor, whereas its glutamate moiety is solvent-exposed and sticks out of the pocket entrance, allowing it to be conjugated to drugs without adversely affecting FRα binding. The extensive interactions between the receptor and ligand readily explain the high folate-binding affinity of folate receptors and provide a template for designing more specific drugs targeting the folate receptor system.

Hum Vaccin. 2011 Feb;7(2):183-90. Epub 2011 Feb 1.

FOLATE RECEPTOR A: A STORIED PAST AND PROMISING FUTURE IN IMMUNOTHERAPY

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ABSTRACT

Folate receptor alpha (FR α) is a membrane-bound transport protein with several features which make it an attractive target for cancer immunotherapy. FR α is largely shielded from the immune system in normal tissue but exposed while expressed on a variety of malignancies; it is functionally active in cancer pathogenesis; and it is immunogenic. A variety of different immunotherapeutic methods targeting FR α are being explored to treat cancer. Passive immunotherapy includes monoclonal antibodies, antibodies modified to deliver treatments, and modified T cell therapy. Active immunotherapy has focused on using FR α to increase the immunogenicity of cancer or to generate active FR α-directed immunity through a range of vaccination techniques. We will review the rationale behind targeting immunotherapy to FR α and cover the various techniques designed to do this. Folate receptor alpha (FRα) is a unique tumor-associated antigen (TAA) with many characteristics that make it an attractive target for immunotherapy in cancer. Many different immunotherapeutic modalities utilizing FRα are being explored to treat cancer. The research is in various stages: some are just beyond conception, others have been tried and abandoned, and others still are progressing through human clinical trials. This review will cover immunotherapeutic methods, both active and passive, that target FRα.

Sci Rep. 2012;2:980. doi: 10.1038/srep00980. Epub 2012 Dec 14.

NUCLEAR LOCALIZATION OF FOLATE RECEPTOR ALPHA: A NEW ROLE AS A TRANSCRIPTION FACTOR

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ABSTRACT

Folic acid (FA) has traditionally been associated with prevention of neural tube defects; more recent work suggests that it may also be involved in in the prevention of adult onset diseases. As the role of FA in human health and disease expands, it also becomes more critical to understand the mechanisms behind FA action. In this work we examined the hypothesis that folate receptor alpha (FRα) acts as a transcription factor. FRα is a GPI-anchored protein and a component of the caveolae fraction. The work described here shows that FRα translocates to the nucleus, where it binds to cis-regulatory elements at promoter regions of Fgfr4 and Hes1, and regulates their expression. The FRα recognition domain mapped to AT rich regions on the promoters. Until this time FRα has only been considered as a folate transporter, these studies describe a novel role for FRα as a transcription factor.