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Juvenile Onset Central Nervous System Folate Deficiency and Rheumatoid Arthritis

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Abstract

Isolated cerebral folate deficiency was detected in a 13-year-old girl with cognitive and motor difficulties and juvenile rheumatoid arthritis. Her serum contains autoantibodies that block membrane-bound folate receptors that are on the choroid plexus and diminish the uptake of folate into the spinal fluid. Whereas her serum folate exceeded 21 ng/mL, her spinal fluid contained 3.2 ng/mL of 5-methyltetrahydrofolate as a consequence of the autoantibodies diminishing the uptake of this folate.

Keywords

folate; rheumatoid; autoantibody

Case Report

A 13-year-old girl had neuropsychiatric disturbances, ataxia, and deterioration in cognitive abilities. Juvenile rheumatoid arthritis was diagnosed at the age of 11 months with clinical manifestations of bilateral knee and ankle swelling, intermittent fevers, and a macular rash. She responded to naproxen; however, a systemic exacerbation at 5 years of age required steroids and methotrexate. At 7 years of age, she complained of neck pain and unusual visual phenomena characterized by colored spots with a firework pattern. Brain magnetic resonance imaging (MRI) showed abnormal enhancement of the soft tissues surrounding the odontoid process, and somatosensory-evoked potentials were abnormal upon left median and posterior tibial nerve stimulation. She was diagnosed with C1–2 arthrosis syndrome[1] (rheumatoid cervical myelopathy). Steroids and methotrexate were discontinued, and anti-inflammatory therapy was initiated with injections of soluble tumor necrosis factor receptor (etanercept) with symptomatic and neuroimaging resolution over several months. At 12 years of age, the patient was re-evaluated for significant behavioral problems characterized by paranoid and suicidal ideations. She also complained of paresthesias in her extremities, intermittent urinary incontinence, impaired writing skills, and deterioration of cognitive abilities at school.

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Clinical Description

At 12 years of age, the patient was a cooperative girl in no distress and with normal speech. General physical and cranial nerve examination was normal. Sensation was intact and bilaterally active to fine touch, pinprick, and proprioception. Motor examination demonstrated normal muscle bulk, tone, and strength. Bilateral fine tremors were apparent in her arms and legs. Deep tendon reflexes were increased throughout; however, plantar responses were flexor. Tandem gait and Romberg testing revealed unsteadiness. Bilateral median and posterior tibial somatosensory-evoked potentials were normal. MRI scans of her brain, craniocervical junction, and entire spinal cord were normal. Serum vitamin E and vitamin B12 levels were normal. Serum folate was >21.7 ng/mL (reference, >5.4 ng/mL). Cerebrospinal fluid contained 3.2 ng/mL of 5-methyltetrahydrofolate (reference range, 18–55 ng/mL, Horizon Molecular Medicine Laboratory, Atlanta, Georgia). Other cerebrospinal fluid studies, including lactate, neurotransmitter metabolites, neopterin, tetrahydrobiopterin, myelin basic protein levels, routine biochemistry, and electrophoresis were all normal. Serum contained folate receptor-1(FR-1) blocking autoantibodies against the plasma side of the folate receptor of the choroid plexus. FR-1 blocking autoantibodies have been found to prevent folate from binding to folate receptors on epithelial cells of the choroid plexus, thus preventing entry of folate into the cerebrospinal fluid.[2]

Discussion

Our child presented with neurologic abnormalities at age 7 years with rheumatoid C1–2 arthrosis syndrome and cervical myelopathy with neck pain and abnormal neuroimaging. She was successfully treated with conservative medical management (etanercept). Up to 70% of rheumatoid patients may develop cervical involvement within 10 years of disease onset.[1,3] Subsequently, at the age of 12 years, she developed ataxia and behavioral, and cognitive changes. Rheumatoid cervical myelopathy was excluded by normal imaging of the craniocervical junction. Previously, she was treated with methotrexate and etanercept; however, she had not received methotrexate for many years. Prior methotrexate use raised the possibility of folate deficiency as a cause of her symptoms. Methotrexate is a known analogue of folic acid and serves to bind dihydrofolate reductase, effectively preventing the systemic metabolism of folate.[4] However, her systemic folate concentration was normal in her serum. Etanercept had been useful in managing her cervical arthrosis and rheumatological manifestations. Etanercept is a dimeric fusion protein of the type II tumor necrosis factor receptor linked to the Fc portion of human IgG1.[5] However, postmarketing observations have occasionally documented inflammatory demyelination with paresthesias, visual disturbances, confusion, gait disturbance, apraxia, facial palsy, and Guillain-Barré syndrome.[6,7] In our patient, these neurological complications seemed unlikely given her normal brain and spine MRI and normal cerebrospinal fluid protein, myelin basic protein, and IgG indices. However, a low concentration of 5-methyltetrahydrofolate was detected in the cerebrospinal fluid with normal serum folate. This finding was confirmed by an elevated autoantibody in the serum that binds to the choroids plexus and diminishes the uptake of folate into the cerebrospinal fluid.

Idiopathic cerebral folate deficiency has been recognized in a cohort of children showing normal development until the age of 4 months.[8] At this age, these children began demonstrating unrest, irritability, and sleep disturbances. Further development was characterized by delayed acquisition of neurodevelopmental milestones, severe cognitive delay, visual and hearing disturbances, progressive ataxia, dyskinesias, and ascending paraparesis leading to spastic tetraplegia if untreated. An autoantibody to the FR-1 located on the plasma side of the choroid plexus epithelium has been identified in these cases.[2] The function of the FR-1 receptor is to transport 5-methyltetrahydrofolate from the blood into the

cerebrospinal fluid by means of receptor-mediated endocytosis. Impaired function of this receptor results in normal to high serum folate level with a low cerebrospinal fluid folate concentration. Although age at diagnosis varied, all identified patients have displayed a form of cerebral folate deficiency with infantile onset. Cerebral folate deficiency was confirmed in our adolescent patient by detection of autoantibodies in the serum against the folic acid receptor.[2] Furthermore, our patient is unusual in that she was developmentally normal and symptom onset did not occur until late childhood. Our patient was started on folinic acid, a reduced methyl-folate metabolite not requiring the FR-1 receptor for transport into the cerebrospinal fluid. There was symptomatic neurological improvement beginning at 3 months after initiation of therapy. Two years later, while on folinic acid 45 mg daily, the cerebrospinal fluid 5-methyltetrahydrofolate level was normal at 50 ng/mL (reference range, 18–55 ng/mL).

Patients with autoimmune disorders are known to produce a wide variety of autoantibodies. Many of these autoantibodies appear unrelated to the pathogenesis of these disorders. We are not aware of any screening that has previously been performed to detect FR-1 autoantibodies in patients with autoimmune disorders. Patients with rheumatoid arthritis are known to produce antibodies to cartilage proteins and fibronectin, in addition to antiphospholipid and antineutrophil cytoplasmic antibodies.[9] It is possible that other autoantibodies are produced and have yet to be elucidated, such as anti–FR-1 autoantibodies. Methotrexate with folate (or folinic acid) is frequently used in the management of rheumatoid arthritis. In addition, autoantibodies can block the uptake of folate through the choroid plexus into the central nervous system. It is therefore important that folate receptor deficiency be considered in the differential diagnosis of neurological symptoms in patients with rheumatoid arthritis.

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