Hereditary Folate Malabsorption with Extensive Intracranial Calcification

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Background: Anemia is a common accompaniment of cerebral palsy, mental retardation and neurodegenerative disorders. **Clinical Characteristics**: A 4-year-old boy with chronic megaloblastic anemia, global developmental delay, seizures, intracranial calcification and new onset neuro-regression. **Observation**: A diagnosis of hereditary folate malabsorption was made, and he was put on oral and injectable folinic acid. **Outcome:** Marked improvement at 6 month follow up. **Message:** Hereditary folate malabsorption should be suspected in any child having megaloblastic anemia and neuro degeneration disorder.

Keywords: *Developmental delay, Megaloblastic anemia, Seizures.*

Hereditary folate malabsorption (HFM) is a rare and specific defect of the absorption of folic acid from the gastrointestinal tract in the absence of malabsorption of any other nutrient [1]. Findings include poor feeding, failure to thrive, and anemia – often accompanied by leukopenia and/or thrombocytopenia – and recurrent infections [2]. Neurologic manifestations include developmental delay, cognitive and motor impairment, behavioral disorder and early-onset seizures [1,3,4].

Diagnosis of HFM is confirmed by impaired absorption of an oral folate load and low cerebrospinal fluid (CSF) folate concentration (even after correction of the serum folate concentration). *SLC46A1*, a gene encoding the proton-coupled folate transporter (PCFT) protein, a member of the superfamily of facilitative carriers, is associated with HFM [5-7]. We report a child who had severe neurological involvement with relative sparing of immunological system, and extensive intracranial calcifications.

CASE REPORT

A 4-year-old child, product of 3rd degree consanguineous marriage, was admitted in our hospital with suspicion of a storage disorder in view of anemia, organomegaly and a neurodegenerative course. He was born at term after an uneventful pregnancy at term with no perinatal complications. At four months of age, he was hospitalized for pneumonia and concurrent anemia. Blood transfusion was given once. He received two more blood transfusions at ages of 18 months and 3 years. He had repeated generalized tonic-clonic seizures at 7 months of age when he was put on oral phenytoin. Phenytoin was changed to sodium valproate after a diagnosis of megaloblastic anemia was made at 18 months of age. However, seizure control was poor despite two anticonvulsants: sodium valproate and levetiracetam at maximum recommended doses. He also had painful oral lesions. Developmental delay was present in all domains of development. In last few months, he became progressively less communi-cative and showed less interest in play; regression was most prominent in motor milestones and was bedridden at the time of hospitalization.

On examination, his weight was at the 10th centile and his height was below the 3rd centile. He looked dull, and had severe pallor and splenomegaly (5 cm below costal margin). His neurological examination revealed hypotonia and hyporeflexia in all four limbs. Blood counts revealed hemoglobin of 4.5 g/dL, total leucocyte count of 4.5×10^9/L and platelet count of 87×10^9/L. Mean corpuscular volume and mean capuscular hemoglobin were 105 and 31, respectively. Bone marrow examination showed features of megaloblastic anemia. Serum folate and cobalamin levels were 1 ng/mL (subnormal) and 2000 pg/mL (above normal), respectively. Serum IgG, IgA and IgM levels were normal. Computed tomography of head revealed diffuse intracranial calcifications in cortex as well as in basal ganglia. Nerve conduction velocity studies suggested peripheral neuropathy. Serum folate level after an oral loading dose of folic acid was 3 ng/mL whereas cerebrospinal fluid (CSF) folate level rose from 1 ng/mL to 1.5 ng/mL. Serum level was 26 ng/mL after parenteral folinic acid. The patient was discharged on oral folinic acid (15 mg/day) and its fortnightly injections. Parents did not consent for repeat CSF analysis for folate measurement to guide therapy. Six months after diagnosis, anemia, oral mucositis and splenomegaly resolved. He had become more interactive and playful, appetite had increased and anthropometric parameters improved. The patient had no seizure episode over next six months. Tone in limbs improved and patient started standing and walking with support.

DISCUSSION

Hereditary folate malabsorption is an autosomal recessive disorder characterized by signs and symptoms of folate deficiency that appear within a few months after birth [7]. Infants exhibit low blood and CSF folate levels. Treatment with folate supplementation results in resolution of the signs and symptoms. The disorder is caused by impaired intestinal folate absorption and impaired transport of folate into the central nervous system [5]. Folate deficiency results primarily in megaloblastic anemia but may affect all three hematopoietic lineages resulting in pancytopenia [2]. Neurological features include developmental delay, cognitive and motor impairment, behavioral abnormalities, ataxia and other movement disorders, peripheral neuropathy, and seizures [8-10]. Diagnosis is confirmed by very low baseline serum folate concentrations (often <1.0 ng/mL; normal: 5-15 ng/mL) and little or no increase after an oral loading dose of 5-formyl-tetrahydrofolate. In unaffected individuals, the serum folate concentration increases to at least 100 ng/mL [3,4,8,9]. CSF folate concentrations are also low and may remain low after normalization of serum folate levels.

Our patient was diagnosed when he presented with severe neurological involvement. He had developed neurological deterioration and was bedridden for last few months, likely due to neuropathy. Our patient also had extensive intracranial calcifications. Congenital infections, neurocutaneous disorders, tumors, traumatic or ischemic insults and endocrine diseases were ruled out in our patient. Though intracranial calcifications have been reported to occur in the cortex or basal ganglia in hereditary folate malabsorption [2,3,9], such extensive calcifications are unusual.

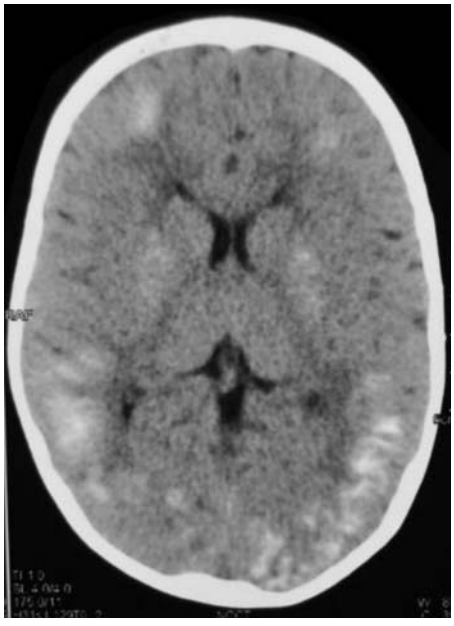

Fig. 1 *Non-contrast computed tomography of head demonstrating extensive intracranial calcifications.*

We conclude that hereditary folate malabsorption is a treatable cause of neurological deterioration in children, and should be suspected in any child having concomitant megaloblastic anemia.

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