Hereditary folate malabsorption: effect of systemic folate supplements on myelination

Folate deficiency is a rare but important cause of macrocytic anaemia in infancy. This article describes folate deficiency in a four-month-old male infant who presented with non-specific symptoms, but was found to have megaloblastic anaemia with very low serum folate due to congenital folate malabsorption. The critical role of folic acid in brain development is highlighted.

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Keywords

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Key points

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1. Hereditary folate malabsorption (HFM) presents clinically from two months with anaemia, immune deficiency and neurological manifestations.
2. In this infant serial MRI scans demonstrated improved myelination with IM folinic acid.
3. Lifelong folate replacement therapy is necessary in HFM.

Folate is known to participate in the *de novo* synthesis of thymidine and adenine, which are constituents of both DNA and RNA, and also of methionine (amino acid) which is required for both protein and S-adenosyl-methionine (SAM) synthesis[1]. SAM is essential for the synthesis of myelin. Mammals are unable to synthesise folate *de novo* and therefore need to obtain a supply of folate from exogenous sources[2]. This paper further highlights the importance of folate in children for cerebral myelination. A four-month-old male infant who presented with a hereditary folate malabsorption (HFM) and in whom the effect of supplementary folinic acid on myelination was documented by serial MRI examinations, is described.

Case study

A four-month-old male infant born to non-consanguineous parents presented with a history of poor feeding and pallor. He was commenced on nasogastric feeds. Blood investigations revealed megaloblastic anaemia with a haemoglobin of 7.1g/dL and a MCV of 96fL (normal range 83 – 101fL). The platelet count was 446x10^9/L, the white cell count was 10.1x10^9/L and C reactive protein 6mg/L. The blood film showed red cell fragmentation. Serum folate concentration was 0.1µg/L (normal range 3-24µg/L) and vitamin B_{12} was 604ng/L (normal range 211-911ng/L). His mother's haemoglobin level was normal during pregnancy and the infant's neonatal haemoglobin was 17.3g/dL, showing that the fetus was not exposed to a folate deficient state *in utero*.

He continued to be non-specifically unwell and developed an oxygen requirement. The formula milk was changed to an amino acid formula (Neocate®) as he was thought to have cow's milk protein intolerance due to an episode of blood streaks in his stool and some vomiting.

The infant was started on intravenous folinic acid at a dose of 1mg once daily. However, his respiratory condition deteriorated with chest X-ray changes compatible with *Pneumocystis carinii* pneumonitis. He was transferred to the paediatric intensive care unit (PICU) for further management following an initial dose of co-trimoxazole (Septrin®). He was electively intubated and ventilated for a short period to support his respiratory condition.

The broncho-alveolar lavage contained *P. carinii* indicating an immunodeficient status. He was continued on oral Septrin and once weekly doses of immunoglobulins. He was referred to a paediatric immunologist and metabolic paediatrician in a tertiary paediatric hospital.

The immunoglobulin levels showed only a mild IgA deficiency and this was later concluded as secondary to folate deficient status leading to transient immunodeficiency. His immunoglobulin and Septrin were subsequently discontinued at later reviews. Red cell folate was found to be low and cerebrospinal fluid (CSF) studies showed no detectable folate at the first lumbar puncture at 17 months of age. Serial red cell folate and CSF folate levels are depicted in **TABLE 1**.

The child had serial MRI brain scans (**FIGURES 1 and 2**) to evaluate the myelination pattern. Initial MRIs showed a

Age of child when sampled	At Dx 4 months	5 months	9 months	17 months	18 months	20 months	2yr 1 month	2yr 8 months	3yr 2 months	4yr 3 months	5yr 3 months	6yr 7 months
Dose and route of administration of folate supplements	None	Folic acid 1.5mg PO daily	Folic acid 5mg PO daily	Folic acid 5mg PO daily	Calcium folinate 5-7.5mg IM daily	Calcium folinate 7.5mg IM daily	Calcium folinate 10mg IM daily	Calcium folinate 10mg IM daily	Calcium folinate 12mg IM daily	Calcium folinate 12mg IM daily	Calcium folinate 12mg IM + Calcium folinate 10mg PO daily	Isovorin 20mg IM
Serum folate (3-24µg/L)	0.1	2.6	5.4	18.9	>20	-	-	-	-	-	>24	>24
Red cell folate (150-650µg/L)	-	-	97	120	802	-	-	-	-	-	-	-
CSF methyl 5-tetra hydrofolate (72-305nmol/L)	-	-	-	<1	-	26	22	19	31	25	14	21

TABLE 1 Red cell and CSF folate levels. Dx = diagnosis.

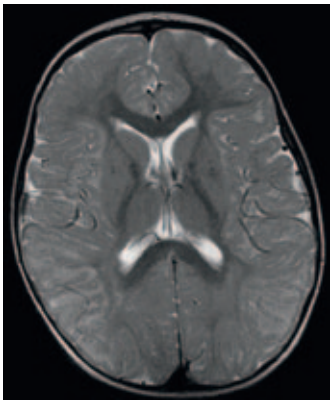

FIGURE 1 T2 weighted MRI scan at two years eight months shows delay in myelination.

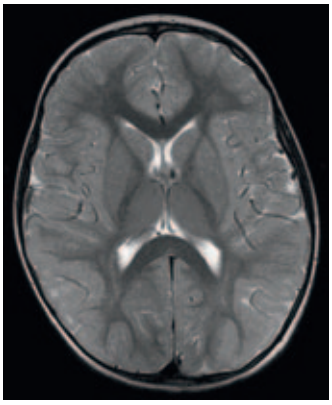

FIGURE 2 T2 weighted MRI scan at four years three months shows progress of myelination.

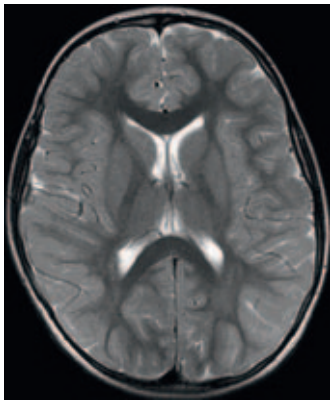

FIGURE 3A T2 weighted MRI scan at six years three months showing completed myelination.

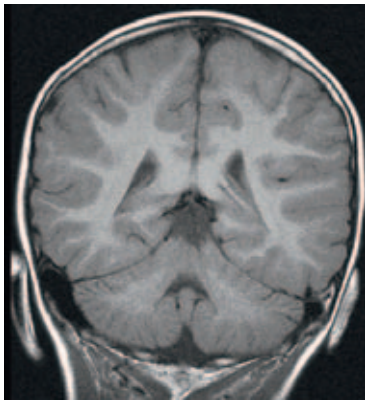

FIGURE 3B T1 weighted MRI scan at six years three months confirms completed myelination.

delayed myelination pattern but no evidence of demyelination. The latest MRI brain scan (**FIGURES 3 A and 3B**) performed at six years three months of age, showed appropriate myelination. It is important to remember that unmyelinated white matter is lighter than grey matter, while myelinated white matter is darker than grey matter[3]. The subcortical white matter should be fully myelinated by 24 months of age and this was clearly delayed in this child with HFM.

He was started on daily intramuscular calcium folinate injections at 18 months of age with dose adjusted by his weight and folate assays. Currently at seven years of age he is on daily IM injections of 20mg Isovorin® (calcium levofolinate). Developmental follow-up at 20 months of age revealed global regression of developmental skills having had normal development till 12 months of age. Delay in social and fine motor skills were noted. The child is currently seven years of age and attending a mainstream school with additional support and has had a statement for educational support.

He has a normal gait, and is able to run and balance on one leg. Although his fine motor and social skills have also improved, he needs extra help with his reading and writing skills. The patient had new onset seizures at six years of age and an EEG was suggestive of complex partial seizures (**FIGURE 4**). He was started on oral sodium valproate but needed changing to carbamazepine (initial choice of anti-epileptics had been guided by his folate deficient state) with good seizure control. Currently he is on a daily dose of 600mg of carbamazepine. It may be noted that the child's CSF folate rose dramatically from less than 1nmol/L at 17 months of age to 30nmol/L at the peak and this possibly coincided with improved myelination. The fact that he has developed epilepsy may be a sign that CSF concentrations are still low as seen in cases of HFM.

Discussion

Folate deficiency has been recognised to play a role in macrocytic anaemia, neural tube defects and neuropsychiatric disorders since the 1940s[4]. Studies in the past have demonstrated the effect of folate deficiency on the CNS antenatally leading to spina bifida[5].

Epidemiology and genetics

HFM has been reported to be panethnic and is inherited in an autosomal recessive fashion[6]. Consanguinity has been reported in half of the HFM affected families[6] and most of the affected children are girls[6]. SLC46A1 is the only gene known so far to be associated with HFM[7]. SLC46A1 encodes the proton-coupled folate transporter (PCFT) protein, a member of the superfamily of solute transporters[8,9].

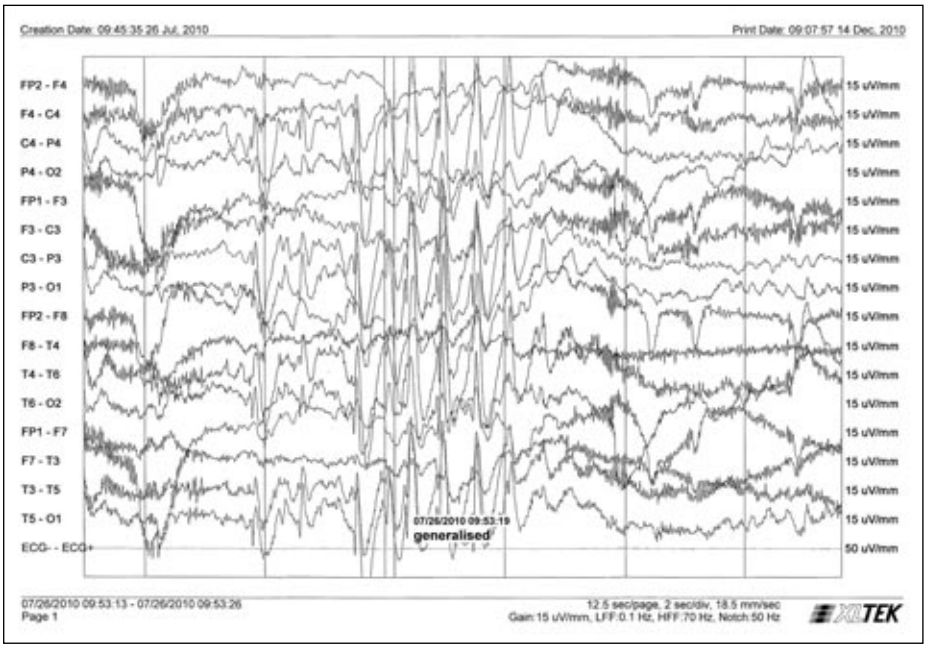

FIGURE 4 EEG showing complex partial seizures.

Folate absorption mechanism

Absorption of folate mainly occurs in the duodenum and upper jejunum and is mediated by PCFT which transports optimally at low pH[8,9]. There is another carrier expressed in the small intestine but it is not functional in the acidic environment. This is the reduced folate carrier (RFC). It functions optimally at pH 7.4. Patients with HFM have defective transport of folate into the CNS and CSF folate is either very low or remains undetectable; this is in spite of a normal level in blood with folate supplementation; as is also evident in our patient. This low CSF/blood folate ratio in HFM indicates the crucial role of PCFT in transporting folate across the blood brain barrier.

Clinical manifestation of folate deficiency

Isolated HFM is a rare disorder characterised by haematological, immunological and neurological manifestations which become manifest from two months onward when intrauterine-acquired stores become exhausted[1,6,7,8].

Anaemia

Folate deficiency primarily manifests as megaloblastic anaemia. It may affect all three haematopoietic cell lines resulting in pancytopenia. The anaemia starts improving within a few days of parental folate replacement, although some cases may need transfusion.

Immunodeficiency

Profound humoral and cellular immunodeficiency state may be present at the initial diagnosis and can be confused with severe combined immunodeficiency (SCID). Leukopenia can result from untreated severe folate deficiency. Hypoimmunoglobulinemia not associated with lymphopenia can lead to infections with *Pneumocystis, Clostridium difficile* and cytomegalovirus infections in the affected infants. Reports have suggested that folate therapy may trigger *Pneumocystis* infection. An early recovery of the immune system following folate therapy may cause *Pneumocystis* infection to become symptomatic.

Neurological presentations

Patients with HFM have defective transport of folate into the CNS in spite of normal levels in the blood. The patient may have neurological signs as part of the initial presentation or later in the course of the disease, notably seizures and developmental delay. Behavioural abnormalities, cognitive impairment, ataxia, other movement disorders and peripheral neuropathy have also been reported. It remains unclear why some children do not have neurological signs since HFM always causes low CSF folate concentrations.

Serial brain imaging with MRI scans in our patient documented the effect of folate deficiency on myelination. The initial studies demonstrated a global delay in the maturation of myelin. These changes were subsequently corrected on treatment, as shown at a later age. Measurement of red cell and CSF folate are essential to differentiate between HFM and cerebral folate deficiency caused by impaired transport across the blood:choroid plexus:CSF barrier where the affected child will have low CSF folate in spite of normal red cell folate levels. Methionine synthetase deficiency will also present as megaloblastic anaemia with developmental delay.

Management

A multi-specialty and multi-disciplinary team is needed to manage cases of HFM. To establish the extent of the disease in a child diagnosed with HFM the following evaluations are recommended[6,7].

- A paediatric neurologist to determine baseline neurological findings and appropriate monitoring of neurological response to folate therapy.
- Initial evaluation and regular follow-up with a metabolic specialist.
- Assessment by a paediatric gastroenterologist to rule out any acquired malabsorption issues and a paediatric dietician to determine any dietary issues.
- Assessment and regular follow-up with a developmental paediatrician to address any underlying developmental delay and help with co-ordinating the overall care of the child in the community. The patient described in the case report showed acceleration of achievement of milestones once folate supplementation was started.

Previous cases in the literature have suggested the use of high dose oral folate in HFM. Our patient required daily intramuscular and oral folate supplementation (recently changed to IM Isovorin) to maintain red cell folate levels and even with this frequency the CSF folate concentrations remained below the normal range.

The most important element for treating children with HFM is the maintenance of adequate CSF folate concentrations and it is necessary to monitor red cell and/or serum folate to ensure the folate stores are well repleted. Serum folate alone is not sufficient for monitoring, as was seen in our case when serum folate was normal at nine months, but RBC folate was still low indicating deficiency of tissue stores. Although HFM patients never achieve a normal level of CSF folate, it should be noted that

without folate supplementation to maintain some level of folate in the CSF, myelination of brain and achievement of developmental milestones is highly unlikely.

Conclusion

Isolated HFM shows how the human physiology reacts to a particular deficiency in its purest form, such as folate deficiency. The diagnosis of HFM depends on demonstrating an impaired folate transport across the gastrointestinal tract and the blood brain barrier. A normal neurological and developmental outcome may be achieved by aggressive folate replacement therapy by the parenteral or oral route. This paper highlights the importance of investigating rare causes of macrocytic anaemia in infancy. Genetic counselling may be necessary for the family members to discuss the effect on future offspring.

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