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. 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. 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 446x10⁹/L, the white cell count was 10.1x10⁹/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 B₁₂ 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 pneumonia. 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 cerebral spinal 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
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 matter3. 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

colate 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 1940s4. Studies in the past have

demonstrated the effect of folate deficiency

on the CNS antenatally leading to spina

bifida5.

Epidemiology and genetics

HFM has been reported to be panethnic

and is inherited in an autosomal recessive

fashion7. Consanguinity has been reported

in half of the HFM affected families6 and

most of the affected children are girls6.

SLC46A1 is the only gene known so far to

be associated with HFM7. SLC46A1

codes the proton-coupled folate

transporter (PCFT) protein, a member of

the superfamily of solute transporters8,9.
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. 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.

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:

- 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 dietitian 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 Isovirin) 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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**References**