Expanding the Phenotypic Spectrum of Methylenetetrahydrofolate Reductase (MTHFR) Deficiency in Childhood: A Case Series

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**Summary (Abstract)**

Methylenetetrahydrofolate Reductase (MTHFR) Deficiency is a rare inborn error of folate metabolism. A number of phenotypic findings have been identified to date, and we hereby wish to expand its phenotype based on our Irish experience of the condition. We follow three children with MTHFR deficiency in our National Centre for Inherited Metabolic Disorders (NCIMD), giving an estimated point prevalence of approx. 0.08 cases per 100,000 in the Republic of Ireland. Our first case was referred for a metabolic opinion at 19 months of age. She had a history of global developmental delay with hypotonia, microcephaly, nystagmus, rash and seizures. The second patient presented at twelve years of age with an osteopenic femoral fracture on the background of low body mass index (BMI). The third case presented at ten and a half years of age with acute mood disturbance with challenging behavior and a history of focal seizures and intellectual disability. It has been reported that early treatment may provide clinical benefit; however, we wish to acknowledge the varying responses to treatment despite pleasing metabolic control in our patients. MTHFR deficiency is a challenging diagnosis in childhood, given its low prevalence, complex phenotypes and varying response to treatment. Presymptomatic treatment further to early diagnosis through newborn screening may further improve outcomes.

**Synopsis**

We examined the paediatric Irish cohort of MTHFR deficiency patients to expand our knowledge of the condition’s phenotypes.

**Key Clinical Message**

MTHFR deficiency is a challenging diagnosis in childhood, given its low prevalence and complex phenotypes. We examined the paediatric Irish cohort of MTHFR deficiency patients to gain new insights into the phenotypic spectrum. We noted varying response to treatment in symptomatic patients; diagnosis through newborn screening may further improve outcomes.

**Keywords**

Folate, homocysteine, methylene tetrahydrofolate reductase deficiency, newborn screening, rare disease

**Introduction**

Methylenetetrahydrofolate reductase (MTHFR) deficiency (OMIM #  [236250](https://www.omim.org/entry/236250)), an inborn error of folate metabolism, is an ultra-rare metabolic disorder.1 MTHFR plays a key role in folate metabolism by catalyzing the reduction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (MTHF), which is required for the remethylation of homocysteine to methionine, generating tetrahydrofolate.2 MTHFR deficiency leads to homocysteinemia with low-normal methionine concentrations in plasma as well as low-normal folate. Individuals with MTHFR deficiency do not usually present with haematological abnormalities.3,4 MTHFR deficiency is an autosomal recessive disorder.5 A number of clinical phenotypes for the condition have been identified from the severe, neonatal onset MTHFR deficiency to incidental findings in adult patients.

Here, we wish to expand the phenotypic spectrum of MTHFR deficiency in the paediatric population by presenting three cases diagnosed and treated at our National Centre for Inherited Metabolic Disorders diagnosed between 2008 and 2023. The National Centre for Inherited Metabolic Disorders, located at Children’s Health Ireland at Temple Street in Dublin, is the national tertiary referral center for all children in the Republic of Ireland with inborn errors of metabolism. The national Metabolic Laboratory and Newborn Blood Spot Screening laboratory are also located on site. Ethical approval was granted by the Institution’s Research/Ethics Committee and written informed consent was taken from parents/families as appropriate. Our database was reviewed and we identified all patients with genetically confirmed childhood-onset MTHFR deficiency. Their medical records were reviewed and clinical, diagnostic biochemical, enzymatic as well as molecular genetics and neuro-radiological findings compiled.

**Case 1: Case History and Examination**

Our first patient was referred to us for further metabolic investigations at 19 months of age with global developmental delay, microcephaly, nystagmus and a history of rash.6 We here report on her clinical course and outcome age 14 years.

She was born at 39 weeks gestation after an uneventful pregnancy and had a normal neonatal course apart from mild jaundice. She was born to Irish non-consanguineous parents. Her head circumference at birth was at the 10th centile and her weight on 50th centile.

She was noted to have an erythematous rash at 6 weeks of age which required emulsifying ointments. At 11 weeks of age she presented with hypotonia, an episode of upper limb tremors and a possible starring episode. Her occipitofrontal circumference was noted to be on <0.4th percentile. She was linked in with services to monitor her developmental progress. She sat unaided at 15 months of age, and had no words. At 18 months of age, she developed a swollen, painful left wrist.

**Case 1: Investigations and Treatment**

Her ANA titre was positive (1:400). In parallel, she was referred for a metabolic opinion in light of her global developmental delay with hypotonia, microcephaly and nystagmus. Contrast MRI of the wrist suggested synovitis with thickening of the subcutaneous tissues with high signal around the carpal bones. She responded to high dose anti-inflammatory medications and intra articular joint injections. MRI brain revealed small cerebral hemispheres with bilateral subdural collections, a thin corpus callosum and it also showed periventricular white matter hyper intense signal areas (Figure 1a). Ophthalmological assessment showed convergent strabismus, delayed visual maturation with evidence of cortical visual impairment. EEG demonstrated generalized seizure activity with immature wave forms and phenobarbitone was initiated, along with pyridoxine and folinic acid for possible vitamin-responsive seizures. She developed a new, severe well demarcated ‘peeling paint’ scaling and erythematous rash. A skin biopsy revealed significant hyper- and para- keratosis.

From a metabolic point of view it was noted that her plasma amino acids revealed a low-normal methionine of 5 umol/L (reference range 5-77 umol/L) and raised total homocysteine of 149 umol/L (3-8 umol/L). Serum folate was low at 2.6 (3.8 - 18.2ug/L). Mean cell volume (MCV) was normal 77 fL (73-86 fL) with normal blood film appearance. There was no increase in excretion of methylmalonic acid (MMA) on her urine organic acid profile and her acylcarnitine profile was also normal. Cerebrospinal fluid (CSF) revealed a MTHF of less than 5 nmol/L (52-178 nmol/L), indicative of MTHFR deficiency. Blood leukocyte-derived DNA gene sequencing subsequently identified two likely pathogenic variants in the *MTHFR* gene, c.386C>A (p.T129N) and c.757G>T (p.V253F), confirming the diagnosis. Parental analysis was carried out and confirmed the presence of a single variant in each parent. MTHFR activity in fibroblasts (Prof. Matthias Baumgartner, Zurich, Switzerland) revealed a very low residual activity of approx. 1% of the mean control activity. She was commenced on additional treatment, including, e.g., folinic acid followed by 5-methyltetrahydrofolate, Vitamin B12, and Betaine. From an epilepsy point of view she developed generalized tonic clonic seizures which were controlled with antiepileptic drugs. Her medications include lamotrigine, levetiracetam, sodium valproate and midazolam if needed. Neuroimaging showed that periventricular white matter hyper intense signal areas had improved with targeted treatments (Figure 1b).

Her metabolic control was pleasing with total homocysteine concentrations < 100 umol/L and free homocysteine <5 after specific treatment commenced (Table 1). She had several lumbar punctures for neurotransmitter and CSF folate studies. Her methyltetrahydrofolate medication dose was increased to up to 15 mgs three times a day. 5-Hydroxyindoleacetic acid was found to be borderline low at 70 nmol/L (89-367 nmol/L) on one occasion. A degree of impaired serotonin turnover was noted, and decreased serotonin has been associated with 5-methyltetrahydrofolate deficiency states.7 However, admissions to hospital for lumbar punctures were more difficult to manage for our patient and there was also no immediate clinical benefit noticeable. She had her menarche at 12 years of age. Now aged 14 yrs, she walks with a crouched gait and requires monitoring for scoliosis. Her head circumference remained <0.4th centile (48.2 cm). She has a special needs assistant in school. In relation to her juvenile arthritis, she has been commenced on Adalimumab, a monoclonal antibody and TNFα inhibitor which contributed to her improvement from an arthritis perspective.

**Case 2: Case History and Examination**

Our second patient, a boy, was born in India at term with no neonatal concerns to non-consanguineous parents. The family moved to Ireland when he was 10 years of age. Prior to moving to Ireland he required no medical intervention. However, he was known to have a low appetite with little interest in food.

The boy presented at 12 years of age with an osteopenic femoral fracture (Figure 2). He was brought to the hospital after he fell on the couch at home and suffered a painful injury.

At presentation he weighed 23.05 kg (<0.4th percentile), his height was 149 cm (50th percentile), and he was noted to have a low Body Mass Index (BMI) (10.4 kg/m2, reference range 15 -24 kg/m2).

**Case 2: Investigations and Treatment**

Bone X-ray showed reduced bone density with thinning of the cortex and an oblique distal femoral metaphysis fracture (Figure 2). Point-of-care blood tests showed a reduced plasma calcium level (2.24mmol/L; reference range 2.25-2.7mmol/L), a low corrected calcium (2.06 mmol/L; 2.25-2.7 mmol/L) and an elevated alkaline phosphatase (488 IU/L; <300). Full blood count was essentially normal including MCV and blood film.

Further biochemical blood tests revealed multiple nutritional deficiencies, e.g., Vitamin D <13 (>50 nmol/L), Folate 2.1 ng/mL (3.8 - 18.2 ng/ml), Vitamin B12 107 (211-760 ng/L) and Ferritin 12 ug/L (15 to 80 ug/L). His initial total homocysteine of 86 umol/L; however, his methionine was normal at 34 as was cystine at 38 (27 - 107 umol/L). Urine organic acid analysis did not show any abnormalities, with no excretion of methylmalonic acid (MMA, 0-8 umol/mmol creatinine).

The boy received orthopedic care and his healing process was uncomplicated; furthermore, he was given a Vitamin D and calcium supplement. Additionally, he was commenced on multivitamin supplements, including folate, Vitamin B12, and Vitamin B6. Upon conformation of his overarching metabolic diagnosis he was also started on betaine and 5- methyltetrahydrofolate. Gene sequencing identified two likely pathologic variants in the *MTHFR* gene, c.589T>G (p.Tyr197Asp) and c.1072C>T (p.Arg258\*) and parental carrier status was confirmed. His baseline MRI brain result showed only mild changes of cerebellar atrophy (Figure 3). CSF neurotransmitter and folate studies were deferred in light of his good clinical progress and at his parents’ request.

Further to commencement of treatment his weight was tracking between 2nd – 9th centile and his height between 75th – 91st centile. At 15 years of age, his BMI had normalized (17 kg/m2). His appetite had further improved and he had made pleasing progress. He enjoyed playing cricket and doing gymnastics in school.

**Case 3: Case History and Examination**

The third patient, a girl, was born at term with no neonatal concerns to Irish non-consanguineous parents. She presented at 5 years of age with focal seizures. During these episodes she became pale, unresponsive and had twitching of her right upper limb with a persistently fixed stare, lasting a few minutes. She also had a mild resting tremor, developmental co-ordination disorder and was noted to have learning difficulties

**Case 3: Investigations and Treatment**

She had previous investigations, including, e.g., a CGH microarray, which were unrevealing from a diagnostic point view. She had an MRI brain which showed a paraventricular left frontal deep white matter T2 hyperintensity of uncertain significance. She also had some subjective volume loss in the body and splenium of the corpus callosum as well as reduced white matter volume in both parieto-occipital lobes posteriorly. Her EEG at this time showed abnormal low amplitude spikes bilaterally in the fronto-central region. Initially, her seizures were well managed on valproate; however, she had worsening of her tremor and was switched to levetiracetam. At this point she was also commenced on Pyridoxine.

By 9 years 5 months she had increasing behavioral difficulties which were difficult to manage and so her levetiracetam was discontinued and she was initiated on oxcarbazepine. Following this medication change was a notable increase in her weight. At ten years, 4 months she was then initiated on brivaracetam with the aim of weaning to a lower dose of oxcarbazepine due to her weight gain and challenging behavior. Over a three month period following this she had a marked deterioration in her behavior with significant aggression, nevertheless she had adequate seizure control. Given her deteriorating behavior one month prior to her admission she was weaned off brivaracetam. She was continued on a lower dose of oxcarbazepine and initiated on clobazam. She was admitted at ten years, eight months of age with an acute episode of aggression, agitation, as well as auditory and visual hallucinations.

Her repeat MRI brain which revealed noticeable generalised supratentorial white matter and grey matter volume loss when compared with previous MRI brain as in figure 4. MR Spectroscopy was normal. She had an EEG which was markedly abnormal with slow and encephalopathic background but with no frank epileptiform discharges. A comprehensive work-up was performed. Plasma amino acids showed an elevated total homocysteine of 330 umol/L, presence of mixed disulphide peak detected with an elevated free homocystine of 36 umol/L and a low methionine of 7 umol/L. There were no abnormalities noted on urine organic acid or dried blood spot acylcarnitine profiles. Normal FBC with no evidence of macrocytosis raised suspicion for MTHFR deficiency rather than intracellular cobalamin (cbl)-related disorders.3,4 Additional CSF amino acids studies revealed an undetectable methionine in CSF. CSF 5-Methyltetrahydrofolate was also low at <10 nmol/L (46 to 160 nmol/L). Her serum folate was reduced at 3.1ug/L (3.8 to 18.2ug/L). Confirmatory molecular genetic analysis demonstrated the homozygous pathogenic variant c.386C>T in the *MTHFR* gene (p.Thr129Ile). The patient was commenced on Pyridoxine 50mg OD, Vitamin B2 10mg OD, Betaine 3grams BD, Methylfolate 15mg OD and Vitamin B12 1mg IM once a month with a significant improvement in her behavior and pleasing clinical progress.

**Conclusion and Results**

MTHFR Deficiency in the Irish population displays heterogeneity in its presentation. It is important that physicians are aware of this disorder and consider the diagnosis in order to aid early initiation of treatment. However, it is a challenging diagnosis given the wide range of symptoms and age of onset of disease. It often has a multisystem presentation, from chronic, to acute and acute on chronic presentations.

Childhood-onset MTHFR deficiency is rare in the Irish paediatric population, with only three patients identified to date, as presented here. The phenotype of MTHFR deficiency may be slowly progressive and non-specific, including developmental delay, behavioral disturbance, or more severe with microcephaly, seizures and other neurological symptoms.8 Many features of MTHFR deficiency overlap with other disorders of the remethylation pathway of homocysteine to methionine, such as cblE/methionine synthase reductase, cblG/methionine synthase deficiency.3,4,9 Absence of macrocytosis is helpful in distinguishing MTHFR deficiency from an intracellular defect but molecular genetic confirmation is essential; however, initiation of early treatment is recommended when diagnostic biochemical findings become available and the clinical suspicion arises.3,4 Low plasma concentration of methionine leads to decreased S-adenosylmethioine which is essential for optimum myelin synthesis.1 It is felt that the neurological sequelae of MTHFR deficiency are as a result of low plasma concentration of methionine and S-adenosylmethionine in the central nervous system.10

When performing a metabolic work up, e.g. in a child with global developmental delay, it is important to note that plasma homocysteine concentration is often not routinely analyzed as part of the quantitative amino acids, as free homocystine deteriorates rapidly in plasma; therefore, (total) plasma homocysteine should be requested specifically, if clinical and/or biochemical suspicion for a re-methylation defect, namely MTHFR deficiency arises.4,6

**Discussion**

In this case series we wish to highlight the varying phenotypes of MTHFR deficiency in our paediatric patient cohort, including an osteopenic femoral fracture as a hitherto undescribed presenting symptom. As presented here, we would like to raise the possibility of an individual range in response to treatment, depending, e.g., on the severity of the underlying defect, presenting clinical features and co-morbidity, as well as age at presentation. However, it has been reported that early treatment with betaine, folinic acid and hydroxycobalamin may significantly improve clinical outcomes and minimize neurological deterioration.11 One study showed a betaine dose of 100mg/kg/day was effective in preventing mortality and, when initiated early, may enable normal psychomotor development.12 Our first case has pleasing biochemical response; however, her clinical course has shown slow clinical progress despite remarkable improvement on neuroimaging. While biochemical improvements were demonstrated, plasma homocysteine never normalized. In light of initial low methionine concentrations in plasma/CSF as well as striking neurological features, two out of three patients (cases 1 and 3, respectively) were advised on a moderate methionine-rich diet (including, e.g., egg yolks) in addition to their medication regimens; however, the beneficial effect of same was difficult to establish.

A number of case reports outline the most common features of MTHFR deficiency, including, e.g., developmental delay, seizures, tremor, microcephaly as well as neuropsychiatric findings, similar to our cases one and three, respectively.13, 14 However, case two, to the best of our knowledge, is a new phenotypic finding. This boy also had evidence of nutritional deficiencies when he was diagnosed which we feel may have also contributed to his pathological fracture.Interestingly, there are some studies examining the effect of MTHFR gene polymorphism on Bone Mineral Density (BMD). One study examined BMD in teenage girls with Anorexia Nervosa (AN) and showed that the presence of the MTHFRgene polymorphism was associated with a lower BMD in teenage girls with AN. It showed a likely dose-response effect as those with only one polymorphic variant had higher BMD than those with two polymorphic variants.15 The MTHFR polymorphism has been shown to have a slight increase in fracture risk.16 It is proposed that the decreased bone mineral density is related to the high homocysteine plasma concentration which interfere with collagen cross linking, an essential part of bone formation.17

Newborn bloodspot screening for classical homocystinuria based on determination of raised blood methionine concentration has been successfully in place in the Republic of Ireland since 1971.18,19 Conversely, newborn screening by means of low methionine blood concentration has been suggested to allow for early diagnosis and intervention in patients with severe MTHFR deficiency.20-22 The exact prevalence of early-onset MTHFR deficiency in childhood in the Republic of Ireland remains unknown; however, we suggest an estimated point prevalence of approximately 0.08 cases per 100,000,23 based on the three confirmed cases in our national center. Furthermore, we would like to suggest that screening for severe MTHFR deficiency could be included in newborn screening, as pre-symptomatic treatment is available and may further improve patient outcomes.

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**Legends to figures**

**Figure 1:**

MRI brain of patient 1 showing some general cerebral atrophy along with periventricular hyperintense signals (arrows) around the time of her diagnosis (a). MRI brain at 9 years of age demonstrated significant improvements of cerebral atrophy and periventricular signals (arrows) (b).

**Figure 2:**

Standard X-ray image of patient 2 aged 12 years demonstrating osteopenia and a fracture involving the left distal femur metaphysis (arrow).

**Figure 3:**

MRI brain of patient 2 showing mild atrophy of the cerebellum with prominent cerebellar folia (thick arrow). Similar findings were noted on neuroimaging of our other cases (images not shown here).

**Figure 4:**

MRI brain of patient 3 at 11 years of age showing cerebral atrophy with an increase in the axial space (arrow) (a). On the right side the MRI was done 7 months after commencing targeted treatment, showing that both widening of axial space and brain atrophy have essentially resolved (arrow) (b).