Molecular Genetics and Metabolism Reports 25 (2020) 100644

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Case Report

Clinical presentation of seven patients with Methylenetetrahydrofolate reductase deficiency

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ARTICLE INFO

Keywords:
Apnea
Homocysteine (HYC)
Hydrocephalus
Methylenetetrahydrofolate reductase (MTHFR)

ABSTRACT

Methylenetetrahydrofolate reductase deficiency; MTHFR (MIM 236250) is widely studied with more than 200 reported cases up to our knowledge from pediatrics to adult patients. Clinical presentation of MTHFR deficiency has a wide spectrum and its severity correlates with the degree of the enzyme activity. We report here seven pediatric cases with variable presentations including apnea at early infancy, in addition to hydrocephalus that needed drainage.

Introduction

Methylenetetrahydrofolate Reductase, MTHFR is a cytoplasmic enzyme that catalyzes the NADPH-linked reduction of methylenetetrahydrofolate, MTHF to methyl-THF. Methyl-THF serves as the methyl donor for the methylation of homocysteine in the reaction catalyzed by methionine synthase (5-methyl-THF: homocysteine methyltransferase. Methionine is then converted to S-adenosylmethionine (SAM). The reaction catalyzed by MTHFR is essentially irreversible under physiological conditions, and enzyme activity is regulated by levels of S-adenosylmethionine (SAM), which acts as negative feedback inhibitor [1].

Demyelination in MTHFR deficiency has been attributed to low SAM levels in the brain and it has been described in several patients with MTHFR deficiency [2].

MTHFR deficiency leads to moderate homocystinuria and hyperhomocysteinemia with low or relatively normal levels of plasma methionine. Clinical manifestations are variable including developmental delay, motor and gait abnormalities, seizures, EEG abnormalities, microcephaly, and hydrocephalus internus [1–3].

We report seven cases from Saudi Arabia (Fig. 1), presented with apnea, hydrocephalus, and neurodevelopmental delay.

CASE REPORTS (Table 1)

PATIENT 1.

A 6 months old boy who was a product of term pregnancy, and spontaneous vertex delivery with unremarkable perinatal history. He has a low hairline, normal hair texture, and skin complexion. No dysmorphic features. At one month of age, he presented with lethargy and seizure. He had difficulty in feeding and delayed development. On examination, he had poor swallowing and fixing, axial hypotonia but normal peripheral tone and normal tendon reflexes. The rest of the systemic examination was unremarkable. Ophthalmology examination revealed mild disc pallor not explaining the poor vision. Brain magnetic resonance imaging (MRI) showed mild brain atrophy. The lactate level was normal. EEG showed multiple epileptiform discharges. At two and a half months of age, he had cyanosis for few seconds and recovered spontaneously. He was witnessed in the emergency to have cyanosis and frothy secretions for 10 min followed by apnea. No chocking or vomiting. Lab tests revealed a high Homocysteine of 135.9 umol/L. MTHFR deficiency was suspected and the gene testing was sent and confirmed. On our last follow up, he was 6 months old on Carbamazepine 5 mg/kg/day with good response and started on Vitamin B12 100 μg weekly intravenous injection, betaine 100 mg/kg/day, pyridoxine oral 100 mg/day and folenic acid oral 15 mg/day. The last homocysteine level is 102.6 umol/L.

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https://doi.org/10.1016/j.ymgmr.2020.100644
Received 28 April 2020; Received in revised form 22 August 2020; Accepted 23 August 2020

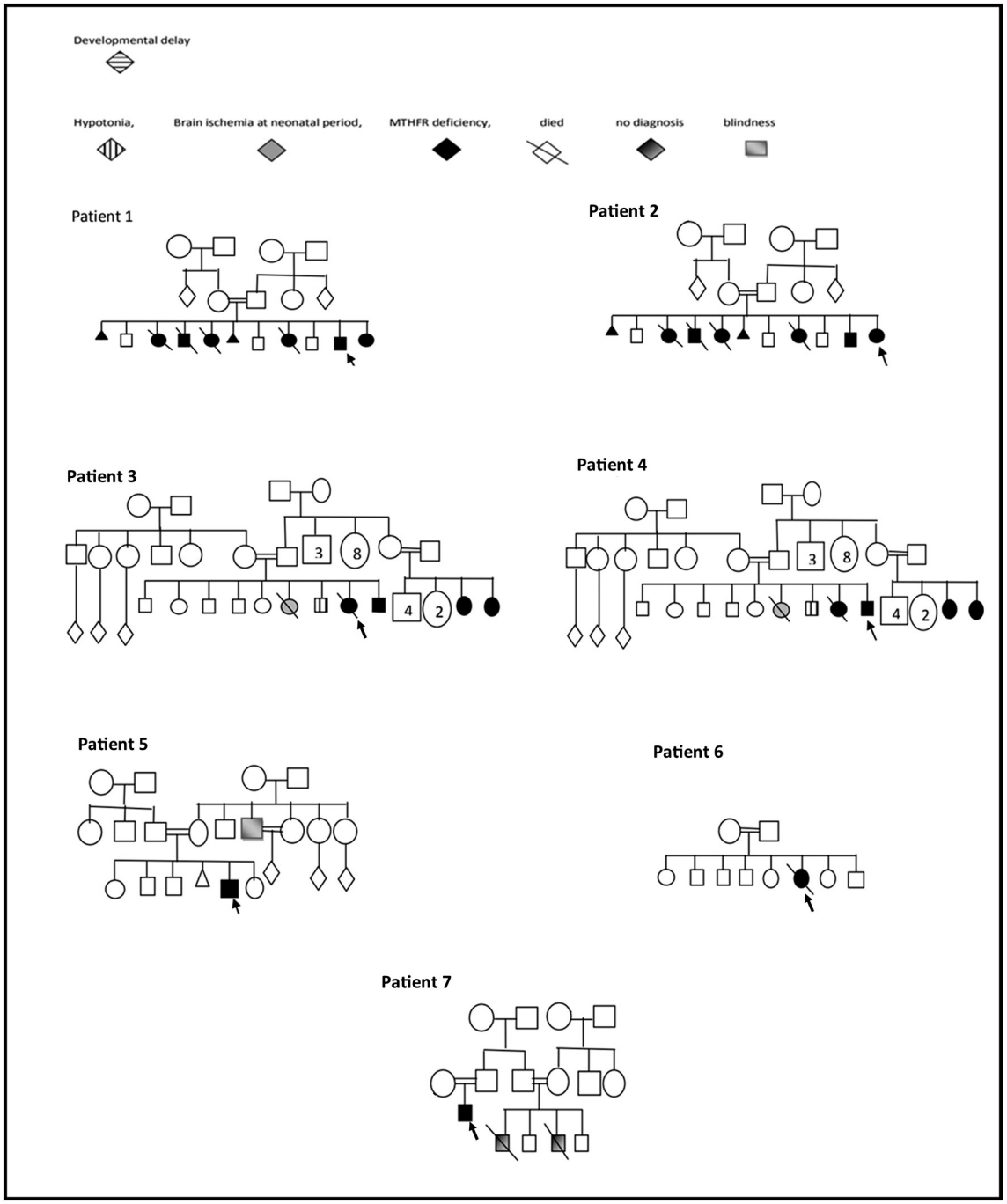

Fig. 1. Family pedigree of all patients.

PATIENT 2.

A 17 months old girl, the sister of patient 1. She is a product of full-term normal spontaneous delivery. She has low set ears, heterochromia. Development is normal. Her homocysteine level was high, 189.97 umol/L since early infancy, and last follow up, when homocysteine level was 115.8 umol/L. MTHFR deficiency was investigated and confirmed. The patient was started on Aspirin 81 mg/ day orally, betaine 100 mg/kg/day, pyridoxine oral 100 mg/day and folinic acid oral 15 mg/day, methionine 50 mg/kg/day. The patient was seen last time at the age of 3 years, she was having a global developmental delay and ataxic gait. Her latest brain MRI showed cerebral and cerebellar atrophy.

PATIENT 3.

A 2 months old girl born at term via normal spontaneous delivery, Apgar score was 9&10 at 1 & 5 min. She had good growth parameters at birth. She had fair skin, down slanted eyes, low set ears, and high arch palate. She presented with hypotonia, developmental delay, and abnormal breathing pattern associated with hypothermia of 34.7 ˚C. She required mechanical ventilation due to hypoventilation. Her parents are first degree cousins and have 5 healthy siblings and one older sibling with hypotonia. On examination, she had microcephaly with a head circumference at 35.2 cm (< 5th percentile) with significant head lag. She was not following, had bilateral red reflex, and equal reactive pupils but with nystagmus. She had increase tone of upper limbs while lower limbs low tone and absent deep tendon reflexes. Brain MRI showed significantly dilated ventricles, a picture of hydrocephalus was suspected. Subsequently, a ventriculoperitoneal shunt was inserted, however, the clinical picture of the patient did not improve after the

Table 1
biochemical parameters & Neurology Findings for all patients.

	Homocysteine HYC (umol/L)	Plasma Methionine (umol/L)	Ammonia (umol/L)	Lactic acid (mmol/L)	Hb (g/L)	MCV (fL)	MTHFR Gene detection	Neurology Findings
Patient 1	135.9	30	63	1.5	99	100	680 T > C (p.Thr227Met) Homozygous	Has seizures Brain MRI: mild brain atrophy.
Patient 2	189.97	4	–	–	193	105	680 T > C (p.Thr227Met) Homozygous	Brain MRI: cerebral and cerebellar atrophy
Patient 3	118.5	low		1.2	106	98.9	680 T > C (p.Thr227Met) Homozygous	Has Apnea. Brain MRI: microcephaly & hydrocephalus.
Patient 4	161.8	33	47	2.58	130	91.7	680 T > C (p.Thr227Met) Homozygous	Has apneas and seizures
Patient 5	88.5 Highest 150.2	1	47	1.5	120	106	680 T > C (p.Thr227Met) Homozygous	Has apneas & seizures. CT head: microcephaly, communicating hydrocephalus, suggestive of Dandy walker.
Patient 6	129.79 Highest 167.62	1	32	–	126	87.2	680 T > C (p.Thr227Met) Homozygous	Brain CT showed global brain atrophy. Later, brain edema
Patient 7	81.6	27	58	1.2	123	82.7	680 T > C (p.Thr227Met) Homozygous	Has seizures. Brain MRI: large right temporo-frontoparietal arachnoid cyst with mass effect

procedure. EEG showed sharp waves. No organomegaly. Tandem mass spectrometry revealed low methionine. The patient was started on betaine 100 mg/kg/day, pyridoxine oral 100 mg/day, folinic acid oral 15 mg/day, and methionine 50 mg/kg/day. She died at 3 months of age after a complicated course end with pulmonary hemorrhage and ARDS.

PATIENT 4.

A 15 days old boy, brother of patient 3. He was born at term with a birth weight of 2.755 kg, length, and head circumferences were average. He was brought to the emergency department due to lethargy and difficulty in feeding. In the hospital, he developed recurrent apneas that required intubation for mechanical ventilation. Later, he developed seizures. The examination was unremarkable. EEG showed a temporal lobe seizure. Homocysteine was 161.8 umol/L. His molecular genetic report expresses an MTHFR deficiency. He was started on betaine, methionine, folinic acid, carnitine, and pyridoxine. On our last follow up, he was 5 years of age with controlled seizures, general well-being, no apnea and he has normal growth parameters. The latest homocysteine level is 83 umol/L. The patient is currently on betaine 100 mg/kg/day, pyridoxine oral 100 mg/day, folinic acid oral 15 mg/day, and methionine 50 mg/kg/day.

PATIENT 5.

A 5 months old boy. He is a product of full-term pregnancy, delivered by CS due to bradycardia. He was brought to the hospital due to recurrent apneas for one day. He had a cough associated with symptoms of upper respiratory tract infections for 3 days without fever. The apnea was not related to feeds and not preceded by abnormal movements. Later, he developed seizures in the form of cyanosis, up rolling of eyes, and drooling of saliva at 1 month of age, which was not controlled by levetiracetam. He was developmentally delayed. His initial homocysteine level was 88.5 umol/L. His CT scan (Fig. 2) showed communicating hydrocephalus, large posterior fossa with vermian agenesis suggestive of Dandy walker. At the age of 5 months, the patient presented to our ER with pallor, respiratory distress on supplemental oxygen saturating 98% with decrease air entry at the right side. He was diagnosed initially to have bronchopneumonia, which was complicated and needed mechanical ventilation. Growth parameters were all at the 5th percentile (head circumference was 39 cm). The brain MRI showed generalized ventriculomegaly and cerebellopontine hypoplasia that may be related to his apnea, in addition to a small infra-cerebellar cyst which might result in partial obstruction. Subsequently, and because the diagnosis was not yet reached, a ventriculoperitoneal shunt was inserted to solve the patient's apnea. His repeated CT brain showed no significant change in the ventricular size. The patient eventually deteriorated during the intensive care admission and developed septic shock, pulmonary hemorrhage, and died. Biochemical investigations

Fig. 2. Patient 5 CT brain showing ventriculomegaly.

sent showed a high homocysteine level of 88.5 umol/L (highest level was 150.2 umol/L) and MTHFR mutation was detected after the patient's death.

PATIENT 6.

A 13-year-old girl was born via spontaneous vertex delivery with normal growth parameters. Her Apgar scores at 1, 5 min were 9&9. She presented at 12 days of age with poor feeding, hiccups, and jaundice since birth. Her examination was unremarkable except for an ejection systolic murmur on the cardiac exam. Echocardiography showed ASD, small VSD & peripheral branch pulmonary artery stenosis. Laboratory workup showed Klebsiella pneumonia in urine culture. She had negative CSF, CMV, Hepatitis & Rubella cultures. CT brain showed profound hypodense white matter. The suggestive family history of an affected sister with MTHFR deficiency, as well as the molecular testing of the patient, confirmed the diagnosis of MTHFR deficiency. The patient was started on medications; folinic acid 15 mg/day orally, betaine 3 g orally twice daily, methionine 250 mg orally four times per day. At 13 years of age, she presented with loss of consciousness after having a sudden chest and abdomen pain associated with seizure for 30 min followed by cardiopulmonary arrest. She had a pulseless electrical cardiac activity. She was resuscitated and intubated for mechanical ventilation. Brain CT showed global brain atrophy and no acute findings but after 5 days there was significant brain edema without hydrocephalus. Brain venogram CT was unremarkable. Despite medical treatment, the homocysteine level remained elevated at 129.79 umol/L. The girl died after aggressive PICU management.

PATIENT 7.

An 11 years old boy who was born at full term via spontaneous vertex delivery to a 39 years old healthy mother. His perinatal history was unremarkable. He was brought to the hospital at 15 days of age with difficulty in breathing and progressive lethargy since birth. History of frequent attacks of cyanosis of the face for 2 days. No history of apneas or abnormal movements. No history of vomiting or diarrhea or characteristic body odors. There was a family history of a cousin, who died at 10 days of age with an unknown diagnosis. On examination, he was lethargic but arousable and has fair skin, colored eyes, long philtrum, and high arch palate. He was hypotonic and had weak reflexes including Moro reflex. His weight was 3.14 kg (5th percentile), length 54 cm (50th percentile) and head circumference was 33.5 cm (10-25th percentile). Vital signs were stable initially. No heart murmur or organomegaly. The baby required emergency management 3 days after admission due to a depressed level of consciousness and high Ammonia of 486 once only but dropped to 30 after immediate Arginine infusion with questionable sampling technique for the high reading. He required intubation electively for mechanical ventilation for 2 days then improved clinically apart from having weak reflexes and absent Moro reflex. Urgent CT scan of the brain was unremarkable and brain MRI showed only prominent sulci. EEG showed no specific encephalopathy. Other labs showed pancytopenia with Hb 93 g/dl and platelets 50,000, No metabolic acidosis, normal TSH, and negative cultures of blood, urine, and CSF. Tandem mass spectrometry showed low methionine and at 30 days of age, the diagnosis of MTHFR deficiency was confirmed. He was started on betaine 100 mg/kg/day, pyridoxine oral 100 mg/day and folinic acid oral 15 mg/day, methionine 50 mg/kg/day. He was active and better upon discharge. He had a febrile seizure at the age of 2 years. His growth parameters were on the 50th percentile. He was developmentally delayed. Neurology examination revealed upper motor neuron lesion findings with brisk reflexes on the left body side. Brain MRI showed a large right temporofrontoparietal arachnoid cyst associated with significant mass effect that was endoscopically drained and the patient improved. On the last follow up, the patient was 11 years with seizure disorders and has special needs in feeding and mobilization.

Discussion

Methylenetetrahydrofolate Reductase (MTHFR) is essential to catalyze the reduction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate which is the major transport form of folate. MTHFR gene is located on chromosome 1p36.3. MTHFR deficiency is inherited as an autosomal recessive trait and it has wide clinical presentations. There are more than 100 cases reported with various clinical presentations. A common mutation is 677C → T was reported previously to cause mild elevation of homocysteine due to thermo-labile enzyme, however, the patients are not at risk to develop a complete picture of MTHFR deficiency [3]. The severity of this disorder varies from case to case and it has been correlated with the residual enzyme activity [4]. Neuropathologic changes in severe MTHFR deficiency are widely variable include dilated cerebral ventricles, internal hydrocephalus, microgyria, EEG abnormalities, progressive brain atrophy and demyelination [3–11]. Other clinical manifestations include developmental delay, motor abnormalities, microcephaly, seizures, and psychiatric manifestations [5]. We report here seven cases from consanguineous families presented to our hospital. All patients were symptomatic since infancy and the MTHFR deficiency was confirmed by molecular testing. All the patients had the same variant c.680C > T, which suggests a founder effect. This mutation was reported previously as a disease-causing mutation in a Caucasian and another African-Indian patient [6]. All the patients had moderate homocystinuria ranging from 88.5 to 189 with low plasma methionine in addition to non-specific dysmorphic features, including low set ears, low hairline, fair skin, colored eyes, long philtrum, and high arch palate. These subtle dysmorphic features, except the microcephaly, were not specific and were not reported previously with MTHFR deficiency and may hardly indicate the disease. Clinical manifestations in current patients are common with the previously reported cases including lethargy, developmental delay, microcephaly, seizure, and EEG changes but most of them were having average growth parameters [6]. However, patients 3 and 5 had hydrocephalus with microcephaly that required drainage with ventriculoperitoneal shunt insertion without reaching a solid reason for the hydrocephalus. Hydrocephalus internus due to MTHFR deficiency, requiring neurosurgical intervention was reported previously [2]. However, in the picture of unexplained hydrocephalus or ventriculomegaly, which could be a result of brain volume loss rather than increased intracranial pressure, MTHFR deficiency should be considered.

The brain MRI of the second patient was suggestive of Dandy-Walker malformation, which was not reported previously in the current mutation [6]. Additional MRI findings in other patients revealed different findings; some were reported before and others were not like prominent sulci and temporofrontoparietal arachnoid cyst that was endoscopically drained in patient 7 which may be related to MTHFR deficiency.

Two of the patients (3 and 5) were having hydrocephalus and died without an apparent cause of the apnea. On the other hand, a third patient, patient 4, who presented early in the neonatal period with recurrent apnea, but had a favorable outcome possibly due to the early intervention because of previous family history. These results support the study of early Betaine treatment and its prevention of mortality and allowance of normal psychomotor development in patients with severe MTHFR deficiency [12]. Our follow up of patients also support that neonatal screening is beneficial to those patients for early diagnosis and treatment. Apnea or abnormal breath pattern and hydrocephalus were reported previously in patients with MTHFR deficiency although the underlying reason is not very clear and more cases are needed to be studied to understand the pathophysiology of hydrocephalus, apnea, and MTHFR deficiency. The two causes of mortality for the patients in the current study were the respiratory failure due to pulmonary hemorrhage and status epilepticus.

Conclusion

The clinical phenotype of MTHFR deficiency has a wide spectrum of presentations. We report herein seven pediatric cases, with a common missense mutation. The early intervention of the patients may result in a better outcome.

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