IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 10 Ser.9 (October. 2022), PP 04-08
www.iosrjournals.org

Methylene tetrahydrofolate reductase deficiency presenting as chronic recurrent myelopathy in an adult - a treatable entity.

Madhusudanan Mohan, Roy Thomas, Rajesh A and Muthukumarasamy B

Date of Submission: 15-10-2022 Date of Acceptance: 31-10-2022

I. Introduction

Methylene-tetrahydrofolate reductase (MTHFR) deficiency is a rare disorder affecting the metabolism of folate and sulfur-containing amino acids[1]. The deficiency of this enzyme results in a reduction in synthesis of 5- methyl-tetrahydrofolate (5MTHF). 5 methyl tetrahydrofolate is the biologically active form of folate, which acts as a cofactor for the re-methylation of homocysteine into methionine.

Biochemical hallmarks of this disease are moderately low plasmatic folate levels, hyperhomocysteinemia, hypomethioninemia and absence of methyl malonic aciduria.

The disease onset is usually in the neonatal period or childhood presenting with encephalopathy, psychomotor delay, gait disorder and epilepsy, all of which may also be associated with thrombotic events[2]. Neonatal forms are usually more severe[1] and are related to the lowest level of residual MTHFR activity[3,4].

Patients with adolescent/adult onset are rare, with varied clinical presentations. They may present with progressive or recurrent spastic paraparesis, psychotic episodes, cognitive disorder, relapsing encephalopathy, language disorder, progressive ataxia, peripheral neuropathy or recurrent thrombotic events.

In this article, we present a middle-aged lady who presented with recurrent myelitis starting from the age of 16, and later on developed features of cognitive decline and psychosis.

II. Case History

A 56-year-old female presented to us initially at her age of 16 years in 1985 with history of weakness of left lower limb of 3 weeks duration. 2 weeks later, she re-presented with weakness of right lower limb and retention of urine. She had one episode of generalised tonic-clonic seizure, 5 days after the onset of illness. Examination at that time revealed pyramidal weakness of both lower limbs with bladder retention. Her blood biochemistry was normal. Since MRI was not available at that time, myelography was done, which did not reveal any spinal block. CSF study was also within normal limits.

She was diagnosed to have spinal cord demyelination treated with medications including intravenous steroid and her weakness improved to a great extent so much so she could walk unsupported but mild weakness and precipitancy in micturition persisted. Subsequently she had two further episodes of worsening in her weakness of lower limbs requiring hospital admission, and each time the paraparesis improved with treatment.

She presented to another hospital again in 2012 with worsening of weakness of lower limbs. Her MRI of the spine was normal. MRI of the brain revealed bilateral asymmetric confluent periventricular lesions which were hyperintense in FLAIR and hypointense in T1 weighted sequence with no contrast enhancement (Fig.1)

In august 2020, patient was admitted with severe diarrhea and improved with treatment over a period of 2 weeks. In November 2020, her weakness of both lower limbs worsened again and became wheelchair bound. Examination revealed total paraplegia of both lower limbs, with impaired posterior column sensation over both feet. Patient was already on urinary catheter. Repeat MRI of the spinal cord with contrast was normal (Fig.2).

Blood investigations revealed an ESR of 40mm/1st hour, with normal hematological parameters. Her CRP was 9mg/L, ANA and rheumatoid factors were normal. Antiphospholipid antibody was normal.

CSF was done which revealed4 cells per cmm, all lymphocytes, with a protein of 48mg/dL and sugar of 86mg/dL. CSF OCB and VDRL were negative. Serum NMO, MOG antibodies were negative. She was given another course of intravenous methyl prednisolone which did not produce any significant improvement.

For the last 6 months, patient was noticed to have episodes of excessive anxiety, palpitations and profuse sweating which was considered due to panic attacks and was prescribed propranolol, and clonazepam. Her symptoms improved, but noticed to have excessively jocularity, progressive decrease in word out with tendency to repeat whatever the examiner says. She was also noticed to have abnormal posturing of both upper limbs and got admitted in the present hospital.

On examination, patient was conscious, with excessive jocularity. At times she goes in to "trance like "state. She had profound echolalia and palilalia, which hindered a proper HMF examination. She could recognize her daughter, but could not name her. Cranial nerves were grossly normal. Motor system examination showed rigidity of both upper limbs with weakness which was more on the right side. Lower limbs were severely spastic with Grade 0 power. Deep reflexes were brisk in both upper and lower limbs with upgoing plantar response. She had exaggerated primitive reflexes including grasp and palmomental reflexes.

Her MRI brain was repeated, which revealed progression of the diffuse confluentT2/FLAIR hyperintense lesions in the periventricular white matter with evidence of cortical atrophy and ventricular dilatation (Fig 3).

EEG showed diffuse slowing in theta range with no epileptiform discharges. Repeat CSF was normal, including CSF lactate and ACE levels. SSEP evoked normal response. Repeat ANA profile was normal.

Since MRI showed symmetrical while matter hyperintensities, possibility of neurometabolic disorder, mitochondrial cytopathy or leukodystrophy was considered and serum was sent for clinical exome sequencing, including mitochondrial gene panel. Genetic analysis identified homozygous mutation in MTHFR gene in exon 4 (c.582 C>G, p.(lle194Met), suggesting homocystinuria secondary to methylene tetrahydrofolate reductase deficiency. Given the genetic report, serum was sent for homocysteine level which was grossly elevated (79.81micromol/L, normal being 3.7 to 13.9).

During the interim period till the genetic results became available, she deteriorated and became stuporous with stiffness of both upper and lower limbs.

Patient was given Injection Vitamin B12(1000 microgram/day), Folic acid 15mg, Riboflavin 500mg daily. and betaine 9 gm per day. After 1week of therapy, she started showing signs of improvement in her encephalopathic symptoms and she started speaking and was able to recognize her children.

III. Discussion;

MTHFR is an important enzyme in homocysteine remethylation to methionine. Defects of remethylation give rise to hyperhomocysteinemia with normal or low methionine.

The clinical presentation can be from infancy to adulthood. The infantile presentation is most common and manifested as hypotonia, lethargy, apnea, seizures, coma, frequently leading to death[2] .

In the later onset presentations, the course is either insidious with gradual progression or relapsing-remitting presentation. They have more variable manifestations including neurocognitive impairment, gait abnormalities, neurological disturbance compatible with myelopathy or ataxia, psychiatric disorders or thromboembolic events[2].

Some of the adult cases can present with spastic paraparesis, psychotic episodes, cognitive disorder, relapsing encephalopathy, polyneuropathy or strokes[5,6,7,8,9].

J M Michot, F Sedel, et al[10] reported a woman with MTHFR deficiency, in whom first symptoms occurred in the fifth decade of life. She presented initially with psychosis, later on evolving into progressive paraparesis and catatonia. The authors stressed the importance of plasma homocysteine testing in any patient presenting with atypical psychosis or unexplained neurological manifestations at any age.

Lossos et al[11] reported two unrelated families, each with two siblings with severe MTHFR deficiency manifesting a spastic paraparesis, polyneuropathy, behavioural changes, cognitive impairment, psychosis, seizures and leukoencephalopathy starting between the ages of 29 and 50 years, responsive to betaine therapy. Their clinical picture mimicked that of adult-onset hereditary spastic paraparesis.

Daniela Vieira, Cristina Florindo et al[12] reported a 23-year- old man with MTHFR deficiency who presented with a 3-week history of speech and gait impairment, and numbness in lower limbs. Neurological examination revealed dysarthria, decreased vibratory sensation in both legs and appendicular and gait ataxia.

Bathgate et al[13] also described two young-adult siblings with a spastic paraparesis who developed cognitive decline and behavioural disturbance, in relation with a severe hyperhomocysteinemia.

Santhakumar Senthilvelan, Sathish Kandasamy et al[14] presented a patient who
had a reversible form of adult-onset leukoencephalopathy resulting from MTHFR deficiency presenting with letter by letter reading, impaired visual recall, and mild to moderate difficulty in delayed visual reproduction tasks and bipyramidal signs.

Kyoko Katsumura, Michiho Sodenaga et al[15] reported a 46-year-old woman who initially presented with seizures at the age of 20 years, later developed dementia with psychotic manifestation in the form of depression and symptoms of schizophrenia. At age 43, she developed muscular hypotonia and gait disturbance. Subsequently investigations revealed marked hyperhomocysteinemia, hypomethioninemia, and decreased folate level. Brain magnetic resonance imaging revealed multiple cerebral infarctions.

Nervous system damage in MTHFR deficiency results from two pathophysiologic mechanisms. Most neurological features of MTHFR deficiency, including myelin pathology (leukoencephalopathy) are thought to be due to hypomethioninemia.
Hypomethioninaemia results in low levels of S-adenosyl methionine, which represents the methyl donor for most methylation reactions, including neurotransmitters and myelin synthesis. Secondly, hyperhomocystinaemia can lead to endothelial dysfunction and injury, followed by platelet activation and thrombus formation, resulting in arterial or venous vasculopathy, and stroke.

The predominance of white matter disease and brain atrophy is caused by a defective myelination due to cerebral deficiency of S-adenosylmethionine, which may be reversed with treatment'[16].

Since causal treatment for MTHFR deficiency is not available, betaine is the mainstay of symptomatic treatment[17].

In conclusion, one should be aware of the possibility of MTHFR deficiency as a cause of recurrent paraplegia and not to miss this eminently treatable entity by screening for homocysteine levels in select cases of non-compressive myelopathies where the diagnosis is not obvious.

References

[1]. Froese DS, Huemer M, Suormala T, Burda P, Coelho D, Gueant JL, et al. Mutation update and review of severe Methylenetetrahydrofolate Reductase deficiency. Hum Mutat. 2016;37(5):427–38.
[2]. Huemer M, Mulder-Bleile R, Burda P, Froese DS, Suormala T, Zeev BB, et al. Clinical pattern, mutations and in vitro residual activity in 33 patients with severe 5, 10 methylenetetrahydrofolate reductase (MTHFR) deficiency. J Inherit Metab Dis. 2016;39(1):115–24
[3]. Goyette P, Frosst P, Rosenblatt DS, Rozen R. Seven novel mutations in the methylenetetrahydrofolate reductase gene and genotype/phenotype correlations in severe methylenetetrahydrofolate reductase deficiency. Am J Hum Genet. 1995;56(5):1052–9.
[4]. Sibani S, Christensen B, O'Ferrall E, Saadi I, Hiou-Tim F, Rosenblatt DS, et al. Characterization of six novel mutations in the methylenetetrahydrofolate reductase (MTHFR) gene in patients with homocystinuria. Hum Mutat. 2000; 15(3):280–7.
[5]. Rosenblatt D, Fenton W. Inherited disorders of folate and cobalamin transport and metabolism. In: Scriver C, Beaudet AL, Sly WS, et al.The Metabolic and Molecular Bases of Inherited Disease. 8th edn. New York: McGraw-Hill, 2001: 3897–911.
[6]. Freeman JM, Finkelstein JD, Mudd SH. Folate responsive homocystinuria and ''schizophrenia''. A defect in methylation due to deficient 5,10 -methylenetetrahydrofolate reductase activity. N Engl J Med 1975; 292:491–6.
[7]. Visy JM, Le Coz P, Chadefaux B, et al. Homocystinuria due to 5,10-methylenetetrahydrofolate reductase deficiency revealed by stroke in adult siblings. Neurology 1991; 41:1313–5.
[8]. Pasquier F, Lebert F, Petit H, et al. Methylenetetrahydrofolate reductase deficiency revealed by a neuropathy in a psychotic adult. J Neurol Neurosurg Psychiatry 1994; 57:765–6.
[9]. Haworth JC, Dilling LA, Surtees RA, et al. Symptomatic and asymptomatic methylenetetrahydrofolate reductase deficiency in two adult brothers. Am J Med Genet 1993; 45:572–6
[10]. J M Michot, F Sedel, S Giraudier, J M Smiejan, T Papo. Psychosis, paraplegia and coma revealing methylenetetrahydrofolate reductase deficiency in a 56-year-old woman. J Neurol Neurosurg Psychiatry 2008; 79:963–964.
[11]. Lossos A, Teltsh O, Milman T, et al. Severe methylenetetrahydrofolate reductase deficiency: clinical clues to a potentially treatable cause of adult-onset hereditary spastic paraplegia. JAMA Neurology 2014; 71:901–4.
[12]. Daniela Vieira, Cristina Florindo, Isabel Tavares de Almeida, Maria Carmo Macário. Adult-onset methylenetetrahydrofolate reductase deficiency. BMJ Case Rep 2020;**13**: e232241.
[13]. Bathgate D, Yu-Wai- Man P, Webb B, et al. Recessive spastic paraparesis associated with complex I deficiency due to MTHFR mutations. J Neurol Neurosurg Psychiatry 2012; 83:115.
[14]. Santhakumar Senthilvelan, Sathish Kandasamy, Ramshekhar N. Menon, · Sheela Nampoothiri, Harikrishnan Ramachandran, Bejoy Thomas, · Chandrasekharan Kesavadas. Methylenetetrahydrofolate Reductase Deficiency as a Cause of Treatable Adult-onset Leukoencephalopathy and Myelopathy. Clin Neuroradiol. 2021 Mar;31(1):277-281.
[15]. Kyoko Katsumura, Michiho Sodenaga, Seiya Miyamoto, Ouga Sasaki, Tomoko Akiyama, Osuke Migita, Koji Hori and Hiroki Kocha. A Case of Methylenetetrahydrofolate Reductase Deficiency with Suspected Early-onset Dementia Associated with Hyperhomocysteinemia Due to Reduced Folate. J Alzheimers Dis Parkinsonism 2019, Vol 9(3): 467
[16]. Strauss KA, Morton DH, Puffenberger EG, et al. Prevention of brain disease from severe 5,10-methylenetetrahydrofolate reductase deficiency. Mol Genet Metab 2007; 91:165–75.
[17]. Froese DS, Huemer M, Suormala T, et al. Mutation update and review of severe methylenetetrahydrofolate reductase deficiency. Hum Mutat 2016; 37:427–38.

Figures and legends

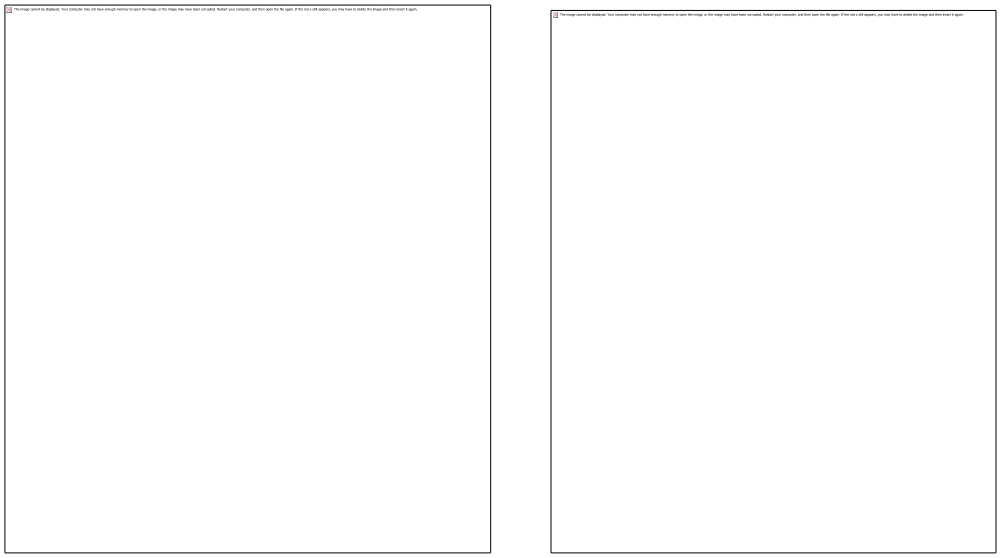

Fig. 1. T2 FLAIR sequence showing bilateral asymmetric confluent periventricular hyperintense lesions

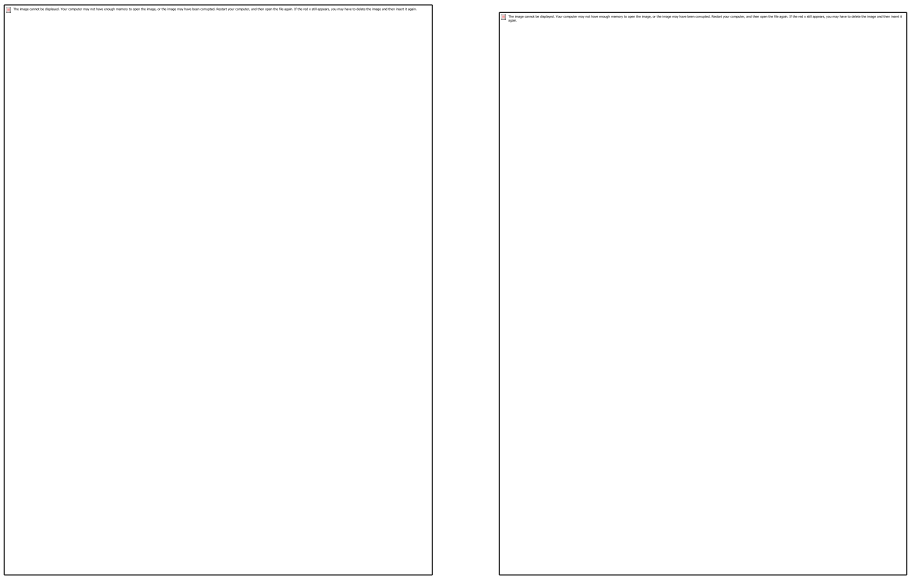

Figure 2. showing normal T2 weighted sagittal MRI of the cervical and thoracic cord

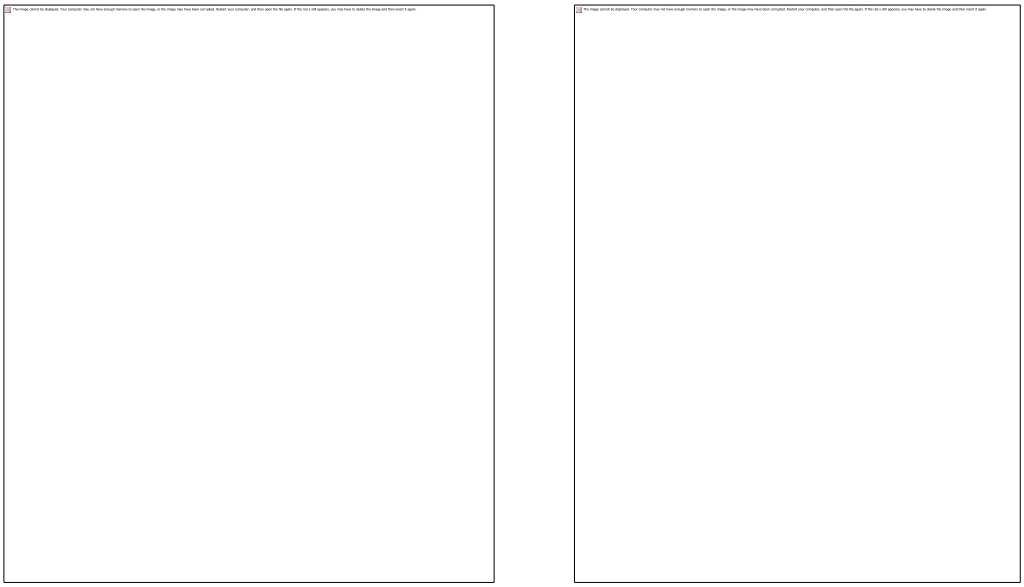

Fig.3. T2-FLAIR MRI taken 8 years later, showing progression of the confluent hyperintense lesions in the periventricular white matter with evidence of cortical atrophy and ventricular dilatation.

Acknowledgement: Nil