Reversible Cerebral White Matter Abnormalities in Homocystinuria

Naila Ismayilova • Andrew D. MacKinnon •
Helen Mundy • Penny Fallon

Received: 20 May 2018 / Revised: 21 July 2018 / Accepted: 10 August 2018 / Published online: 06 September 2018
© Society for the Study of Inborn Errors of Metabolism (SSIEM) 2018

Abstract Striking MRI brain changes resembling leukoencephalopathy are rarely seen in classical homocystinuria. Our case suggests that reversible white matter changes (WMC) are linked to elevated plasma methionine levels arising during treatment.

A 6-year-old boy with learning difficulties and a normal MRI brain scan was diagnosed with homocystinuria (initial total homocysteine 344 $\mu\text{mol/L}$ and methionine 64 $\mu\text{mol/L}$). At the age of 6.5 years, he developed superior sagittal sinus (SSS) thrombosis. Antithrombotic and homocysteine-lowering treatments were started. Due to poor dietary compliance and betaine treatment, his methionine level reached 1,285 $\mu\text{mol/L}$, and left side weakness developed. Repeat MRI scan revealed new confluent WMC in previously myelinated brain areas. Further 3-month treatment with tighter dietary control significantly dropped his methionine level (233 $\mu\text{mol/L}$) with resolution of his neurological deficit and of radiological changes.

We suggest a reversible toxicity from hypermethioninaemia as a possible source of cerebral WMC (secondary to a demyelinating process) in patients with homocystinuria.

It highlights the importance of homocysteine-lowering treatment as a prevention and complete resolution of neurological complications. It also demonstrates the need to consider homocystinuria in a differential diagnosis of paediatric leukoencephalopathy.

Abbreviations

CBS	Cystathionine beta-synthase
ICP	Intracranial pressure
MTHFR	5,10-Methylenetetrahydrofolate reductase
SSS	Superior sagittal sinus
WMC	White matter changes

Introduction

Classical homocystinuria is an autosomal recessive disorder of methionine metabolism secondary to deficiency of cystathionine beta-synthase (CBS) resulting in multisystemic impairment (Mudd et al. 1985). There are a wide range of neurological presentations, but the most common are psychomotor retardation and focal neurological deficit secondary to infarction. Brain imaging may demonstrate cerebral infarction, atrophy or venous occlusion (Van den Knaap and Valk 2005). Rarely, patients with abnormalities of methionine metabolism have presented with striking cerebral WMC on MR brain imaging resembling a leukoencephalopathy. A variety of different mechanisms have been proposed based on the methionine metabolic pathway. However, myelinopathy caused by hypermethioninaemia in children with homocystinuria has been sparsely reported in the literature. We demonstrate a case, where white matter abnormalities are likely linked to elevated plasma methionine levels, arising during the course of treatment, with subsequent resolution.

Communicated by: Brian Fowler, PhD

N. Ismayilova (✉) • P. Fallon
Department of Paediatric Neurosciences, St George's University
Hospitals NHS Foundation Trust, London, UK
e-mail: Naila.ismayilova@chelwest.nhs.uk;
ismayilova@doctors.org.uk

A. D. MacKinnon
Department of Neuroradiology, Atkinson Morley Regional
Neuroscience Centre, St George's University Hospitals NHS
Foundation Trust, London, UK

H. Mundy
Department of Paediatric Inherited Metabolic Disease, Evelina
London Children's Hospital, Guy's and St Thomas' NHS Foundation
Trust, London, UK

Case

A 6-year-old boy was born in good condition by a normal delivery to healthy non-consanguineous Caucasian parents. He had unremarkable family and postnatal history. His early development was normal, but deterioration of speech and language skills was noted from the age of 2 years requiring educational support at school. On examination at age of 6 years and 4 months, the child was tall and had hypermetropia, a conductive hearing loss, pectus excavatum, large ears, high forehead, and a mild scoliosis. A detailed neurological assessment was limited due to his attention and coordination difficulties. He had impaired gross and fine motor skills (but no focal neurological deficit) together with delayed speech and language, reminiscent of a child <2-year-old.

In a month, the patient underwent a complete investigation for his developmental delay. His biochemical investigations revealed grossly elevated total homocysteine (344 $\mu\text{mol/L}$, normal range 0–15 $\mu\text{mol/L}$) and a mildly raised methionine levels (64 $\mu\text{mol/L}$, normal range

10–53 $\mu\text{mol/L}$), consistent with homocystinuria later confirmed by detecting a CBS gene mutation (heterozygous for the pathogenic mutation c.919G>A; p.G307S). His MRI brain scan was normal. He was also a carrier for MTHFR 677CT variant. Due to detected homocysteinaemia, his serum vitamin B12 levels (42 pmol/L, normal range 200–500 pmol/L) and folate levels (>20.0 ng/mL, normal range 2–20 ng/mL) were checked. Shortly before his next hospital presentation, he was commenced on pyridoxine, folic acid and a methionine-restricted diet.

Three weeks later, at the age of 6.5 years, he developed symptoms and signs of a raised intracranial pressure (ICP) caused by an acute SSS thrombosis confirmed on MRV/MRI scans with normal brain appearances and myelinated white matter elsewhere (Fig. 1a, c). At that time, his total homocysteine levels slightly reduced (339 $\mu\text{mol/L}$) and methionine levels increased (647 $\mu\text{mol/L}$). He was rehydrated and treated with subcutaneous dalteparin. As dietary compliance was suboptimal, he was also commenced on betaine hydrochloride adjuvant to his diet. Following 1 month of this treatment, his total homocysteine levels

Fig. 1 Axial FLAIR images (a, b): (a) showed normal brain structures in November 2013; (b) detected diffuse white matter changes with predominance in anterior areas in February 2014.

Coronal T2-weighted images (c, d): (c) a thrombus in the anterior and mid-portions of the superior sagittal sinus detected in November 2013; (d) the thrombus later started to recanalise in February 2014

rapidly reduced to $<100 \mu\text{mol/L}$. However, his plasma methionine levels reached $1,285 \mu\text{mol/L}$ and his development did not improve. At this time, he developed left-sided weakness with reduced muscle power (MRC score 4/5) but no evidence of other neurological signs and symptoms. A follow-up MRI scan revealed new confluent widespread T2 hyperintensity in previously myelinated white matter prominent in the anterior supratentorial regions with involvement of deep juxta cortical, subcortical, periventricular, capsular and brainstem areas including central tegmental tracts. The SSS thrombosis had started to recanalise (Fig. 1b, d). Within further 3-month treatment and tighter dietary control, there was a significant drop in methionine levels ($233 \mu\text{mol/L}$), resolution of his neurological deficit and improvement in his cognition, speech and motor skills. At that time, there was resolution of previous WMC and significant recanalisation of the SSS thrombosis. Following further treatment, his plasma homocysteine and methionine levels continued to fall, and our patient remained clinically well and made good developmental progress.

In the view of his diagnosis, his asymptomatic 3-year-old sister with a normal development was screened for homocystinuria and found to have hypermethioninaemia ($669 \mu\text{mol/L}$) and homocysteinaemia ($180 \mu\text{mol/L}$). She was subsequently started on a low-methionine diet and on homocysteine-lowering treatment but became symptomatic

(paroxysmal episodes of falls, leg pains, clumsiness and urinary incontinence) once betaine was commenced. However, she required extra-educational support for difficulties in speech and fine motor skills at 4 years. Her brain scan was normal even though her hypermethioninaemia peaked at $917 \mu\text{mol/L}$. This was possibly due to much tighter control of her biochemical results, timely modifications of betaine doses and compliance with low-methionine diet.

Discussion

Our paediatric case demonstrates reversible diffuse brain WMC in classical homocystinuria with a significant hypermethioninaemia probably secondary to both betaine treatment and poor dietary compliance. It also highlights the importance of screening children with learning difficulties for amino acid disorders. These MRI changes were correlated with left-sided weakness and coincided with high methionine and mildly raised plasma homocysteine levels following homocysteine-lowering treatment. Clinical and radiological abnormalities resolved after a significant drop in plasma methionine levels.

In homocystinuria, a CBS deficiency impacts the transsulfuration pathway causing hyperhomocysteinaemia. This leads to hypermethioninaemia secondary to activation of the remethylation pathway (Fig. 2). Successful remethylation process requires betaine or 5-methyltetrahydrofolate to

Fig. 2 Transsulfuration pathway

donate a methyl group to homocysteine causing an elevation of plasma methionine levels. Our patient, therefore, had a dramatic increase in methionine and a significant drop in homocysteine plasma levels once betaine treatment was initiated. Brenton et al. (2014) reported similar changes with progressive unilateral weakness, developmental delay and a marked increase of homocysteine and methionine but prior to homocystinuria treatment. By contrast, our patient developed a focal neurological deficit together with WMC on MRI scan on the background of poor dietary compliance and betaine treatment resulting in hypermethioninaemia.

Cerebral WMC are uncommon findings in classical homocystinuria, which were associated with hypermethioninaemia. However, Vatanavicharn et al. (2008) demonstrated an adult case with diffused reversible white matter changes in the brain and neurological deficits. Similar to our case, these radiological findings and clinical deterioration were correlated with highly elevated levels of methionine (1,282 $\mu\text{mol/L}$) and total homocysteine (266.3 $\mu\text{mol/L}$). They resolved following normalisation of methionine levels. The authors proposed that observed leukoencephalopathy was due to demyelinating process secondary to hyperhomocysteinaemia and hypermethioninaemia.

Sasai et al. (2015) also presented another adult case with reversible diffuse WMC on the background of elevated levels of plasma methionine (904.2 $\mu\text{mol/L}$) and total homocysteine (166.5 $\mu\text{mol/L}$) but with no associated neurological abnormalities. The authors proposed that treatment with betaine and elevated plasma methionine could increase a risk of the cerebral WMC. Interestingly, in patients with MAT I/MAT III deficiency, Chien et al. (2015) suggested that betaine works as an intracellular osmolyte. It causes a development of brain oedema in its high plasma levels.

Yaghmai et al. (2002) and Devlin et al. (2004) also demonstrated widespread WMC with a cerebral oedema and acute symptoms of ICP in two cases with marked hypermethioninaemia (2,272–3,037 $\mu\text{mol/L}$) and hyperhomocysteinaemia (1,190–1,205 $\mu\text{mol/L}$). These changes were detected with commencing betaine treatment and resolved following its discontinuation. Devlin et al. (2004) justified these changes by high brain intracellular concentrations of betaine secondary to its treatment whereas Yaghmai et al. to methionine toxicity (Yaghmai et al. 2002). In contrast, our case did not show any evidence for a cerebral oedema and had significantly lower levels of amino acids. Moreover, there was no evidence of betaine toxicity as hypomethioninaemia, and clinical improvement was achieved with perseverance with betaine treatment and a low-methionine diet. We, therefore, suggest that significant hypermethioninaemia secondary to betaine treatment

in homocystinuria contributed to the evolution of the brain WMC. Betaine remains a beneficial medicine for homocystinuria treatment. However, with growing evidence in the literature of its neurological complications and our patient's sibling example, we support Devlin et al.'s suggestion to control plasma methionine levels targeting $<1,000 \mu\text{mol/L}$ by both modifying the dietary intake and judicious use of betaine (Devlin et al. 2004). Moreover, a current recommendation in the management of cystathionine beta-synthase deficiency in patients treated with betaine is to avoid plasma methionine levels $>1,000 \mu\text{mol/L}$ (Morris et al. 2017).

In patients with MAT I/III deficiency, mean methionine values $>800 \mu\text{mol/L}$ had central nervous system (CNS) presentation, whereas $<800 \mu\text{mol/L}$ were associated with no CNS signs or symptoms (Chien et al. 2015). Moreover, patients with $>800 \mu\text{mol/L}$ methionine levels became free from CNS abnormalities after initiation of a methionine-restricted diet. The authors explained neurological deficits with a brain oedema secondary to hypermethioninaemia ($>800 \mu\text{mol/L}$) while on betaine therapy.

This toxicity from hypermethioninaemia could be explained by methionine competition for “large neutral amino acid” (LNAA) system (Chien et al. 2015). Since methionine is transported by the LNAA transporter through the blood-brain barrier, it would compete with other amino acids and inhibit their transport to the brain.

In conclusion, our case contributes to the scarce literature on the aetiology of cerebral WMC in patients with abnormal methionine metabolism and homocystinuria. It identifies a reversible toxicity from hypermethioninaemia as the likely source of demyelinating process. Our report also underlines the importance of monitoring the dose of betaine together with a tight methionine-restricted diet. This should normalise plasma methionine levels with the aim of preventing or complete resolution of neurological complications. Importantly, this case highlights the need to consider homocystinuria in a differential diagnosis of paediatric leukoencephalopathy and to screen patients with developmental delay for amino acid disorders.

Synopsis

A reversible toxicity from hypermethioninaemia is a possible source of cerebral WMC in patients with homocystinuria.

Conflict of Interest

Naila Ismayilova, Andrew D. MacKinnon, Helen Mundy and Penny Fallon declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Informed consent was obtained from a patient's parent before submitting this manuscript.

Naila Ismayilova – Contributed pertinent aspects of the planning, conduct and reporting of the work described in the article *Guarantor*

Andrew D. MacKinnon – Contributor in analysis and interpretation of data and revising it critically for the important intellectual content

Helen Mundy – Contributor in analysis and interpretation of data

Penny Fallon – Contributor in analysis and interpretation of data and revising it critically for the important intellectual content revising it critically for the important intellectual content

References

- Brenton JN, Matsumoto JA, Rust RS, Wilson WG (2014) White matter changes in an untreated, newly diagnosed case of classical homocystinuria. *J Child Neurol* 29(1):88–92
- Chien YH, Abdenur JE, Barono F, Bannick AA, Corrales F, Couce M, Donner MG, Ficicioglu C, Freehauf C, Frithiof D, Gotway G, Hirabayashi K, Hofstede F, Hoganson G, Hwu WL, James P, Kim S, Korman SH, Lachmann R, Levy H, Lindner M, Lykopoulou L, Mayatepek E, Muntau A, Okano Y, Raymond K, Rubio-Gozalbo E, Scholl-Burgi S, Schulze A, Singh R, Stabler S, Stuy M, Thomas J, Wagner C, Wilson W, Wortman S, Yamamoto S, Pao M, Blom HJ (2015) Mudd's disease (MAT I/III deficiency): a survey of data for MAT1A homozygotes and compound heterozygotes. *Orphanet J Rare Dis* 10:99
- Devlin AM, Hajipour L, Gholkar A, Fernandes H, Ramesh V, Morris AA (2004) Cerebral edema associated with betaine treatment in classical homocystinuria. *J Pediatr* 144(4):545–548
- Morris AAM, Kozich V, Santra S, Andria G, Ben-Omran TIM, Chakrapani AB, Crushell E, Henderson MJ, Hochul M, Huemer M, Janssen MCH, Maillot F, Mayne PD, McNulty J, Morrison TM, Ogier H, O'Sullivan S, Pavlikova M, Tavares De Almeida I, Terry A, Yap S, Blom HJ, Chapman KA (2017) Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. *J Inher Metab Dis* 40:49–74
- Mudd SH, Skovby F, Levy HL, Pettigrew KD, Wilcken B, Pyeritz RE, Andria G et al (1985) The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet* 37(1):1–31
- Sasai H, Shimozawa N, Asano T, Kawamoto N, Yamamoto T, Kimura T, Kawamoto M, Matsui E, Fukao T (2015) Successive MRI findings of reversible cerebral white matter lesions in a patient with cystathionine β -synthase deficiency. *Tohoku J Exp Med* 237:323–327
- Van den Knaap MS, Valk J (2005) Hyperhomocysteinemias. In: *Magnetic resonance of myelination and myelin disorders*. Springer, Berlin, pp 342–359
- Vatanavicharn N, Pressman BD, Wilcox WR (2008) Reversible leukoencephalopathy with acute neurological deterioration and permanent residua in classical homocystinuria: a case report. *J Inher Metab Dis* 31(Suppl 3):S477–S481
- Yaghmai R, Kashani AH, Geraghty MT, Okoh J, Pomper M, Tangerman A, Wagner C et al (2002) Progressive cerebral edema associated with high methionine levels and betaine therapy in a patient with cystathionine beta-synthase (CBS) deficiency. *Am J Med Genet* 108(1):57–63