Brain Magnetic Resonance Imaging Findings in Poorly Controlled Homocystinuria

Charles Q Li[1*], Bruce A Barshop[2], Annette Feigenbaum[2], Paritosh C Khanna[3]

1. Department of Radiology, University of California, San Diego, San Diego, USA

2. Department of Pediatrics, University of California, San Diego, La Jolla, USA

3. Department of Radiology, Rady Children's Hospital-San Diego, San Diego, USA

* **Correspondence:** Charles Q Li, MD, University of California, San Diego, Department of Radiology, 200 W Arbor Dr MC 8756, San Diego, CA 92103-8756, USA
(*charlesqli@alumni.ucsd.edu*)

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ABSTRACT

Homocystinuria is an inherited metabolic disorder most commonly caused by cystathionine β-synthase deficiency. Severe cases can cause white matter abnormalities that can mimic other vascular, toxic and metabolic disorders on computed tomography and magnetic resonance imaging. We present such a case which demonstrates not only extensive white matter abnormalities on magnetic resonance imaging, but also previously unreported basal ganglia signal abnormalities and imaging manifestations of increased intracranial pressure, likely caused by elevated methionine and betaine therapy. We also review the literature and discuss the potential underlying biologic mechanisms of these imaging findings.

CASE REPORT

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A two-year-old female with homocystinuria due to cystathionine β-synthase (CBS) deficiency was admitted to improve metabolic control after incidentally finding mild asymptomatic bilateral papilledema on routine ophthalmologic examination. Initial laboratory analyses (Table 1) revealed poorly controlled disease (suspected to have been caused by poor treatment compliance) characterized by elevated plasma homocysteine and markedly elevated plasma methionine concentrations. Plasma methionine had also been markedly elevated (1007–1211 μmol/L, normal 7–47 μmol/L) for six months preceding admission. Lumbar puncture revealed elevated intracranial pressure (ICP) and elevated methionine concentration in the cerebrospinal fluid (CSF). Ophthalmologic examination revealed edema of the optic nerve heads, greater on the left, without ectopia lentis, visual field or acuity deficits.

Magnetic resonance imaging (MRI) of the brain performed on a 1.5 T scanner (Figure 1) revealed diffuse T1 and T2 prolongation and diffusion restriction throughout the white matter, bilateral globi pallidi, and bilateral dorsolateral thalami. The brain was diffusely swollen with effacement of the cerebral sulci and ventricular system. Bilateral papilledema and mild dilation of the optic nerve sheaths were present. The lenses were normally positioned without ectopia lentis. No abnormal enhancement occurred after administration of intravenous gadolinium-based contrast. Magnetic resonance spectroscopy (MRS) of the left frontal lobe corona radiata (single voxel, TE = 144 ms) revealed decreased N-acetylaspartate (NAA) and increased choline without a lactate peak to suggest necrosis. No venous filling defects were present on magnetic resonance venography (MRV).

Whole protein consumption was held during hospitalization to decrease methionine intake and homocysteine production, and betaine dosage was decreased to reduce methionine synthesis. Plasma concentrations of homocysteine and methionine at discharge declined to 189 μmol/L (203 μmol/L on admission) and 724 μmol/L (1182 μmol/L on admission), respectively. The patient was

discharged with a lower dose home betaine regimen and eventually received a gastrostomy tube to assure reduced methionine intake.

DISCUSSION

Etiology & Demographics:

Homocystinuria is a rare disorder of metabolism characterized by elevated plasma concentration of homocysteine and urine concentration of its oxidation product, homocystine. Homocystinuria is most commonly caused by autosomal recessive inheritance of a deficiency of CBS; however, other enzymatic abnormalities including defective synthesis of methylcobalamin (a form of vitamin B12) and methylenetetrahydrofolate reductase (MTHFR) deficiency cause this condition as well [1].

CBS is an enzyme which converts homocysteine to cystathionine in the metabolism of the essential amino acid methionine to cysteine (Figure 2). In CBS deficiency, plasma homocysteine and urine homocystine concentrations are elevated, with increased plasma and urine methionine as well. The frequency of the CBS deficiency form of the disease within the global population is unknown, but is estimated to range from 1:1,800 to 1:900,000 [2]. The imaging manifestation of brain white matter changes on MRI, as demonstrated in the presented case, is exceedingly rare, with only five other reports in the literature [3–8].

Numerous pathophysiologic mechanisms have been proposed as the cause of white matter abnormalities in poorly controlled CBS deficiency. Three prior reports have demonstrated imaging evidence of brain swelling with clinical signs of ICP elevation, presumably due to cerebral edema [3, 4, 7]. While the presented case shares similar findings of cerebral edema and additional imaging evidence of increased ICP, which are discussed further in the next section, two other cases have exhibited decreased brain volume, one attributed to atrophy [5, 6]. When present, cerebral edema may also be a multifactorial complication. One contributing factor may be direct cellular injury from the intrinsically toxic amino acid methionine, an intermediate metabolite that also accumulates in CBS deficiency [3]. Braverman, et al. theorized that oral betaine may also contribute to cerebral edema by acting as an intracellular osmolyte [8]. In fact, a minireview by Lawson-Yuen, et al. recommends close clinical monitoring of ICP in patients receiving betaine therapy [9].

Similar to two prior reports, the presented case also demonstrates extensive diffusion restriction throughout the white matter, implying accumulation of water within cells and/or in confined extracellular spaces between cell membranes [6, 7]. Although diffusion restriction is most commonly caused by cellular energetic failure leading to decreased Na+/K+ ATPase activity and subsequent cytotoxic cell swelling, osmotic imbalances induced by the intracellular osmolyte betaine could conceivably also produce similar changes in diffusion measurements. The involvement of several basal ganglia nuclei in the presented case may be due to the same process, although this has not been previously described in the literature.

Other authors have speculated that abnormal accumulation of homocysteine, methionine, and S-adenosylmethionine in the CSF secondary to decreased CBS activity causes white matter diffusion restriction via inhibition of Na+/K+ ATPase and resultant cytotoxic edema [10]. While at least four animal studies have shown reduction of Na+/K+ ATPase activity by artificially adding these metabolites to reach certain threshold concentrations, it appears that the experimental concentrations (either in μmol/g of wet brain tissue or μmol/L of solution) are markedly higher than the typical CSF concentrations (in μmol/L of CSF) in actual patients with homocystinuria, both with and without white matter abnormalities [4, 7, 11–15].

Vacuolating myelinopathy, characterized by the accumulation of water into extracellular intramyelinic vacuoles, is another potential mechanism of white matter diffusion restriction [16]. Myelin vacuolization is a well-known cause of white matter diffusion restriction observed in several metabolic disorders, such as Canavan disease and phenylketonuria. While this process may also occur in other disorders of methionine metabolism, such as methionine adenosyltransferase (MAT) I/III deficiency, it has been associated with CBS deficiency only via pathologic examination without radiologic correlate [7, 17, 18].

Case reports of other errors in methionine metabolism also imply demyelination as an alternate cause of white matter diffusion restriction [19]. This pattern of tissue injury has also been demonstrated on neuropathologic examination in severe CBS deficiency and is further substantiated by the MRS findings of our case, which demonstrates decreased NAA and increased choline in a pattern suggestive of increased cell membrane turnover [18]. However, all prior reports of white matter abnormalities in CBS deficiency have also demonstrated eventual signal normalization, which is unusual for most demyelinating diseases [3–8].

Despite the differing theories explaining the observed imaging findings, abnormal accumulation of methionine, not homocysteine, is generally accepted as the causative agent. As seen in the presented case, white matter abnormalities in other reports coincided with significantly elevated plasma methionine levels (904–2823 μmol/L) [3–8]. In several instances, they also resolved after plasma methionine decreased, although this was accompanied by reducing or ceasing betaine therapy, a potentially confounding factor [3, 4, 7]. Sasai, et al. most clearly illustrated the correlation between plasma methionine concentration and white matter abnormalities, specifically diffusion restriction, by concurrently acquiring both serial MR imaging and plasma methionine and homocysteine measurements in a single patient [7]. Several authors have also reported similar imaging findings in cases of markedly elevated plasma methionine (960–6830 μmol/L) and only mildly elevated homocysteine, caused by other metabolic derangements such as diet-induced hypermethioninemia and MAT I/III deficiency [10, 17, 20].

Clinical & Imaging findings:

Deficiency of the CBS enzyme results in a wide spectrum of abnormalities affecting multiple organ systems, the most common of which are ectopia lentis, osteoporosis, thinning and

lengthening of the long bones, mental retardation, and arterial and venous thromboembolism [1]. Severity of symptoms also greatly varies, ranging from asymptomatic to debilitating seizures and fatal thromboembolic disease [2]. Classic radiologic findings in homocystinuria due to CBS deficiency include arterial and venous neurovascular infarctions in infancy through adulthood, as well as morphological abnormalities of the skeleton and lesions of the pulmonary and peripheral vasculature [21, 22].

As described in the presented case, rare instances of poorly controlled CBS deficiency have been associated with nonspecific, but sometimes extensive, bilateral and symmetrical T2 prolongation and water diffusion restriction in the cerebral white matter, without evidence of an instigating neurovascular occlusion or abnormal enhancement with intravenous contrast [3–8]. Of the five case reports describing these findings, three also note clinical evidence of increased ICP manifested by elevated lumbar puncture opening pressure, papilledema, emesis and/or headaches. Diffuse brain swelling was also evident on MRI [3, 4, 7].

The presented case demonstrates not only severe and rare white matter changes in poorly controlled CBS deficiency, but also additional similar signal abnormalities in the basal ganglia not described in prior case reports [3–8]. In addition, papilledema, optic nerve sheath dilation and brain swelling provide specific imaging evidence of ICP elevation in this case, radiologically manifested in prior cases only as reversible brain swelling [3, 4, 7].

Treatment & Prognosis:

The primary treatment goal is to lower homocysteine concentrations throughout the body. The mainstays of therapy are pyridoxine (vitamin B6) supplementation, in cases that are pyridoxine-responsive, and dietary restriction of methionine. Betaine (trimethylglycine) may also be used for an alternate pathway to lower homocysteine and form methionine (Figure 2). Prognosis can be predicted by responsiveness to pyridoxine therapy, compliance with treatment regimen, and age of detection. Pyridoxine-unresponsive patients that are inadequately treated carry markedly reduced life expectancies and elevated risk of catastrophic complications, including potentially fatal thromboembolic events. While adequately treated patients with pyridoxine-responsive disease are at decreased risk of serious complications, overall long-term outcomes are not yet known [2].

In contrast, the primary treatment goal for the rare cases with white matter abnormalities is to lower methionine, not homocysteine, due to the postulated role of methionine in this complication. This is typically achieved by reducing or withdrawing betaine therapy and tightening control of dietary methionine intake. If methionine concentrations are successfully reduced, short-term prognosis is typically good. After initiating methionine-lowering therapy, all five previously reported cases demonstrated reversal of white matter signal changes on MRI, and four of the five prior cases demonstrated clinical resolution of the various signs and symptoms that prompted imaging workup [3, 4, 6, 7]. Long term prognosis, however, is not known.

Differential Diagnoses:

White matter changes in poorly controlled CBS deficiency are a rare complication with mixed imaging appearances and likely complex multifactorial pathophysiology. These findings have been shown to resolve with improved disease control and reduction/cessation of betaine therapy, and therefore should not be mistaken for other vascular, toxic or metabolic disorders.

The most acutely treatable differential diagnosis is dural venous sinus thrombosis, which can also present with clinical manifestations of increased ICP and imaging findings of bilateral white matter vasogenic and cytotoxic edema. An abnormal computed tomography (CT) scan or MRV, with or without gadolinium-based contrast, can generally confirm venous thrombosis. Venous infarction can also cause intraparenchymal hemorrhage, which has never been described in cases of white matter changes from poorly controlled CBS deficiency.

Hypoxic-ischemic injury is another cause of diffuse cerebral edema and increased ICP, characteristically with focal imaging abnormalities of the basal ganglia as well. Acutely, however, cerebral involvement more commonly affects gray matter than white matter due to increased cellular metabolic demands, which is opposite of findings seen in poorly controlled CBS deficiency. Spectroscopy can show increased lactate in the affected brain, which is also a distinguishing feature.

Other inborn errors of metabolism can also produce symmetrical and sometimes diffuse white matter signal changes on brain MRI that mimic poorly controlled CBS deficiency, including metachromatic leukodystrophy, Canavan disease, urea cycle defects, and maple syrup urine disease [23]. Several of these diseases, however, can be characterized by additional MRI findings that are more specific. Urea cycle defects can cause more localized edema of the insular cortex, perirolandic cortex, and basal ganglia. Metachromatic leukodystrophy can sometimes result in concentric stripes of normal and abnormal myelination in the periventricular white matter, typically accompanied by progressive brain volume loss. Others demonstrate specific MRS abnormalities, such as a characteristically high NAA peak in Canavan disease, or the presence of a branched chain ketoacid peak in maple syrup urine disease.

TEACHING POINT

Poorly controlled homocystinuria due to cystathionine β-synthase deficiency can develop varying degrees of T1 hypointensity, T2 hyperintensity, and diffusion restriction in the white matter of the brain that should not be mistaken for other vascular, toxic or metabolic disorders. While the underlying pathophysiology of these imaging findings is poorly understood and likely multifactorial, hypermethioninemia (and not hyperhomocysteinemia) is believed to be the major contributor to white matter abnormalities.

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FIGURES

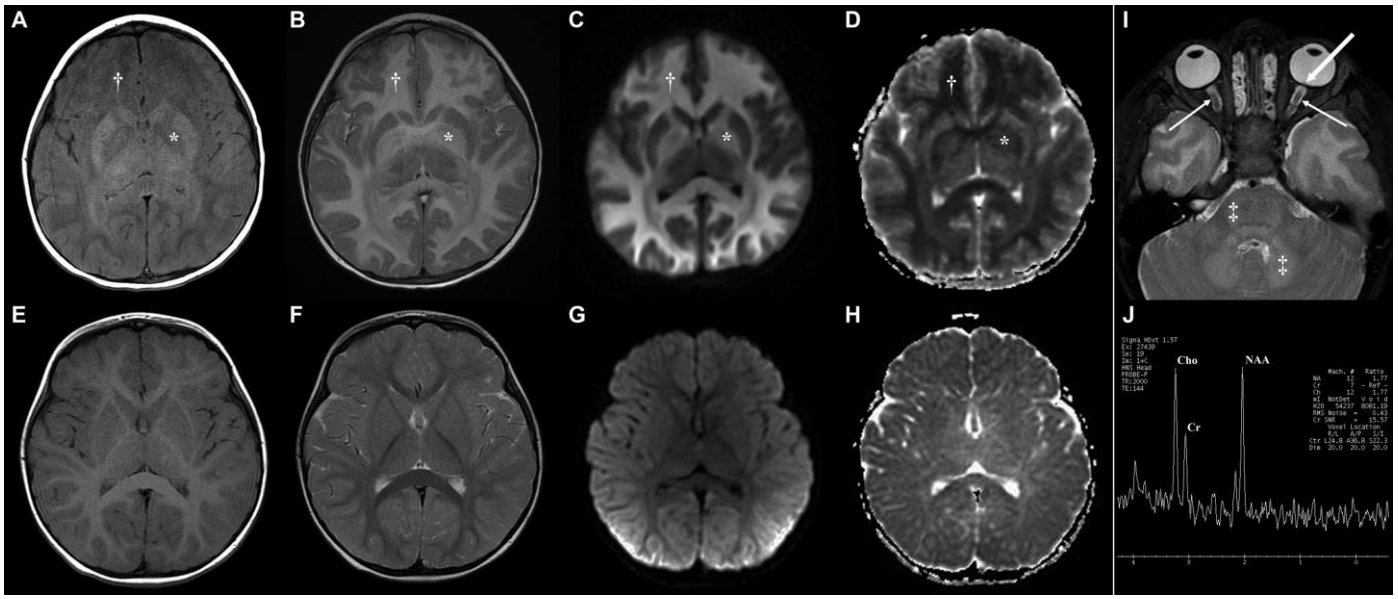

Figure 1: Two-year-old female with poorly controlled homocystinuria.
FINDINGS: Brain MRI showing signal abnormalities throughout white matter (†) and bilateral globi pallidi (*) (top row, A-D). Age-matched normal is shown for comparison (bottom row, E-H). White matter was abnormally dark on T1-weighted images (A) and bright on T2-weighted images (B) due to prolonged T1 and T2 relaxation. Diffusion weighted images (C) and calculated apparent diffusion coefficient maps (D) revealed diffusion restriction throughout the white matter. High-resolution T2-weighted images of the orbits (I) showed papilledema (thick arrow) and dilated optic nerve sheaths (thin arrows) without ectopia lentis. The white matter of the pons and cerebellum was also abnormally T2-bright (‡). MRS (J) of the left frontal lobe white matter shows small NAA and large choline peaks without a lactate peak.
TECHNIQUE: All sequences acquired at 1.5 T field strength. T1-weighted: TR 350 ms, TE 14 ms. T2-weighted: TR 4093 ms, TE 84 ms. DWI: TR 8000 ms, TE 84 ms, b=1000 s/mm2. T2-weighted orbits: TR 2858 ms, TE 69 ms, chemical fat saturation. MRS: single voxel, TE 144 ms.

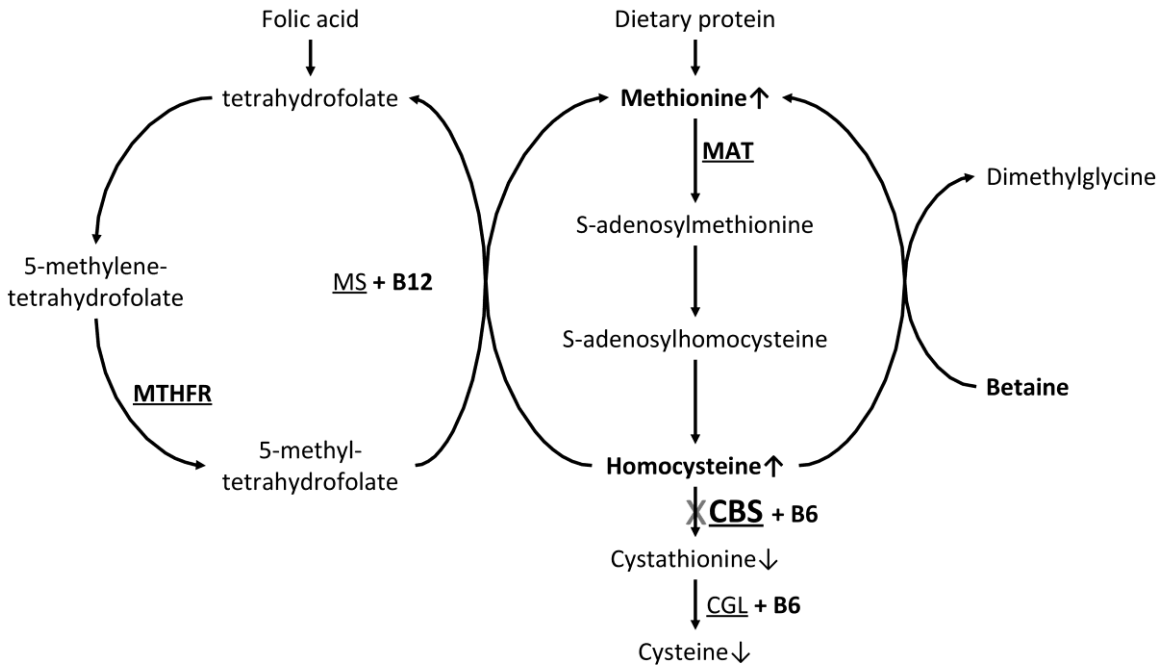

Figure 2: Homocysteine and methionine metabolism. Enzymes are underlined and all components pertinent to this case are bolded. CBS deficiency disrupts the conversion of homocysteine to cystathionine (denoted by an "X") and results in accumulation of homocysteine and methionine. B6: vitamin B6. B12: vitamin B12, or methylcobalamin. MS: methionine synthase. MTHFR: methylenetetrahydrofolate reductase. MAT: methionine adenosyltransferase. CGL: cystathionine γ-lyase.

	Our patient	Normal range
Plasma homocysteine (µmol/L)	203	3.4–11.8
Plasma methionine (µmol/L)	1182	7–47
CSF methionine (µmol/L)	199	0–5.8
CSF glucose (mg/dL)	76	40–70
CSF protein (mg/dL)	<10	15–45
Lumbar puncture opening pressure (cm)	28	10–20

Table 1: Laboratory values on admission. Plasma and CSF concentrations of homocysteine and methionine were elevated, as was lumbar puncture opening pressure.

Etiology	• Autosomal recessive inheritance of a deficiency of CBS • Brain MRI findings may be caused by a combination of: o Direct cellular toxicity of elevated methionine o Intracellular fluid shift caused by betaine therapy o Vacuolating myelinopathy o Demyelination
Incidence	• Overall frequency of CBS deficiency ranges from 1:1,800 to 1:900,000 [2] • Only five other reported cases of white matter abnormalities in the setting of poor disease control
Gender ratio	• N/A, autosomal recessive inheritance
Age predilection	• CBS deficiency is present at birth • No clear age predilection of white matter abnormalities
Risk factors	• Consanguineous, Celtic and Qatari populations have higher frequency of CBS deficiency [1, 2] • Poor treatment compliance may increase risk of white matter abnormalities
Treatment	• Pyridoxine supplementation, dietary methionine restriction, and betaine are mainstays of homocysteine-lowering therapy • White matter abnormalities require methionine-lowering therapy, typically by reducing or withdrawing betaine therapy and tightening control of dietary methionine intake
Prognosis	• Overall varied based on responsiveness to pyridoxine therapy, compliance with treatment regimen, and age of detection [2] • White matter abnormalities have shown to be reversible with successful lowering of methionine levels
Findings on imaging	• Classic radiologic features of CBS deficiency include osteoporosis, thinning and lengthening of the long bones, arterial and venous neurovascular infarctions in infancy through adulthood, and pulmonary and peripheral vascular disease [1] • When present, nonspecific but sometimes extensive white matter T2 prolongation and diffusion restriction without evidence of an instigating neurovascular occlusion, sometimes with diffuse brain swelling and evidence of increased ICP [3–8] • Possible involvement of the basal ganglia as demonstrated in the presented case

Table 2: Summary table for brain magnetic resonance imaging findings in Homocystinuria.

	CT	MRI
CBS deficiency (white matter disease only)	• Brain swelling • Symmetrical/diffuse cerebral white matter hypoattenuation, possibly involving cerebellum	• Brain swelling • Symmetrical/diffuse cerebral white matter T1 and T2 prolongation with diffusion restriction • May involve cerebellum and basal ganglia • May see papilledema and optic nerve sheath dilation • No contrast enhancement
CBS deficiency (acute neurovascular disease)	• Potentially bilateral and symmetrical white matter hypoattenuation and brain swelling in setting of dural venous sinus thrombosis • Territorial infarcts in arterial thrombosis • Arterial/venous filling defect on CT angiography/venography • May see intraparenchymal hematomas with dural venous sinus thrombosis	• Potentially symmetrical white matter T1 and T2 prolongation, potentially with diffusion restriction and/or intraparenchymal hematoma, in the setting of dural venous sinus thrombosis • Territorial diffusion restriction in arterial thrombosis • Arterial/venous filling defect on MR angiography/venography • No contrast enhancement (acutely)
Hypoxic-ischemic injury	• Brain swelling • Loss or reversal of grey-white attenuation differences • Decreased basal ganglia attenuation • Sometimes increased attenuation of the cerebellum relative to cerebrum	• Brain swelling • Possible basal ganglia T1 shortening and T2 prolongation • Diffusion restriction in basal ganglia, cerebral cortex, vascular watershed territories • Elevated lactate peak on MRS • No contrast enhancement (acutely)
Metachromatic leukodystrophy [23]	• Symmetrical central cerebral white matter hypoattenuation • Progressive brain volume loss	• Symmetrical central cerebral white matter T1 and T2 prolongation, as well as diffusion restriction, initially sparing the subcortical white matter, sometimes with concentric stripes of normal and abnormal signal • Progressive brain volume loss • Decreased choline peak on MRS • No contrast enhancement
Canavan disease [23]	• Diffuse symmetrical cerebral and cerebellar white matter hypoattenuation, involving subcortical white matter and globi pallidi	• Diffuse symmetrical cerebral and cerebellar white matter T1 and T2 prolongation, as well as diffusion restriction, involving subcortical white matter and globi pallidi [24] • Elevated NAA peak on MRS • No contrast enhancement
Urea cycle defects [23]	• Brain swelling • Diffuse cerebral edema	• Brain swelling • Localized T1 and T2 prolongation in the insular cortex, perirolandic cortex, and basal ganglia, with greater involvement of the frontal lobe cortex in older patients
Maple syrup urine disease [23]	• Possible brain swelling • Hypoattenuation of the deep cerebellar white matter, dorsal brainstem, cerebral peduncles, posterior limb of the internal capsule and perirolandic white matter • Possible generalized white matter hypoattenuation	• Possible brain swelling • T1 and T2 prolongation, as well as diffusion restriction, of the deep cerebellar white matter, dorsal brainstem, cerebral peduncles, posterior limb of the internal capsule and perirolandic white matter • Presence of a branched chain ketoacid peak on MRS

Table 3: Differential diagnosis table for brain magnetic resonance imaging findings in Homocystinuria.

ABBREVIATIONS

CBS = cystathionine β-synthase
CGL = cystathionine γ-lyase
CSF = cerebrospinal fluid
CT = computed tomography
ICP = intracranial pressure
MAT = methionine adenosyltransferase
MRI = magnetic resonance imaging
MRS = magnetic resonance spectroscopy
MRV = magnetic resonance venography
MS = methionine synthase
MTHFR = methylenetetrahydrofolate reductase
NAA = N-acetylaspartate

KEYWORDS

homocystinuria; cystathionine beta synthase deficiency; magnetic resonance imaging; brain; cerebral edema; intracranial pressure; white matter; diffusion restriction