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Case Report

Severe cystic degeneration and intractable seizures in a newborn with molybdenum cofactor deficiency type B

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ABSTRACT

Newborns with cystic degeneration with or without intractable seizures should be investigated for inborn errors of metabolism, including molybdenum cofactor deficiency (MoCoD). MoCoD may present with non-specific hypoxic ischemic injury in the neonatal period with MRI showing extensive prenatally acquired cystic encephalomalacia involving grey and white matter. Most newborns with MoCoD will present with normal head size and brain appearance at birth and postnatally rapidly develop cystic encephalomalacia. A significant minority will present with signs of prenatal brain injury or malformation. It is important to consider the diagnosis in both scenarios. Low plasma urate and homocysteine may help direct the diagnostic evaluation. Herein, we describe the clinical, radiological and biochemical features of a newborn with MoCoD that was initially suspected of having the condition on biochemical screening and confirmed on rapid whole exome sequencing.

1. Introduction

Seizures are the most common neurological manifestation in newborns with a brain abnormality. Neonatal seizures increase the risk for death, while survivors may experience developmental delay or neurologic impairment, including epilepsy. Causes of neonatal seizures include hypoxic-ischemic injury, hypoglycemia, stroke, infection, inborn errors of metabolism (IEM), and brain malformations [1].

Rare IEM, including molybdenum cofactor deficiency (MoCoD), may present similar to non-specific hypoxic ischemic injury in the neonatal period, with MRI showing extensive prenatally acquired cystic lesions involving grey and white matter. MoCoD does not present with non-specific hypoxic-ischemic encephalopathy (HIE) and one single MRI cannot determine the etiology of cystic lesions. Such imaging findings in the neonatal period may help prioritize the workup of IEM [2].

2. Case report

A one-day-old term male infant presented for evaluation of encephalopathy and intractable seizures. His mother noted in-utero hiccups and abnormal movements in the 3rd trimester. Antenatal ultrasound on week 25 demonstrated a cystic structure in the posterior fossa (4.9x3x4.3 cm), suspected to be an arachnoid cyst. He was born at 37 weeks +2 days gestational age to consanguineous parents with a family history of unexplained infantile deaths and developmental delay. He was microcephalic with myoclonic jerks including facial twitching, and dysmorphic features were absent. Brain MRI obtained on the first day of life showed severe atrophy of the corpus callosum and thalami, with a slender brainstem and shortened heights of the vermian (Fig. 1A and B). Cavitary changes were demonstrated in the frontal lobe white matter, the caudate nuclei and putamina (Fig. 1B). There were multifocal foci of hemosiderin in the frontal lobes, head of caudate nucleus, ependyma of the lateral ventricles, the posterior horns and tentorial incisura (Fig. 1C). No diffusion restriction was identified, confirming chronicity of findings. Taken together, these findings were consistent with severe intrauterine acquired brain damage resulting in cystic encephalomalacia.

Screening for IEM showed a low plasma and urine urate, high xanthine and hypoxanthine, undetectable homocysteine and a positive urinary sulfite (initially negative) and sulfocysteine (Table 1). His urine sulfocysteine was only mildly increased and given the consistently low

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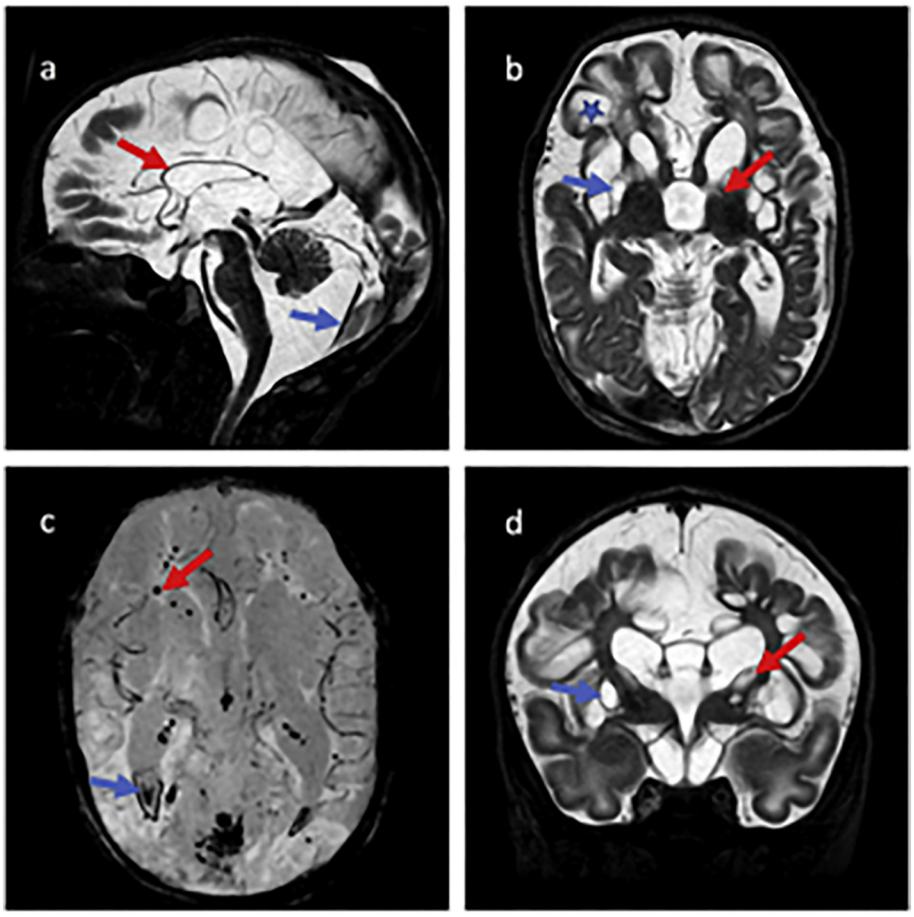

Fig. 1. Legend MRI Day 0: Sagittal T2 weighted image (a) demonstrates severe atrophy of the corpus callosum (red arrow). The brainstem is slender and the vermian height is short. Blood layers in the posterior fossa cyst (blue arrow). Axial and coronal T2W images (b, d) demonstrate cavitary changes of the frontal lobe white matter (star), the caudate nuclei (red arrows) and putamina (blue arrows). The thalami are atrophied. Axial susceptibility weighted image (c) reveals multifocal foci of hemosiderin in the frontal lobes (red arrow) and head of caudate nucleus. Hemosiderin also stains the ependyma (blue arrow) of the lateral ventricles, the posterior horns and tentorial incisura. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Biochemical laboratory analysis since birth.

Test	Day 1	Day 2	Day 17
Homocysteine (2.9–10 μmol/L)		< 1	< 1
Urine Sulfite (0 mg/L)	Negative		80
Urine sulfocysteine (1–15 mmol/mol creatinine)	26		180
Plasma urate (156–732 μmol/L)		31	34
Urine uric acid (166–1222 μmol/mmol creatinine)		85	
Urine xanthine (11–42 μmol/mmol creatinine)		282	
Urine hypoxanthine (3–39 μmol/mmol creatinine)		115	

urate levels, a high index of suspicion for MoCoD led to a repeat urinary sulfite and sulfocysteine. These tests came back strongly positive, confirming the diagnosis of MoCoD. Three different gene defects can cause MoCoD, with one form (MoCoD-A, caused by disease-causing variants in the *MOCS1* gene) being a treatable disease. Therefore, a rapid whole exome sequencing was pursued, with a turnaround time of approximately 2 weeks, which identified a known homozygous likely pathogenic variant in *MOCS2* (c.*146G > A, p.?). The patient was diagnosed with molybdenum cofactor deficiency type B (MoCoD-B). His last clinical evaluation was at the age of 6 months; he has had recurrent hospital admissions for intractable seizure disorder that is difficult to control on several antiepileptic therapies. He has 2 siblings that developed appropriately without concerns. The family received a genetic consultation, genetic testing was offered, and both parents were heterozygous for the pathogenic variant.

3. Discussion

The clinical and laboratory findings for our patient were typical of an IEM. Plasma urate is the metabolic product of purine metabolism in humans; low levels are suggestive of rare IEM, including MoCoD. The biochemical profile of xanthine oxidase deficiency (low plasma and urine urate, elevated xanthine or hypoxanthine) and sulfite oxidase deficiency (undetectable homocysteine and elevated urinary sulfite and sulfocysteine) are characteristic of MoCoD [1,3]. Molybdenum is an essential trace element that is incorporated into a cofactor for several enzymes, including xanthine oxidase, sulfite oxidase and aldehyde oxidase [1]. The functional deficiency of sulfite oxidase causes sulfite intoxication, which is thought to be the primary pathophysiology event in MoCoD. The urine sulfite test is a screening dipstick test that can be done at the patient's bedside leading to rapid results. However, using this test, one should be aware of the possibility of both false negative and false positive results. Urine sulfocysteine is a more sensitive diagnostic tool, however the number of centers offering this test is limited and long turnaround time can prevent the rapid evaluation of IEM (Table 1).

Altered serum and urine uric acid levels are indispensable markers in detecting rare IEM. We have presented a case of severe intrauterine presentation of MoCoD-B. Clinical presentation and imaging studies led us to further investigate the possibility of MoCoD. The suspicion of MoCoD was based on further metabolic testing, which might not always be available or might not be performed in many health care facilities. Cystic brain transformation related to MoCoD are difficult to distinguish from acquired causes, such as asphyxia and infections, or other IEM, such as thiamine transporter defect due to disease-causing variants in the *SLC19A3* gene [4,5] and mitochondrial disorders [6]. In this case, the initial urine sulfite stick results were negative. However, repeatedly low urate levels led us to further investigate the diagnosis of MoCoD. Clinicians should pursue the possibility of MoCoD in all neonatal cases with severe cystic brain transformation to avoid missing this diagnosis

and despite a negative urine dipstick test. In this case, the clinical presentation is less common than what is expected in HIE without adequate perinatal history.

MoCoD presents with severe neonatal seizures, mimicking HIE secondary to perinatal asphyxia, feeding difficulties, hypotonia, lens dislocation, coarse features, severe developmental delay, brain atrophy and early childhood death [1,7]. Our patient's MRI showed extensive chronic cavitary encephalopathy of white and grey matter, reflecting brain damage that began in-utero. Additionally, the extensive hemorrhagic deposits observed are non-specific but could be seen in MoCoD. Interestingly, there was no diffusion restriction detected in the MRI on the first day of life. Typically, brain MRI abnormalities in MoCoD evolve sequentially with time into global cerebral infarction with edema and restriction in diffusion-weighted images followed by severe cystic leukomalacia [7,8]. Other abnormalities include dysgenesis of corpus callosum, distinctive band of intermediate signal intensity at the grey-white junction, pontocerebellar atrophy, retrocerebellar cyst and isolated hyperintensities of globus pallidus [7,8].

Most disease-causing variants are at the *MOCS1* gene, corresponding with MoCoD-A. Unlike other published cases of MoCoD [3,7,9], this patient's diagnosis was confirmed with rapid whole exome sequencing with a turnaround time of ~2 weeks. His known homozygous likely pathogenic missense variant in *MOCS2* (c.*146G > A, p.?) is found at an allele frequency of 0.0049% in the gnomAD control database, with no homozygotes present. Using variant prediction models, this variant has been hypothesized to abolish the canonical splicing at the donor sites of exon 4, resulting in the activation of a cryptic splice site 4 bp upstream in exon 4 and a potential frameshift and premature truncation of the protein.

Daily intravenous administration of cyclic pyranopterin monophosphate (c-PNP) has been effective in *Mocs1* knockout mice and MoCoD-A patients, particularly if initiated before the development of significant encephalopathy [10]. However, no successful therapies are available for MoCoD-B, and death in early infancy has been the usual outcome. This has been recently recapitulated in *Mocs2* knockout mice that failed to thrive and died within 11 days after birth [11]. The confirmation of MoCoD was followed by subtyping of disease to determine if our patient had MoCoD-A or MoCoD-B to help inform treatment decisions as c-PNP is only effective in type A. In our case, rapid whole exome sequencing confirmed MoCoD-B diagnosis and further informed our supportive approach for seizure management for this patient. Establishing a molecular diagnosis in a timely manner is an important consideration for disease treatment and prognosis.

Informed consent

Informed consent was obtained from the participant's parents.

Author contributions

FHS: analysis and interpretation of the data, drafting and revising the manuscript for intellectual content. LM: analysis and interpretation of the data, drafting the manuscript for intellectual content. MP: analysis and interpretation of the data, revising the manuscript for intellectual content. RJ: analysis and interpretation of the data, including rapid whole exome sequencing, drafting the manuscript for intellectual content. SL: analysis and interpretation of the data, including radiographs, drafting the manuscript for intellectual content. GY: analysis and interpretation of the data, drafting the manuscript for intellectual content SB: analysis and interpretation of the data, including radiographs, drafting the manuscript for intellectual content. MIF: design and conceptualization of the study, analysis and interpretation of the data, revising the manuscript for intellectual content.

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Disclosure

The authors declare that they have no conflict of interest.

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