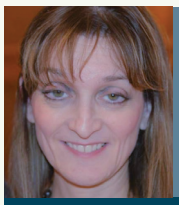
Molybdenum Cofactor Deficiency (MoCD): A Rare Genetic Disorder in Newborns



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Introduction

The detection of inborn errors of metabolism (IEM) depends upon a high index of suspicion. In the case below, one must keep in mind that neonates with intractable seizures are often given a diagnosis of hypoxic ischemic encephalopathy (HIE). However up to 20%-35% of cases may be due to an underlying metabolic etiology. Given that many IEMs are treatable, it is important to include IEMs in the differential diagnosis of any child being considered for HIE. Important details from the medical history and the timing of appearance of lesions on magnetic resonance imaging (MRI) can provide important clues.

The following case report emphasizes key aspects of the history that warrant further diagnostic evaluation for an IEM.

Case Report

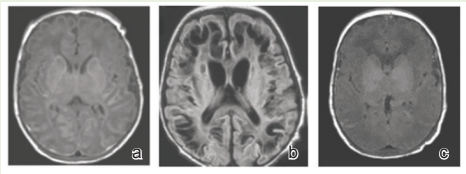
A neurological consultation is requested for a baby under the following scenario:

A 3600-g female infant was born at 38 weeks' gestation to a 26-year-old G1P0 mother by spontaneous vaginal delivery at a local community hospital. The mother was healthy, and the pregnancy had been uncomplicated. There were no concerning events during the delivery. Apgar scores were 8 and 8 at 1 and 5 min, respectively. On day of life (DOL) 2, the infant developed intractable seizure activity requiring a phenobarbital load and was intubated for development of apnea. Head ultrasound showed "swelling." The diagnosis was coded as HIE, and the infant was transferred to a tertiary care NICU for further management and possible cooling. At the second hospital, computed tomography (CT) showed a small subdural hemorrhage. Continuous electroencephalographic (cEEG) monitoring showed left hemispheric seizures (50% with clinical correlates and dysmaturity; L>R hemispheric dysfunction). The seizures were initially refractory to multiple antiepileptic medications including phenobarbital, levetiracetam, fosphenytoin, pyridoxine, lorazepam, and oxcarbazepine. Finally, on DOL 3, the seizures were significantly reduced, and MRI and magnetic resonance spectroscopy (MRS) were performed, demonstrating diffuse, global diffusion abnormalities with a significantly elevated lactate peak on MRS. Diffusion tensor imaging showed restricted diffusion involving deep nuclei and the cortex. The diagnosis provided to the family was an acute and partial prolonged asphyxia event. Since IEM may mimic HIE, genetics was consulted. Plasma amino acids on DOL 7 revealed the following results: low cystine, 1* µmol/L (normal range, 17-98) and low uric acid, 0.5 mg/dL (normal range, 2-7). Urine purine/pyrimidine panel on DOL 8 revealed that urinary xanthine was 8× the upper limit of normal. There were no sulfite dipsticks available. Urine S-sulfocysteine (SSC) and genetic sequencing of *MOCS1* and *MOCS2* were ordered. Results ultimately showed a homozygous *MOCS1* gene variant consistent with a diagnosis of molybdenum cofactor deficiency (MoCD) Type A (OMIM 252150).

The sulfite intoxication disorders isolated sulfite oxidase deficiency (ISOD) (OMIM 272300) and MoCD can present in the newborn period and mimic HIE. ISOD is an IEM of sulfated amino acids. The most common presentation is in the neonatal period with intractable seizures, encephalopathy, and characteristic dysmorphic features. It is associated with poor outcome and profound intellectual disability. MoCD, which affects the functioning of sulfite oxidase (SOX), has a similar phenotype. Both conditions are autosomal-recessive disorders and should be considered in the differential diagnosis of a neonatal seizures or neonatal birth injury, especially when the history does not fit the presentation of asphyxia.

In this clinical scenario, one must consider the sulfite intoxication disorders ISOD and MoCD in the differential diagnosis. In a neonate such as this with early-onset, intractable epilepsy and an MRI showing global injury (**Figure 1**), the timing of the abnormalities seen on CT (showing swelling on DOL 1 and global injury on DOL 3) is too early to be attributed to HIE.[1,2]

FIGURE 1. T1 MRI shows edema (a) and subsequent necrotic lesions (b) of the basal ganglia. After 2 months (c), there is ventricular dilatation, dramatic cerebral cortical atrophy and multicystic lesions.



What are the striking features of this presentation? Is this merely HIE, or should one consider an IEM?

(Images courtesy of Andrea Gropman, MD.)

Individuals affected with sulfite intoxication disorders most commonly present in the neonatal period with a broad range of signs including encephalopathy, intractable seizures, feeding difficulties, high-pitched cry, metabolic acidosis, intracranial acidosis, exaggerated startle response, axial hypotonia, and characteristic dysmorphic facial features. Patients ultimately have profound intellectual disability and high mortality. The most common features in the neonatal period are intractable seizures (often of prenatal onset) and severe neurologic abnormalities. In those infants that survive, subsequent lens dislocation may occur, with the youngest report of dislocation occurring at 8 weeks of age. The neuropathologic findings

in ISOD resemble those seen in severe perinatal asphyxia.[3,4] Cystic brain destruction might already be present prenatally, and subsequent development of gyration and differentiation of the cortical layers in the developing brain can be affected by sulfite accumulation early during the third trimester.[5]

The phenotypic spectrum of MoCD was recently further delineated by Misko, et al. into 2 phenotypes based on clinical and radiographic distinctions.[6] In the first group are those who have "classic MoCD" defined as clinical presentation from DOL 1-50 with acute onset of neurologic symptoms. MRI findings in early-onset cases show diffuse brain injury with cystic leukomalacia.[6] In this case scenario, MoCD may mimic HIE in the newborn and needs to be considered. Typical brain MRI findings include cerebral edema, cystic encephalomalacia, and involvement of the globus pallidus and subthalamic nuclei, with cortical and white matter atrophy.[6] Proton MRS (1H-MRS) shows an elevated lactate level, a decrease in the ratio of N-acetylaspartate to creatine, and a rise in the ratio of choline to creatine.[7] The second group of patients with MoCD, accounting for 13% of patients, present between 50 days and 23 years. The prominent neurologic condition involves a movement disorder, and MRI shows selective injury of the basal ganglia and cerebellum. This overlaps clinically with many other IEMs and needs to be included in the differential. Biochemical diagnosis may not distinguish between the 2 groups. Group 2 has a better prognosis and life expectancy.[6] Key features seen on examination are described in **Table 1**.

Natural History and Clinical Presentation

Duran, et al. described the first patient with MoCD in 1978, a neonate with intractable seizures associated with feeding difficulties and a high-pitched cry. Subsequently, the infant was noted to have lens dislocation, facial dysmorphism, and significant intellectual disability.[8] Pregnancy and delivery history were unremarkable. At the time, the biochemical pathway was not known.

The "classic presentation" of sulfite intoxication includes intractable seizures in the first days or weeks of life and abnormal tone (particularly opisthotonos). Feeding difficulties are common shortly after birth. Growth is typically normal at birth but may subsequently be poor with secondary microcephaly. Affected individuals continue to manifest severe psychomotor retardation, spasticity, and/or hypotonia as well as significant intellectual disability. Initial features may appear in the first days of life and include feeding difficulties and intractable seizures, sometimes with opisthotonos and exaggerated startle reaction/myoclonus.[9] Eventually, there is progressive cerebral atrophy, cystic encephalomalacia, and lack of developmental progress. Previously described radiologic features have included global cerebral edema, cystic encephalomalacia, ventriculomegaly, both cortical gray and white matter atrophy, focal or bilateral signal abnormality in the globus pallidus and subthalamic nuclei, and dysgenesis of the corpus callosum and basal ganglia.[1,10,11]

Etiology of Sulfite Oxidase and Molybdenum Cofactor Deficiencies

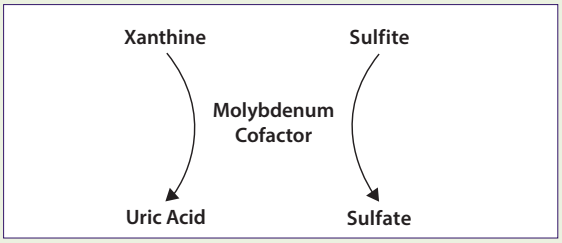
SOX is a molybdenum cofactor–dependent enzyme, and loss of its activity is sufficient to cause the neurodegenerative phenotype of both ISOD and MoCD. SOX is an intramitochondrial enzyme that leads to oxidation of sulfite to sulfate.[12] The enzyme SOX requires the molybdenum-containing pterin cofactor. Molybdenum cofactor (MoCo) is also required for xanthine dehydrogenase and aldehyde oxidase. Xanthine dehydrogenase catalyzes the hydroxylation of hypoxanthine and xanthine, producing uric acid, and aldehyde oxidase oxidizes aldehydes to carboxylic acids in the cytoplasm and functions in detoxification. Deficiency of either xanthine oxidase or aldehyde oxidase is not known to be associated with neurologic disorders[13] **(Figure 2)**. ISOD affects the metabolism of sulfated amino acids due to SOX deficiency, while MoCD affects SOX and xanthine dehydrogense **(Figure 3)**. Both disorders have a common phenotype thatincludes intractable seizures, characteristic facial dysmorphic features **(see Table 1)**, and severe intellectual disability. Rarely, milder cases have been reported.[14-18]

MoCo is a complex molecule made by a 3-step biosynthetic pathway **(Figure 3)**. The pathway involves gene products from 4 distinct loci: *MOCS1*, *MOCS2*, *MOCS3*, and *GPHN*. MoCD is due to the simultaneous deficiency to complete loss of function of all MoCo-dependent enzyme activity due to decreased

TABLE 1. MoCD: Key Findings on Examination

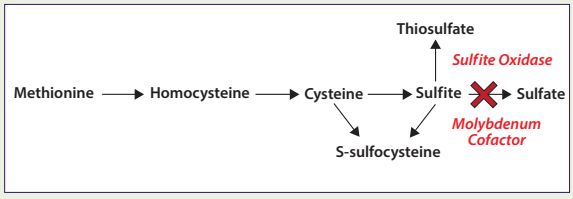
Neurologic
• Axial hypotonia with peripheral hypertonia
• Intractable tonic/clonic seizures
• Myoclonus
• Opisthotonos
• Movement disorder
• Hyperekplexia
• Hyperreflexia
• Apnea
• Encephalopathy
Cranial dysmorphic features
• Narrow bifrontal diameter
• Frontal bossing
• Depressed nasal bridge
• Deep-set eyes
• Full cheeks
Eye findings
• Dislocated lenses (may develop after the neonatal period)
• Lack of response to light
Cardiovascular
• Hypotension
Gastrointestinal
• Feeding difficulties
Renal
• Nephrolithiasis

FIGURE 2. Key biochemical pathways where MoCo is involved. MoCo is necessary for conversion of xanthine to uric acid and sulfites to sulfate.[26]



or absent biosynthesis of MoCo. This process occurs via 3 steps involving cyclic pyranopterin monophosphate (cPMP; previously called precursor Z)[19,20] and the metal-binding pterins: molybdopterin (MPT),[21] pyranopterin triphosphate,[20] thio-pyranopterin phosphate,[22] and adenylated MPT.[20,23] MoCD types A and B are clinically indistinguishable. Type C presents with a more severe neurologic phenotype. This has been attributed to the loss of synaptic inhibition, which is dependent on gephyrin function. The estimated prevalence of MoCD is 1 per 100,000-200,000 newborns worldwide.[24] More than 100 cases of MoCD have been reported, and Type A is the most common type.[9,14]

FIGURE 3. Synthetic pathway of MoCo. When SUOX is deficient, alternate metabolic pathways for sulfite are enhanced, including the formation of the metabolites SSC and thiosulfate.[26]



Diagnosis and Testing

When sulfite intoxication is in the differential diagnosis, specific laboratory testing may offer clues. One should consider screen for the presence of urine sulfite and low or decreasing plasma urate. The potential for a false negative sulfite by dipstick may necessitate repeat assessments with fresh urine, with reports of false positives.[25] Next, one should screen for elevations of purine metabolites (xanthine and hypoxanthine) and elevations of SSC, which are due to the deficiency of MoCo-dependent enzymes. Tests and sample requirements for testing are shown in Table 2. These tests are available in most hospitals, although several may require samples to be sent out.

It should be noted that plasma urate can be normal in milder phenotypes.[12,16] This may also be the case in the first day or two for severe cases due to maternal influence; thus, a repeat urate test is important if high clinical suspicion exists. In ISOD, as opposed to MoCD, there is no xanthine oxidase deficiency, so the urate and purine metabolites are normal. These 2 conditions are often not clearly distinguished in the literature, leading to potential confusion when interpreting results.[17]

Brain Imaging

Brain imaging may be critical in distinguishing sulfite intoxication from other etiologies such as glycine encephalopathy (OMIM 605899), pyridoxamine 5′-phosphate oxidase deficiency (OMIM 610090), and asparagine synthetase deficiency (OMIM 615574) with intracranial hemorrhage.[27] ISOD and MoCD should be considered when HIE is in the differential diagnosis.

Though clinical features may overlap, the MRI findings that distinguish sulfite intoxication from HIE are the involvement of pallidi and subthalamic nuclei. HIE involves deep gray matter: posterolateral putamina and ventrolateral thalami or more diffuse basal ganglia injury. Prenatal enlarged cisterna magna has been observed in a patient who was ultimately diagnosed with an *MOCS1* gene mutation.[28]

It is important to obtain a complete history, including birth history, to help differentiate from HIE. This is because SSC is a structural analog of glutamate that accumulates in the plasma and urine of patients. Studies show it can function as an N-methyl-d-aspartate receptor (NMDA-R) agonist, thereby promoting calcium influx and downstream events leading to neurotoxicity. It is believed that SSC is responsible for progressive excitotoxic neurodegeneration.[29]

Genetic Testing

Patients with ISOD carry biallelic mutation in SUOX. Patients with MoCD harbor mutation in one of the molybdenum cofactor synthesis genes *MOCS1, MOCS2, GPHN*, or *MOCS3* (Table 3).

Note: Patients with GPHN deletions and splice site mutations show hyperekplexia. Patients with missense mutations, which do not affect the receptor cluster function of the protein product

TABLE 2. Testing Requirements for Diagnosis of of MoCD[26]

	Quantity	Notes
Urine studies		
Sulfite dipstick	N/A	Fresh urine
S-sulfocysteine	1 mL	Frozen
Uric acid	1 mL	Frozen
Xanthine	1 mL	From purine/pyrimidine panel
Plasma studies		
S-sulfocysteine	1 mL	EDTA tube
Uric acid	1 mL	EDTA tube
Xanthine	1 mL	From purine/pyrimidine panel

Abbreviation: EDTA, ethylenediabminetetraacetic acid.

TABLE 3. MoCD Subtypes, Genes, and Loci

Complementation Group	Gene Symbol	Chromosomal Locus	Protein Name
Isolated sulfite oxidase	*SUOX*	12q13.2	Sulfite oxidase
Complementation group A	*MOCS1*	6p21.3	MoCo synthesis protein 1 A and AB
Complementation group B	*MOCS2*	5q11	MoCo synthesis protein 2
	MOCS3	20q13.13	MoCo synthesis protein 3
Complementation group C	*GPHN*	14q23.3	Gephyrin

TABLE 4. Metabolic Differences Between Subtypes of MoCD[26]

Molybdenum cofactor deficiency type		*A*	*B*	*C*
Routine laboratory	Uric acid (P)	↓↓	↓↓	↓↓
Special laboratory	cPMP (U)	N	↑↑	n-↑
	Cystine (P)	↓↓	↓↓	↓↓
	Homocysteine (P)	↓↓	↓↓	↓-↑
	PLP (P)	↓	↓	↓
	Sulfocysteine (P, U)	↑↑↑	↑↑↑	↑↑↑
	Sulfite (U)	+++	+++	+++
	Taurine (P, U)	↑	↑↑	↑↑
	Urothione (U)	↓↓↓	↓↓	n-↑
	Xanthine (P, U)	↑↑↑	↑↑↑	↑↑↑

Abbreviations: P, plasma; U, urine

gephyrin, do not. Patients with *GPHN* deletions and splice mutations or with only deletions will not survive beyond infancy.

There are metabolic differences between the subtypes (Table 4) despite the similar clinical phenotype.

Molecular Testing

Prenatal molecular testing can be performed on chorionic villus or cultured amniocytes.

Most patients with MoCD have causative variants in *MOCS1* (Type A) and *MOCS2* (Type B). The *GPHN* gene encodes gephyrin, an organizational protein that clusters and localizes the inhibitory glycine and GABA receptors to the microtubular matrix of the neuronal postsynaptic membrane (summary by Reiss et al., 2003).

Differential Diagnosis

The differential diagnosis of other intractable neonatal epileptic encephalopathies includes the voltage gated potassium channels (KCNQ2/KCNQ3) and epileptic encephalopathy syndromes caused by metabolic disorders such as nonketotic hyperglycinemia, pyridoxine dependency, propionic aciduria, Menkes disease, and Zellweger syndrome.

Treatment

In the absence of treatment, patients with MoCD typically die within the first few years of life without achieving developmental milestones. A dietary approach with low-cysteine and methionine-containing foods has been tried but has not resulted in any significant improvements in symptoms. The first mechanistic therapy for MoCD type A patients was recently approved in the US and involves treatment with synthetic cPMP, the first intermediate in the MoCo synthesis pathway.[31,32] As it is believed that sulfite and related compounds account, in part, for disease-related neurotoxicity, early diagnosis is likely to be essential to maximize outcomes. In support of this theory, retrospective data on patients treated shortly after birth suggested that early treatment appeared to be associated with better seizure control and required fewer anticonvulsants, and with improved clinical and neurodevelopmental outcomes.[32,33] Therefore, rapid recognition and diagnosis is critical to allow for early treatment and to maximize clinical treatment outcomes.

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