Research Article

Clinical and Biochemical Spectrum of Molybdenum Cofactor Deficiency Due To *MOCS2* Mutations

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Abstract

Background: Molybdenum cofactor deficiency (MoCD) is a neurometabolic disorder with presenting symptoms such as severe congenital microcephaly, severe global developmental delay, intractable seizure disorder, and spastic quadriplegia. Magnetic resonance imaging of the brain of patients with MoCD indicates brain atrophy, delayed myelination, and cystic leukomalacia.

Materials and Methods: We evaluated 3 patients with MoCD and their clinical, biochemical, and molecular findings. The results were compared with previously reported cases. One of these patients was prescribed a low-methionine diet, and the clinical and biochemical changes observed in this case are presented in this article.

Results: In all 3 patients with MoCD, uric acid and homocysteine levels were low, and sulfocysteine, urinary hypoxanthine, and xanthine levels were elevated. We also noticed homozygous mutations in the *MOCS2* gene of these patients. Methionine-restricted diet in 1 patient with a milder mutation showed good clinical response with improvement in head control and reduced frequency of seizures. Biochemical investigations showed improvement in decreased sulfocysteine level in the plasma and urine along with disappearance of sulfites in the urine.

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Conclusions: Clinicians should suspect MoCD in any newborn or neonate presenting with severe congenital microcephaly, followed by severe epileptic encephalopathy and global developmental delay. Our case study shows that instituting dietary therapy early in life might be useful in improving the outcomes, at least in cases of milder forms of *MOCS2* deficiency.

Key Words: Molybdenum cofactor deficiency, *MOCS2*, methionine-restricted diet, dietary therapy, milder mutations, congenital microcephaly, epileptic encephalopathy

Introduction

Molybdenum cofactor deficiency (MoCD; OMIM #252150) is an ultrarare life-threatening, neurogenetic disorder with endogenous intoxication pathology due to accumulation of sulfite at toxic levels.[1] This condition is characterized by the onset of encephalopathy in infancy that worsens over time. Newborns with this condition appear normal at birth, but they exhibit difficulty in feeding and develop intractable seizures within a week. Brain abnormalities, including atrophy of the brain tissue, lead to severe developmental delay; affected individuals usually do not learn to sit unassisted or to speak. A small percentage of affected individuals exhibit other features such as microcephaly, ectopia lentis, and coarse facial features.[2-4]

Mutations in the *MOCS1*, *MOCS2*, *MOCS3*, and *gephyrin* (*GPHN*) genes cause MoCD.[5] Types A, B, and C are the 3 forms of the disorder (or complementation groups A, B, and C). Although the signs and symptoms are same in all 3 types, they are distinguished by their genetic cause, that is *MOCS1* gene mutations cause type A, *MOCS2* and *MOCS3* gene mutations cause type B, and *GPHN* gene mutations cause type C deficiency (Figure 1).[6,7] Each of these genes produces the proteins required for the biosynthesis of molybdenum cofactor. The molybdenum cofactor contains molybdenum, which is essential for the functioning of several enzymes such as sulfite oxidase, xanthine oxidase, and aldehyde oxidase.[8]

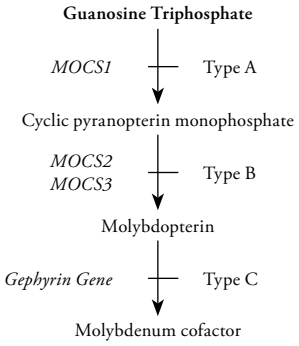

Figure 1. Molybdenum Cofactor Biosynthesis

Guanosine triphosphate is converted to cyclic pyranopterin monophosphate by *MOCS1*, which is subsequently converted to molybdopterin by *MOCS2* and *MOCS3*. Gephyrin mediates the conversion from molybdopterin to molybdenum cofactor. Based on these 3 major steps, MoCD is categorized into 3 subtypes, A, B, and C, involving genetic mutations in *MOSC1*, *MOSC2*, *MOCS3*, and *GPHN*.
Adapted from: Reiss J.[6]

Mutations in the *MOCS1*, *MOCS2*, *MOCS3*, or *GPHN* genes alter functioning of the associated proteins that are responsible for molybdenum cofactor biosynthesis.[9-11] This in turn results in accumulation of certain chemicals such as sulfites, S-sulfocysteine, xanthine, and hypoxanthine in the urine and reduction of uric acid and homocysteine levels in the blood.[11]

MoCD is a distinct form of severe encephalopathy associated with congenital microcephaly, progressive brain atrophy, intractable seizures, and profound developmental delay.[7] Substrate reduction therapy, that is, substitution of cyclic pyranopterin monophosphate (cPMP), has been evaluated in single cases of MoCD type A (*MOCS1* gene mutations), and clinical trials

for drug registration are ongoing.[12-15] Currently, there is no treatment for MoCD types B and C. However, a methionine-restricted diet has been attempted in a few reports, with uneven results. Boles et al[16] reported short-term clinical improvements in their patients with *MOCS2* deficiency with methionine restriction. Similar findings have been reported by Touati et al[17] in 2 patients with sulfite oxidase deficiency.

In this study, the clinical, biochemical, and molecular findings of 3 patients with MoCD due to mutations in *MOCS2* were analyzed in detail. These study results were compared with those of previously reported cases. We also present the observations of effects of methionine-restricted diet in 1 patient.

Materials and Methods

Measurement of biochemical parameters

Freshly collected urine samples were analyzed for sulfite levels by dip stick method. Urinary levels of xanthine and hypoxanthine along with other purines and pyrimidines and sulfocysteine levels in plasma and urine samples were analyzed by ultra–high-performance liquid chromatography and photo diode array detection. Serum levels of uric acid were measured using Dry Chemistry Analyzer (Fujifilm Corporation, Tokyo, Japan). Homocysteine level was analyzed using chemiluminescence assay.

Genetic studies

In all 3 patients, genetic studies were done using Applied Biosystems® 3130xl Genetic Analyzer (Centogene AG, Rostock, Germany). In patients 1 and 2, *MOCS1* and *MOCS2* genes were analyzed by PCR, and sequencing of both DNA strands of the entire coding region and the highly conserved intron–exon splice junctions was done. In patient 3, the sequencing of *MOCS1*, *MOCS2*, and *GPHN* genes was done by NGS panel (CentoDx®, Centogene AG). Entire coding regions, including 10bp of intronic flanking sequences, were targeted. The sequence variants were interpreted based on the ACMG standards and guidelines.[18]

Dietary management

The methionine-restricted diet (HCYS-1 metanutrition) was procured from Pristine Organics Limited (Bengaluru, Karnataka, India). The breastfeeds and dietary supplements were formulated to provide the patient with 2 to 2.5 g of protein/kg/day, ~ 250 mg of methionine/day, and 45 mg of taurine/day. The biochemical and clinical response in the patient was evaluated at every 3-month interval. The patient is currently on the same diet plan and is being monitored by the primary physician.

Results

Patient 1 (K.P.) was a full-term male neonate born to nonconsanguineous parents by lower-segment cesarean section (LSCS) after previous 2 children by LSCS. The neonate had seizures on the third day of life and had poor feeding since birth. He was managed on multiple antiepileptics, which did not show any effect. The brain magnetic resonance imaging (MRI) showed cystic leukomalacia.

The biochemical investigations showed normal basic workup. In view of the seizures, the neonate was evaluated more specifically for conditions associated with recurrent seizures. The sulfite level was found to be elevated in the urine (60 mg/L); further investigations were undertaken to analyze MOCS deficiency. Uric acid was low and hypoxanthine and xanthine levels were high in the urine (576.59, 882.06, and 3135.96 µmol/mmol creatinine, respectively). Uric acid and homocysteine levels were significantly reduced in the serum (0.2 mg/dL and 1 mmol/L, respectively). Plasma and urinary sulfocysteine levels were also increased (155.06 and 269.5 µmol/mmol creatinine, respectively). Analysis of the *MOCS2* gene showed a homozygous mutation in the exon 2: c.45T > A, which resulted in a change of p. Ser15Arg protein. This mutation is reported in the literature and is associated with *MOCSB* deficiency (Table 1).[8]

Patient 2 (S.A.) was a female preterm neonate born at 36 weeks and 6 days by LSCS because of fetal tachycardia and previous LSCS. The neonate developed seizures within an hour of birth and was managed on

antiepileptics and antibiotics. The neonate was started on L-carnitine, L-arginine, and benzoate as hyperammonemia was noted. The neonate remained encephalopathic and was found to have low serum uric acid level on day 5 of life. She was started on full feeds, but the condition remained the same with no improvement and intermittent seizures. The muscle tone had increased with spontaneous eye opening and a shrill cry.

The biochemical investigations showed sulfites (80 mg/L) in the urine. Urinary uric acid level was low (0.17 μmol/mmol creatinine), and xanthine level was high (468.73 μmol/mmol creatinine). Serum uric acid

Table 1. Clinical and Biochemical Parameters in All 3 Patients With *MOCS2* Gene Mutations

Parameter	Patient 1	Patient 2	Patient 3	Reference Range
Consanguinity	No	No	No	—
Birth History	Full term	Preterm (37 wk)	Full term	—
Mode of Delivery	LSCS	LSCS	LSCS	—
Antenatal Complications	No	Fetal tachycardia	No	—
Age at Onset of Symptoms	Day 3	Day 1 (1 h after birth)	Month 5	—
Gender	Male	Female	Female	—
Presenting Symptoms	Seizures on day 3, poor feeding since birth	Seizures at 1 h after birth (then intermittent), encephalopathy, increased tone, and shrill cry	LRTI followed by uprolling of eyeballs, seizures, and loss of head control	—
Family History	No	No	Elder male sibling expired at 9 mo with severe seizure disorder	—
MRI	Diffuse cerebral hypoxic injury, and cystic leukomalacia	—	—	—
Ectopia Lentis	No	No	No	—
Urinary Sulfite Level, mg/L	60	80	40	Not detectable
Urinary Uric Acid Level, μM/mmol Creatinine	567.59	0.17	333.54	1803 ± 1446
Urinary Hypoxanthine Level, μM/mmol Creatinine	882.06	33.04	375.76	69.47 ± 60.19
Urinary Xanthine Level, μM/mmol Creatinine	3135.9	468.73	861.99	72.13 ± 69.02
Serum Uric Acid Level, mg/dL	0.2	0.2	0.4	2.5–5.8
Serum Homocysteine Level, μmol/L	1	0.5	6.9	4–8
Plasma Sulfocystine Level, μmol/L	155.06	140.39	55.65	0–5.39
Urinary Sulfocysteine Level, μM/mmol Creatinine	269.5	353.51	21.61	0.26–20
Gene Affected	*MOCS2*	*MOCS2*	*MOCS2*	—
Zygosity	Homozygous	Homozygous	Homozygous	—
Mutation	Exon 2: c.45T > A/ p.Ser15Arg	Exon 4: c.194delC/ p. Thr50Metfs*7	Exon 4: c.218T>C/ p.Leu73Pro	—
Treatment	Multiple antiepileptics	Multiple antiepileptics, carnitine	Methionine-restricted diet with taurine supplementation	—
Outcome	Died	Global developmental delay, spastic diplegia, severe microcephaly, dysmorphic features	Partial head control, reduced frequency of seizures, and slowly gaining milestones	—

LRTI, lower respiratory tract infection; LSCS, lower segment cesarean section; MRI, magnetic resonance imaging.

and homocysteine levels were significantly reduced (0.2 mg/dL and 0.5 µmol/L, respectively). Plasma and urinary sulfocysteine levels had also increased (140.39 µmol/L and 353.51 µmol/mmol creatinine, respectively). The *MOCS2* gene analysis showed a homozygous frameshift mutation in the exon 4: c.149delC, which resulted in a change in p.Thr50Metfs*7 protein. This mutation creates a shift in the reading frame starting at codon 50. The new reading frame ends in a stop codon, 6 positions downstream. This is a truncating mutation, and thereby resembles the majority of variants reported so far.

The neonate is now 6.5 months old with global developmental delay, spastic diplegia, severe microcephaly (head circumference: 38.5 cm), and dysmorphic features (Table 1).

Patient 3 (P.R.) was a female full-term neonate born to a nonconsanguineous couple by LSCS (because of previous LSCS) and was apparently normal till 5 months of age. Her elder male sibling expired at 9 months of age with severe seizure disorder. At 5 months, she presented with lower respiratory tract infections (LRTIs), followed by uprolling of the eyeballs, seizures, and then loss of head control. The reports of electroencephalogram (EEG) and MRI performed at the age of 5 months (just after the first attack of seizures) were available. The EEG report showed bilateral frontal slow wave discharges, but no focal epileptiform discharges. The MRI report showed subtle altered signal intensities in the left cerebellar hemisphere and adjacent vermis with mild diffusion restriction. The rest of the brain parenchyma was normal, and no cystic leukomalacia was seen at this stage. The biochemical investigations showed sulfites (40 mg/L) in the urine. Urinary uric acid level was low (333.54 µmol/mmol creatinine), and hypoxanthine and xanthine levels had increased (375.76 and 861.99 µmol/mmol creatinine, respectively). Serum uric acid level was 0.4 mg/dL. Plasma and urine sulfocysteine levels had also increased (55.65 µmol/L and 21.61 µmol/mmol creatinine, respectively). The analysis of the *MOCS2* gene showed a homozygous variant of an unknown significance in the exon 4: c.218T > C, which resulted in a change of p.Leu73Pro protein (PMID 29696052; Table 1).

She was then given a trial of the methionine-restricted diet. Details of methionine restriction and its effects were provided to the parents, and the trial was started after their consent to the therapy. After 2 months of therapy with low-methionine diet consisting of calculated breastfeeds, fruits, and methionine-free formula (2–2.5 g protein/kg/d and ~ 250 mg methionine/d) and taurine supplementation (45 mg/100 g of HCYS-1 powder), there was some improvement in her biochemical and clinical parameters (Table 2 and Figure 2). She achieved partial head control, rolling over, sitting with support, and reduced frequency of seizures. There was no further deterioration and loss of milestones, after which she was lost to follow-up.

Discussion

MoCD deficiency is a rare inherited autosomal recessive disorder that results in deficiencies of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. Accumulation of sulfites and its toxicity are because of the absence of sulphite oxidase, which leads to severe neurologic impairment. Neonates with these abnormalities are usually born after an uneventful pregnancy and delivery. Most of the neonates show symptoms after

Table 2. Improvement in Biochemical Parameters in Patient 3

Age	Urine Sulfites, mg/L	Plasma Sulfocysteine, µmol/L	Urine Sulfocysteine, µmol/mmol Creatinine	Plasma Methionine, µmol/L	Plasma Total Amino Acids, µmol/L
Reference Range	Not detectable	0–5.39	0.26–20	13–60	3000–5000
July 7, 2017, 5 mo	Present, 40	55.65	21.61	36	2562
January 24, 2018, 11 mo	Trace, 10	29.78	36.65	40	2656
Methionine-restricted diet initiated					
May 28, 2018, 1 y 3 mo	Not detectable	15.17	0.68	2	2617

Methionine-restricted diet was started at the age of 1 y, after which there was a significant improvement in the biochemical parameters.

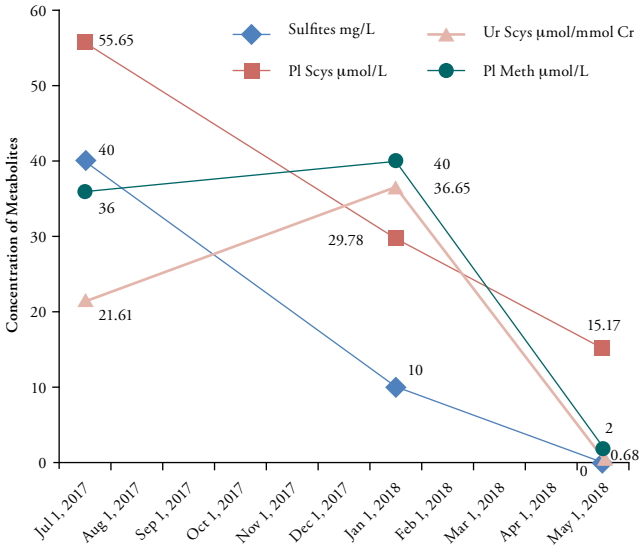

Figure 2. Improvement in Biochemical Parameters in Patient 3

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several days, whereas others suffer from late-onset diseases after the neonatal period. Seizures refractive to therapy, myoclonic spasms, axial hypotonia, hypertonicity, and feeding difficulties are a few clinical symptoms observed in affected neonates.[1]

Mechler et al[7] reported a natural history of MoCD with pooled data of 82 children.[7] They reported seizures at birth (75%), feeding difficulties (25%), and hypotonia (11%) as a few cardinal features of the disease. In addition, developmental delay (9%), hemiplegia (2%), lens dislocation (2%), and hyperreflexia (1%) were also reported. The median age at presentation was day 1 of life and overall median survival was 36 months. Our study results also showed similar findings. Table 3 compares the clinical findings of this study with a few other studies. Our patient 3 presented a milder phenotype with seizures at the age of 5 months, which were precipitated probably by LRTI. Her biochemical markers also showed mild abnormalities. We could hence attempt dietary therapy in this patient.

The primary feature showed in the EEG findings was multiple independent spike foci (8/12, 67%); the other findings include hypsarrhythmia, burst suppression, and disorganized background.

Table 3. Comparison of Our Study Results With That of Mechler et al's[7] Study

Parameter	Our Report	Mechler et al[7]
No. of Patients	3	82
Age at Presentation	Patient 1, poor feeding since birth; patient 2, seizures within 1 h; patient 3, normal till 5 mo	—
Sex (M:F)	1:2	37:34 (11 unknown)
Ethnicity	Indian	Variable
Consanguinity	No	No
Developmental Delay	Severe in all 3	7
Microcephaly	Yes, in all 3	—
Hypotonia	Yes, in all 3	9
Seizures	Yes, in all 3	59
Types of Seizures	—	—
Feeding Difficulties	Since birth in patient 1	21
Lens Dislocation	No	2
Hemiplegia	1	2
Hyperreflexia	—	1
EEG Pattern	—	—
MRI Pattern	MRI showed cystic leukomalacia	—
MOCS Mutation Type	*MOCS2* in all 3	*MOCS1* in 12; *MOCS2* in 8; *GPHN* in 5; unspecified in 57
Mutation	Patient 1: Exon 2: c.45T > A/p.Ser15Arg; Patient 2: Exon 4: c.149delC/ p.Thr50Metfs*7; Patient 3: c.218T > C/ p.Leu73Pro	—
Outcome	Patient 1 died; patient 2 is alive at 6.5 mo with global developmental delay, spastic diplegia, severe microcephaly (HC: 38.5 cm), and dysmorphic features; patient 3 is 1.25 y with developmental delay and hypotonia	42 alive and 40 dead

EEG, electroencephalogram; HC, head circumference; MRI, magnetic resonance imaging.

Radiologically, all patients had severe microcephaly, brain atrophy, delayed myelination, demyelination, cerebral atrophy, thinning of the corpus callosum, cystic leukomalacia, gliosis, and axonal loss.

The catalytic activity of enzymes xanthine oxidase, sulfite oxidase, nitrogenases, and nitrate reductase require molybdenum cofactor. Sulfites are detoxified by sulfite oxidase, the terminal enzyme. Xanthine dehydrogenase plays a role in purine metabolism and converts xanthine and hypoxanthine to uric acid. Aldehyde dehydrogenase converts aldehyde to acids.[19] Brain autopsy findings mirror the MRI findings. There is an extensive neuronal loss, reactive astrogliosis, and spongiosis. Abnormal accumulation of sulfite because of loss of sulfite oxidase activity in MoCD is responsible for excitotoxic neuronal injury.[19]

MoCD has a poor prognosis. Uric acid is an antioxidant and scavenges excitotoxic-free radicals. Theoretically, uric acid supplementation may reduce or limit neuronal injury occurring in MoCD due to hypouricemia and increased oxidative stress. Its practical utility remains to be established. Anti-N-methyl-D-aspartate receptor inhibition with dextromethorphan, thiamine, and cysteine supplementation and a diet low in sulfur-containing amino acids have been tried, which did not show any benefit. Seizures are often therapy-resistant; however, seizures can be controlled in some patients by novel antiepileptic drugs such as vigabatrin.[1] Pyridoxine is shown to improve seizure frequency without affecting the underlying metabolic defect. In 2004, Schwarz et al[20,21] showed that injecting cPMP (previously identified as precursor Z) repeatedly into *MOCS1*-deficient mice results in extension of life span and normal development. Recently, the first patient with MoCD type A was successfully treated based on these results.[12]

This experimental therapy with IV cPMP is shown to benefit only patients with MoCD type A.[14] This compound is ideally injected at birth at a dose of 80 mg/kg/d and increased to 240 mg/kg/d. Neurocognitive outcome improves markedly, and lifelong therapy is recommended.[14] Molybdate therapy may benefit those with mutations in the *GEPH* gene.

Several attempts, such as dietary intervention or absorbing excessive sulphite with cysteamine administration, have been made to reduce sulfite production. Boles et al[16] reported that dietary methionine restriction with cysteine supplementation is associated with moderate short-term clinical improvement, including a resumption in predicted head growth, modest developmental progress, and a reduction in irritability in their patients with MoCD. Clinical relapse was noticed after 2 months with noncompliance of dietary therapy.[16] Touati et al[17] reported normal growth, no neurologic deterioration, and progress of psychomotor development in 2 patients with sulfite oxidase deficiency after prescribing a methionine-restricted diet. However, a recently reported mild case of MOCS1 deficiency did not show any significant progress in motor or cognitive development.[22] Our patient with MOCS2 deficiency showed improvement in clinical as well as biochemical parameters. There was a reduction in frequency of seizures and improvement in milestones such as head control. Biochemical improvement was evident, that is, reduction in sulfocysteine level in plasma and urine and disappearance of sulfites from urine.

Thus, our results indicate that dietary protein restriction may help in the reduction of toxic metabolites' production (ie, sulfites and sulfocysteine). The long-term effect of this treatment needs to be evaluated for the resulting outcome. We still need to analyze the sustainability of the gain in milestones in this child and role of methionine-restricted diet in neurologic improvement in a mild *MOCS2* case like this.

We recommend all clinicians must consider MoCD in any neonate presenting with congenital microcephaly, epileptic encephalopathy, and severe developmental delay. We also suggest to attempt dietary therapy in patients with *MOCS2* gene defect.

Conclusion

MoCD is characterized by severe congenital microcephaly followed by a global developmental delay, central hypotonia, spastic quadriplegia, and intractable seizure disorder. Sulfite and sulfocysteine levels are high in patients with this disorder. The brain MRI shows

microcephaly, cystic leukomalacia, brain atrophy, delayed myelination, and simplified gyriform pattern. A methionine-restricted diet supplemented with taurine may be instituted early in the treatment to prevent neurologic deterioration.

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