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Original Article

The Clinical and Molecular Characteristics of Molybdenum Cofactor Deficiency Due to *MOCS2* Mutations

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ABSTRACT

Background: We explored the clinical and molecular characteristics of molybdenum cofactor deficiency due to *MOCS2* muations.
Methods: We summarize the genetic and clinical findings of previously reported patients with a *MOCS2* mutation. We also present a new patient with novel neuroradiological findings associated with molybdenum cofactor deficiency due to a novel homozygous variant in the 5′ untranslated region of the *MOCS2* gene.
Results: The study population comprised 35 patients with a *MOCS2* gene mutation. All reported children had delayed motor milestones. The major initial symptom was seizures in neonatal period. Facial dysmorphism was present in 61% of the patients. Only one patient had ectopia lentis. Agenesis of the corpus callosum and an associated interhemispheric cyst in our case are novel neuroradiological findings.
Conclusions: The occurrence of neonatal seizures and feeding difficulties can be the first clinical signs of molybdenum cofactor deficiency. Although there is no effective therapy for this condition, early diagnosis and genetic analysis of these lethal disorders facilitate adequate genetic counseling.

Introduction

Molybdenum cofactor deficiency is a rare autosomal recessively inherited disease leading to loss of activity of molybdenum cofactor-dependent enzymes including sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase.[1] The main pathogenic mechanism for the neurological dysfunction may relate to accumulation of toxic levels of sulfite resulting from the deficient activity of sulfite oxidase.[2]

The clinical manifestations include seizures refractive to therapy, severe developmental delay, distinctive facial features, lens dislocation, and feeding difficulties.[3] Laboratory abnormalities in molybdenum cofactor deficiency include very low levels of serum and urinary uric acid, positive urinary sulfite test, and increased urinary levels of xanthine, hypoxanthine, and S-sulfocysteine.[4,5] Molybdenum cofactor deficiency is caused by mutations in four genes involved in molybdenum cofactor biosynthesis: *MOCS1*, *MOCS2*, *MOCS3*, and *GEPH*. Mutations in *MOCS1* are responsible for two thirds of the reported cases, followed by *MOCS2* and then *GPHN*.[6,7]

We summarize the reported patients with molybdenum cofactor deficiency, harboring mutations of the *MOCS2* gene and describe the genetic and clinical findings of patients with a *MOCS2* gene mutation. We also report a new patient with molybdenum cofactor deficiency because of a novel homozygous variant in *MOCS2* gene with novel neuroradiological findings.

Methods

We created a database including collected data from all published reports of patients with molybdenum cofactor deficiency harboring mutations in the *MOCS2* gene. We examined the reported patients with a *MOCS2* mutation for demographic details, clinical features, neurodevelopmental outcome, and results of investigations.

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TABLE.
Clinical and Molecular Characteristics of Patients With *MOCS2* Mutations

References	Case No	Sex	Age of Onset	Consanguinity	Origin	Mutations	Exon	Clinical Findings	Clinical Severity	Cranial Imaging
Reiss et al.[1]	1		Newborn		Egyptian	M1I	1	Seizures, facial dysmorphism	Severe	
	2		Newborn		Portuguese	252insC	3	Seizures, facial dysmorphism	Severe	
	3		Newborn		Italian	533del4	5	Seizures, facial dysmorphism	Severe	
	4		Newborn		French	726del2	7	Seizures, facial dysmorphism	Severe	
	5		Newborn		Portuguese	726del2	7	Seizures, facial dysmorphism	Severe	
	6		Newborn		English	726del2	7	Seizures, facial dysmorphism	Severe	
	7		Newborn		German	E168K/726del2	7	Seizures, facial dysmorphism	Severe	
Johnson et al.[8]	8	F	11 months	No	Chinese	V7F/Q6X	1	Sacrocephaly, hypotonia	Mild	Abnormal BG, cortical dysplasia
Reiss and Johnson[6]	9					S15R	2			
	10					Q30X	2			
	11					Q36X	2			
	12					G76R	4			
	13					G126A	5			
	14					658_664del7insG	6			
	15					c.635__637del3	6			
	16					c.714_718del5	7			
Leimkühler et al.[9]	17				English	Y11X	2	Seizures, psychomotor retardation	Severe	
	18				Mexican	X189Y	7	Facial dysmorphism, psychomotor retardation	Severe	Cerebral atrophy, thinned CC
Hahnewald et al.[10]/ Serrano et al.[11]	19	M	Newborn	No	Senegalese	9_14del23	1a	Seizures, feeding difficulties	Severe	Cerebral atrophy, cystic encephalomalacia, abnormal BG
Per et al.[12]	20	M	Newborn	Yes	Turkish	A44X	2	Seizures, feeding difficulties	Severe	Cerebral atrophy, cystic encephalomalacia, cerebellar hypoplasia
Sie et al.[13]	21	M	Newborn	Yes	Afghan	Q74X	3	Seizures, facial dysmorphism	Severe	White matter abnormalities, abnormal BG
Reiss and Hahnewald[4]	22					Q74X	3			
	23					c.564+1G>A	Intron5			
	24					501delA	5			
Vijayakumar et al.[14]	25		Newborn	Yes	Afghan	c.226G>A	4	Seizures, facial dysmorphism	Severe	Pontocerebellar hypoplasia, cerebral atrophy, abnormal BG
	26		Newborn	Yes	Pakistani	c.226G>A	4	Seizures, facial dysmorphism	Severe	Cystic encephalomalacia, abnormal BG
Struys et al.[15]	27	F	Newborn	Yes		c.564+1G>A	Intron 5	Seizures, feeding difficulties, microcephaly	Severe	Cortical edema, white matter abnormalities
	28	M		Yes		c.564+1G>A	Intron 5	Seizures, developmental delay	Severe	Subcortical cysts, cerebral atrophy, thinned CC, abnormal BG
Kikuchi et al.[16]	29	M	Newborn	No		c.265T>C/266A>G	3	Seizures, feeding difficulties	Severe	Cystic encephalomalacia, cerebral atrophy, agenesis of the corpus callosum
Edwards et al.[17]	30	F	Newborn	No	Samoan and Caucasian	S140F/c.501+2delT		Seizures, feeding difficulties	Severe	Thinned CC, subependymal cyst, cerebral edema
Megahed et al.[18]	31	F	Newborn	Yes	Egyptian	M1I	1	Developmental delay, facial dysmorphism	Mild	Cerebral and cerebellar atrophy
Zaki et al.[19]	32	F	12 months	Yes	Egyptian	M1I	1	Seizures, feeding difficulties	Severe	Cystic encephalomalacia, cerebral atrophy, thinned CC abnormal BG

(*continued on next page*)

TABLE. (*continued*)

References	Case No	Sex	Age of Onset	Consanguinity	Origin	Mutations	Exon	Clinical Findings	Clinical Severity	Cranial Imaging
Yoganathan et al.[20]	33	M	Newborn	No	Indian	L73P	4	Seizures, feeding difficulties	Severe	Cystic encephalomalacia, abnormal BG, diffusion restriction along the corticospinal tract
Duman and Gençpinar[21]	34	M	5 months	No	Turkish	G3A	1	Seizures, developmental delay, facial dysmorphism	Mild	Abnormal BG and cerebellum
Our Case	35	M	Newborn	Yes	Turkish	c.-9G>C	1a	Seizures, feeding difficulties, facial dysmorphism	Severe	Cystic encephalomalacia, cerebellar hypoplasia, agenesis of the corpus callosum with interhemispheric cyst

Abbreviations:
BG = Basal ganglia
cc = Corpus callosum

Duplicate reports of the same patients were excluded and only patients were included for whom genetic information was available. Furthermore, we identified a new patient with a novel homozygous *MOCS2* variant. Finally, we analyzed the assembled cohort and sought to establish genotype-phenotype correlations in individuals with a *MOCS2* mutation.

Results

The study population comprised 35 patients with a *MOCS2* gene mutation. Individual clinical and genetic features of these 35 patients are summarized in Table. Our patient was admitted to the hospital with myoclonic seizures and feeding difficulties at age three months. He had mild facial dysmorphic features: a long philtrum, a broad nasal bridge, and prominent cheeks. Serum uric acid was nondetectable (0.0 mg/dL). At age six months, brain magnetic resonance imaging revealed symmetric subcortical cystic white matter changes and an enlarged cisterna magna. Agenesis of the corpus callosum and an associated interhemispheric cyst in our patient are novel neuroradiological findings (Figure). In our patient, a homozygous novel variant was detected in 5′ untranslated region (5′ UTR) of *MOCS2* (NM_004531.4): c.-9G>C. This variant has not

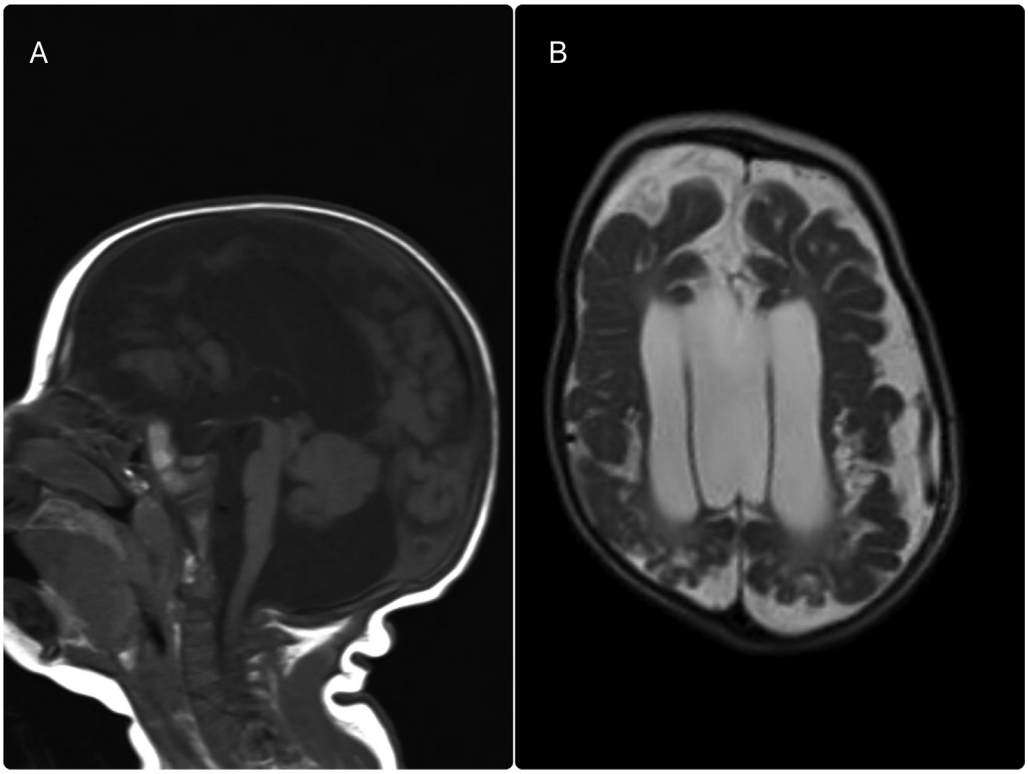

FIGURE. Brain magnetic resonance imaging at age six months. (A) Sagittal T1-weighted image shows agenesis of the corpus callosum and enlarged cisterna magna. (B) Axial T2-weighted image shows symmetric subcortical cystic white matter changes and an interhemispheric cyst. Central and peripheric cerebrospinal fluid spaces were dilated secondary to atrophy.

been previously reported in the 1000 genome population database (GnomAD, 1000 genom).

Because of its retrospective design, some published reports had missing demographic and clinical data. The cohort was analyzed according to available data in the literature. Eighteen children had symptom onset at birth, and only three children had symptom onset after age one month. All reported children had delayed motor milestones. Twenty-one patients had seizures during the neonatal period. Facial dysmorphism including puffy cheeks, microcephaly, microphthalmia, broad nasal bridge, long philtrum occurred in 14 patients. Eight patients experienced feeding difficulties. Only one patient had ectopia lentis.

In total, 29 different *MOCS2* mutations have been described, including deletions, duplications, missense, nonsense, and frameshift variations. Of the 35 patients, four patients carried compound heterozygous mutations and 31 patients carried homozygous mutations.

Discussion

The molybdenum biosynthetic pathway can be divided into three steps: synthesis of cyclic pyranopterin monophosphate (cPMP) from guanosine triphosphate by *MOCS1*, conversion of cPMP to molybdopterin by *MOCS2* and *MOCS3*, and insertion of molybdenum to form molybdenum cofactor by *GEPH*.[1,4] This study reports a systematic analysis of the genotypes in correlation to the phenotypes in patients with a *MOCS2* mutation while integrating all published cases with clinical and genetic data. We also described novel neuroradiological findings in our patient with a novel variant.

Most of the patients with a *MOCS2* mutation were diagnosed during the neonatal period. The predominant initial symptom was seizures in neonatal period. Facial dysmorphism was present in 61% patients. Two different phenotypes related to *MOCS2* were reported: 21 patients presented with a severe form (intractable neonatal seizures and multiple cystic cavities on magnetic resonance imaging) and three patients presented with a milder form (global developmental delay without seizures). The common clinical findings in *MOCS2* deficiency including neonatal seizures, feeding difficulties, and distinctive facial features were similar to *MOCS1* deficiency.[3] Ectopia lentis has been described in individuals with molybdenum cofactor deficiency because of *MOCS1* gene mutations.[3,14] However, only one patient with *MOCS2* mutation was found to have ectopia lentis.

Neuroradiological findings initially involve cerebral edema without cystic changes. Cerebral and cerebellar atrophy and subcortical cystic changes are the most commonly described lesions in the course of the disease. Other reported radiological changes include hypoplasia of the corpus callosum and brainstem, basal ganglia abnormalities, and diffusion restriction along the corticospinal tract. Agenesis of the corpus callosum and an interhemispheric cyst associated with agenesis of the corpus callosum in our case are novel neuroradiological findings.

The *MOCS2* gene was mapped to the long arm of chromosome 5 and comprises seven exons.[1] In our study, the reported mutations were detected in all exons of the *MOCS2* gene. *MOCS2* mutations have been reported from different countries around the world. Our results show no founder mutation in the *MOCS2* gene for any population. The variant in our patient was interpreted as having uncertain significance according to The American College of Medical Genetics and Genomics criteria; however, it was not found in population studies, it was detected in a homozygous state, and the child's clinical features were highly consistent with the disease. We suggest that this variant was causative. Our patient is the first patient with a causative variant in the 5′ UTR region of the gene. Because 5′ UTR variants can damage critical sequences such as Kozak consensus sequence (which contains the initiation codon), *cis*-acting regulatory elements (which are called upstream open reading frames), upstream AUGs and termination codons (which have a great impact on the regulation of translation), 5′ UTR variants have significant importance in the etiology of some diseases.

Genotype-phenotype correlations are hindered because 29 different *MOCS2* mutations have been described in 35 patients. Furthermore, the same mutations sometimes led to different phenotypes whereas different mutations led to the same phenotypes. Genotype-phenotype correlations should be considered with caution in patients with *MOCS2* gene mutations.

Treatment of patients with a *MOCS1* mutation by cPMP supplementation has been performed, but currently there is no effective therapy for patients with a *MOCS2* gene mutation. Management for patients with *MOCS2* mutations largely remains supportive and the prognosis is poor.[3,22,23]

In conclusion, the occurrence of neonatal seizures and feeding difficulties can be the first clinical signs of molybdenum cofactor deficiency. Serum uric acid levels should be performed in all patients who present with intractable seizures and developmental delay. Multiple cystic encephalomalacic changes and hypoplasia of the corpus callosum are important diagnostic clue in molybdenum cofactor deficiency. Although no effective therapy has been found for individuals with a *MOCS2* dysfunction, early diagnosis and genetic analysis of these lethal disorders facilitate adequate genetic counseling.

References

1. Reiss J, Dorche C, Stallmeyer B, Mendel RR, Cohen N, Zabot MT. Human molybdopterin synthase gene: genomic structure and mutations in molybdenum cofactor deficiency type B. Am J Hum Genet. 1999;64:706–711.
2. Zhang X, Vincent AS, Halliwell B, Wong KP. A mechanism of sulfite neurotoxicity: direct inhibition of glutamate dehydrogenase. J Biol Chem. 2004;279:43035–43045.
3. Atwal PS, Scaglia F. Molybdenum cofactor deficiency. Mol Genet Metab. 2016;117:1–4.
4. Reiss J, Hahnewald R. Molybdenum cofactor deficiency: mutations in GPHN, MOCS1, and MOCS2. Hum Mutat. 2011;32:10–18.
5. Hinderhofer K, Mechler K, Hoffmann GF, Lampert A, Mountford WK, Ries M. Critical appraisal of genotype assessment in molybdenum cofactor deficiency. J Inherit Metab Dis. 2017;40:801–811.
6. Reiss J, Johnson JL. Mutations in the molybdenum cofactor biosynthetic genes MOCS1, MOCS2, and GEPH. Hum Mutat. 2003;21:569–576.
7. Huijmans JG, Schot R, de Klerk JB, et al. Molybdenum cofactor deficiency: identification of a patient with homozygote mutation in the MOCS3 gene. Am J Med Genet A. 2017;173:1601–1606.
8. Johnson JL, Coyne KE, Rajagopalan KV, et al. Molybdopterin synthase mutations in a mild case of molybdenum cofactor deficiency. Am J Med Genet A. 2001;104:169–173.
9. Leimkühler S, Charcosset M, Latour P, et al. Ten novel mutations in the molybdenum cofactor genes MOCS1 and MOCS2 and in vitro characterization of a MOCS2 mutation that abolishes the binding ability of molybdopterin synthase. Hum Genet. 2005;117:565–570.
10. Hahnewald R, Leimkühler S, Vilaseca A, Acquaviva-Bourdain C, Lenz U, Reiss J. A novel MOCS2 mutation reveals coordinated expression of the small and large subunit of molybdopterin synthase. Mol Genet Metab. 2006;89:210–213.
11. Serrano M, Lizarraga I, Reiss J, et al. Cranial ultrasound and chronological changes in molybdenum cofactor deficiency. Pediatr Radiol. 2007;37:1043–1046.
12. Per H, Gümüş H, Ichida K, Çağlayan O, Kumandaş S. Molybdenum cofactor deficiency: clinical features in a Turkish patient. Brain Dev. 2007;29:365–368.
13. Sie SD, de Jonge RC, Blom HJ, et al. Chronological changes of the amplitude-integrated EEG in a neonate with molybdenum cofactor deficiency. J Inherit Metab Dis. 2010;33:401–407.
14. Vijayakumar K, Gunny R, Grunewald S, et al. Clinical neuroimaging features and outcome in molybdenum cofactor deficiency. Pediatr Neurol. 2011;45:246–252.
15. Struys EA, Nota B, Bakkali A, Al Shahwan S, Salomons GS, Tabarki B. Pyridoxine-dependent epilepsy with elevated urinary α-amino adipic semialdehyde in molybdenum cofactor deficiency. Pediatrics. 2012;130:e1716–e1719.
16. Kikuchi K, Hamano SI, Mochizuki H, Ichida K, Ida H. Molybdenum cofactor deficiency mimics cerebral palsy: differentiating factors for diagnosis. Pediatr Neurol. 2012;47:147–149.
17. Edwards M, Roeper J, Allgood C, et al. Investigation of molybdenum cofactor deficiency due to MOCS2 deficiency in a newborn baby. Meta Gene. 2015;3:43–49.

18. Megahed H, Nicouleau M, Barcia G, et al. Utility of whole exome sequencing for the early diagnosis of pediatric-onset cerebellar atrophy associated with developmental delay in an inbred population. Orphanet J Rare Dis. 2016;11:57.
19. Zaki MS, Selim L, EL-Bassyouni HT, et al. Molybdenum cofactor and isolated sulphite oxidase deficiencies: clinical and molecular spectrum among Egyptian patients. Eur J PaediatrNeurol. 2016;20:714–722.
20. Yoganathan S, Sudhakar S, Thomas M, Dutta AK, Danda S, Chandran M. Novel imaging finding and novel mutation in an infant with molybdenum cofactor deficiency, a mimicker of hypoxic-ischaemicencephalopathy. Iran J Child Neurol. 2018;12:107.
21. Duman F, Gençpinar P. Molibden Kofaktör Eksikliği ve Lens Dislokasyonu: Olgu Sunumu. J Glaucoma Cataract. 2018;13:38–41.
22. Schwahn BC, Van Spronsen FJ, Belaidi AA, et al. Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study. Lancet. 2015;386:1955–1963.
23. Bayram E, Topcu Y, Karakaya P, et al. Molybdenum cofactor deficiency: review of 12 cases (MoCD and review). Eur J Paediatr Neurol. 2013;17:1–6.