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Sundal Aziz

*The Children's Hospital & the Institute of Child Health Lahore*

Javeria Raza Alvi

*The Children's Hospital & the Institute of Child Health Lahore*

Tipu Sultan

*The Children's Hospital & the Institute of Child Health Lahore*

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# MOLYBDENUM COFACTOR DEFICIENCY CAUSING NEONATAL SEIZURES AND GLOBAL DEVELOPMENTAL DELAY

Sundal Aziz<sup>1</sup>, Javeria Raza Alvi<sup>2</sup>, Tipu Sultan<sup>3</sup>

<sup>1,2,3</sup>Department of Pediatric Neurology, The Children's Hospital & the Institute of Child Health Lahore

**Correspondence to:** Javeria Raza Alvi, Department of Pediatric Neurology, The Children's Hospital & the Institute of Child Health, Lahore. E-mail: jra\_28@hotmail.com

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## ABSTRACT:

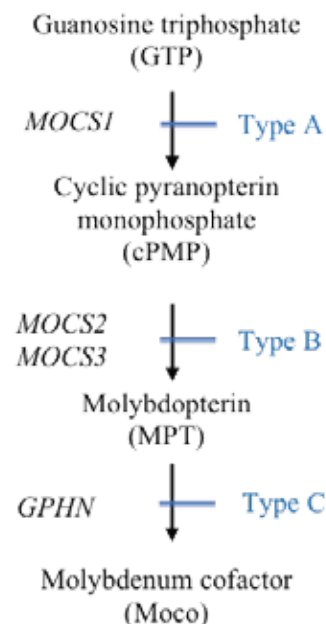
Molybdenum cofactor deficiency is a rare degenerative brain disorder with autosomal recessive inheritance. It presents early in neonatal life with seizures, feeding difficulty and spasticity, sometimes misdiagnosed as neonatal hypoxic ischemic encephalopathy. Neuroimaging findings are consistent with loss of white matter and volume along with cystic encephalomalacic changes. Most of the patients have mutations in the MOCS1 and MOCS2 genes causing imbalance in the sulfur-containing amino acid metabolism leading to progressive neurological damage and early childhood death in majority of cases. We report a case of a 7 months old child, product of non-consanguineous marriage with history of neonatal seizures and global developmental delay. Examination showed facial dysmorphism and spasticity with neuroimaging showing marked cortical atrophy and agenesis of corpus callosum.

**KEY WORDS:** Molybdenum cofactor deficiency, MOCS1, MOCS2, neonatal seizures

## INTRODUCTION:

Molybdenum cofactor deficiency (MoCo) is a rare neuro-degenerative condition which is inherited in an autosomal recessive pattern. It is characterized by neonatal seizures, which often become refractory, feeding difficulties, facial dysmorphism, spasticity and opisthotonic posturing along with global developmental delay and cerebral atrophy. Molybdenum is involved in the functioning of four different enzymes including sulfite oxidase, aldehyde oxidase, xanthine oxidase, and mitochondrial amidoxime reducing component (mARC), each harboring the pterin-based molybdenum cofactor (MoCo).<sup>1</sup> Of these enzymes, sulfite oxidase is known to be crucial for neurological functioning. The common mutations leading to MoCo deficiency have been identified in the genes MOCS1 (type A), MOCS2 (type B) and rarely GPHN (type C).<sup>2</sup> Genetic mutation results in the loss of sulfite oxidase activity leading to buildup of certain chemicals, including sulfite and S-sulfocysteine that causes severe neurologic dysfunction in the affected individuals. MoCo deficiency also affects the xanthine pathway leading to an accumulation of hypoxanthine and xanthine, and low to undetectable uric acid levels in blood.<sup>3</sup>

**FIG 1: Molybdenum Cofactor Biosynthesis**



Abbreviations: MOCS (Molybdenum Cofactor Synthesis Protein), GPHN (Gephyrin Protein)

## CASE REPORT

A 7 months old boy, product of a non-consanguineous marriage but with significant deaths and miscarriages on the paternal side, 2nd in order in a family of 2 siblings, born at term to a healthy mother. There was significant antenatal history of mild polyhydramnion and brain anomaly was detected on 36 weeks gestational scan showing ventriculomegaly. The baby had immediate cry and was born with an APGAR score of 9 at 1 min and 5 min. Physical examination showed normal facies, birth weight of 2.8kg (10th centile), length of 51cm (50th centile) and head circumference of 33.5cm (10th centile). He was admitted in the nursery for four days because of poor suckling and multi-focal clonic and tonic seizures. MRI brain on 2nd day of life showed severe brain atrophy, agenesis of corpus callosum, bilateral symmetrical T1W hyperintense signals in basal ganglia, cystic enlargement in posterior fossa and giant cisterna magna. Seizures were controlled with medication namely levetiracetam at 40mg/kg/day and child was discharged on 5th day of life. At 2nd month of age the child developed inconsolable cry, arching episodes and opisthotonic posture for which he was started on muscle relaxant tizanidine 1 mg/day and clonazepam 0.2mg/day. At 7 months follow up, child had delayed milestones, microcephaly with overriding of sutures, facial dysmorphism which was initially not present, spasticity in all four limbs and severe muscle wasting. On reviewing the family tree, there was death of a previous child and multiple miscarriages from the first consanguineous marriage of father. Although this child was a product of a non-consanguineous marriage, but considering the paternal history and early presentation, feeding issues, seizures and cerebral atrophy of this child, genetic work up was done.

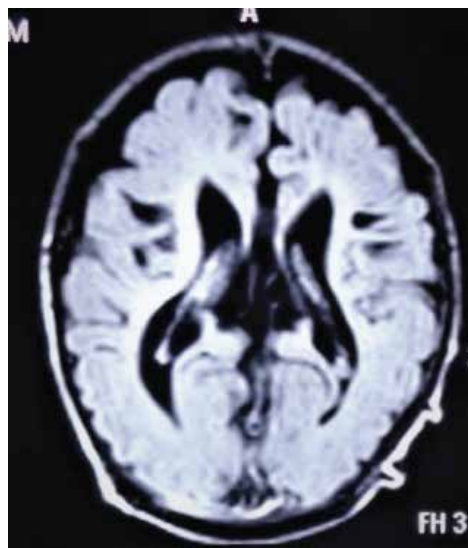
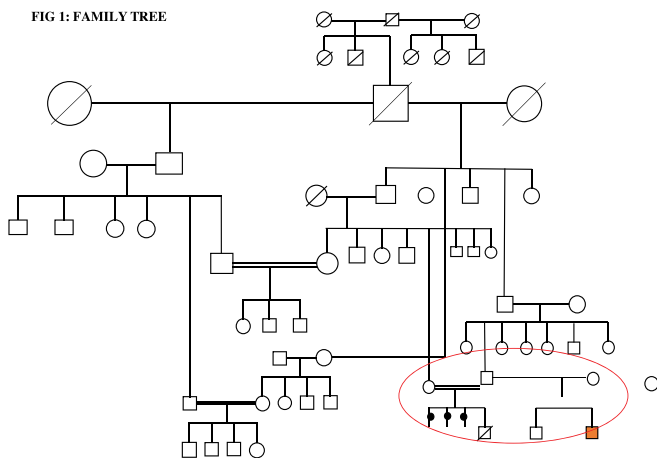


FIG 2: Cortical atrophy and ventriculomegaly

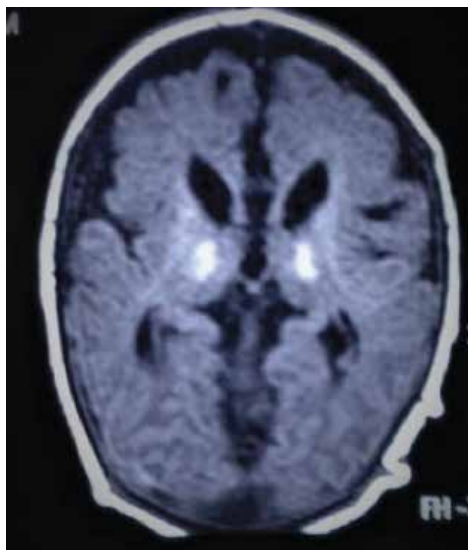


FIG 3: Bilateral T1W hyperintensities in basal ganglia

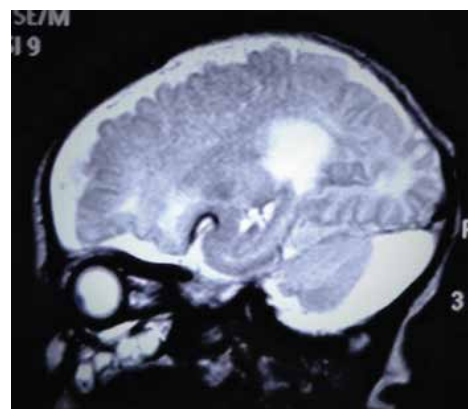


FIG 4: Arachnoid cyst (Blue arrow) Agenesis of corpus callosum (Green arrow)

His whole exome sequencing revealed a missense homozygous pathogenic variant in the MOCS2 gene causing an amino acid change from Gly to Arg at position 76 as shown in Table 1 and genetic diagnosis of autosomal recessive Molybdenum cofactor deficiency type B was confirmed despite a non-consanguineous marriage. His uric acid level was low (<1 mg/dl; Range: 2-5mg/dl) which corresponded with the disease. At present at the time of case report, child is 15 month old, thriving well with weight of 10 kg (50th centile), OFC of 47 cm (between 25th – 50th centile). He having global developmental delay with no gaze fixation or neck holding, poor auditory and feeding difficulties. His seizures are well controlled but there is spasticity which is also improved. Nature of genetic origin has been explained to the family.

**TABLE: Results of Genetic Testing**

GENE	VARIANT COORDINATES	AMINO ACID CHANGE	ZYGOSITY	TYPE AND CLASSIFICATION***
MOCS2	NM_004531.3:c.226G>A	p.(Gly 76 Arg)	homozygous	Missense Pathogenic (class 1)

## DISCUSSION

Molybdenum cofactor deficiency is a rare autosomal recessive condition of sulfur-containing amino acid metabolism. It has an estimated prevalence of 1 in 100,000 to 200,000 newborns worldwide<sup>4</sup> and nearly only 100 cases have been reported in literature.<sup>5</sup> It classically occurs in early infancy with majority of patients presenting with epileptic encephalopathy along with feeding difficulties and facial dysmorphism<sup>6</sup> like our index case, although late presentation with global developmental delay including motor, visual and language impairment<sup>7</sup> and atypical presentation with movement disorder have also been described.<sup>8</sup> Typical neuroimaging findings include loss of white matter and volume, cystic encephalo-malacic changes and ventriculomegaly but novel findings of agenesis of corpus callosum and interhemispheric cyst similar to our index case have also been reported.<sup>3</sup> MoCo deficiency has overlapping phenotypic features with sulfite oxidase deficiency and is sometimes differentiated only biochemically by low serum uric acid concentrations due to loss of function of xanthine dehydrogenase in MoCo deficiency.<sup>3</sup> Clinical features can also be mistaken for neonatal hypoxic ischemic encephalopathy<sup>6,9</sup> and children presenting late with spastic quadriplegia and intellectual disability are usually labelled as cerebral palsy. Treatment with exogenous cyclic pyranopterin monophosphate (cPMP) for type A deficiency is present.<sup>10</sup> Since patients with

type B deficiency (MOCS2 gene) do not lack this molecule, hence they cannot benefit from this treatment. However, supplementation with pyridoxine could reduce the frequency of seizures in these patients.<sup>11</sup> The deficiency can also be diagnosed prenatally by monitoring the sulfite oxidase activity on chorionic villous sampling tissue and subsequent mutational analysis can be done.<sup>12</sup> Although therapeutic options are yet to be ascertained, early detection and genetic testing in such degenerating brain disorder is important for genetic counselling.<sup>13</sup>

Our case report emphasizes that refractory neonatal seizures without a clear documented hypoxic ischemic event, progressive microcephaly, spasticity and specific neuroimaging findings can be clinical clues to early diagnosis. Even in the absence of consanguinity, in the families where there are unexplained death and miscarriages, a high index of suspicion is needed as most cases are otherwise labelled as hypoxic ischemic encephalopathy and managed as cerebral palsy. Thus, a genetic diagnosis is mandatory and important for genetic counselling.

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## REFERENCES:

- Schwarz G. Molybdenum Cofactor and Human Disease. *Curr Opin Chem Biol.* 2016;31:179-87.
- Reiss J, Hahnwald R. Molybdenum Cofactor Deficiency: Mutations in GPHN, MOCS1, and MOCS2. *Hum Mutat.* 2011;32(1):10-18.
- Arican P, Gencpinar P, Kirbiyik O, Bozkaya Yilmaz S, Ersen A, Oztekin O, Olgac Dundar N. The Clinical and Molecular Characteristics of Molybdenum Cofactor Deficiency Due to MOCS2 Mutations. *Pediatr Neurol.* 2019;99:55-59.
- Zaki MS, Selim L, El-Bassyouni HT, Issa MY, Mahmoud I, Ismail S, et al. Molybdenum Cofactor and Isolated Sulphite Oxidase Deficiencies: Clinical and Molecular Spectrum Among Egyptian Patients. *Eur J Paediatr Neurol.* 2016;20(5):714-22.
- Ichida K, Aydin HI, Hosoyamada M, et al. (2006). "A Turkish Case with Molybdenum Cofactor Deficiency". *Nucleos, Nucleot & Nucleic Acids.* 2006;25(9-11):1087-91.
- Bayram E, Topcu Y, Karakaya P, Yis U, Cakmakci H, Ichida K, Kurul SH. Molybdenum Cofactor Deficiency: Review of 12 Cases (MoCD and Review). *Eur J Paediatr Neurol.* 2013;17(1):1

7. Vijayakumar K, Gunny R, Grunewald S, Carr L, Chong KW, DeVile C, et al. Clinical Neuroimaging Features and Outcome in Molybdenum Cofactor Deficiency. *Pediatr Neurol.* 2011;45(4):246-52.
8. Alkufri F, Harrower T, Rahman Y, Hughes E, Mundy H, Knibb JA, et al. Molybdenum Cofactor Deficiency Presenting with a Parkinsonism-Dystonia Syndrome. *Mov Disord.* 2013 Mar;28(3):399-401.
9. Durmaz SM, Ozbakir B. Molybdenum cofactor deficiency: Neuroimaging findings. *Radiol Case Rep.* 2018 Jun;13 (3): 592-595.
10. Struys EA, Nota B, Bakkali A, Al Shahwan S, Salomons GS, Tabarki B. Pyridoxine-dependent epilepsy with elevated urinary  $\alpha$ -amino adipic semialdehyde in molybdenum cofactor deficiency. *Pediatrics.* 2012;130(6):1716-1719.
11. Johnson LJ. Prenatal Diagnosis of Molybdenum Cofactor Deficiency and Isolated Sulfite Oxidase Deficiency. *Prenat Diagn.* 2003 Jan;23(1):6-8.
12. Zahid M, Khan HA, Yunus ZM, Chun BC, Steinmann B, Johannes H, et al. Inherited metabolic disorders presenting as hypoxic ischemic encephalopathy: A case series of patients presenting at a tertiary care hospital in Pakistan. *JPMA.* 2019 Mar;69(3):432-436.
13. Kikuchi K, Hamano S, Mochizuki H, Ichida K, Ida H. Molybdenum cofactor deficiency mimics cerebral palsy: differentiating factors for diagnosis. *Pediatr Neurol.* 2012 Aug; 47(2):147-9.

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Author's contribution:

**Sundal Aziz;** concept, data collection, data analysis, manuscript writing, manuscript review

**Javeria Raza Alvi;** data collection, data analysis, manuscript writing, manuscript review

**Tipu Sultan;** data collection, data analysis, manuscript writing, manuscript review