Molybdenum cofactor deficiency (MoCD) is a rare inherited metabolic disorder characterized by neonatal onset intractable seizures, severe psychomotor retardation, dysmorphic facies, and dislocated ocular lenses. A characteristic biochemical profile permits early diagnosis. Although more than 100 genetically characterized patients have been reported, this number is discrepant with the actual prevalence as MoCD is often mistaken for hypoxic-ischemic encephalopathy (HIE) secondary to perinatal asphyxia. It is important to recognize MoCD to provide appropriate genetic counseling and prenatal diagnosis. Effective pharmacotherapies that overcome the primary biochemical defect are also in the pipeline. We present a child with biochemically and genetically confirmed MoCD and discuss the clinical, imaging, biochemical, and genetic profile of this disorder.

CASE REPORT A 4-year-old boy from the south Indian state of Kerala presented with developmental delay and seizures. He was the only child of consanguineous parents (first cousins). He was born at term following an uneventful antenatal period with a birthweight of 3.25 kg, cried immediately at birth, and did not have features of birth asphyxia. He developed generalized seizures on the fifth day of life. The seizures remained refractory to multiple anticonvulsants at optimal dosages. He also developed episodes of intermittent sudden flexion of trunk and limbs once in 1–2 minutes. The frequency of these episodes was reduced with time and occurred in response to sound only. Since 6 months of age, he developed progressive stiffness with intermittent posturing of neck and trunk. There was no history of neurologic illness in the family.

On examination, he was irritable and poorly nourished with intermittent stridor. He had microcephaly with head circumference of 46 cm, bilaterally dislocated lenses, and could not fix or track light. He had exaggerated startle to sound. There was severe spasticity, cervical dystonia, and opisthotonus. Investigations showed normal hemogram, renal and hepatic function tests, serum vitamin B₁₂, folic acid, and biotinidase levels. Cytogenetic study showed normal male karyotype. Screening for amino-acidemias, organic acidemias, and disorders of fatty acid oxidation by tandem mass spectrometry drew negative results. Urine analysis for abnormal metabolites, glycosaminoglycans, total mucopolysaccharides, and organic acids was normal. Lactate (32.9 mg/dL; ref 4.5–20 mg/dL) and ammonia (67.7 mg/dL; ref 11–35 mg/dL) were mildly elevated. Mild laryngomalacia was detected on bronchoscopic examination. Brain MRI done at fourth month of life showed severe diffuse cerebral atrophy, areas of T2 shortening in bilateral basal ganglia suggestive of intracranial haemorrhage, and pontine hypoplasia with enlargement of the prepontine cistern (figure, A–D). EEG showed recurrent multifocal epileptiform discharges.

Serum homocysteine was markedly reduced (0.9 μmol/L; ref 4–12 μmol/L), and uric acid was undetectable. Examination of purine metabolites in urine showed the following: xanthine (259 mmol/mol creatinine; ref 0–43 mmol/mol creatinine), hypoxanthine (83 mmol/mol creatinine; ref 0–56 mmol/mol creatinine), inosine (5 mmol/mol creatinine; ref 0–4 mmol/mol creatinine), orotic acid (4 mmol/mol creatinine; 0–3 mmol/mol creatinine), uracil (48 mmol/mol creatinine; 0–26 mmol/mol creatinine), and dihydrothymine (11 mmol/mol creatinine; 0–10 mmol/mol creatinine). The biochemical abnormalities were characteristic of MoCD. Sequencing of coding region of MOCS1 and MOCS2 showed homozygous mutation in MOCS2 c.252insC, resulting in a frameshift and early termination. This confirmed the diagnosis of MoCD.

DISCUSSION The differential diagnosis in a child presenting with neonatal seizures are listed in table e1 on the Neurology® Web site at Neurology.org. An important diagnostic clue on general physical examination was the presence of dislocated ocular lenses. Lens dislocation characterizes sulfite oxidase deficiency, MoCD, Marfan syndrome, and homocystinuria. The combination of severe global developmental delay, seizures, and dislocated ocular
lenses is characteristic of MoCD and isolated sulfite oxidase deficiency. The clinical and imaging profiles of both these disorders are similar and they can be distinguished based on the biochemical and genetic abnormalities.

MoCD is a rare autosomal recessive neurometabolic disorder of childhood. Patients reported so far belong to diverse ethnic backgrounds, but the incidence in the general population is not known due to lack of epidemiologic studies. The disorder presents classically with neonatal onset refractory seizures, marked global developmental delay, microcephaly, abnormal muscle tone, and markedly reduced lifespan. Clinical signs of progressive pyramidal and extrapyramidal dysfunction ensue. Dysmorphic features include long face, puffy cheeks, widely spaced eyes, elongated palpebral fissure, thick lips, long philtrum, and small nose. Feeding difficulty, failure to thrive, and screaming episodes are common. Cortical damage, myopia, and lens dislocation contribute to impaired vision, which is universal. Other uncommon features include renal stones, intermittent microscopic hematuria, skeletal abnormalities, laryngomalacia, autonomic dysfunction, and metabolic and lactic acidosis. Macrocephaly may occur exceptionally due to hydrocephalus. Clinical phenotype is expanding with recognition of lens dislocation as forme fruste of neurologic manifestations, neonatal hyperekplexia with startle and flexor spasms leading to apnea without any electrographic seizure, and adult-onset progressive parkinsonism-dystonia syndrome. The majority of the affected individuals die of the illness within the first few days or weeks of life. Late-onset, milder phenotype with survival into adult life and neurologically asymptomatic patients detected during sibling screening are also reported.

Brain MRI abnormalities evolve sequentially with time. Global cerebral infarction with edema and restriction in diffusion-weighted images are noted in early stages. Basal ganglia, thalami, cerebral peduncles, and subthalamic nuclei are also affected early. This is eventually replaced by severe cystic leukomalacia with an antero-posterior gradient and greater involvement of the posterior regions of cerebral cortex. Dysgenesis of corpus callosum, and a distinctive band of intermediate signal intensity at the boundaries of the posterior horns of the lateral ventricles are noted. The majority of the affected individuals die of the illness within the first few days or weeks of life. Late-onset, milder phenotype with survival into adult life and neurologically asymptomatic patients detected during sibling screening are also reported.
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. NMDA receptor inhibition with dextromethorphan, thiamine, and cysteine supplementation and diet low in sulfur-containing amino acids have been tried without any benefit. Pyridoxine has been shown to improve seizure frequency without affecting the underlying metabolic defect. Experimental therapy with IV cyclic pyrophosphoryl monophosphate has been shown to benefit MoCD type A only. This compound is ideally initiated at birth at a dose of 80 µg·kg⁻¹·d⁻¹ and increased to 240 µg·kg⁻¹·d⁻¹. Neurocognitive outcome is markedly improved and lifelong therapy is recommended. Molybdate therapy may benefit those with mutations in the GEPH gene. It is now possible to establish diagnosis in the prenatal period by mutation analysis or linkage studies in families where the specific genetic defect is known or by estimating sulfite oxidase in chorionic villus tissue. Prenatal diagnosis has the advantage of permitting decision regarding continuation of pregnancy and initiation of early treatment in the newborn child to arrest the illness.

MoCD should be considered in any child with global developmental delay and seizures in the setting of dysmorphic facies, dislocated ocular lenses, and hypouricemia. Brain MRI should be used judiciously to distinguish MoCD from HIE, with a close differential diagnosis. Early diagnosis is essential to avail benefit of emerging therapies.

**AUTHOR CONTRIBUTIONS**

M. Nagappa: wrote the first draft. P.S. Bindu: study concept and design, data analysis and interpretation, approved final draft. A.B. Taly: study supervision, critical revision of the manuscript for important intellectual content. S. Sinha: study supervision, critical revision of the manuscript for important intellectual content. Rose D. Bharath: analyzed and interpreted MRI data.

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