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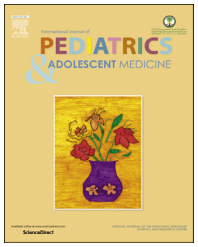

CASE REPORT

Neonatal molybdenum cofactor deficiency and ectopia lentis in a Saudi Arabian patient

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KEYWORDS
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Abstract Molybdenum cofactor deficiency (MCD) is a rare and ultimately fatal metabolic disease that results in extensive neurodegeneration in early infancy. The causal association of MCD with sulfite oxidase deficiency, a known cause of subluxed lenses (ectopia lentis), has only been recently defined. We report a 16-month-old Saudi Arabian male product of a consanguineous union, who presented as a neonate with intractable seizures and a failure to thrive. Subsequent examinations revealed hypotonia, laryngomalacia, global developmental delay, progressive neurodegeneration and ectopia lentis. Urine analysis revealed elevated sulfocystiene, xanthine and hypoxanthine, which suggested MCD. This diagnosis was confirmed by subsequent genetic analysis, which disclosed a homozygous MOCS1 mutation. A significant family history of sibling death, prior to diagnosis, from intractable seizures and respiratory distress at three months of age, most likely represents the same affliction and suggests an underestimation of MCD worldwide. This case underscores the need to consider and investigate MCD in all cases of intractable infantile seizures. Thus, early diagnosis and confirmatory gene analysis before permanent neurodegeneration is imperative for potential therapeutic intervention.

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Introduction

Molybdenum cofactor deficiency (MCD) is a rare and fatal metabolic disorder, which manifests in early childhood with seizures refractory to medical intervention. First reported in 1978 [1], the precise nature of the disease was only recognized in 1980 [2]. Molybdenum cofactor is a crucial component and is necessary for the synthesis of three enzymes: sulfite oxidase, xanthine dehydrogenase and aldehyde oxidase. However, only sulfite oxidase deficiency (SOD) appears to be responsible for the serious neurodegenerative decline that ultimately leads to early mortality [3]. Thus, SOD and MCD have similar clinical manifestations, including ectopia lentis. It is possible but highly rare to have isolated SOD without MCD.

Differentiation of MCD from isolated SOD is determined using urinalysis. Both diseases have increased levels of thiosulfate, but MCD also exhibits increased levels of xanthine and hypoxanthine. In addition, plasma and urinary uric acid levels are typically low or low-normal in MCD, while it is normal in isolated SOD. Abnormal xanthine, hypoxanthine and uric acid levels result from xanthine dehydrogenase deficiency. Current hypotheses of the pathogenetic mechanisms resulting in neurodegeneration are beyond the scope of this paper, although it is sufficient to say that either diminished levels of sulfates or toxic accumulation of sulfa-containing metabolites are likely candidates [4].

MCD is an autosomal recessive disease. Thus, its prevalence is higher in isolated areas and where consanguinity is common. Four genes are required for the production pathway of molybdenum cofactor; MOCS1, MOCS2, MOCS3, and GEPH. The most common mutation observed is in the MOCS1 gene, followed by MOCS2 [4]. Less than 150 cases [5] have been reported worldwide. Importantly, the incidence is most likely an underestimation because many patients with MCD die in early neonatal period without a diagnosis. Due to the low incidence, a high index suspicion is required prior to confirmatory tests. The diagnosis is made by the clinical picture of intractable seizures that are mostly unresponsive to anti-convulsant therapy, urinalysis and low plasma and urinary uric acid. Neuro-radiology typically reveals non-specific changes similar to ischemic/hypoxic encephalopathy. A finding of concurrent ectopia lentis supports the clinical diagnosis of MCD. Prenatal diagnosis is possible with an assay of sulfate oxidase activity and genetic analysis of chorionic villus specimens [6,7].

Although effective treatment has not been established, early diagnosis is important for providing information for genetic counseling, screening of pregnant mothers suspected of being heterozygous carriers and to help determine the real incidence of MCD. Furthermore, stable molybdenum cofactor intermediates or dietary modifications, once identified, might help to ameliorate further neurodegeneration or help to abate the seizures. Early identification of ectopia lentis along with typical urinary chemistry and neuroradiological changes is an important complementary finding instrumental in making a timely diagnosis of MCD. In this study, we describe a patient with a complex combination of clinical signs, including intractable seizures and ectopia lentis who was ultimately diagnosed with molybdenum cofactor deficiency.

Case report

A sixteen-month-old male, full-term product of a consanguineous union was referred to our clinic for ophthalmic assessment. He was transferred from a local hospital in the northern region of Saudi Arabia to King Faisal Specialist Hospital at the age of 18 weeks for examination of neonatal seizures, hypotonia, feeding difficulties and respiratory distress. At birth, following an uneventful pregnancy and delivery, he was noted to have meconium aspiration syndrome and developed intractable seizures. These were successfully managed in the neonatal ICU with carbamazepine and antibiotics. He was then readmitted soon after discharge for poor sucking, hypotonia, and a failure to thrive. He was diagnosed with infantile spasm-like seizures and treated in the pediatric ICU with levetiracetam (Keppra) and vigabatrin. Concomitant stridor and respiratory distress was assessed and subsequently attributed to laryngomalacia.

Importantly, the family history revealed a brother who likewise developed intractable seizures, respiratory distress and hypotonia in the neonatal period and died at three months of age without a syndromic designation or initiation of investigations. The parents are healthy second degree cousins. The mother, a 25-year-old $P_2G_2A_0$, had two brothers and one sister who died in early infancy without diagnoses. They were previously healthy. The father's family is completely healthy with no reported early deaths. Consanguinity is an acceptable practice in this family and region.

On examination, the patient had a dysmorphic face with a broad nasal bridge, deep seated eyes, prominent cheeks, micrognathia and large ears. Severe delay in developmental milestones was also observed. There was no spontaneous smile, no fixation or grasping of objects and no head control. Neurological examination revealed axial hypotonia and peripheral spasticity with hyper-reflexia. The rest of the systemic examination was normal and no organomegaly was detected.

An EEG showed polyspikes with posterior dominance of the left compared to the right. CSF analysis revealed decreased glycine and uric acid, and non-ketotic hyperglycinemia was ruled out. Urinary xanthine, hypoxanthine, and S-sulfocysteine levels were elevated. Tandem mass spectrometry of the blood was negative for organic acids and very long chain fatty acids, which simultaneously ruled out several other inborn errors of metabolism. An MRI was performed at five weeks of age, which revealed extensive cortical atrophy, cystic degeneration of the white matter, small brainstem and cerebellum, basal ganglion atrophy, thin corpus callosum, and enlargement of the ventricles and subarachnoid and peri-cerebellar CSF spaces (Fig. 1a and b). A subsequent CT scan, at sixty weeks of age, revealed further global encephalomalacia with a collapse of the cystic white matter, enlarged ventricles and subarachnoid spaces (Figs. 2 and 3a), and small, superiorly subluxed lenses.

Ophthalmic examination, at sixteen months of age, revealed no fixation or following in both eyes. The anterior chambers were white and quiet with superiorly subluxed lenses bilaterally (Figs. 3 and 4a,b). The dilated fundoscopy was normal. Although the clinical manifestations, urinary

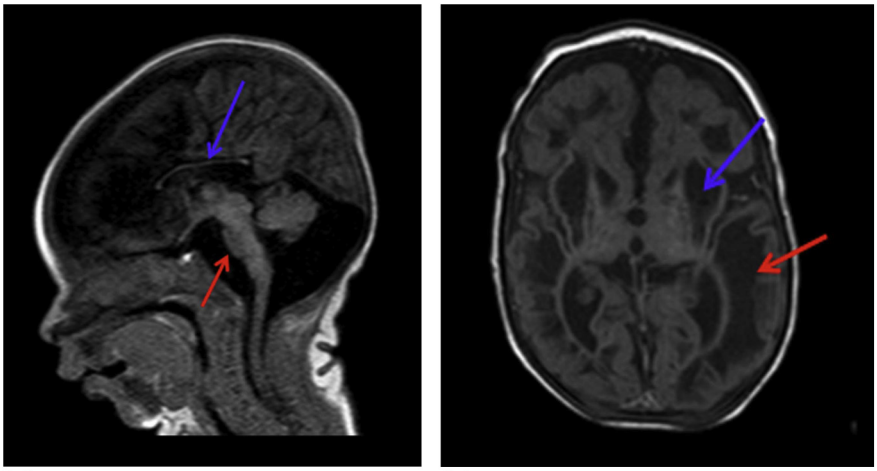

Figure 1 Five weeks of age — T1-weighted MRI of brain (a) sagittal view showing thin corpus callosum (blue arrow), small brainstem (red arrow), cerebellum and enlarged ventricles and subarachnoid spaces; (b) axial views at the level of the thalamus, demonstrating cystic changes in the bilateral basal ganglion (blue arrow), and cerebral white matter (red arrow) and dilated lateral ventricles.

chemistry and neuroradiology established the diagnosis of molybdenum cofactor deficiency, a blood specimen was submitted for genetic analysis (Mayo Clinic, USA) and a homozygous MOCS1 mutation was detected, which confirmed the diagnosis of MCD. The parents have not been investigated for heterozygosity and whether this case represents a new mutation cannot be determined at this time.

Multiple episodes of aspiration pneumonia from gastroesophageal reflux necessitated a Nissen fundoplication and the placement of a feeding tube through which he receives various fortified infant milk formulae. He is currently oxygen-dependent and exhibits severe psychomotor retardation. Phenobarbital was added to levetiracetam (Keppra) and vigabatrin to control his seizures.

Discussion

Molybdenum cofactor deficiency is a severe progressive, neurodegenerative, inborn error of metabolism, which ultimately results in death in early childhood. Early diagnosis is essential but, due to its rarity and phenotypic variability, it requires a high index of suspicion when a neonatologist is presented with complex and wide-ranging clinical manifestations, which include intractable seizures. Indeed, neonatal deaths may occur without syndromic designation as might have occurred in our patient's immediate family, including a sibling who died of respiratory distress, hypotonia and intractable seizures. His clinical picture and course make MCD the mostly likely diagnosis. The maternal siblings were described as "normal" prior to their untimely demise and cannot be presumed to have had MCD.

Because the predominant clinical manifestations of MCD are neurological and arise from SOD, the clinical course of MCD and SOD are virtually identical. Ectopia lentis, a known association of SOD is likewise observed in MCD and plays an important role in establishing the diagnosis. Immediate post-birth presentations have been reported [8—10] but typically, clinical manifestations of MCD begin two weeks after birth and early infancy [1,2,10]. In the initial descriptions of MCD [1,2], the neonate had ectopia lentis at the outset, while others have reported its development at a later date. Although the patient had ectopia lentis at sixty weeks, the small, malformed lens observed on the CT scan in our patient indicates earlier subluxation (Fig. 3); thus its precise onset is indeterminate.

Phenotypic variability is recognized and has been reported in both MCD and SOD. In a cohort of ten patients, Vijayakumar [10] recognized two forms of MCD: the more common classical form presenting with neonatal rapidly

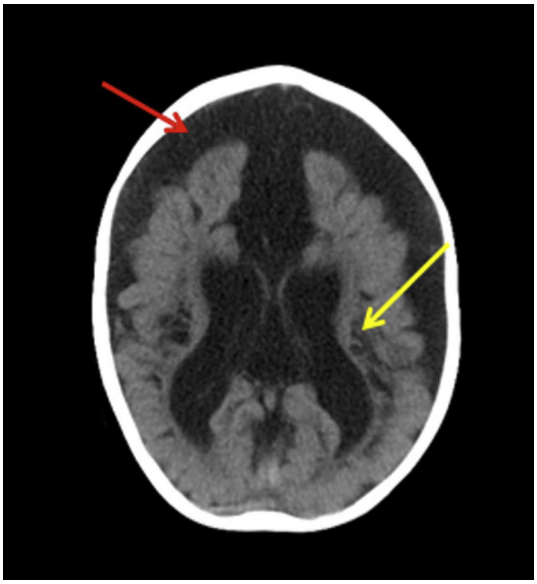

Figure 2 60 weeks of age — axial CT scan of the brain revealing progressive neurodegeneration with severe global encephalomalacia, collapse of cysts in the cerebral white matter (yellow arrow), enlarged lateral ventricles and subarachnoid spaces (red arrow).

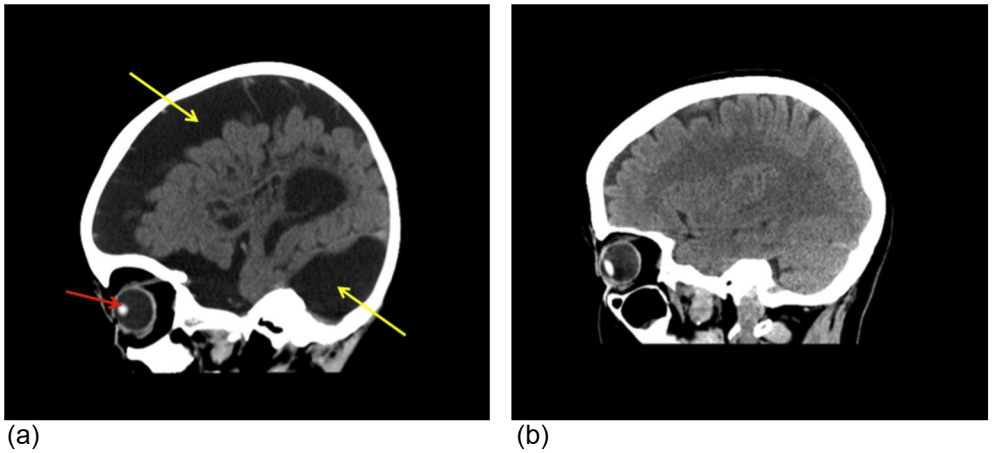

Figure 3 60 weeks of age — sagittal CT scan (a) revealing severe global volume loss, enlarged ventricles, subarachnoid space and retro-cerebellar space (yellow arrows) and small, superiorly displaced lens — ectopia lentis (red arrow); (b) is a sagittal CT scan of a normal baby, demonstrating normal brain development and normal shape, size and location of lens, for comparison.

progressive neurodegeneration and the mild atypical form that presents later in life with a developmental delay. Milder forms diagnosed after the incidental discovery of ectopia lentis have been reported [10—12]. Our case represents the classical early-onset form.

Currently, there is neither an evidence-based treatment regime for the management of MCD nor a means of delaying progressive neurodegeneration. Molybdenum cofactor is not sufficiently stable for systemic administration, but there appears to be therapeutic potential in utilizing biosynthetic intermediates or dietary modification. Anecdotal reports of successful treatments include the administration of cPMP (cyclic pyranopterin monophosphate), an intermediate in molybdenum biosynthesis [13], NMDA (*N*-methyl-D-aspartate) receptor inhibition with dextromethorphan, thiamine and cysteine supplementation and methionine-restricted diet [14]. Improvement of biochemical profiles and neurological manifestations, including a decline or complete cessation of seizures has been reported. Thus, additional research is required before a therapeutic regime can be established and universally adopted. However, it is clear that the potential exists for early intervention once individuals with this disorder are identified. This makes early diagnosis of MCD, before permanent brain damage, imperative.

This report of a very rare and ultimately fatal metabolic disease represents the need for a heightened index of suspicion for MCD for all cases on intractable seizures. Furthermore, this report underscores the similarities between MCD and isolated SOD. Both syndromes are likely

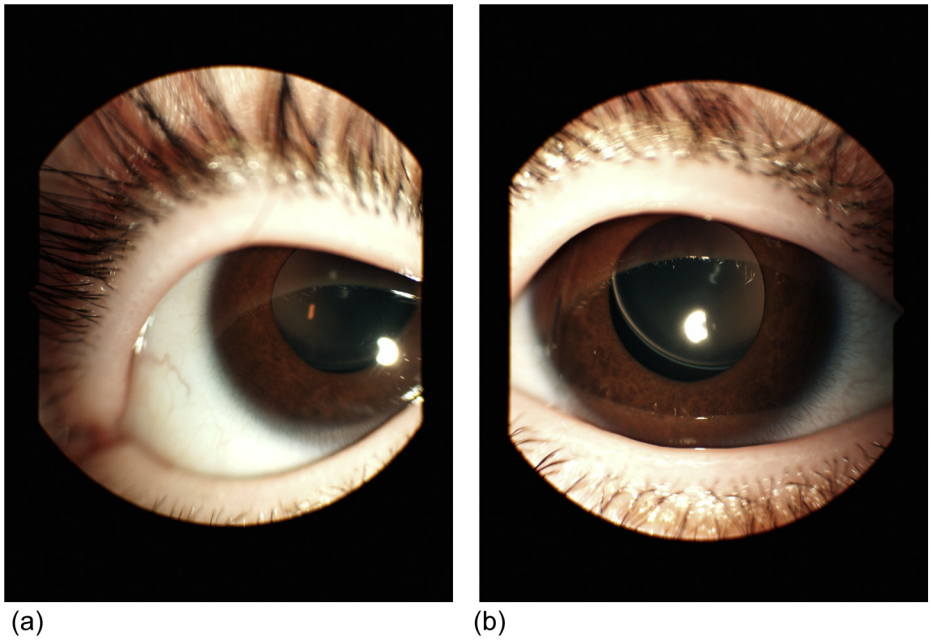

Figure 4 Bilateral ectopia lentis in a 16-month-old baby boy with molybdenum cofactor deficiency (a) right eye and (b) left eye show superiorly subluxed lenses.

under-diagnosed and under-reported particularly in isolated areas and where consanguinity is common. The addition of this confirmed case of molybdenum cofactor deficiency to the current database, while adding to the incidence and prevalence rates, will also help to establish the phenotypic spectrum, detail the natural clinical course and will enable an earlier recognition with implications for future therapeutic intervention.

Conflict of interest

The authors have no funding or conflicts of interest to declare.

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