Mild phenotype of Molybdenum cofactor (MoCo) deficiency Type B among Egyptian patients

Original Article

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ABSTRACT

MoCD is a rare autosomal recessive neuro-metabolic disorder which results from the absence of the three molybdenum requiring enzymes. It is caused by mutations in *MoCS1, MoCS2, MoCS3* and *GPHN* genes. Therefore, there are four forms of this disorder namely type 1, 2, 3 and 4. All forms have the same clinical signs and symptoms, but differ by their genetic mutations. We present the clinical, neurological, neuro-radiological and molecular genetic analysis of two female Egyptian patients diagnosed with the rare form of MoCD type B disorder. They were subjected to detailed family history, clinical, neurological, and neuro-radiological investigations. Their diagnosis was MoCD type B with mild phenotype and confirmed by genetic mutation analysis through whole exome sequencing (WES). MoCD should be considered in all cases with neuro-developmental delay and neonatal convulsions. Therefore, MoCD analysis should be included in the neonatal screening to establish early diagnosis and potentially proper management.

Key Words: *GPHN*, *MoCS1, MoCS2, MoCS3* genes, molybdenum cofactor, neurodevelopmental delay, prenatal genetic diagnosis, whole exome sequencing.

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INTRODUCTION

MoCD is a rare autosomal recessive neuro-metabolic disorder resulting from mutations in *MOCS1, MOCS2, MOCS3* and *GPHN* genes which result in the absence of molybdenum-complex protein factor. This causes deficiency of one of the four molybdenum enzymes namely; aldhyde oxidase, mitochondrial amidoxine reducing component (mARC), xanthine oxido reductase and sulphite oxidase (**Scelsa *et al*., 2019**). The first case of MoCD was reported by Duran, 1978, yet its clinical features were described on 1980 by Johnson and colleagues (**Johnson *et al*., 1980**).

MoCD type B results from mutations in *MOCS2* gene (**Mechler *et al*., 2015**). More than 100 patients of MoCD type A have been reported in the medical literature, while no more than 30 patients of MoCD type B have been recognized worldwide (**Huijmans *et al*., 2017**). The prevalence of MoCD is not ascertained, however, it is estimated to be 1: 100000 to 200000 newborns world-wide (**Schwahn *et al*., 2015**).

Clinically, most patients are usually presented within the first week of life by intractable neonatal seizures, exaggerated startle reflexes, progressive encephalopathy, facial dysmorphism, and failure to thrive. Microcephaly, abnormal tone, renal stones and lens dislocation could be associated. Most cases are misdiagnosed as hypoxic ischemic encephalopathy (HIE) and die early in childhood. However, late onset type has been reported (**Megahed *et al*., 2016; Zaki *et al*., 2016; Scelsa *et al*., 2019**). Neuro-radiologically, cerebral and cerebellar atrophy, basal ganglia calcifications are detected on MRI studies. Cystic encephalomalacia, ventriculomegaly, hypoplasia of the corpus callosum and delayed myelination resembling hypoxic ischemic encephalopathy, perinatal multicystic leukomalacia are also reported (**Higuchi *et al*., 2014**).

2. Clinical Report

Two female Egyptian patients represent the core of this study.

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Patient 1:

A female patient presented at the age of 3.8 years was referred to our clinic in the clinical genetics department at the National Research Centre (NRC) complaining of gradual progressive deterioration of her acquired developmental milestones. She is a product of first degree consanguineous parents (Figure 1). She was born after full term normal pregnancy and delivery with unremarkable neonatal history. Her birth weight was 3 kilograms on the mean for her age, her head circumference was just below normal standard deviation (-2D) with a tendency to microcephaly. She had a normal Apgar score, was not dysmorphic, and had normal ophthalmic examination.

The parents did not seek any medical advice at that time. She developed normally till the age of 3 years when her developmental milestones gradually deteriorated following recurrent chest infection. She was delayed in walking, followed by inability to sit and could only crawl, although she was on physiotherapy. She has cognitive deterioration with delayed language development. At the age of 3.5 years she developed generalized tonic-clonic convulsions, which responded adequately to proper antiepileptic therapy. Neurologically, she had normal cranial nerves with bilateral normal fundi, but she was hypertonic with exaggerated deep tendon reflexes more on the left side. Routine metabolic laboratory investigations were done on both blood and urine. Electro-encephalography (EEG) showed right fronto-temporal epileptogenic dysfunction with secondary generalization. MRI showed right frontal subdural hygroma with mild frontal lobe atrophy and severe cerebellar atrophy as shown in (Figure 2). On regular follow-up visits she showed a stationary course. She was last seen alive at age of 6 years unable to walk unsupported and had delayed language development but her convulsions were well controlled on antiepileptic therapy. Diagnosis of MoCD was suspected due to the low level of blood uric acid. Using whole exome sequencing (WES) the diagnosis of MoCD type B was confirmed.

Patient 2:

A female patient aged 1.6 years presented to our clinic. Her parents reported that their child was complaining of progressive global developmental delay with convulsions. She is the first child of non-consanguineous parents with no family history of any neurological problems (Figure 3). She had full term normal pregnancy and delivery. At birth there were no hypoxia, convulsions, fever or jaundice with a normal Apgar score. There were no dysmorphic features. She had normal anthropometric measurements with her head circumference on the mean standard deviation. She had congenital heart defect in the form of pulmonary stenosis, which was diagnosed by echocardiographic imaging. She developed normally till the age of one year when she had fever with convulsions followed by coma for three days. She had difficulty in feeding and started to lose her acquired developmental milestones and lost the ability to stand or sit and could not recognize her mother. Laboratory investigations for infection were all negative. On neurological examination she had normal cranial nerves with bilateral normal fundi. But she had opisthotonus posture with dystonia and brisk deep tendon reflexes. She developed generalized tonic clonic convulsions, which responded to antiepileptic therapy. Routine laboratory investigations of blood and urine were done. Electro-encephalography showed abnormal tracings in the form of generalized epileptogenic dysfunction. MRI of the brain revealed bilateral abnormal signals in the globus pallidus with bilateral basal ganglia calcification and cerebellar atrophy as shown in (Figure 4). MoCD was suspected and DNA analysis by whole exome sequencing, revealed MoCD type B. On routine follow up visits her convulsions were controlled and her developmental milestones showed a stationary course. After one year she was failing to thrive and died at the age of 2.8 years.

Table 1: List of patients of mild phenotype of MOCD described in the literature and present two patients.

Case No.	1 Shih *et al.*, 1977	2 Mize *et al.*, 1995	3 Graf *et al.*, 1998	4 Hughes *et al.*, 1998	5 Alkufri *et al.*, 2013	6 Johnson *et al.*, 2001	7 Vijayakumar *et al.*, 2011	8 Zaki *et al.*, 2016	9 Huijuma *et al.*, 2017	10 Mayr *et al.*, 2018	11 Scelsa *et al.*, 2019	12 Current study	13 Current study
Age at onset (months)	17	24	6	12	28	15	15	16	18	24	16	44	16
Dysmorphism	-ve	Marfanoid	-ve	-ve	-ve	Macro-cephaly	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Psychomotor development	delay	delay	delay	delay	delay	delay	delay	delay	delay	delay	delay	delay	delay
Behavior disorders	+	+	+	+	+	+	+	+	+	+	+	+	+
Extra pyramidal signs	+	+	+	+	+	+	+	+	+	+	+	+	+
Pyramidal signs	+	+	+	_	_	_	+	+	+	+	+	+	+
Ophthalmic signs	lens dislocation	lens dislocation	lens dislocation	_	lens dislocation	_	_	_	_	lens dislocation	_	_	_
Seizures	+	_	_	+	_	_	+	+	+	+	+	+	+
Independent walking	+	+	_	_	unstable	+	+	+	_	+	_	+	+
Feeding difficulties	_	_	_	+	+	_	_	+	_	+	_	_	+
Language development	aphasia	delayed	normal	regression	regression	delayed	delayed	delayed	delayed	delayed	normal	delayed	delayed
Uric acid	normal	decreased	decreased	decreased	decreased	normal	decreased	decreased	decreased	decreased	decreased	decreased	decreased
S Sulpho-cystine	increased	increased	increased	normal	normal	increased	increased	increased	increased	increased	increased	increased	increased
Sulfite test	+	+	+	+	+	+	+	+	+	+	+	+	+
MRI brain	normal	lentiform nucleus	basal ganglia+ white matter	basal ganglia+ dentate nucleus	basal ganglia	basal ganglia	Severe	basal ganglia+ globas pallidus lentiform	Moderate	mild	Globus pallidus + dentate nucleus	Basal ganglia+ frontal hygroma	Basal ganglia+ Globus pallidus
Antiepileptic treatment	+	_	_	+	_	_	+	+	+	_	+	+	+
Molecular analysis	_	_	_	MOCS2	MOCS2	MOCS2	MOCS2	MOCS2	MOCS3	MOCS1	MOCS2	MOCS2	MOCS2

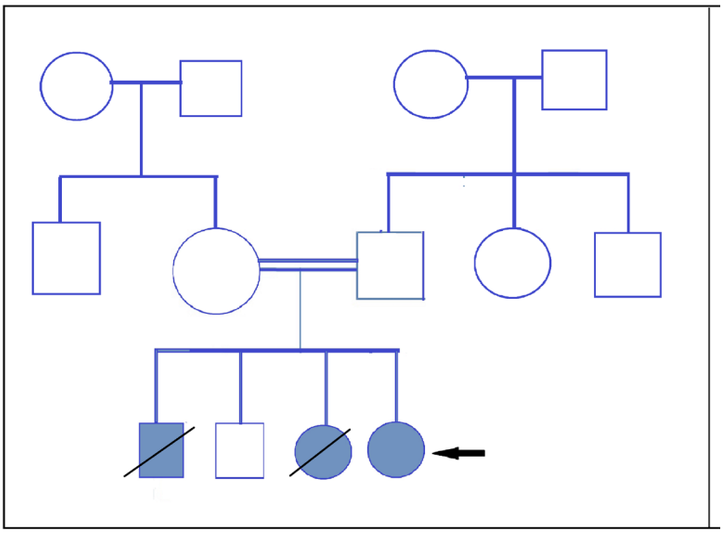

Fig. 1: Pedigree of patient 1 showing positive consanguinity and 2 similarly affected siblings

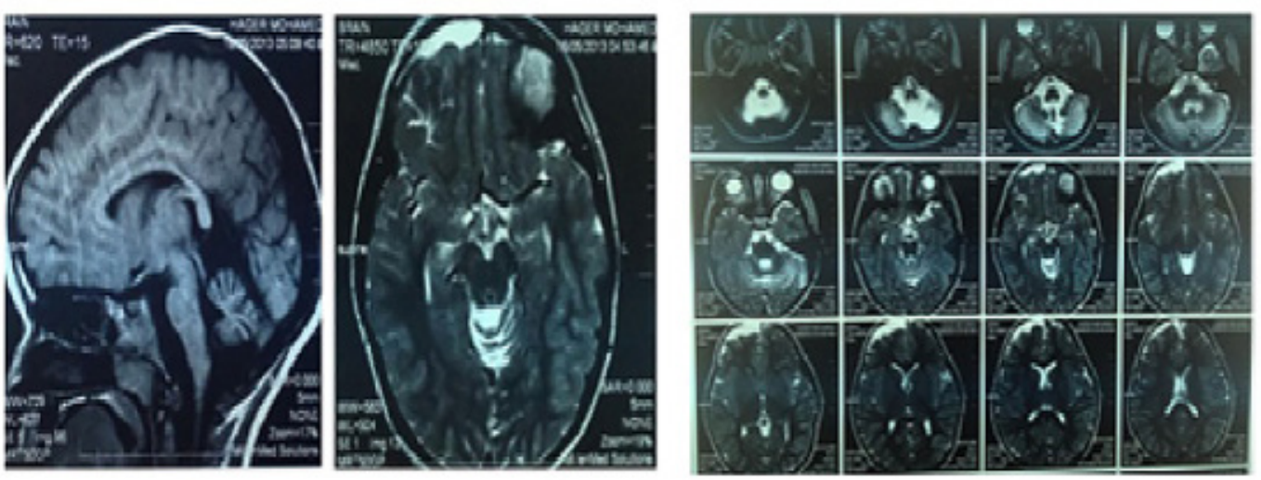

Fig. 2: MRI brain of patient 1, showing right frontal subdural hygroma, severe cerebellar atrophy, cortical atrophy and white matter abnormalities.

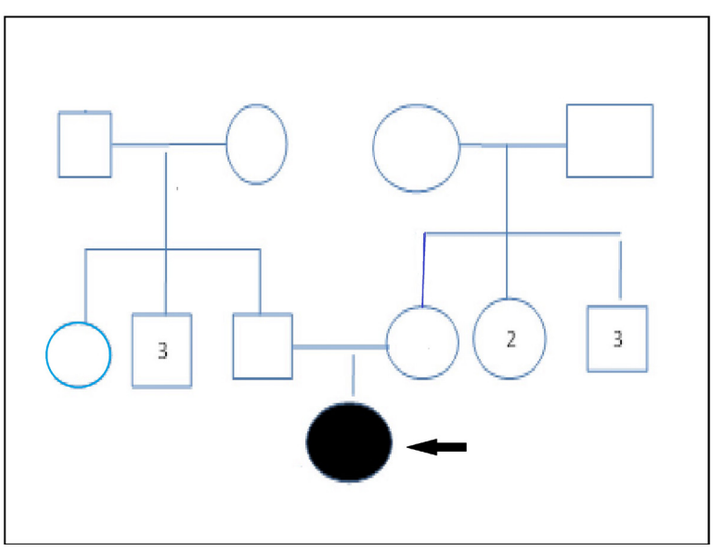

Fig. 3: Pedigree of patient 2 showing non consanguineous parents and no other affected family members.

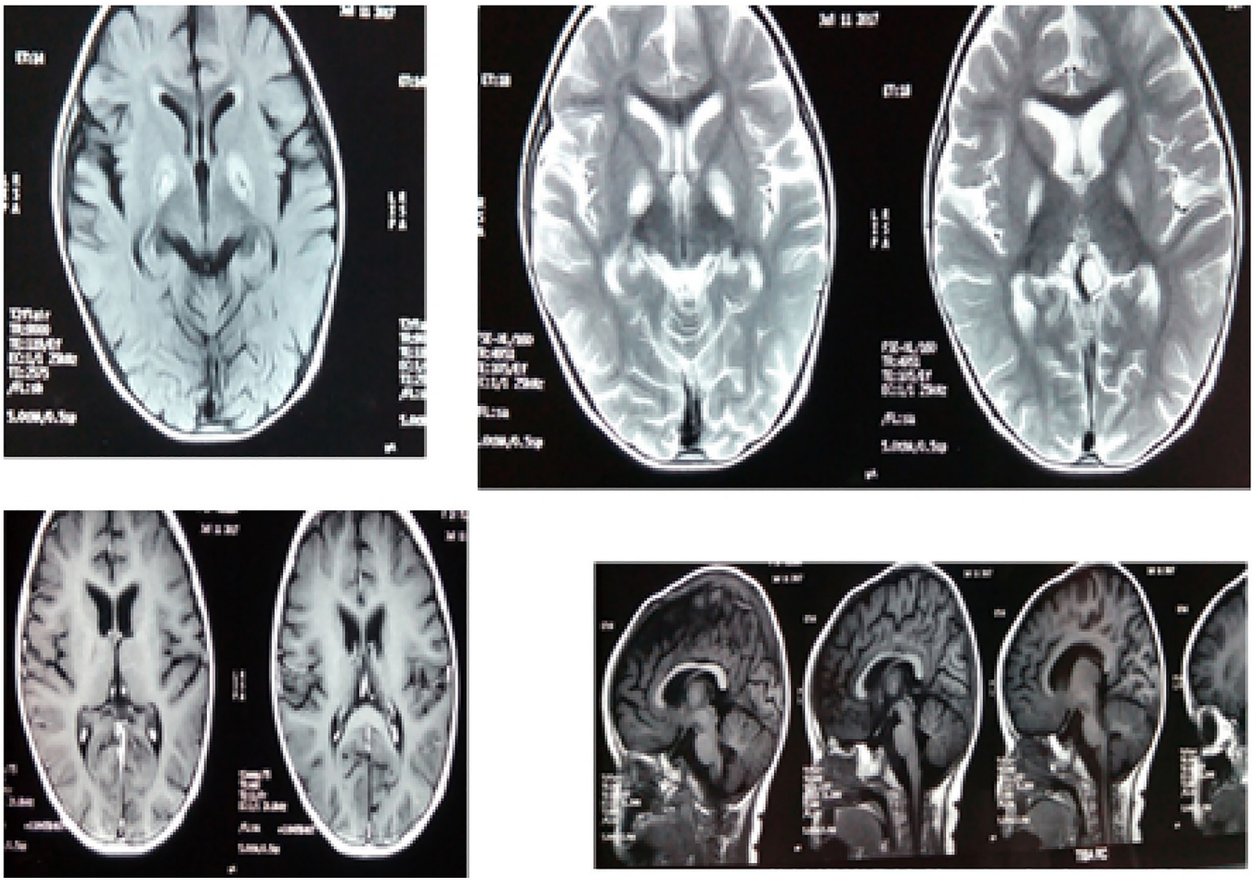

Fig. 4: MRI brain of patient 2 showing mild cerebellar atrophic changes, cortical brain atrophy and calcification of the basal ganglia bilaterally.

PATIENTS AND METHODS:

The study was carried out according to the standers of the Egyptian government's protocols approved by the Medical Research Ethics Committee of the Egyptian National Research Centre. Informed consents were obtained from patients' guardians. Patients were subjected to detailed family history, pedigree analysis, clinical, neurological and neurophysiological assessments.

Biochemical analysis of sulphite was done. Purines and Pyrimidines were measured by HPLC, thiosulfate measured by ion chromatography, plasma homocysteine was measured with tandem mass spectrometry, uric acid in plasma and freshly voided uric acid was measured with an enzymatic colorimetric assay. MRI of the brain, electro-encephalography, electro-cardiography, visual evoked response and electroretinography were also done.

Whole exome sequencing was done to our two patients:

DNA was extracted from the blood and the sequencing core facility and WES were performed at the Imagine Institute, Paris, France. Briefly, WES libraries were prepared from 3 µg of genomic DNA sheared by ultrasonication (Covaris S220 Ultrasonicator). Exome capture was performed with the 51 Mb SureSelect Human All Exon kit V5 (Agilent technologies). Sequencing of the WES libraries was carried out on a HiSeq2500 (Illumina). Paired-end reads were generated and mapped on the human genome reference using Burrows-Wheeler Aligner (BWA). The mean depth of coverage obtained for each sample was > 160x with >97 % of the exome covered at least 30x. SNP and indel calling were made using GATK tools (**Li H *et al*., 2009**).

Bioinformatics, databases A variant filtering pipeline was systematically applied to narrow down the number of putative causative variants. All the possible inheritance patterns were tested. Briefly, common (>1 % minor allele frequency) variants were filtered out by using dbSNP, 1000 genomes databases and our in house exome collection, which includes more than 7000 exomes. Functional (protein-altering) alleles were prioritized versus non-functional. Potentially pathogenic variants in known disease genes were identified if flagged as damaging by polyphen2 (http://genetics.bwh. harvard.edu/pph2/), Sift http://sift.jcvi.org/) or mutation taster (http://www.mutationtaster.org/). Remaining variants were compared with those in the public databases EXAC (http://exac.

broadinstitute.org/) and EVS (http://evs.gs.washington.edu/EVS/) exome database. The presence of candidate recessive variants in homozygous intervals was checked by identifying predicted regions of SNP homozygosity from exome data with the unified genotyper tool from GATK (https://www.broadinstitute.org/gatk/). In order to identify fully penetrant dominant mutation in singleton WES data we used the following method. We filtered out variants that were present in control individuals from our in house exome database and not predicted to be pathogenic by at least two prediction programs: PolyPhen, SIFT or Mutation-Taster.

We validated potential de novo mutations by using Sanger sequencing on the patients and parents' DNA. However, considering the large number of variants generated by this method, it is considered efficient only for the identification of mutations in known disease genes.

RESULTS:

The clinical findings for brain MRI, encephalogram, electrocardiography results are detailed in the previous section describing the patients, as shown in Table 1, Fig. 2 and Fig. 4.

The biochemical findings showed high levels of plasma s-sulfocystine, plasma xanthin, and decreased plasma uric acid

Whole exome sequencing showed *MOCS2* variant NM-176803 homozygous mutation c.3G>A p.Metl? for both patients (Figure 5).

Segregation analysis was done in both patients to confirm that the identified mutation was segregating in other family members, as confirmed by sanger sequencing. Data may be obtained upon request from the performing labs.

Fig. 5: Bioinformatics' analysis for the WES data showing *MOCS2* gene prioritisation.

DISCUSSION

MoCD is a rare autosomal recessive neuro-metabolic disorder due to mutations in *MOCS1, MOCS2, MOCS3* and *GPHD* genes. This causes absence of molybdenum-complex protein factor which leads to deficiency of the four molybdenum enzymes and causes decreased conversion of xanthine to Uric acid and toxic sulfite accumulation in the brain (**Reiss *et al*., 2011**). This causes cellular damage, neuronal death, severe neurological impairment and intractable seizures, (**Schwartz *et al*., 2009**). Accumulation of sulfite in the basal ganglia causes extrapyramidal manifestations (**Alkufri *et al*., 2013**). Sulfite accumulation also inhibits mitochondrial metabolism in particular glutamate dehydrogenase causing Glutamate toxicity, which could be responsible for the ischemic lesions

described, or through the action of other insults for instance intercurrent illness (**Zhang *et al*., 2004**). Activation of inflammatory cascade causes additional brain damage and neuronal dysfunction (**Scelsa *et al*., 2019**).

MoCD mostly present in the neonatal period with intractable seizures and early death despite all supportive measures and are misdiagnosed as Hypoxic-Ischemic Encephalopathy (HIE) due to the similarly clinical picture and MRI findings (**Topcu *et al*. 2001**; **Per *et al*. 2007; Yoganathan *et al*. 2018**). Our patients presented in early childhood by progressive deterioration of acquired global developmental milestones with seizures, and were initially misdiagnosed as HIE despite of their normal pregnancy and labour history.

MoCD usually occurs in consanguineous parents but it can still occur in non-consanguineous parents due to novel mutations as the case of our second patient (**Yoganathan *et al*., 2018). Scelsa *et al*., (2019)** reported one patient with MoCD type B with late onset and milder phenotype who presented at age of 16 months and was last seen at the age of 6.11 years. **Zaki *et al*., (2016)**, presented an Egyptian female patient at the age of 2 years diagnosed with MoCD type B presenting with rapid deterioration of milestones of development and seizures and died at the age of 5.6 years. She had positive consanguineous parents and other three similarly affected siblings.

A late onset form has also been reported in the literature in 13 cases (including our 2 current cases) (Table 1). (**Alkufri *et al*., 2013, Graf *et al*., 1998, Hughes *et al*., 1998, Huijmans *et al*., 2017, Johnson *et al*., 2001, 1988, Mayr *et al*., 2018, Megahed *et al*., 2016, Mize *et al*., 1995, Shih *et al*., 1977, Vijayakumar *et al*., 2011, Zaki *et al*., 2016**). These cases are similar to our patients and our findings. Both of our patients were from remote geographical regions in Egypt, excluding the possibility of a founder effect.

MoCD has a spectrum of manifestations starting from the neonatal period to adulthood. When the disease begins early in the neonatal life the phenotype is severe with rapid neurological deterioration. However, when the disease begins after the first year of life the patients have a milder phenotype with pyramidal and extrapyramidal manifestations. Residual activities of molybdenum cofactor enzymes are responsible for the late onset of this milder phenotype (**Mayr *et al*. 2018**). The role of other factors including inter-current infection may trigger an exacerbation for the neurological symptoms.

Neuro-radiology, MRIs of the brain of our Egyptian cases revealed frontal hygroma, cortical and severe cerebellar atrophy, abnormal white matter signals in the globus pallidus and bilateral basal ganglia calcifications, which are similar to the MRI picture of the case reported by **Higuchi *et al*., (2014)** and **Zaki *et al*., (2016)**. While, the usual MRI picture of the brain of the MoCD patients resembles that of HIE including perinatal multiple cystic encephalomalacia with various degrees of cortical involvements (**Vijayakumar *et al*. 2011**).

Since, MoCD is a rare autosomal recessive neuro-metabolic disorder which is clinically miss-diagnosed as HIE, the possibility of lack of diagnosis or underdiagnoses might be the cause of its inaccurate estimation. Therefore, MoCD should be considered in all patients with neuro-developmental delay, neonatal insults and HIE especially if there are no obvious causes. We recommend that MoCD should be included in the neonatal screening tests with measurements of blood uric acid and urinary sulfite oxidase levels to establish early diagnosis and potential proper management.

The prognosis of the disease including that of our cohort is still very unfavourable, our first patient was last seen alive at the age of 6 years, and the second patient died at the age of 2.8 years.

Prenatal diagnosis should be recommended if the diagnosis of MoCD has been previously confirmed in the family (**Johnson 2003**). More investigations, including whole exome sequencing is required to establish better effective diagnosis for this severe disorder. Despite the clinical investigations, effective treatment strategies have not yet been reached. Diet low in sulphur amino acids has potentially proved to cause a decrease in the sulphur metabolites. Pyridoxine supplementation may improve the neurological manifestations but not the previously established cerebral injuries (**Schwartz *et al*., 2004**). **Valdman *et al*., (2010)** proved that IV administration of cyclic pyranopterin monophosphate (Cpmp) showed favourable clinical response in cases of *MOCS1* gene mutation. But *MOCS2* gene mutations appear to be incurable. Further trials using MoCS2 proteins and gene therapy are under trials.

It is possible that biochemical testing supported by molecular genetic testing may be required for any infant with unexplained neuro-developmental delay.

CONFLICT OF INTEREST

There are no conflicts of interest.

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