Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

A case report of molybdenum cofactor deficiency type A: the first case diagnosed in Syria

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Introduction: Molybdenum cofactor deficiency (MoCD) type A, a rare mitochondrial disorder with characteristic clinical presentation and imaging findings, is one of the forms of molybdenum cofactor deficiency. It presents with seizures, psychomotor delay, and breastfeeding difficulties. Seizures are especially prominent in patients with MoCD.

Case presentation: A 3-month-old girl presented with refractory generalized tonic-clonic seizures since the third day of life. Her parents were third-degree relatives. On physical examination, she demonstrated psychomotor delay, breastfeeding difficulties, seizures, doll-like facial features, and other neurological abnormalities. Her brain MRI scan revealed cortical and white matter atrophy of the cerebral hemispheres. Metabolic workup revealed elevated levels of liver enzymes, lactic acid, and ammonia. These results were inconclusive. She received anticonvulsants and vitamin therapy to manage her seizures. Based on a suspicion of mitochondrial disease, genetic analysis was performed, revealing a homozygous variant of uncertain significance in the MOCS1 gene associated with autosomal recessive molybdenum cofactor deficiency type A.

Conclusion: MoCD is a rare disease. Early diagnosis should be considered based on the patient's medical history and MRI findings, after excluding other possible diagnoses. The definitive diagnosis relies on genetic testing results.

Keywords: molybdenum cofactor deficiency, MoCD, MOCS1, neonate, seizures

Introduction

Molybdenum cofactor deficiency (MoCD) is an autosomal recessive disorder causing a deficiency in molybdenum-dependent enzymes like sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase[1,2]. Mutations in MOCS1, MOCS2, MOCS3, or GEPH genes impair molybdenum cofactor production, leading to neurological disorders, feeding difficulties, intractable seizures, and encephalopathy[3–5]. Some rare symptoms are also reported (Table 1)[6,7]. Type A, caused by MOCS1 mutations, results in sulfite oxidase dysfunction and accumulation of toxic sulfites, causing encephalopathy and other neurological symptoms[3]. This report aims to investigate the first case reported in Syria, presenting with delayed psychomotor development and generalized tonic-clonic seizures.

HIGHLIGHTS

- Molybdenum cofactor deficiency (MoCD) is an autosomal recessive disorder that results in a concomitant deficiency of molybdenum-dependent enzymes.
- Type A is the most common type, which is caused by a mutation in the MOCS1 gene.
- The genetic analysis confirmed the diagnosis of molybdenum cofactor deficiency.
- There is currently no effective treatment for the disease.

Case presentation

Clinical history and investigations

A 3-month-old girl presented with generalized tonic-clonic seizures since the third day of life. Her vaginal delivery yielded a birth weight of 3.4 kg. The mother was 29 years old and the parents were third-degree relatives. Physical examination revealed psychomotor delay, doll-like facial features, mild general status, hyperthermia (39°C), cervical lordosis, mild spasticity in the limbs, hyperreflexia, positive plantar reflex, and hepatomegaly 2 cm below the costal margin. The head circumference was 36 cm. She also had breastfeeding difficulties. Her brain computed tomography (CT) scan showed generalized cerebral oedema without midline deviation and millimetre-size haemorrhagic foci in the thalamus. Her brain MRI scan showed atrophy in the cortex and white matter of the cerebral hemispheres, as well as dilation of the subarachnoid space and lateral ventricles (Fig. 1).

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2024) 86:1762–1765

Received 28 November 2023; Accepted 23 January 2024

Published online 30 January 2024

http://dx.doi.org/10.1097/MS9.0000000000001778

Table 1

Symptoms of molybdenum cofactor deficiency

The common symptoms	The rare symptoms
• Seizures. • Psychomotor delay. • Intellectual disability. • Breastfeeding difficulties. • Hypotonia. • Apnoea. • Lens dislocation.	• Status dystonicus. • Parkinsonian features. • Abnormal facial features.

Biochemistry and blood tests

The patient's tandem mass spectrometry (TMS) and urine amino acid electrophoresis were within the normal range. Blood glucose, lactic acid, and ammonia showed high values, while the uric acid test was slightly low. Liver enzymes were elevated, while total protein and albumin were low. Inflammatory markers and cerebrospinal fluid (CSF) analysis were normal. All other biochemical tests were within the normal range (Table 2).

Genetic analysis

The patient was referred to Centogene Center for genetic testing. The results identified a variant in the MOCS1 gene: c.470G > A p. (Gly157 Asp). This variant has been associated with autosomal recessive molybdenum cofactor deficiency of complementation group A.

Diagnostic strategy

Early refractory seizures and psychomotor delay prompted investigation without evidence of hypoxic or haemorrhagic features on MRI and CT findings. Biochemical results ruled out hypocalcemia and hypoglycemia as potential causes. Specific metabolic disorders were considered as differential diagnoses for early refractory seizures (Table 3)[8]. Experimental treatment with magnesium and vitamin B6 to rule out pyridoxine deficiency did not improve symptoms. While metabolic workup revealed elevated liver enzymes (gamma-glutamyltransferase, serum glutamic-oxaloacetic transaminase, and serum glutamic-pyruvic transaminase), lactic acid, and ammonia, these findings offered limited diagnostic guidance. The normal result of urinary amino acid electrophoresis ruled out malignant phenylketonuria. Due to the early onset of seizures and psychomotor delay, Canavan disease, a rare leukodystrophy with similar but often more distinct features like macrocephaly and optic nerve involvement, could be considered a less likely differential diagnosis[9]. However, mitochondrial and Krebs cycle diseases were the most likely suspects, and genetic analysis was recommended to

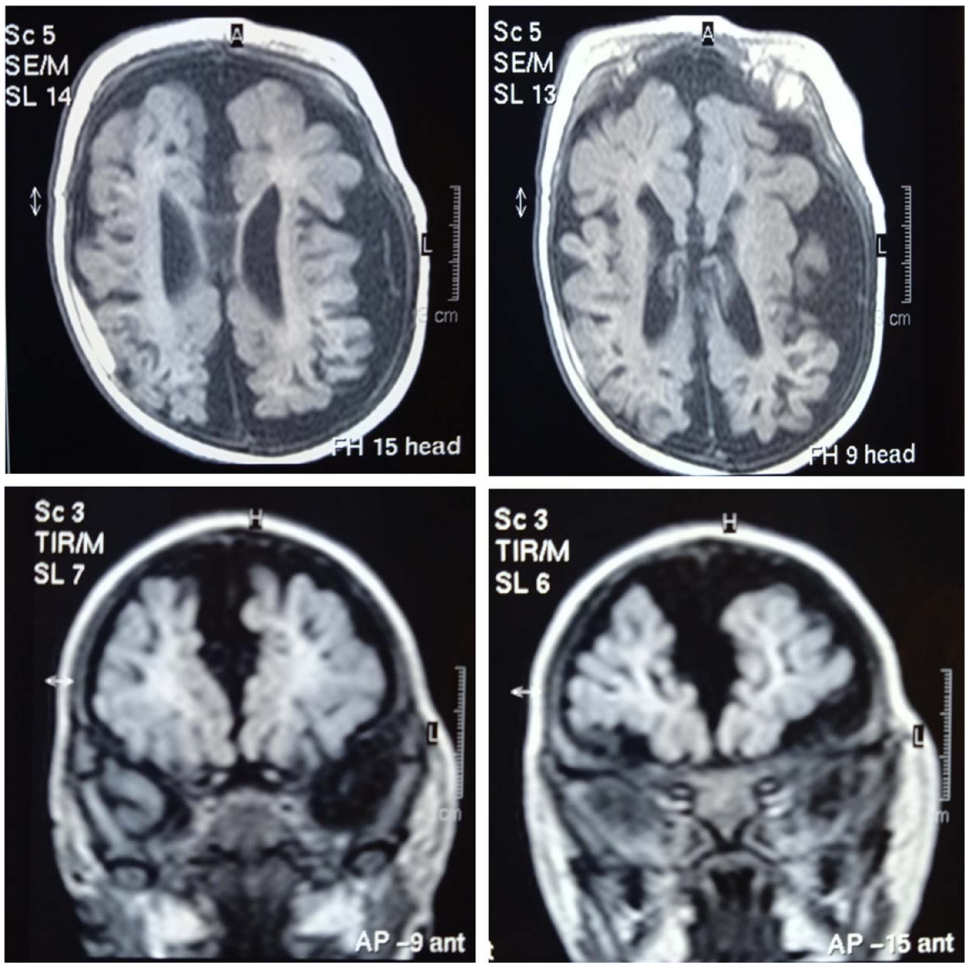

Figure 1. MRI revealed an atrophy in the cortex and white matter of the cerebral hemispheres, as well as dilation of the subarachnoid space and lateral ventricles.

Table 2

Biochemistry and blood tests

Lab test	Results	Reference range
CRP	1 mg/l	0–5 mg/l
Blood glucose	230 mg/dl	70–99 mg/dl
Lactic acid	31 mg/dl	5–20 mg/dl
Ammonia	142 mol/l	11–35 mol/l
Uric acid	2 mg/dl	2.5–6.6 mg/dl
Liver enzymes		
GGT	260 U/l	1–70 U/l
SGOT	70 U/l	6–18 U/l
SGPT	72 U/l	7–56 U/l
Total protein	5.7 mg/dl	6.0–9.0 mg/dl
Albumin	3.5 mg/dl	2.9–5.5 mg/dl
Electrolytes		
Na	137 mEq/l	135–147 mEq/l
Ca	10.7 mg/dl	8.5–10.5 mg/dl

CRP, C-reactive protein; GGT, gamma-glutamyltransferase; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.

diagnose these disorders. Eager to understand the cause, the patient's parents opted for genetic testing. This identified a homozygous variant of uncertain significance in the MOCS1 gene, known to impair molybdenum formation and lead to molybdenum cofactor deficiency. In MoCD, malfunctions in specific enzymes involved in purine metabolism lead to impaired breakdown and, consequently, reduced uric acid production. Therefore, low uric acid levels can be a valuable clue suggesting further investigation for MoCD[1]. However, in our case, the uric acid test result was only slightly low, providing limited diagnostic value. Ultimately, it was the genetic analysis that delivered the definitive diagnosis of molybdenum cofactor deficiency.

Management and follow-up

The patient was treated with levetiracetam (75 mg/kg/day), clonazepam (0.05 mg/kg/day), and a vitamin cocktail [vitamin B1 (300 mg/day), vitamin B2 (30 mg/day), pyridoxine (50 mg/day), coenzyme Q10 (10 mg/kg), biotin (5000 mcg/day), and carnitine (50 mg/kg)] to control seizures. Following initiation of this therapy, a significant reduction in seizure frequency was observed. This clinical improvement allowed for the patient's safe discharge from the hospital after 10 days, continuing the same therapy regimen outside the hospital.

During the 6-month post-discharge follow-up, the patient's symptoms demonstrated partial improvement, although psychomotor delay remained evident. At 5 years old, the characteristic doll-like face and limb spasticity were still present (Fig. 2).

Table 3

Different metabolic diagnoses for early refractory seizures

Malignant PhynelKetonUria (PKU)
Pyridoxine deficiency
Non-ketonic hyperglycaemia (NKHG)
Folinic acid responsive seizures
Isolated sulfite oxidase deficiency (ISOD)

Figure 2. At the age of 5, the patient exhibited a characteristic doll-like facial expression and marked spasticity in the extremities.

Discussion

This is the first case of MoCD type A reported in Syria caused by a mutation in MOCS1 gene. MoCD is an uncommon disease first described in 1978[10]. Molybdenum biosynthesis involves three phases: (1) MOCS1-mediated production of cyclic pyranopterin monophosphate (cPMP) from guanosine triphosphate, (2) MOCS2 and MOCS3-facilitated conversion of cPMP to molybdopterin, and (3) GEPH-driven incorporation of molybdenum to form the cofactor[11]. Lack of this cofactor triggers rapid and severe neuronal damage in the brain due to toxic sulfite accumulation. The most common symptoms of molybdenum cofactor deficiency type A can vary widely and occur shortly after birth or in early infancy. The mean age at diagnosis is 12.5 months. The median survival time was 36 months[12]. The patients with MoCD type A had MRI results, which included abnormal white matter, cortical atrophy, abnormal corpus callosum, cyst formation, abnormal basal ganglia, and hydrocephalus[6,13].

In this case, a child suffered from molybdenum cofactor deficiency and was diagnosed based on the child's symptoms, which included generalized seizures, psychomotor delay, muscle weakness, microcephaly and difficulty breastfeeding. The diagnosis was confirmed by a genetic test that showed a mutation in the MOCS1 gene. This mutation in MOCS1 lead to MoCD type A, the most common form of MoCD, affecting ~50–60% of all known patients to date. The latest and comprehensive review of all reported MOCS1 variants lists a total of 32 disease-causing variants, of which 20 mutations represent loss-of-function variants that result in a complete absence of MoCD and thus

complete penetrance of the disease[14]. There is currently no effective treatment for the disease. In cases where the MOCS1 gene is altered, there is a deficiency of cPMP, the more stable precursor to the molybdenum cofactor, which has shown promising results in treating the disease. Other subtypes can be treated with a cysteine-restricted diet. Usual treatment for people with this disorder may include medication to relieve symptoms; In the case of seizures, antispasmodic medications are primarily used[6,11,12]. In our case, the patient received a high-dose regimen of vitamins and anticonvulsant therapy.

Finally, we emphasize the importance of Genetic testing when suspecting metabolic disorders, as it facilitates accurate identification of genetic defects and development of appropriate treatment plans.

Conclusion

The rarity of MoCD necessitates diagnosis based on a detailed medical history and MRI findings after excluding other possible conditions. While definitive diagnosis relies on genetic testing, identifying the specific type of MoCD mutation informs both appropriate treatment choices and the disease's progression. Early diagnosis and intervention remain critical for managing MoCD.

Ethical approval

Ethical approval was also taken from the Faculty of Medicine at Damascus University. Written informed consent was obtained from the patient's parents for publication of this case report and any accompanying images.

Consent

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal on request.

Sources of funding

No funding resources.

Author contribution

All the authors participated in writing and reviewing the manuscript. Diana Alasmar supervised the conduction of this paper.

Conflicts of interest disclosure

Authors declare no conflicts of interest.

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Research Registration Unique Identifying Number (UIN)

No registration was needed, because it's a case report not clinical trial.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

All data are available.

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