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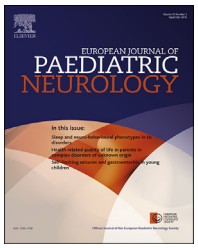

Original Article

Molybdenum cofactor and isolated sulphite oxidase deficiencies: Clinical and molecular spectrum among Egyptian patients

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ABSTRACT

Aim: Molybdenum cofactor deficiency (MoCD) and Sulfite oxidase deficiency (SOD) are rare autosomal recessive conditions of sulfur-containing amino acid metabolism with overlapping clinical features and emerging therapies. The clinical phenotype is indistinguishable and they can only be differentiated biochemically. *MOCS1*, *MOCS2*, *MOCS3*, and *GPRN* genes contribute to the synthesis of molybdenum cofactor, and *SUOX* gene encodes sulfite oxidase. The aim of this study was to elucidate the clinical, radiological, biochemical and molecular findings in patients with SOD and MoCD.

Methods: Detailed clinical and radiological assessment of 9 cases referred for neonatal encephalopathy with hypotonia, microcephaly, and epilepsy led to a consideration of disorders of sulfur-containing amino acid metabolism. The diagnosis of six with MoCD and three with SOD was confirmed by biochemical tests, targeted sequencing, and whole exome sequencing where suspicion of disease was lower.

Results: Novel *SUOX* mutations were detected in 3 SOD cases and a novel *MOCS2* mutation in 1 MoCD case. Most patients presented in the first 3 months of life with intractable tonic–clonic seizures, axial hypotonia, limb hypertonia, exaggerated startle response, feeding difficulties, and progressive cystic encephalomalacia on brain imaging. A single patient with MoCD had hypertrophic cardiomyopathy, hitherto unreported with these diseases.

Interpretation: Our results emphasize that intractable neonatal seizures, spasticity, and feeding difficulties can be important early signs for these disorders. Progressive

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microcephaly, intellectual disability and specific brain imaging findings in the first year were additional diagnostic aids. These clinical cues can be used to minimize delays in diagnosis, especially since promising treatments are emerging for MoCD type A.

1. Introduction

Molybdenum cofactor deficiency (MoCD, OMIM 252150) and isolated Sulphite oxidase deficiency (SOD, OMIM 272300) are rare recessive disorders of sulfur-containing amino acid metabolism with an overlapping clinical phenotype and severe neurodegeneration in newborns.[1] Due to the large clinical overlap between MoCD and SOD, they can only be differentiated biochemically. Both disorders show elevated urinary sulfite levels and lead to an accumulation of S-sulphocysteine, as well as elevated levels of thiosulfate and taurine. MoCD differs from SOD in that elevations of urinary xanthine and hypoxanthine concentrations, and low serum uric acid concentrations are observed due to loss of function of xanthine dehydrogenase. So far, about 100 MoCD and 30 SOD patients have been reported in the literature with different ethnic backgrounds, mostly from Europe and North America.[2] The prevalence of MoCD is not ascertained, but is considered to be in between one in 100,000–200,000 newborns worldwide.[3] The aim of this study is to showcase the clinical and molecular findings in our cohort in order to expand shared knowledge in these ultra-rare disorders.

MoCD patients have a wide spectrum of clinical findings including facial dysmorphism, early refractory seizures, severe psychomotor retardation, failure to thrive,

Table 1 – Clinical and radiological data of patients.

Disease	Patient 1 MoCD	Patient 2 MoCD	Patient 3 MoCD	Patient 4 MoCD	Patient 5 MoCD	Patient 6 MoCD	Patient 7 SOD	Patient 8 SOD	Patient 9 SOD
Age at diagnosis	8m	2m	2m	5m	7m	2y	10m	4m	2m
Sex	F	F	F	F	M	F	M	M	F
Consanguinity	+	+	+	+	+	+	+	+	+
Affected siblings	+	–	+	+	+	+	+	–	–
Severe developmental delay	+	+	+	+	+	+	+	+	+
Failure to thrive	+	+	–	–	+	+	+	+	+
Seizures	+	+	+	+	+	+	+	+	+
Onset age	D2	D5	D2	D12	D3	1 year	D50	D15	D40
Response to AED	No	Fairly	No	No	No	No	No	No	No
Hyperekplexia	+	–	+	+	–	–	+	+	–
EEG	Focal	Focal	Focal	Hypsarrhythmia	Focal	Focal	Focal	Hypsarrhythmia	Focal
Head circumference (SD)	−5	−6	−4	−3.5	−5	−4	−5.5	−3	−2.6
Facial dysmorphism	+	–	+	+	–	+	+	+	–
Axial hypotonia	+	+	+	+	+	+	+	+	+
Spastic quadriparesis	+	+	+	+	+	+	+	+	+
Extrapyramidal	+	+	+	+	+	+	+	+	+
Lens dislocation	–	–	–	–	–	–	–	–	–
Renal stones	+	–	+	+	–	–	–	–	–
Cardiomyopathy	–	–	–	+[a]	–	–	–	–	–
Neuroimaging									
Calcifications	Thalami/BG	–/–	–/–	–/–	Thalami	–/–	Thalami	Thalami	–
Subcortical cysts	+	+	+	+	+	–	+	+	+
Abnormal BG	+	+	+	+	–	+	+	Atrophy	–
Cerebral atrophy	+	+	+	+	+	+	+	+ (Severe)	+
Wide IHF	+	+	+	+	+	+	+	+	–
Thinned CC	+	+	+	+	+	+	+	+	+
WM volume loss	+	+	+	+	–	+	+	+	+
CB/BS atrophy	+/–	+/+	–/–	–/–	–/–	+/+	+/–	+/+	+/+

AED: antiepileptic drug, BG: basal ganglia, BS: brain stem, CB: cerebellar, CC: corpus callosum, CT: computerized tomography, D: day, EEG: electroencephalography, F: female, IHF: interhemispheric fissure, M: male, MoCD: molybdenum cofactor deficiency, MR: magnetic resonance imaging, SD: standard deviation, SOD: Sulphite oxidase deficiency, WM: white matter.

[a] Echocardiogram revealed hypertrophic cardiomyopathy with severe left ventricular outlet (LVOT) obstruction with a gradient of 122 mmHg. Following beta blocker treatment it was improved at 3 and 4 years old to 50 mmHg and 12 mmHg, respectively.