P0134

A Natural History Study of Molybdenum Cofactor and Isolated Sulfite Oxidase Deficiencies

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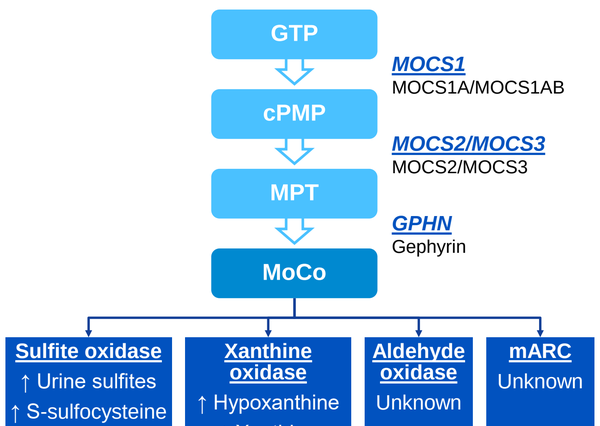
INTRODUCTION

- Molybdenum cofactor deficiency (MoCD) is a rare, autosomal, recessive, inborn error of metabolism caused by disruption in MoCo synthesis which is vital for sulfite oxidase (SOX) activity[1,2]
- In infants, both MoCD and isolated sulfite oxidase deficiency (ISOD) present with severe encephalopathy, intractable seizures, burst suppression or multifocal epileptic EEG, exaggerated startle reactions, axial and limb hypertonia, and feeding difficulties.[3-5]
  - Neuronal injury is severe and rapidly progressive as a result of accumulation of toxic concentrations of sulfite in the brain and subsequent formation of SSC leading to increased risk of mortality within the first year of life.[6]
- The objective of this study was to characterize the natural history of patients with MoCD and document its natural progression, develop a more complete understanding of the phenotype, and describe the clinical and biochemical variability of the condition



METHODS

Study Design

- Noninterventional, observational, natural history, multinational, multicenter study

Documented clinical and biochemical or genetic diagnosis of MoCD *or* ISOD

Retrospective data collection: Complete history including demographic data, genotype, disease onset, medical history, family information, biochemical markers, growth parameters through time of enrollment

Deceased cohort

Living cohort

12 month prospective data collection: Prospectively for 12 months, including survival data

End of the study: Last patient last visit (LPLV) for the last patient enrolled in the prospective arm of the study

Primary Objective

- To characterize the natural history of MoCD Type A, in pediatric patients, in terms of survival

Secondary Objectives

- Evaluate S-sulfocysteine (SSC), uric acid, and xanthine levels in blood and urine in patients with MoCD and ISOD
- Quantitate the natural history of MoCD and ISOD by changes in head circumference, seizure frequency, and neurocognitive outcomes
- Evaluate changes in CNS morphology by brain MRI in patients with MoCD and ISOD
- Correlate biochemical markers with changes in head circumference, seizure frequency, neurocognitive outcomes, and MRI findings
- Quantitate natural history of MoCD and ISOD in terms of survival

Primary Endpoint

- Survival at end of 1 year

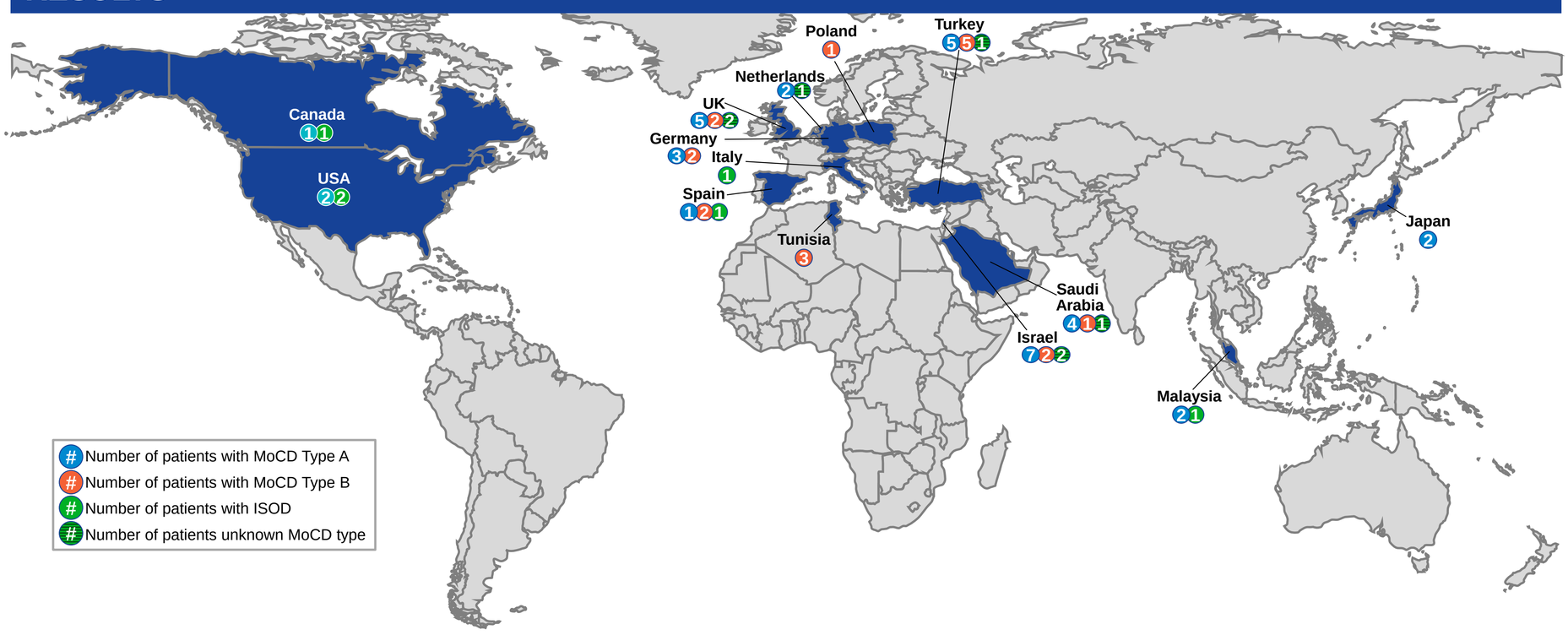
Populations Evaluated

- All Patient Set (APS) = 65 patients
- Prospective Set (PS; living prospective data) = 24 patients
- Full Analysis Set (FAS; Type A; symptom onset by Day 28) = 33 patients
- Data collected retrospectively for all patients and prospectively for patients in living cohort

Statistical Analysis

- Data were summarized for each disease subgroup (MoCD Type A, Type B, and "other" [Type C, ISOD, or unknown type were combined due to small sample sizes]) and the overall population
- All patients enrolled in either deceased or living cohorts were included in APS. All patients enrolled in the living cohort and providing any prospective data were included in the PS. All patients enrolled in either the deceased or living cohorts with a diagnosis of MoCD Type A and onset of symptoms by day 28 following delivery were included in the FAS
- Continuous data were described with descriptive statistics and categorical data were summarized using frequencies and percentages

RESULTS



Patient Demographics and Other Baseline Characteristics

		Type A N = 37	Type B N = 16	Other[a] N = 12
Patient Disposition, n [%]				
Enrolled		37 (100)	16 (100)	12 (100)
Deceased cohort		20 (54)	7 (44)	9 (75)
Living cohort		17 (46)	9 (56)	3 (25)
Not enrolled in prospective data collection		3 (8)	2 (13)	0 (0)s
Enrolled in prospective data collection		14 (38)	7 (44)	3 (25)
Completed prospective data collection		13 (35)	5 (31)	2 (17)
Discontinued prospective data collection		1 (3)	2 (13)	1 (8)
Reason for discontinuation:				
Death		1 (3)	2 (13)	0 (0)
Withdrawal by patient or patient's representative		0 (0)	0 (0)	1 (8)
Demographic and Other Baseline Characteristics, n [%]				
Gender [n (%)]	Male	28 (76)	10 (63)	9 (75)
	Female	9 (24)	6 (38)	3 (25)
Race [n (%)]	White	21 (57)	9 (56)	8 (67)
	Black or African-American	0 (0)	1 (6)	0 (0)
	Asian	10 (27)	4 (25)	2 (17)
	Other	6 (16)	2 (13)	2 (17)
Ethnicity [n (%)]	Hispanic	2 (5)	2 (13)	1 (8)
	Non-Hispanic	31 (84)	13 (81)	11 (92)
	Not reported	1 (3)	0 (0)	0 (0)
	Unknown	3 (8)	1 (6)	0 (0)
Gestational age at birth (weeks)	N	30	10	10
	Mean (SD)	39.0 (1.19)	38.2 (2.76)	38.3 (1.42)
Age at onset of first MoCD signs and symptoms (days)	N	36	15	12
	Mean (SD)	56.6 (195.21)	162.3 (507.05)	3.5 (6.39)
	Median	2.0	5.0	1.5
Presenting Signs and Symptoms				
MoCD presenting signs and symptoms [n (%)]	Seizures	34 (92)	15 (94)	12 (100)
	Feeding difficulties	31 (84)	12 (75)	12 (100)
	High pitched cry	16 (43)	6 (38)	3 (25)
	Exaggerated startle response	12 (32)	4 (25)	5 (42)
	Metabolic acidosis	7 (19)	3 (19)	2 (17)
	Intracranial hemorrhage	2 (5)	2 (13)	3 (25)
	Other	11 (30)	7 (44)	7 (58)

[a]The MoCD type "Other" consisted of 5 patients with ISOD, 4 patients with probable MoCD Type A, 1 patient with probable MoCD Type B, and 2 patients with unknown MoCD type.

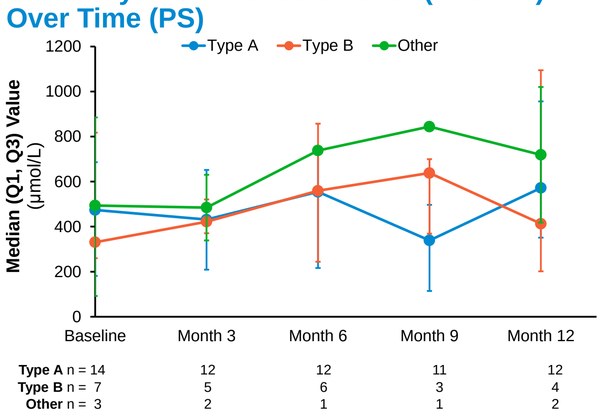
Note: Patient percentages are based on the total number of patients in each group.

Country of Origin and Alleles

Allele	Allele Count	Country
Type A		
c.99_100del2	2	UK
c.130C>T	2	Turkey
c.217C>T	8	Saudi Arabia, Turkey
c.251del169	2	Israel
c.256T>G	1	Germany
c.271C>T	2	USA
c.367C>T	2	Turkey
c.377G>A	1	USA
c.394C>T	2	Malaysia
c.418+1G>A	2	Netherlands
c.586A>G	2	Israel
c.589+1G>A	1	Canada
c.645+2T>G	4	Tunisia
c.757+1G>C	3	Saudi Arabia
c.949C>T	2	Netherlands
c.956G>A	2	UK
c.970G>A	1	Spain
c.971G>A	6	Israel
c.1000insT	2	Malaysia
c.1015del4	1	UK
c.1102+1G>A	3	Tunisia
c.1150G>T	3	Germany, Spain
c.1338del1	2	Germany
c.1508del2	2	Turkey
c.1523del2	2	Germany
c.1643C>A	4	Japan
c.1660C>T	4	Israel
c.1777G>A	2	UK
MCOS1 G.IVS9+6T>C	2	UK
WT/Unkown	2	Canada, Saudi Arabia

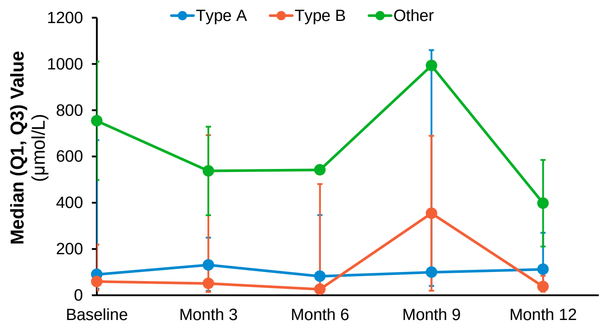
Allele	Allele Count	Country
Type B		
c.3G>A	5	Israel, Turkey
c.9del23	1	UK
c.57A>T	2	Spain
c.140+1G>A	2	Israel, Poland
c.226G>A	2	UK
c.252insC	2	Saudi Arabia, Turkey
c.314delA	2	Turkey
c.413G>A	6	Germany, Spain, UK
c.539del2	2	Poland, Saudi Arabia
c.564+1G>A	1	Canada
c.658del7insG	2	Turkey
c.726del2	1	Germany
c.1508del2	2	Turkey
c.1667G>A	1	Turkey
WT	1	Turkey
ISOD		
c.141insT	1	Italy
c.234del2	2	Spain
c.671del2	2	USA
c.805C>A	1	Italy
c.1029C>G	2	Malaysia
c.1142del4	2	USA

S-Sulfocysteine Measurements (in Urine) Over Time (PS)



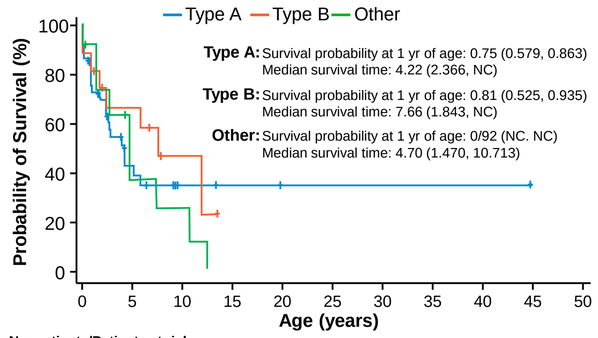
	Baseline	Month 3	Month 6	Month 9	Month 12
Type A n =	14	12	12	11	12
Type B n =	7	5	6	3	4
Other n =	3	2	1	1	2

Uric Acid (in Urine) Over Time (PS)



	Baseline	Month 3	Month 6	Month 9	Month 12
Type A n =	11	10	10	7	11
Type B n =	4	3	3	2	3
Other n =	2	2	1	1	2

Kaplan-Meier Estimates of Survival Probability (APS)

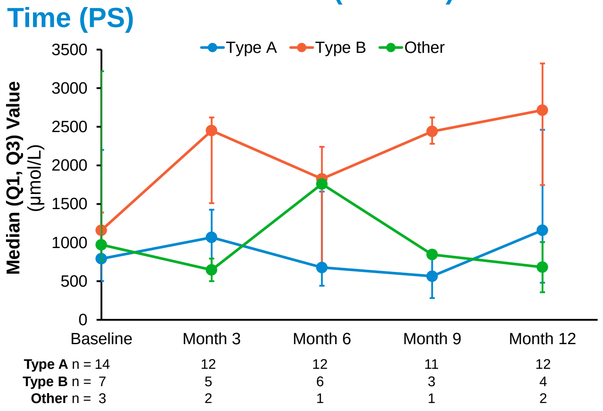


No. patients/Patients at risk

Type A: 0/37	19/11	21/3	21/2	21/1	21/1	21/1	21/1	21/1	21/0	21/0
Type B: 0/16	5/8	7/2	8/0	8/0	8/0	8/0	8/0	8/0	8/0	8/0
Other: 0/12	6/3	7/2	9/0	9/0	9/0	9/0	9/0	9/0	9/0	9/0

Note: Kaplan-Meier curves step down at time points at which a death has been observed; slashes represent patients whose observation time was censored as of the last contact date.

Xanthine Measurements (in Urine) Over Time (PS)



	Baseline	Month 3	Month 6	Month 9	Month 12
Type A n =	14	12	12	11	12
Type B n =	7	5	6	3	4
Other n =	3	2	1	1	2

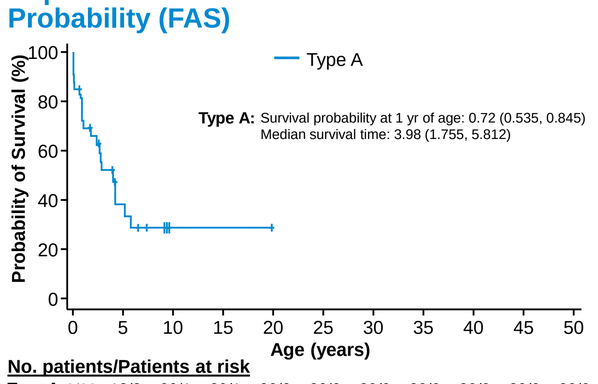
MoCD Sequelae (APS)

Characteristic, n (%)[a]	Type A N = 37	Type B N = 16	Other[b] N = 12
Patients with any MoCD sequelae	34 (92)	14 (88)	10 (83)
Hypertonicity	32 (86)	12 (75)	9 (75)
Developmental delay	31 (84)	11 (69)	9 (75)
Hypotonia	26 (70)	14 (88)	5 (42)
Microcephaly	23 (62)	10 (63)	8 (67)
Dysmorphic features	22 (59)	12 (75)	7 (58)
Myoclonus	20 (54)	3 (19)	6 (50)
Spastic tetraplegia	19 (51)	9 (56)	8 (67)
Opisthotonos	15 (41)	7 (44)	4 (33)
Cortical blindness	13 (35)	3 (19)	8 (67)
Spastic diplegia	11 (30)	3 (19)	3 (25)
Nystagmus	10 (27)	2 (13)	4 (33)
Enophthalmos	9 (24)	2 (13)	0 (0)
Ectopic lenses	8 (22)	3 (19)	3 (25)
Stroke-like episodes	3 (8)	0 (0)	1 (8)

[a]One patient reported to have MoCD sequelae but not included in this summary table because they were incorrectly reported in the database.

[b]5 patients with ISOD, 4 patients with probable MoCD Type A, 1 patient with probable MoCD Type B, and 2 patients with unknown MoCD type.

Kaplan-Meier Estimates of Survival Probability (FAS)



No. patients/Patients at risk

Type A: 0/33	18/8	20/1	20/1	20/0	20/0	20/0	20/0	20/0	20/0	20/0

Note: Kaplan-Meier curves step down at time points at which a death has been observed; slashes represent patients whose observation time was censored as of the last contact date.

Gross Motor Function (APS)

	Type A N = 37					Type B N = 16					Other N = 12				
Level:	I	II	III	IV	V	I	II	III	IV	V	I	II	III	IV	V
Prospective Baseline	1 (11)	0 (0)	1 (11)	0 (0)	7 (78)	0 (0)	0 (0)	0 (0)	1 (20)	4 (80)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Month 6	0 (0)	0 (0)	0 (0)	0 (0)	7 (100)	0 (0)	0 (0)	0 (0)	0(0)	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Month 12	1 (13)	0 (0)	0 (0)	1 (13)	6 (75)	0 (0)	0 (0)	0 (0)	1 (25)	3 (75)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)

Grade I indicates mild disability and Grade V indicates the highest level of disability

Neuroimaging Findings

- A total of 31/33 patients in the FAS had abnormal findings on neuroimaging with 29/29 having abnormal findings on MRI
- Abnormal white matter and cortical atrophy were the most frequently reported abnormalities for all modalities

CONCLUSIONS

- Biochemistry in patients with MoCD Type A showed persistently elevated concentrations of urinary SSC and xanthine, and low concentrations of uric acid
  - Patients with ISOD also had raised concentrations of SSC; however, they did not have low concentrations of uric acid or elevated concentrations of xanthine, which are differentiating features between MoCD and ISOD
- Sequelae were also reported in most patients, with hypertonicity and developmental delay the most frequent
- All the patients with MoCD type A who had MRI scans had abnormal findings with abnormal white matter changes, progressive cortical atrophy and thinning of the corpus callosum being the most common
- Our results confirm that with no disease-modifying treatment the vast majority of cases of MoCD and ISOD are severe, rapidly progressive, neurodegenerative disorders which cause severe disability in almost all cases from the neonatal age. Survival probability is reduced to 75-81% at age 1 year and 40-60% at age 5 years

SCAN ME

References

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