Clinical, Radiological and Genetic Characteristics of Molybdenum Cofactor Deficiency (MoCD) Type A Patients in Israel

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Y Zehavi[1], H Mandel[2], N Confer[3], R Spiegel[1]

[1]Emek Medical Center, Afula, Israel; [2]Galilee Medical Center, Nahariya, Israel; [3]Origin Biosciences, San Francisco, United States

BACKGROUND

- MoCD Type A is a severe autosomal recessive inborn error of metabolism caused by mutations in *MOCS1* gene resulting in a deficiency of molybdenum cofactor dependent enzymes activity.
- The resultant accumulation of toxic metabolites in the brain leads to severe neonatal neurological impairment characterized by intractable seizures, feeding difficulties, no achievement of developmental milestones and regression. Accumulation of urinary xanthine results in urolithiasis.

METHODS

- Clinical, biochemical, radiological and genetic data of 9 patients from Northern Israel were retrospectively collected.

RESULTS

- The cohort included 6 males and 3 females.
- All patients presented in the first week of life.
- The main presenting manifestations: seizures (9/9), feeding difficulties (6/9), exaggerated startle response (6/9) high pitched cry (4/9).
- The main types of seizures were myoclonic and generalized tonic-clonic (8/9).
- All patients featured severe global developmental delay and truncal hypotonia.
- Other neurological features included: spasticity (7/9), myoclonus (5/9), microcephaly (5/9) and cortical blindness (3/9).
- Brain MRI, performed in 6 patients, typically revealed abnormal white matter and cerebellar hypoplasia. Other radiological findings included: enlarged ventricles (5/6), abnormal corpus collosum (4/6), cortical atrophy (4/6) and cyst formation (3/6).
- Urinary sulfite stick was positive in the 1st-2nd days of life; Serum uric acid levels were practically undetectable since age 3-7 days.
- 8/9 died: 4 during the first year of life; 4 within their first decade of life.
- 4 different MOCS1 homozygous mutations were identified in the studied cohort.

Table 1: Genetic characteristics and presenting symptoms:

Pt.	MOCS1 Mutation	Gender	Age of onset (days)	Age of death (days)	Presenting Symptoms			
					seizures	Feeding difficulties	exaggerated startle response	High pitch cry
1	c.251_418del	M	2	369	+	-	+	+
2	c.971G>A	F	1	31	+	+	+	-
3	c.971G>A	M	4	1549	+	+	+	+
4	c.971G>A	F	1	325	+	+	+	+
5	c.1660C>T	M	1	1022	+	+	+	-
6	c.1660C>T	M	1	864	+	+	-	+
7	c.586A>G	M	2	11	+	-	+	-
8	c.586A>G	M	1	2963	+	-	-	-
9	c.586A>G	F	1	Alive at 8 y.o	+	+	-	-

Table 2: Neurologic features and sequalae:

Pt.	Developmental Delay	Dysmorphic facies	Hypertonicity	Hypotonia	Microcephaly	Myoclonus	Type of Seizures	Others
1	+	+	+	+	+	+	generalized tonic clonic	
2	+	+	+	+	-	+	generalized tonic clonic	
3	+	+	+	+	+	+	generalized myoclonic	cortical blindness + opisthotonus
4	+	+	+	+	+	+	generalized myoclonic	nystagmus
5	+	+	+	+	-	+	generalized	
6	+	+	+	+	-	-	generalized tonic clonic	
7	+	+	+	+	-	+	generalized myoclonic	
8	+	+	+	-	+	-	generalized tonic clonic	cortical blindness
9	+	+	+	+	+	-	generalized tonic	cortical blindness+ ectopic lenses

Table 3: MRI findings:

Pt.	Age at MRI Examination (months)	Abnormal White Matter	Cerebellar Hypoplasia	Hydro-cephalus	Cortical Atrophy	Abnormal Corpus Callosum	Mega Cisterna Magna	Cyst Formation	Abnormal Basal Ganglia
1	4	+	+	+	-	+	+	-	-
3	9	+	+	+	+	+	-	+	-
4	5	+	+	+	+	-	-	-	-
6	2	+	+	+	-	+	+	-	-
8	2	+	+	-	+	+	+	+	+
9	68	+	+	+	+	-	-	+	-

CONCLUSIONS

- The present Israeli MoCD Type A cohort highlights the typical disease features with neonatal presentation including intractable seizures, feeding difficulties and hypotonia with rapidly evolving limb spasticity, microcephaly and no achievement of developmental milestones.
- No genotype-phenotype correlation was observed. All the mutations identified should be considered severe.
- High index of suspicion among neonatologists and pediatricians is crucial for early diagnosis since a promising disease modifying treatment is already in clinical trials.

SCAN ME