Newborn with neonatal form of molybdenum cofactor deficiency – the first patient in the Slovak Republic

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Abstract

OBJECTIVE: To present the case of a term newborn with rapid progression of signs of neurodegenerative disease.
RESULTS: In a case of a term newborn with numerous dysmorphic features, with seizure activity from the 3rd day of life, hypertonia and serious changes on brain parenchyma were presented. Diagnosis of molybdenum cofactor deficiency was confirmed by the decreased level of uric acid, 31 μmol/l, in serum, increased excretion of thiosulfate and S-sulfocysteine in urine, taurine (1729.3 μmol/mmol crea; normal range 30–300 μmol/mmol crea) and xanthine (276.9 μmol/mmol crea; normal range < 25 μmol/mmol crea) in urine. Sulfite oxidase activity on skin fibroblasts in culture was not detectable. The patient died at the age of 28 days of life.
CONCLUSION: Deficiency of molybdenum cofactor leads to accumulation of toxic metabolites (levels of sulfite), which causes disturbances of neurotransmitters even before delivery. Therapy is symptomatic, no effective therapy is available. Seizures are difficult to suppress. This case report is about the first patient in Slovakia.

Abbreviations:

SO	- Sulfite oxidase
XD	- Xanthine dehydrogenase
AO	- Aldehyde oxidase
MoCoD	- Molybdenum cofactor deficiency

CASE REPORT

INTRODUCTION

Molybdenum is an essential element. The liver and kidney retain the highest amount of molybdenum. It is required to form molybdopterin, a cofactor essential to the human enzymes sulfite oxidase (SO), xanthine dehydrogenase (XD) and aldehyde oxidase (AO) that are involved in catabolism, including the catabolism of purine and sulfur amino acids.

XD is a soluble enzyme, which is important for the hydroxylation of hypoxanthine and xanthine to produce uric acid. It is located mainly in the liver and intestine; lower levels are detected in the kidney, spleen, skeletal and heart muscle. The deficiency of this enzyme is benign. XD is not expressed in cultured human cell lines.

AO is a part of the body´s general detoxification system. The main function of AO concerns hydroxylation of hypoxanthine to yield xanthine, but it cannot convert the latter to uric acid. It is found mostly in the liver and spleen, less in the kidney, skeletal and heart muscle. Due to its instability, the activity is difficult to assay directly in human tissues.

SO is the terminal enzyme in the pathways of degradation of sulfur amino acids, it is thus needed for elimination of endogenously produced sulfite by conversion to sulfate. SO is located in the intermembrane space of mitochondria. In comparison with XD and AO, is located mostly in the heart, lung, kidney and liver, with no detectable activity in blood and skeletal muscle. SO is expressed in fibroblasts, cultured amniotic fluid cells and lymphoblasts (Tan *et al.* 2005).

Molybdenum cofactor deficiency (MoCoD) in humans results in loss of the activity of molybdenoenzymes SO, XD and AO (Schwarz & Mendel 2005). All forms of MoCoD are inherited as autosomal recessive traits (Reiss & Johnson 2003). Over 100 cases of MoCoD have been diagnosed, many cases remain unrecognized. Patients belong to a variety of ethnic groups. Most mutations have significant geographical concentrations in Europe, North America, Northern Africa, Turkey and Asia. No de-novo mutation leading to MoCoD has been described (Duran *et al.* 1978).

The main reason for severe neurological abnormalities is the absence of sulfite oxidase activity. The consequence of this absence is the accumulation of toxic metabolites (sulfite) or the deficit in the reaction product (sulfate). The CNS is especially sensitive to sulfite, which is toxic to the nervous system. The most dangerous condition is the accumulation of sulfite before birth. Certain parts of the brain are affected more than others because of local differences in sulfite production or supply of the precursor cysteine.

Two forms of presentations are described: early and late onset. The early onset form of MoCoD is presented in more than 90%. The early onset of signs (during the first days of life), is one of the characteristics. Delivery is with adequate value of Apgar score. The newborns are mostly born after an uneventful pregnancy with dysmorphic facial features. The main problems concern neurological manifestations such as tonic/clonic seizures, axial hypotonicity, peripheral hypertonicity. The patients die at an early age. The late onset form of MoCoD involves about 10%. This form presents with ophthalmologic abnormalities, lens dislocation, spherophakia, nystagmus, cortical blindness, enophthalmus or iris coloboma.

CASE REPORT

The patient was the first child of unrelated parents of Caucasian origin. It was a term newborn with birth weight 4650 grams, birth length 55 cm, value of Apgar score 7/8. He was delivered spontaneously. The patient had facial dysmorphic features: a long face with puffy cheeks, thick lips, a long philtrum, a small nose, widely spaced eyes, elongated palpebral fissures with normal value of head circumference.

Laboratory findings confirmed decreased values of uric acid (31 μmol/mmol creatinine), increased excretion of thiosulfate in urine, S-sulfocysteine, taurine (1729.3 μmol/mmol creatinine; normal value: 30–300 μmol/mmol creatinine) and xanthine (276.9 μmol/mmol creatinine; normal value: <25 μmol/mmol creatinine). We found also elevated levels of lactate in blood (4.97; 2.82; 2.79 mmol/l) and in cerebrospinal fluid (2.93; 5.11; 7.45 mmol/l). The test for sulfite determination in urine was not available at the time of investigation. Activity of SO was not detected in cultured fibroblasts.

Neurologic investigation confirmed axial hypotonia, peripheral hypertonia, later serious hypotonia, and the presence of tonic/clonic convulsions. Ultrasonic investigation of the CNS confirmed a diffuse hyperechogenic structure without differentiation of white and gray matter, multiple subcortical and juxtacortical focal lesions in the white matter, cerebral atrophy, extreme microgyria and enlargement of the lateral ventricles.

Cardiac symptoms were associated with attacks of paroxysmal supraventricular tachycardia (Brucknerová *et al.* 2009). The patient died at the age of 28 days.

DISCUSSION

Molybdenum is an essential component of SO, XD and AO. The authors described the first patient in the Slovak Republic with MoCoD. The diagnosis was confirmed by physical and laboratory findings (increased excretion of S-sulfocysteine and thiosulfate in urine; decreased value of uric acid in plasma) and by investigation of skin fibroblasts (not detectable value of SO). In the case of our patient with typical dysmorphic features, the increased intensity of convulsions could not be suppressed. We confirmed characteristic rapid changes of CNS parenchyma as a consequence of massive destruction of the white matter along with enlargement of the

ventricles and cerebrospinal fluid spaces. Neurological signs are the result of accumulation of toxic levels of sulfite in the brain before birth, as reported by Ngu *et al.* (2009).

In the treatment of our patient we tried to diminish sulfite production by restriction of intake of precursors of sulfur-containing amino acids. The convulsion activity failed to be suppressed by antiepileptic drugs. In general, seizures are considered to be refractive to therapy because they are a consequence of accumulation of toxic levels of sulfite in the brain, which causes massive destruction of the white matter, along with enlargement of the ventricles and cerebrospinal fluid spaces. No effective therapy is available. Purified cyclic pyranopterin monophosphate appears to be the drug of choice, as described by Veldman *et al.* (2010), with a positive effect on the activity of molybdenum cofactor-dependent enzymes. MoCoD is a serious and fatal disease. MoCoD can also imitate primary mitochondrial disorder. The lactate accumulation might result from failure of energy metabolism caused by severe encephalopathy (Behúlová *et al.* 2005).

This case report is about the first patient with MoCoD in the Slovak Republic. In a case of seizures, activity of unknown etiology with rapid changes of brain parenchyma or attacks of supraventricular tachycardia, investigation of thiosulfate in urine is recommended. The authors point out that clinical manifestations of neurodegenerative disease are variable.

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REFERENCES

1 Behúlová D, Brucknerová I, Škodová J, Ponec J, Bzdúch V, Šebesta I, Dorche C (2005). Molybdenum cofactor deficiency mimicking mitochondrial disorder. Journal of Inherited Metabolic Disease. **28**, Suppl. 1: 56.
2 Brucknerová I (2009). Intrauterine and neonatal period asphyxia; what can be hidden behind heart rhythm disturbances in asphyxiated newborns? Archives. The International Journal of Medicine. **Vol II**(2): 250–253.
3 Duran M, Beemer FA, van der Heiden *et al.* (1978). Combined deficiency of xanthine oxidase and sulphite oxidase: a defect of molybdenum metabolism or transport? J Inher Metab Dis. **1**: 175–178.
4 Ngu LH, Afroze B, Chen BC, Affandi O, Zabedah MY (2009). Molybdenum cofactor deficiency in a Malaysian child. Singapore Med J. **50**(10): 365–367.
5 Reiss J, Johnson JL (2003). Mutations in the molybdenum cofactor biosynthetic genes MOCS1, MOCS2, and GEPH. Human Mutation. **21**: 569–576.
6 Schwarz G, Mendel RR (2006). Molybdenum cofactor biosynthesis and molybdenum enzymes. Annu Rev Plant Biol. **57**: 623–647.
7 Tan WH, Eichler FS, Hoda S, Lee MS, Baris H, Hanley CA, Grant PE, Krishnamoorthy KS, Shih VE (2005). Isolated sulfite oxidase deficiency: a case report with a novel mutation and review of the literature. Pediatrics. **116**(6): 1616.
8 Veldman A, Santamaria-Araujo JA, Sollazzo S, Gianello R, Yaplito-Lee J, Wong F, Ramsden CA, Reiss J, Cook I, Fainwether J, Schwarz G (2010). Successful treatment of molybdenum cofactor deficiency type A with cPMP. Pediatrics. **May**: 125.