ORIGINAL ARTICLE

Conjugated hyperbilirubinaemia as the first manifestation of mevalonic aciduria in a term newborn

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Abstract

OBJECTIVES: To present clinical and laboratory findings in the case of a term newborn with conjugated hyperbilirubinaemia and to stress the importance of differential diagnosis.

RESULTS: A term newborn delivered by caesarean section (birth weight 2550 g, birth length 47 cm, value of Apgar score 9/10) with good direct adaptation had on the first day of life increased levels of conjugated bilirubin (23 μmol/l), unconjugated bilirubin (55 μmol/l) and C-reactive protein 39.4 g/l. The diagnosis of mevalonic aciduria was confirmed by urine analysis (mevalonolactone 393 μmol/mmol crea, normal range <2.0 μmol/mmol crea; mevalonic acid 40.5 μmol/mmol crea, normal range <0.04 μmol/mmol crea).

CONCLUSION: Mevalonic aciduria can be clinically distinguished based on symptoms of neurological involvement. It can also present itself with hepatosplenomegaly, lymphadenopathy, anaemia, leukocytosis, increased sedimentation rates and levels of C-reactive protein. In cases of conjugated hyperbilirubinaemia of unknown aetiology it is important to exclude mevalonic aciduria by urine investigation for organic acids.

Abbreviations & units
MVA – mevalonic aciduria
MKD – mevalonate kinase deficiency

INTRODUCTION

Disorders of cholesterol biosynthesis form a wide group of diseases. These can be classified as "pre-squalene" and "post-squalene" disturbances. Squalene is an important intermediate in the biosynthesis of cholesterol. The only pre-squalene disorder known is mevalonate kinase deficiency (MKD). MKD is manifested as severe mevalonic aciduria (MVA), and at the milder end of the phenotypic spectrum as hyper-IgD syndrome with periodic fever (Hoffmann *et al.* 1986; Waterham, 2006; Waterham & Gibson, 2008).

MVA is an autosomal recessive inherited disorder. To date only 30 patients have been identified worldwide. Typical features of MVA include significant neurological involvement, with psychomotor retardation, hypotonia, myopathy, cerebellar atrophy, dysmorphic features (low set and

posteriorly rotated ears, downslanted palpebral fissures, blue sclerae, microcephaly, dolichocephaly and wide irregular fontanels), recurrent crises (fever, diarrhoea, vomiting) (Prietsch *et al.* 2003). Clinical signs include hepatosplenomegaly, lymphadenopathy, anaemia, increased erythrocyte sedimentation rate, leukocytes and level of C-reactive protein. Characteristic result can be obtained from urine analysis for organic acids, which confirms mevalonate excretion in urine (Hoffmann *et al.* 1993). The diagnosis is confirmed by pathologically low activity of mevalonate kinase in blood.

CASE REPORT

Our patient was a term male newborn of unrelated parents of Caucasian origin, delivered by caesarean section with birth weight 2550 g, birth length 47 cm, value of Apgar score 9/10, with good direct postnatal adaptation. On the first day of life, increased levels of conjugated bilirubin 23 μmol/l (normal range <5 μmol/l), unconjugated bilirubin 55 μmol/l (normal range <20 μmol/l), C-reactive protein 39.4 g/l (normal range <10 g/l) were detected. After 19 days of prolonged conjugated hyperbilirubinaemia the child was admitted to our department.

The results of the laboratory findings at the time of admission to our department confirmed increased levels of conjugated bilirubin 41.5 μmol/l, unconjugated bilirubin 71.9 μmol/l, alanine aminotransferase 1.5 μkat/l (normal value 0.29±0.04 μkat/l), aspartate aminotransferase 4.3 μkat/l (normal value 0.8±0.12 μkat/l), C-reactive protein 43.1 g/l, leukocytosis 19.5×10^9/l, erythrocyte sedimentation rate (80/94). The child was normoglycaemic, without finding of metabolic acidosis, with negative results for hepatitis A, B, C, HIV-1 or 2, syphilis, viral infection (cytomegalovirus, varicella-zoster, herpes simplex), deficiency of alpha-1-antitrypsin, haemochromatosis, cystic fibrosis, galactosaemia and tyrosinaemia. Routine newborn screening tests for metabolic disorders as phenylketonuria, hypothyroidism and cystic fibrosis, were negative. There were no cultivation signs of inflammation. Levels of plasma and urine amino acids were negative.

Ultrasonic investigation of the liver confirmed increased echogenicity of the parenchyma, enlargement of the spleen, without focal changes, and the cholecysta with thickened wall and without pathological contents. Ultrasonic investigation of the brain parenchyma confirmed hyperechogenic areas in the cortex, basal ganglia and capsule. The diagnosis of metabolic disease was confirmed by investigation of urine using gas chromatography – mass spectroscopy, increased level of mevalonolactone (393 μmol/mmol crea; normal value <2.0) and mevalonic acid (40.5 μmol/mmol crea; normal value <0.04). Ultrasonic investigation of the heart confirmed open ductus arteriosus (1.7 mm) and foramen ovale (4 mm). Investigation of the eyes revealed presence of embryotoxon posterior on the left eye and coloboma maculae on the right eye. The child had skin exanthema. All the time the lymph nodes were enlarged and the child had typical peaks of temperature (38.3 °C). We did not confirm the presence of hyper-IgD syndrome. The diagnosis was confirmed by genetic investigation, which showed the presence of mutation 1006 G>A in heterozygous status.

DISCUSSION

Mevalonic aciduria has a clinical heterogeneity. Predominant are neurological symptoms and frequent crises with fever, vomiting and diarrhoea, which are frequently accompanied by subcutaneous oedema and morbilliform rash. These are the most frequently described features in case reports in the literature (Neven *et al.* 2007). In our patient the dominant feature was the finding of conjugated hyperbilirubinaemia, leukocytosis, recurrent fever, increased sedimentation rates and elevated C-reactive protein immediately after the birth.

Cholestatic liver disease as the main feature was described in two patients by Hinson *et al.* (1998). In mildly affected patients who survive infancy, ataxia due to cerebellar atrophy and mental retardation are seen to be the predominant findings in comparison with something that is present in cases of the severe form of the disease (Martinez *et al.* 2007; Prietsch *et al.* 2003; Hoffman *et al.* 1993). Recurrent febrile crises during childhood have to be distinguished from hyper-IgD syndrome, which is defined by elevated serum IgD and IgA levels (Kovacs *et al.* 2003; Waterham, 2006; Waterham & Gibson, 2008). In the case of our patient, we did not find elevated levels of IgD and IgA. In contrast to other severe metabolic diseases, such as the neonatal form of deficiency of carnitine palmitoyltransferase II which is invariably fatal immediately after delivery of the newborn, our patient did not show signs of severe asphyxia (Brucknerová *et al.* 2008).

CONCLUSION

Mevalonic aciduria can be clinically distinguished by features of neurological involvement. This disease can also manifest with hepatosplenomegaly, lymphadenopathy, anaemia, increased sedimentation rates and levels of C-reactive protein, and leukocytosis. In cases of conjugated hyperbilirubinaemia of unknown aetiology, all infectious, congenital or autoimmune diseases, chromosomal aberrations, congenital infections, myelodysplastic syndromes (also of metabolic origin) and especially mevalonic aciduria must be excluded. Investigation of urine sample for organic acids is crucial for establishing the diagnosis. Mevalonate kinase deficiency represents a single-gene abnormality, which is confirmed by genetic analysis. MVA presents a severe metabolic disease with poor prognosis. Causal therapeutic possibilities do not exist. Intervention with corticosteroids

(2mg/kg/per day) during clinical crises, administration of ubiquinone-50 together with vitamin C is only supportive. Life expectancy is reduced by infections or the development of renal amyloidosis (Haas & Hoffmann, 2006).

Prenatal diagnosis is possible by isotope-dilution gas chromatography/mass spectrometry by determination of mevalonate kinase activity in cultured amniocytes and biopsied chorionic villus and by mutational analysis in families (Hofffmann *et al.* 1992; Mancini *et al.* 1993).

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