

CASE REPORT

Novel genotype of mevalonic aciduria with fatalities in premature siblings

P Raupp, E Varady, M Duran, R J A Wanders, H R Waterham, S M Houten

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Mevalonic aciduria is described in two very low birthweight siblings with unspecific clinical signs and recurrent septicaemia. Both died within the first 2 months of life. DNA analysis showed a novel mutation in the gene encoding mevalonate kinase.

Mevalonic aciduria (MA; McKusick 251170) is a very rare inborn error of isoprene biosynthesis; so far only 20 cases have been reported, and six different disease-causing mutations identified.¹ The earliest age at death of published cases of liveborn infants is 4.5 months.²

CASE 1

A female infant (28 weeks gestation, 1100 g birth weight) was born to a consanguineous Arab couple who had a healthy son. Hepatosplenomegaly, raised levels of C reactive protein (53 mg/l), and thrombocytopenia (47 000/μl) were noted, but the initial blood and surface cultures and the differential white cell count did not suggest infection. Cytomegalovirus and *Toxoplasma gondii* IgM was negative. A blood culture taken on day 7 grew coagulase negative staphylococci. From day 12, while being treated with teicoplanin and amikacin, the patient deteriorated, with increasing abdominal distension, rising C reactive protein concentration, and radiological evidence of a low ileal obstruction. She was considered unfit for operation. She died on day 15 from multiorgan failure. Blood cultures taken on day 11 and 12 grew *Candida parapsilosis*. Throughout her life, she showed thrombocytopenia (10 000–64 000/μl) and hyperbilirubinaemia (conjugated bilirubin 46 μmol/l on day 1, maximum 151 μmol/l on day 12) with normal liver enzymes and plasma coagulation. Gas chromatography and mass spectrometry showed urinary excretion of mevalonic acid and mevalonolactone consistent with MA (courtesy of J. Calvin, Biochemical and Genetics Unit, Peterborough Hospital, Peterborough, UK).

CASE 2

A male infant (26 weeks gestation, birth weight 660 g) was born to the same parents. There was no evidence of infection initially, and the platelet count remained normal during the first two weeks. *Acinetobacter species* was cultured from endotracheal secretions on day 10, and from a blood culture taken on day 19, when he deteriorated with thrombocytopenia and raised C reactive protein (193 mg/l). In spite of treatment with meropenem, the blood culture remained positive for *Acinetobacter sp* on day 28. During this septic episode, profound and prolonged neutropenia and thrombocytopenia was seen. After a transient improvement, he developed septicaemia caused by coagulase negative staphylococci, and died from multiorgan failure at 2 months of age, two days after vancomycin had resulted in a sterile blood

culture. As in case 1, the parents did not grant permission for a post mortem examination. Hepatosplenomegaly and thrombocytopenia were not seen initially in this patient, but developed simultaneously with septicaemia. Hyperbilirubinaemia was unconjugated initially, and fell to a nadir of 39 μmol/l on day 9. Pronounced conjugated hyperbilirubinaemia (maximum 572 μmol/l total, 392 μmol/l conjugated bilirubin) only developed later, with unremarkable liver enzymes and ammonia. Serum cholesterol was low (1.07 mmol/l while the patient was receiving 3 g/kg/day intravenous lipids). The organic acid profile of the urine indicated MA. On day 20, skin biopsies from the patient, and blood and urine samples from the patient, his mother, and his brother were taken. The patient's urinary excretion of mevalonic acid (3.6 mol/mol creatinine) was within the range seen in the severe phenotype of MA.³ Mutation analysis was performed on genomic DNA extracted from leucocytes. The patient was homozygous for a T→C transition at nucleotide 104 of the gene encoding mevalonate kinase, which changes the leucine at position 35 of the enzyme into a serine (L35S). Both the mother and the brother were heterozygous for the same mutation. The activity of mevalonate kinase in the patient's fibroblasts was less than 1% of the value in controls.

DISCUSSION

Data on the phenotype and laboratory indicators of MA mainly refer to long term observations, and emphasise the absence of hypoglycaemia, metabolic acidosis, or lactic acidemia.⁴ In affected families, prenatal diagnosis has been achieved, and stillbirths of malformed fetuses have been described.⁴ Reports on live births in whom MA was diagnosed during the neonatal period are scarce,⁵ and deaths within the first 4 months of life have not been published.^{2,3} In case 1, the parental consanguinity, congenital hepatosplenomegaly, and thrombocytopenia without definite evidence of infection made us consider an inborn error of metabolism. Although the clinical course in siblings has been claimed to be very similar,⁴ the hepatosplenomegaly, conjugated hyperbilirubinaemia, and thrombocytopenia in case 2 were not congenital as in case 1, but developed later during septicaemia and parenteral nutrition, as is commonly seen in very preterm infants. Intercurrent infections are known to trigger crises in MA.¹ Apart from cataracts, cerebellar atrophy, skin rash, and dysmorphic features,³ which were not seen in our patients, hepatosplenomegaly, cholestatic liver disease, and thrombocytopenia have been associated with MA.^{5,6} Unexplained periodic fever has been described as the main presenting feature in hyperimmunoglobulinaemia D (McKusick 260920), a distinct, mild form of mevalonate kinase deficiency. The L35S mutation of mevalonate kinase found in this family has not been reported before and affects a conserved amino acid. As a consequence the activity of mevalonate kinase in fibroblasts of the homozygous offspring was severely reduced.

Owing to its rarity and unspecific symptoms, MA is probably underdiagnosed, especially in preterm infants who die early. The severity of the patient's condition, parenteral nutrition, and prematurity do not interfere with the diagnosis of MA by determination of organic acids in urine. Our observation suggests that MA deserves to be considered in neonates who are born to consanguineous parents, and who suffer from recurrent life threatening infections or unexplained "sepsis-like" disease.

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CORRECTION

The paper by Whitby *et al* (Low field strength magnetic resonance imaging of the neonatal brain *Arch Dis Child Fetal Neonatal Ed* 2003;**88**:F203–F208) was missing an acknowledgement. The authors wish to thank the "Babes in Arms" charity to whom they are extremely grateful for funding the work.



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