Cerebral energy metabolism in isovaleric acidaemia


Abstract
A newborn infant with an acute metabolic encephalopathy caused by isovaleric acidaemia had severe impairment of cerebral energy metabolism. This was detected by phosphorus and proton magnetic resonance spectroscopy. After treatment she made excellent clinical recovery, her spectroscopic abnormalities resolved, and she was neurologically normal at the age of 1 year.

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Keywords: isovaleric acidaemia, magnetic resonance spectroscopy, cerebral energy metabolism.

Isovaleric acidaemia is a rare inborn error of organic acid metabolism, caused by deficiency of isovaleryl CoA dehydrogenase. Some patients present in the neonatal period with a progressive encephalopathy and non-specific symptoms such as poor feeding, weight loss, and vomiting. The characteristic odour of 'sweaty feet' may feature. The mechanism for the encephalopathy is not known, but raised concentrations of isovalerate and hyperammonaemia are likely to be important. The effect of these may be mediated through disordered mitochondrial metabolism, so we assessed cerebral metabolism before and after treatment in an acutely sick neonate with isovaleric acidaemia using phosphorus (31P) and proton (1H) magnetic resonance spectroscopy (MRS).

Case report
A girl was born to non-consanguineous African parents by caesarean section following prolonged rupture of the fetal membranes and induction of labour at 37 weeks of gestation. Her birthweight was 3.5 kg. She was initially in good condition (Apgar scores of 7 at one and 10 at five minutes), but at 3 days of age, poor feeding, vomiting, and weight loss necessitated transfer to the neonatal intensive care unit. On admission she was hypotonic, hypothermic (rectal temperature 34.5°C), and lethargic with signs of respiratory distress and severe dehydration. The blood glucose concentration was less than 2 mmol/l and the venous blood pH was 7.18, with a base deficit of −15.6 mmol/l. She was resuscitated with intravenous glucose, albumin, and sodium bicarbonate solutions and given broad spectrum antibiotics. Intravenous calcium gluconate was administered because plasma calcium was 1.34 mmol/l (plasma albumin 37 mmol/l). The plasma ammonia was 144 μmol/l. At about 95 hours of age, the infant became apnoeic, and required ventilation in addition to further calcium and bicarbonate. The head ultrasound appearance suggested cerebral oedema. Isovaleric acidaemia was provisionally diagnosed because of the characteristic odour, and an intravenous infusion of carnitine was started at 200 mg/kg/l over 24 hours, to reduce intracellular isovaleryl-Co A. Subsequent gas chromatography of urine with confirmation by mass spectrometry showed a large peak of isovaleric acid (2.4 mmol/mmol creatinine), isovaleryl glycerine, and other conjugates, confirming the diagnosis.

At the age of 108 hours the first 31P and 1H MRS studies of the brain were performed, using a specialised transport incubator to maintain intensive support throughout the procedure.1 The infant was subsequently transferred to Great Ormond Street Hospital for Sick Children where treatment with sodium bicarbonate, calcium, and α-calcidol was administered, in addition to a dopamine infusion for circulatory support. After a further five days, her level of consciousness improved and the neurological abnormalities resolved. The baby was discharged home on reduced protein intake, supplemented with glucose polymer and carnitine. The second MRS studies were carried out at 18 days of age.

At 1 year of age the infant underwent a neurological examination (Amiel-Tilson) and neurodevelopmental assessment (Griffiths).

Magnetic Resonance Spectroscopy
Brain spectra were acquired using a 2.4 T Bruker Biospec spectrometer (1H frequency 100.3 MHz, 31P 40.6 MHz) equipped with actively shielded gradient coils. For the first study, an inductively coupled, series tuned, 1H Helmholtz transmitter coil of 18 cm in diameter was used in conjunction with a separate, inductively coupled, double tuned (31P and 1H) surface receiver coil of 10 cm in diameter. For the second study, a specially designed double tuned (31P and 1H) Helmholtz coil of 15 cm in diameter was used.2 The head was positioned supine and studies were performed without sedation.

During the first 31P study, data were acquired from the occipital region of the brain using the surface coil. Acquisition conditions were: single pulse (90° coil centre flip angle); recovery time (TR) 20 seconds; 64 averaged free induction decays. For all the other studies, 1H and 31P spectra were acquired using the
Acetoacetate (AA) and acetone

Figure 2

Spec 1 2 ppm. The resonance at 0 9 ppm indicates a low [PCr]:[Pi] ratio of 0.37; control data have 95% confidence limits 0.70 to 1.36.

In the second cerebral MRS study, performed at 18 days of age, both 1H and 31P spectra had returned to normal (fig 3A and B); the lactate:NAA peak area ratio had fallen to 0.22 and the [PCr]:[Pi] was 1.72, indicating normal cerebral energy metabolism. Intra-cellular pH remained normal; it was 7.14 at 108 hours and 7.18 at 18 days.

At 1 year of age neurological assessment was normal, and the Griffiths quotient was, overall, within the normal range, but with some sub-score variability.

Discussion

We have demonstrated profound abnormalities of cerebral metabolism in a newborn infant with acute encephalopathy due to isovaleric acidemia. The acute metabolic encephalopathy is likely to be multifactorial; in this case the infant was initially hypoglycaemic and acidic with a mildly raised ammonia, as well above the mean of age matched controls. The lactate:NAA peak area ratio (0.5) was also raised compared with age matched controls.

The peak at 0 9 ppm (U) was possibly attributable to isovaleric acid, and a peak at about 1 5 ppm was probably alanine. High resolution 1H MRS of cerebrospinal fluid (CSF) taken at 96 hours of age (fig 2) showed raised isovalerate concentrations at 0 9 ppm, confirming the in vivo assignment, as well as acetone and acetacetate (2 2–2 3 ppm), and 3-hydroxybutyrate (1 2 ppm). Inositol and glucose were also present. The 31P spectrum acquired in vivo at 108 hours of age (fig 1B) revealed a major impairment of oxidative phosphorylation, as judged by the severely reduced [PCr]:[inorganic phosphate (Pi)] ratio of 0.37 (control data have 95% confidence limits 0.70 to 1.36).

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Discussion

We have demonstrated profound abnormalities of cerebral metabolism in a newborn infant with acute encephalopathy due to isovaleric acidemia. The acute metabolic encephalopathy is likely to be multifactorial; in this case the infant was initially hypoglycaemic and acidic with a mildly raised ammonia, as well
as having raised isovaleric acid and probable cerebral oedema. The encephalopathy persisted despite correction of systemic acidosis and hypoglycaemia. A reduced [PCr]:[Pi] ratio at age 108 hours indicated impaired oxidative phosphorylation. The raised alanine may reflect protein catabolism or be secondary to the lactic acidosis. The increased lactate:NAA peak area ratio could be consistent with a compensatory increase in anaerobic glycolysis, but could also be associated with reduced NAA due to neuronal loss. Normal progress of the infant at age 1 year would suggest the former. The increased glutamate and glutamine peak at about 2-03 ppm is likely to be a consequence of increased ammonia and may have contributed to the encephalopathy. However, acetone and acetoacetate resonances, which were observed in the CSF, may have contributed to these peaks. The normal spectrum at 18 days of age contrasts with metabolic abnormalities following neonatal hypoxic-ischaemic injury in which there are reports of an increase in cerebral lactate at 7 days, and reduced NAA concentrations at 13 days. In the only other MRS study of a child with isovaleric acidemia, a well infant aged 5 months was studied by 1H MRS and found to have normal spectra. Although two different techniques were used to obtain the 31P spectra, data from normal controls were available for both methods. The 31P surface coil spectrum at 108 hours was deemed to be very abnormal on the basis of low [PCr]:[Pi] when compared with data acquired in extensive previous studies. 31P PRESS results from five normal infants (GPA range 34 to 40 weeks) give a [PCr]:[Pi] of 1.59 (SD 0.57) (Cady EB, unpublished data), implying that the impairment of energy metabolism had resolved by 18 days of age. We have already seen catastrophic failure of cerebral energy generation and subsequent death in two infants; one with argininosuccinic aciduria and one with propionic acidemia. However, in the infant described here the spectroscopic abnormalities resolved two weeks after the start of treatment, suggesting that no permanent injury had occurred. This study shows that in isovaleric acidemia, while many factors may contribute to the encephalopathy, these are potentially reversible, provided that the production and accumulation of toxic metabolites can be attenuated – for example, by removal of isovalerate as isovaleryl carnitine – and that measures are taken to protect cerebral perfusion and provide substrate for energy production early in the encephalopathy. Thus damage caused by release of excitatory neurotransmitters (with consequent cellular damage and programmed cell death) will not be initiated. These observations also show the potential of 31P and 1H MRS in acute neonatal encephalopathy to investigate abnormal cerebral metabolism, as well as provide diagnostic information. MRS could also be used to monitor response to treatment, and hence help determine optimal treatment of some inborn errors of metabolism.

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