Cerebral energy metabolism in isovaleric acidaemia

A K Lorek, J M Penrice, E B Cady, J V Leonard, J S Wyatt, R A Iles, S P Burns, E O R Reynolds

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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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 (^{31}P) 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 $\mu\text{mol/l}$. 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 glycine, and other conjugates, confirming the diagnosis.

At the age of 108 hours the first ^{31}P 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, ^{31}P 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 (^{31}P and ^1H) surface receiver coil of 10 cm in diameter. For the second study, a specially designed double tuned (^{31}P 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 ^{31}P 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 ^{31}P spectra were acquired using the

Department of
Paediatrics, University
College London School
of Medicine, London
A K Lorek
J M Penrice
J S Wyatt
E O R Reynolds

Department of
Medical Physics and
Bioengineering,
University College
Hospitals NHS Trust,
London
E B Cady

Metabolic Unit, Great
Ormond Street
Hospital for Children
NHS Trust, London
J V Leonard

Department of
Medicine, The Royal
London Hospital,
London
R A Iles
S P Burns

Correspondence to:
Dr Ann Lorek, The
Children's Hospital
Lewisham, Lewisham High
Street, London SE13 6LH.

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Figure 1 ^1H (A) and ^{31}P (B) in vivo spectra acquired at 108 hours of age. The ^1H spectrum shows a high lactate peak in addition to abnormal resonances at about 1.5 ppm and at 0.9 ppm (attributed to alanine and isovaleric acid, respectively). The ^{31}P spectrum indicates a low $[\text{PCr}]:[\text{Pi}]$ suggesting impaired cerebral oxidative phosphorylation.

point resolved spectroscopy (PRESS) localisation technique.^{2,3} ^1H PRESS spectra were collected from an 8 ml cubic volume of interest (VOI) positioned in the thalamus with the aid of a sagittal scout magnetic resonance image coplanar with the mid line. ^1H PRESS acquisition conditions were: echo time (TE) 270 ms; TR 1730 ms, with 256 echoes averaged. ^{31}P PRESS acquisition conditions were: $4 \times 5 \times 5 \text{ cm}^3$ central VOI; TR 2 seconds; TE 12 ms, with 512 echoes averaged. Pulse amplitudes for ^{31}P were scaled from those optimised for ^1H using a previous calibration.² All spectra were analysed by Lorentzian fitting in the frequency domain using χ^2 minimisation with a gradient-search technique and prior knowledge.⁴

Results

Figure 1A shows the brain ^1H spectrum obtained at 108 hours of age. In addition to the detection of major peaks due to choline containing compounds (cho), creatine (Cr; including phosphocreatine (PCr)), and N-acetyl aspartate (NAA), several abnormalities were present.

The broad peak at 2.3 ppm, due mainly to glutamate and glutamine, had a peak area 1.4 times that of (NAA) at about 2.0 ppm. This ratio was more than five standard deviations

above the mean of age matched controls. The lactate:NAA peak area ratio (0.5) was also raised compared with age matched controls.⁵ 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 acetoacetate (2.2–2.3 ppm), and 3-hydroxybutyrate (1.2 ppm). Inositol and glucose were also present. The ^{31}P spectrum acquired in vivo at 108 hours of age (fig 1B) revealed a major impairment of oxidative phosphorylation, as judged by the severely reduced $[\text{PCr}]:[\text{inorganic phosphate (Pi)}]$ ratio of 0.37 (control data have 95% confidence limits 0.70 to 1.36).⁵

In the second cerebral MRS study, performed at 18 days of age, both ^1H and ^{31}P spectra had returned to normal (figs 3A and B); the lactate:NAA peak area ratio had fallen to 0.22 and the $[\text{PCr}]:[\text{Pi}]$ was 1.72, indicating normal cerebral energy metabolism. Intracellular 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 multifactorial⁷; in this case the infant was initially hypoglycaemic and acidotic with a mildly raised ammonia, as well

Fig 2 ^1H CSF spectrum at 96 hours. Isovalerate (IV) is detected at 0.9 ppm. Acetoacetate (AA) and acetone (A) are seen at 2.2–2.3 ppm, and 3-hydroxybutyrate (HB) at 1.2 ppm.

Figure 3 ^1H (A) and ^{31}P (B) in vivo spectra obtained at 18 days of age. The abnormal peaks seen in the ^1H spectrum at age 108 hours are no longer detectable; lactate:NAA is now normal. In the ^{31}P spectrum $[\text{PCr}]:[\text{Pi}]$ has now become normal. These observations indicate that both glycolysis and oxidative phosphorylation are functioning normally.

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.⁸ 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.⁹ 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,¹⁰ and reduced NAA concentrations at 13 days.¹¹ In the only other MRS study of a child with isovaleric acidaemia, a well infant aged 5 months was studied by ¹H MRS and found to have normal spectra.¹²

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.⁶ ³¹P PRESS results from five normal infants (GPA range 34 to 40 weeks) give a [PCr]:[Pi] of 1.59 (SD 0.37) (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 acidaemia.¹³ 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 acidaemia, 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 isovalerylcarnitine – 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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