31P magnetic resonance spectroscopy of the liver in an infant with galactosaemia

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Sequential studies of the liver of an infant with galactosaemia were made by phosphorus magnetic resonance spectroscopy (31P MRS). A peak attributable to galactose 1-phosphate (gal 1-P) was seen in early liver spectra. This peak diminished during dietary therapy in the early months of life, corresponding to a falling level of gal 1-P in red blood cells.

Keywords: spectroscopy, galactosaemia, liver, infant, galactose 1-phosphate.

INTRODUCTION

Classical galactosaemia is caused by deficiency of the enzyme galactose-1-phosphate uridyl transferase, which leads to clinical manifestations including liver disease, cataracts, failure to thrive, susceptibility to sepsis and cerebral damage [1]. The precise aetiology of the clinical picture is not known, but elevated tissue levels of gal 1-P and galactitol have been implicated and blood levels of the former are a convenient means of monitoring dietary therapy. Intracellular gal 1-P can also be detected by phosphorus magnetic resonance spectroscopy (31P MRS), which can therefore be used to monitor hepatic gal 1-P levels non-invasively [2].

METHODS

31P MRS studies of the liver were performed in a specially designed foam cradle with the upper right abdomen and lower chest resting on a 2 cm diameter surface coil. The cradle lay in the bore of a 1.9 T superconducting magnet which was attached to a Biospec spectrometer. Each spectrum was derived from 1024 free induction decays. The pulse length was chosen to give a flip angle of about 180° at the centre of the coil in order to minimize the signal from muscle phosphocreatine, and a pulse interval of 1 s was used. Spectra were processed using a Lorenzian to Gaussian transformation. Peak areas were determined using a computer-assisted, manually operated curve-fitting programme (Glinfit).

Peak assignments are shown in Fig. 1. A correction was made for adenosine triphosphate (ATP) peak area to account for the contribution from skeletal muscle, based on the area of the phosphocreatine (PCr) peak and the PCr/ATP ratio in skeletal muscle at this repetition rate. The relative amount of PCr was similar in all the spectra, thus the variations in the corrected peak area ratios were not critically dependent on the correction factor used. Galactose 1-phosphate is known to have a similar resonance frequency to inorganic phosphate (Pi) [2]. The two peaks cannot be distinguished with the resolution achieved in vivo, so the peak has been attributed to (Pi + gal 1-P).

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Fig. 1. MRS spectra of the liver at (A) 15 days, (B) 73 days and (C) 149 days. Peak assignments: ATP – adenosine triphosphate (beta, alpha and gamma phosphorus nuclei from right to left), PCr – phosphocreatine, PDE – phosphodiesters, Pi + G1P – overlapping peaks of inorganic orthophosphate and galactose 1-phosphate, PME – phosphomonoesters. ppm – parts per million.

CASE REPORT

A male infant weighing 2765g was born to consanguinous Pakistani parents by vaginal delivery at 39 weeks gestation. He was noted to be jaundiced at 26h of age when serum bilirubin was 189 #mol/L. No cause for haemolysis was found and phototherapy was commenced. By day 9 skin colour suggested conjugated hyperbilirubinaemia, and total bilirubin was 395 #mol/L with a conjugated fraction of 192 #mol/L. Aspartate transaminase and alkaline phosphatase levels were elevated at 114 iu/L and 3684 iu/L respectively, prothrombin time was prolonged and fibrinogen levels were low. There was a family history of a female sibling dying at six weeks of age in Pakistan with jaundice and presumed sepsis, but three other siblings were alive and well.

Investigations for conjugated hyperbilirubinaemia showed reducing substances in the urine, and a low blood sugar. Galactose-1-phosphate uridyl transferase activity in red blood cells was very low and blood gal 1-P elevated, consistent with a diagnosis of galactosaemia. Lactose-free feeds were started on day 12. He began to thrive, the jaundice resolved and liver function tests improved. At two weeks ophthalmoscopy revealed bilateral central lens opacities, but these resolved by ten weeks.

At ten weeks of age his mother found him cyanosed and gasping in his cot. He was stiff with rolling eyes for fifteen minutes, but conscious level was normal by the time of arrival in hospital. No similar episodes have occurred since, an electroencephalogram was normal, and he is now healthy and neurologically intact at 18 months of age.

Magnetic resonance spectroscopy was performed on days 15, 22, 39, 73 and 149 of life. Spectra on days 22 and 39 had poor resolution, so metabolite ratios are less reliable. Spectra from the 3 other scans are shown in Fig. 1, and show a fall in the (Pi + gal 1-P)/ATP ratio with age. Changes in the (Pi + gal 1-P)/ATP ratio are shown in Fig. 2 together with blood gal 1-P levels, which showed an exponential fall over the same period, during the initiation of dietary therapy. The upper limit of blood gal 1-P in galactosaemic patients with good dietary control is shown. The upper limit of normal for Pi/ATP in the liver of young infants, derived from Moorcraft and Dixon (unpublished observations), is also shown.

DISCUSSION

Reports of 31P MRS studies of the neonatal liver have mainly been concerned with phosphodiester and phosphomonoester concentrations in a very small number of subjects [3, 4]. Larger numbers of adults have been studied and significant changes have