Intensive Care Med (1995) 21:266–268

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In vivo proton magnetic resonance spectroscopy in a case of Reye's syndrome

Received: 8 July 1993
Accepted: 11 February 1994

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Abstract A case of a 14-year-old boy with Reye's syndrome (RS) and complete neurologic recovery is presented. ^{1}H magnetic resonance spectroscopy was performed on days 1 (admission to ICU), 8 and 62: During the acute phase of RS substantial cerebral metabolic imbalances were observed and their normalization monitored. The spectra from day 1 featured extremely high glutamine content (~18 mmol/kg excess) and low concentrations of choline compounds (~1 mmol/kg deficit). Also some excess lactate was present. The subsequent spectra demonstrated the return to an almost normal brain metabolite profile.

Key words Proton magnetic resonance spectroscopy · Reye's syndrome · Glutamine · Choline · Coma

Introduction

Reye's syndrome (RS) is characterized by encephalopathy and fatty degeneration of the viscera. It occurs in children following an initially mild infectious disease. Etiology and pathogenesis of RS, first described in 1963 [1] and well studied ever since [2, 3], are still unresolved. The advent of ^{1}H magnetic resonance spectroscopy (MRS) as a clinical tool [4] promises new insight into the pathophysiology of RS.

Case report

A 14-year-old boy was admitted to our hospital because of acute encephalopathy of unknown origin. Family and personal history were unremarkable except for an acute hepatitis at the age of 5 years. The present illness started with symptoms and signs of a common cold. Symptomatic treatment was initiated with salicylates. Four days later, persistent vomiting began, which was treated by antiemetics, including injection of metoclopramide. Four hours later the boy was extremely agitated, confused and no longer followed commands. Side effects from metoclopramide were suspected, and biperidin was given as a potential antidote. However, the neurological state of the patient deteriorated further, and coma with diminished protective reflexes of the upper airways was noted. Endotracheal intubation was performed, artificial ventilation started, and the child was transferred to our ICU.

At this stage (day 6 of the present illness = day 1 in ICU) the patient was in deep coma (Glasgow Coma Score 4), pupillary size and reactions normal, cardiovascular and pulmonary functions adequate (heart rate 84/min, blood pressure 135/75 mmHg, plasma pH 7.45, $PaCO_2$ 27 mmHg, HCO_3^- 16 mmol/l, PaO_2 115 mmHg on mechanical ventilation with FIO_2 0.4). Computerized tomography of the skull revealed compressed lateral ventricles, but patent basal cisterns. Analysis of cerebrospinal fluid (CSF) was unremarkable (one leucocyte/mm^3, protein 238 mg/l). Hemoglobin was 15.5 g%, white blood cell count 11.8×10^9/l with unremarkable distribution, platelets 352×10^9/l. Blood chemistry: Na^+ 140 mmol/l, K^+ 4.2 mmol/l, glucose 5.5 mmol/l, urea 5 mmol/l, creatinine 56 µmol/l, SGOT (ASAT) 3040 IU/l, SGPT (ALAT) 2530 IU/l, bilirubin 13 µmol/l, NH_4^+ 178 µmol/l (normal values are indicated in Table 1). A moderate coagulation abnormality was noted with a prothrombin time of 33% of normal, a diminution of activity of factors II, V, VII and X to 21 to 40% of normal, and a fibrinogen level of 2 g/l. Inborn errors of metabolism, particularly in beta-oxidation of fatty acids and organic acidemias were excluded by blood and urine analyses. The following amino acids were elevated: Gln (791 µmol/l), Phe (108 µmol/l) and Lys (462 µmol/l) in plasma; Ser, Gln, Ala, Leu, Lys and His in urine.

Treatment consisted of mechanical ventilation with moderate hypocapnia and hyperoxemia, fluid restriction (70% of normal maintenance), diuretics (mannitol and furosemide), maintenance of normoglycemia, sedation (midazolam), anticonvulsive prophylaxis (phenytoin), lactulose (by enema and nasogastric tube) and cefurox-

Table 1 Clinical course in ICU

	Day1[a]	Day 2	Day 3	Day 4	Day 5	Day 6
Glasgow coma scale	4–6	5–6	6–8	9–10	13–15	15
SGOT (ASAT) (IU/l)	3040	1550	317	217	208	
SGPT (ALAT) (IU/l)	2530	2540	1630	1044	813	
NH_4^+ (μmol/l)	178	159	42	55		
Prothrombin time (%)	33	27	59			

Normal values: 0–35 IU/l for SGOT and SGPT; <50 μmol/l for NH_4^+; 70–130% for prothrombin time
[a] Day 1 = day of admission to ICU

ime against aspiration pneumonia. Continuous neurological monitoring was performed using the cerebral function monitor.

The clinical course was favorable and is summarized in Table 1. Extubation was performed on day 6. The following day the patient was discharged from ICU to the regular ward, where he stayed for 4 days. He went back to normal school 2 weeks later and performed as well as before the acute illness.

^{1}H MRS and MR Imaging (MRI) was performed on day 1, 8, and 62. Two cerebral regions of interest (ROI) were examined, one midline in grey matter (GM) of the occipital cortex (8.9 cm^3), the other in left parietal white matter (WM, 5.4 cm^3). The spectra were recorded using a double echo technique with phase rotation [5] and outer volume suppression (20 ms echo time, 3 s repetition time, 128 averages, 1.5 T GE signa system, standard head coil). Metabolite quantification was accomplished using the unsuppressed water signal as an internal standard and to differentiate between tissue water and CSF [6]. Normal values had been obtained from a study of ten healthy young adults (5 male, 5 female, 23±2 years). Relative standard deviations (SD, derived from 100 measurements for the occipital ROI and 20 spectra for the parietal location) of the normal absolute metabolite concentrations varied from 7–16%, depending on metabolite and ROI. Single measurements outside the range (mean±2 SD) were regarded as statistically significant deviations from normal. The difference in age between control group and patient is not expected to account for the reported abnormalities.

Figure 1 contains 3 GM spectra from the RS patient and an equivalent spectrum from a healthy 22-year-old control subject. Additionally Fig. 1 includes the difference of the spectra from day 1 and day 62, as well as spectra from aqueous Gln and Glu solutions. The spectrum of day 1 is marked by substantially elevated regions from 2.0 to 2.6 ppm and 3.6 to 3.9 ppm, in agreement with an increase in Glx (Gln and/or Glu). The choline (Ch) peak is only ~50% of normal and a small signal of lactate (Lac), identified by chemical shift and characteristic splitting, is visible. The subsequent spectra of days 8 and 62 demonstrate the return of the cerebral metabolite profile to normality: Glx levels appear normal on day 8 already. Ch is transiently above normal on day 8, but within normal limits on day 62. Lac diminished with time. No significant changes were observed for the absolute levels of N-acetyl group (NA) containing metabolites (mostly N-acetylaspartate, NAA). The sum of creatine puls phospho-creatine (Cr), as well as myo-inositol (mI) appeared relatively constant in grey matter, though the absolute level of Cr was two SD below the normal mean at day 62. The CSF volume content in the located region in occipital GM was only 1.5% on day 1, increasing to 10% on day 62 (norm 10±4%).

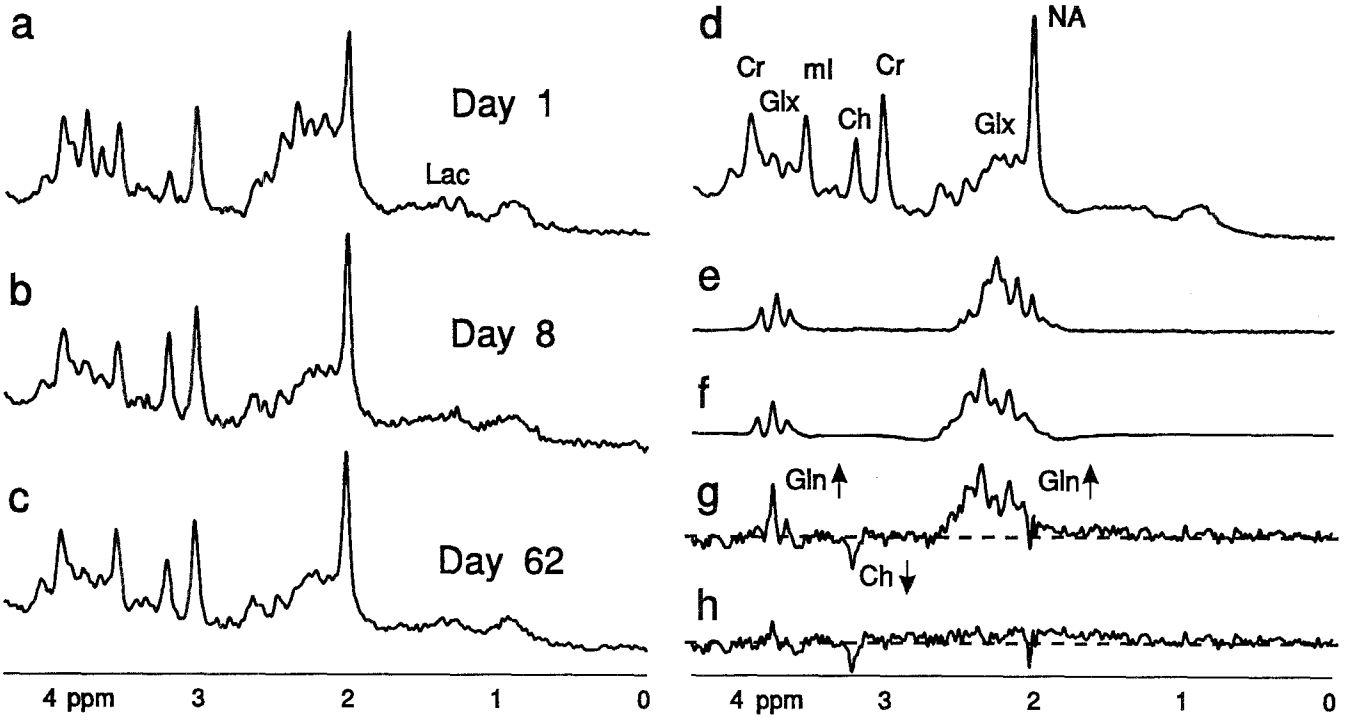

Fig. 1 In vivo ^{1}H MR spectra of the brain documenting the clinical course of a patient with Reye's syndrome: spectra from occipital grey matter of the patient on day 1 (*a*), while in coma, day 8 (*b*) and day 62 (*c*), when recovered, compared to a spectrum from a normal subject (*d*, average of 10 studies). From the difference spectrum between days 1 and 62 (*g*) and spectra from aqueous Glu (*e*) and Gln solutions (*f*), it is evident that a substantial Gln increase and a Ch depletion are the major metabolic abnormalities in the acute phase of RS. *Trace h* contains the above difference spectrum after subtraction of the appropriately scaled Gln spectrum. For abbreviations see Text

The spectral changes in parietal WM were comparable to those shown in occipital GM. The temporal course of Glx and Ch was very similar to that in GM. While NA remained in the low normal range, Cr decreased between day 1 and day 62 from 90–80% of normal. mI fluctuated somewhat but was normal after recovery. No indications of ketone bodies [7] were found in either location.

Discussion

Using clinical criteria this boy was diagnosed to have suffered from RS (non-inflammatory encephalopathy, 50–100 fold increase in SGOT and SGPT, hyperammonemia) [2, 3, 8]. Liver biopsy was not thought to be necessary for clinical management of this patient. Inborn errors of metabolism which can mimic RS were excluded, with the only possible exception of urea cycle defects [9]. However, the relatively low NH_4^+ plasma concentrations in relation to the extremely elevated liver enzymes make such a defect very unlikely (for active exclusion metabolic studies of liver tissue would have been necessary [9]). Increased concentrations of amino acids in the plasma and urine are part of RS, but non-specific. Intracerebral concentration changes of the most abundant metabolites, however, can now be monitored by ^{1}H-MRS.

The most striking variation in the chemical composition of both cerebral locations during the acute phase of RS is the drastic increase of the Glx level. Comparisons of difference spectra (day 1 versus day 62) with appropriate model solutions (cf Fig. 1), showed that the increase in Glx was due to an increase in Gln, while Glu, featuring a distinctly different spectral pattern (Fig. 1E versus Fig. 1F), appears largely unchanged. The surplus of Gln amounted to ~18 mmol/kg brain tissue (wet weight) in occipital GM and 11 mmol/kg in parietal WM (up to 3 times the normal concentration). The measured Gln concentration is an average over different cell types and also intra- and extracellular space. Taking into account the water content of brain and assuming that the normal concentration gradients of Gln between different cell types [10] is conserved in hyperammonemia, it can be speculated that the Gln concentrations within glial cells, the site of glutamine synthetase, may well have been in the range of 50 mmol/l. This can be a substantial factor for the brain swelling observed in CT, MRI and confirmed by the vanishingly small CSF content in the occipital ROI.

The second remarkable observation in the proton spectrum of the comatose patient is a 50% reduction in the concentration of choline. Due to the fact that 9 equivalent protons contribute to this single peak (consisting mainly of phosphocholine and glycerophosphocholine), this reduction translates into a deficit of less than 1 mmol/kg choline residues. As the neurotransmitter acetylcholine is only present in micromolar concentrations, no direct conclusions about its concentration or changes thereof can be drawn from this MRS result. The presence of lactate on day 1 in the occipital cortex is a hint for anaerobic metabolism.

The complete clinical recovery is accompanied by the normalization of the cerebral MR spectrum. In both cerebral locations the only persistent changes two months after the present illness are a small, but significant deficit in total Cr (more than two standard deviations below the norm), as well as marginally low NA and Ch concentrations. This contrasts to findings in chronic hyperammonemia (chronic hepatic encephalopathy [11] and partial ornithine-transcarbamylase deficiency [4]), where the spectrum is characterized by a large reduction in mI (and low choline). Also the results reported for a single case of suspected RS [12] differ from the present long term findings. While initial spectral changes were similar to the present case (high Gln and some Lac on day 2), the later sequelae are strikingly different. Abnormal neurological findings were accompanied by reductions of 30–50% in NA, Cr and mI. The missing marked NA deficit in our case probably indicates that neurons were largely spared from injury. The small continuing cerebral Cr depletion may suggest a persistent, but compensated liver damage. The fact that despite the enormous cerebral Gln accumulation during the acute phase a complete clinical recovery ensued, proves that it is probably not the extent of the short term glutamine increase which is responsible for long term neuronal damage, but either the length of exposure or other factors, like secondary hypoxic-ischemic lesions due to increased intracranial pressure. One of the most salient theories for the pathogenesis of RS, however, is that of a primary mitochondrial metabolic defect which may decompensate during/after a viral illness and salicylate therapy [2].

Whether the pattern of cerebral changes detected in this single case will turn out to be specific for RS is uncertain. We are quite confident, however, that from correlating MRS findings with clinical data much can be learned about the pathophysiology of RS in particular and hyperammonemia in general.

Acknowledgement We thank Prof. Schroth for bringing this patient to the attention of the Department of Magnetic Resonance Spectroscopy and acknowledge the financial support of the Swiss National Science Foundation (# 31-30909.91 NH).

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