Proton MR Spectroscopy and Imaging of a Galactosemic Patient before and after Dietary Treatment

SUMMARY: We describe how proton MR spectroscopy (1H-MR spectroscopy) was useful in elucidating the diagnosis of galactosemia in an undiagnosed 6-month-old infant. In vivo 1H-MR spectroscopy of the brain showed a doublet at 3.7 parts per million, which was identified as galactitol (Gal-ol) by in vitro 1H-MR spectroscopy of the urine. Galactosemia was subsequently confirmed by laboratory tests and treatment was initiated. A follow-up brain MR imaging and 1H-MR spectroscopy study revealed resolution of white matter lesions and disappearance of Gal-ol peaks.

| Metabolite ratios in the parieto-occipital white matter measured by the STEAM technique (TE/TR = 30/1500 ms) before and after patient’s treatment |
|---|---|---|---|---|
| | NAA/Cr | Cho/Cr | ml/Cr | Gal-ol/Cr |
| Patient before treatment | 1.45 | 1.04 | 0.19 | 14.30 |
| Patient after treatment | 1.57 | 0.87 | 0.50 |
| Controls* | 1.53 ± 0.22 | 0.89 ± 0.14 | 0.48 ± 0.07 |

Note:—Control mean values are included for comparison purposes. Cho/Cr indicates choline/creatine; Gal-ol/Cr, galactitol/creatine; ml/Cr, myo-inosito/creatine; NAA/Cr, N-acetylaspartate/creatine.

* Control group consisted of 10 healthy volunteers (3 boys and 7 girls) of mean age of 6 ± 1 years (range, 4–9 years).

for carbohydrate signals. For a more detailed study of the carbohydrate composition, an in vitro 1H-MR spectroscopy of the urine was acquired by using a high-resolution 500-MHz spectrometer, and the result was compared with the urine of a normal volunteer. We could observe a group of multiple peaks in the region of 3.6 to 3.9 ppm (Fig 3) and a triplet at 3.98 ppm, which were absent in the normal spectrum. We found also 2 clearly resolved doublets at 4.57 and 5.25 ppm in the patient’s urine, which were absent in the normal spectrum. The in vitro urine spectrum suggested the presence of high concentrations of galactose (Gal-ose) and galactitol (Gal-ol) in the patient’s urine. The diagnosis of galactosemia was later confirmed by the finding of low levels of galactose-1-phosphate uridyl transferase in the erythrocyte. Subsequently, the patient started a restricted lactose-free diet. At the age of 2 years, the follow-up MR imaging of the patient showed marked atrophy, more evident in the frontal lobes with enlarged sulci and dilation of the lateral ventricles more prominent in the anterior horns. There was marked improvement of the lesions with almost complete resolution of white matter signal intensity abnormalities. The sparse residual lesions were located in the basal temporal lobes and periventricular frontal regions, presenting hypointensity on T1-weighted and hyperintensity on T2-weighted (Fig 4) and FLAIR images, without gadolinium enhancement. On DWI, the lesions presenting increased ADC values on the previous examination had resolved. In vivo 1H-MR spectroscopy of the parieto-occipital white matter did not show evidence of Gal-ol signal intensity (Fig 5). Metabolite ratios appeared to be normal when compared with control group (Table).

Discussion

Galactosemia is a disorder caused by a deficiency of any of the 3 possible enzymes involved in the metabolism of galactose: galactokinase, transferase, or epimerase. Any single defi-
cient enzyme can result in accumulation of Gal-ol in the lenses, causing cataracts, and in the brain, leading to cerebral edema, probably due to an osmotic effect. The most common type of galactosemia, known as classic galactosemia, is caused by the deficiency of galactose 1-phosphate uridyltransferase (GALT). In humans, GALT deficiency leads to significant neonatal morbidity and mortality, which depends on Gal-ose ingestion, as well as long-term complications of primary ovarian failure and cognitive dysfunction, which are independent of diet. Although potentially lethal, neonate screening and Gal-ose restriction prevent neonatal hepatotoxic syndrome, but total exclusion of Gal-ose from the diet does not ensure the absence of all symptoms. Two different metabolites are potentially toxic: Gal-ol is responsible for the cataracts, whereas galactose-1-phosphate causes the rest of the clinical symptoms. Through measurement of urine and plasma Gal-ol levels, it is possible to distinguish galactosemic patients from normal subjects.

Patients with galactosemia have been previously studied by MR imaging and 1H-MR spectroscopy. The MR imaging of galactosemic patients can present cerebral and cerebellar atrophy and multiple small hyperintense lesions in the white matter on T2-weighted images. Berry et al reported the first in vivo 1H-MR spectroscopy evidence of Gal-ol accumulation in a galactosemic patient in 2001. Gal-ol appears in the 1.5T 1H-spectrum as 2 peaks at 3.67 and 3.74 ppm, which can be observed in several locations of the brain. To be able to detect Gal-ol in the in vivo brain 1H-MR spectroscopy examination high Gal-ol levels still need to be present in the patient’s urine. Galactosemic patients, who have been following a Gal-ose-restricted diet for several years, and therefore present controlled levels of Gal-ol in the urine, do not present Gal-ol in the brain by in vivo 1H-MR spectroscopy.

In our case, the patient performed the first MR imaging and 1H-MR spectroscopy examination without having a diagnosis, and we described how it was possible to aid in the diagnosis by
performing in vivo and in vitro $^1$H-MR spectroscopy. Furthermore, we also showed how the $^1$H-MR spectroscopy reversed to normal once the patient was under dietary treatment.

The unusual peaks encountered around 3.7 ppm in the brain $^1$H-MR spectroscopy of our patient suggested the accumulation of carbohydrates, probably due to a failure in the patient’s carbohydrate metabolism. There are several metabolic diseases, which could lead to elevation of carbohydrates in the spectrum, like glucose in diabetes mellitus, Gal-ol in galactosemia, and arabitol, and ribitol in a recently reported inborn error of the polyol metabolism.1,11 All of these sugars present multiple peaks in the region of 3.7 ppm. To distinguish between these conditions by $^1$H-MR spectroscopy it is necessary to work with a higher spectral resolution than the one obtained in vivo at 1.5T. For this reason an in vitro analysis of the urine sample was performed. Moolenaar et al1 acquired in vitro urine spectra from a patient with an inborn error in the arabitol/ribitol metabolism, a patient with diabetes mellitus, and an untreated galactosemic patient. By comparing the latter one with the urine spectrum of our patient, we could observe many similarities in the region of 3.4 – 4.0 ppm, including the presence of the characteristic Gal-ol triplet at 3.98 ppm.11 It is difficult to correlate the peaks around 3.7 to a specific molecule, because they are multiple, and several of the sugars and polyols, like Gal-o-se, Gal-ol, and galactonate resonate in this region, leading to an overlap of different peaks. Gal-o-se presents doublets at 4.57 and 5.25 ppm.9 We could observe the presence of these doublet peaks in the in vitro spectrum, also confirming high levels of Gal-o-se in the urine of our patient. In cases of GALT deficiency, initially there is an accumulation of Gal-o-se, which is then reduced to Gal-ol.9

The presence of Gal-ol in high concentrations in the urine of our patient explains the prominent doublet observed at 3.7 ppm in the in vivo spectrum of the brain. Gal-ol peaks in this region show J-coupling effects, which explain the inversion of these peaks by using a TE of 135 ms. Polyols, such as Gal-ol, can easily penetrate the cellular membrane. With the increase in Gal-ol, we expect to see a decrease of ml, to compensate the osmotic pressure.1 This could explain the low ml/Cr ratio found in the parieto-occipital white matter of our patient before treatment (Table).

The MR imaging and $^1$H-MR spectroscopy results obtained at the age of 2 years are consistent with other reports of treated galactosemic patients: normal brain $^1$H-MR spectroscopy spectrum9 and atrophy and sparse residual lesions on the MR imaging.8

Conclusion

$^1$H-MR spectroscopy was very useful in the diagnosis of this galactosemic patient. The detection of unknown peaks in the spectrum must be considered and investigated. The in vitro MR spectroscopy was a very important tool to aid in this investigation.

Acknowledgments

The MRUI software package was kindly provided by the participants of the EU Network programs: Human Capital and Mobility, CHRX-CT94 – 0432, and Training and Mobility of Researchers, ERB-FMRX-CT970160.

References