Proton magnetic resonance spectroscopic imaging in the clinical evaluation of patients with Niemann-Pick type C disease

G Tedeschi, S Bonavita, N W Barton, A Bertolino, J A Frank, N J Patronas, J R Alger, R Schifffman

Abstract

Objectives—10 patients with Niemann-Pick disease type C (NP-C) were studied by proton magnetic resonance spectroscopic imaging ('1H-MRSI') to assess the biochemical pathology of the brain and to determine whether this method can be useful to clinically evaluate these patients.

Methods—'1H-MRSI permits the simultaneous measurement of N-acetyl aspartate (NA), compounds containing choline (Cho), creatine plus phosphocreatine (Cre), and lactate (Lac) signal intensities from four 15 mm slices divided into 0.84 ml single volume elements. Spectroscopic voxels were identified from seven regions of interest.

Results—In patients with NP-C, NA/Cre was significantly decreased in the frontal and parietal cortices, centrum semiovale, and caudate nucleus; Cho/Cre was significantly increased in the frontal cortex and centrum semiovale. Significant correlations were found between clinical staging scale scores and '1H-MRSI abnormalities.

Conclusion—'1H-MRSI showed diffuse brain involvement in patients with NP-C consistent with the pathological features of the disease. '1H-MRSI is an objective and sensitive tool to neurologically evaluate patients with NP-C.

Keywords: proton magnetic resonance spectroscopy; Niemann-Pick; clinical stage

Niemann-Pick disease type C (NP-C) is an autosomal recessive lipidosis, characterised by a unique error in the intracellular trafficking of lysosomal cholesterol. This abnormality forms the basis for the biochemical diagnosis of the disease, which requires confirmation of both impaired cholesterol esterification by cultured skin fibroblasts and visualisation (by filipin staining) of excess accumulation of free cholesterol in their lysosomes. The disease shows a broad clinical range with diverse neurological manifestations including pyramidal, cerebellar, and developmental delay. Conversely, pathological and histological abnormalities are more unifying features, with the presence of storage material in ballooned neurons in the brain. Ultrasstructurally, the storage material occurs as membranous and osmiophilic granules in lysosomes. Subsequently there are destructive and degenerative abnormalities with widespread neuronal loss, and to a minor extent, astrogliosis and demyelination.

Niemann-Pick type C disease is a diffuse, degenerative brain disease, and although a clinical staging scale has recently been published, it has a relatively limited sensitivity as a measure of the degree of brain involvement. Thus there is a need for a technique that could accurately assess the amount of brain involvement.

Proton magnetic resonance spectroscopic imaging ('1H-MRSI) provides a non-invasive method to obtain information on brain metabolism, and has been successfully applied to the study of CNS disorders. The principal metabolite signals detected by '1H-MRSI at long echo time (TE) are compounds containing the N-acetyl group with N-acetyl aspartate (NA) as the prominent contributor, compounds containing choline (Cho), creatine plus phosphocreatine (Cre), and lactate (Lac). The multislice '1H-MRSI technique used in the present study permits simultaneous acquisition of NA, Cho, Cre, and Lac signal intensities from four brain sections, and enables spatial mapping of metabolic abnormalities.

In the present study of patients with NP-C, our goals were to determine whether multislice '1H-MRSI could (a) detect specific cortical and subcortical neuronal loss or damage, and regionally specific chemical changes associated with astrogliosis and demyelination, and (b) to correlate '1H-MRSI findings with the degree of clinical impairment.

Subjects and methods

We studied 10 patients with NP-C, six males and four females, aged 6 to 39 years, and 15 healthy volunteers as controls (15 to 40 years old).

Patient characteristics and clinical rating scale

Table 1 shows the clinical and MRI characteristics of the patients. A clinical stage was assigned to each patient based on both a previously published clinical staging classification for NP-C and on the clinical characteristics of each patient at the time of the '1H-MRSI. The clinical stages scale has five stages ranging from stage 0, with only biochemical evidence of NP-C, and no neurological abnormality, to stage 4, which is the end stage of neurological involvement.
### Table 1 Clinical data on patients with NP-C in the study

<table>
<thead>
<tr>
<th>Patient/sex</th>
<th>Age studied (y)/onset of neurological disease</th>
<th>Clinical findings/clinical stage</th>
<th>MRI findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F</td>
<td>10/8</td>
<td>VSNGP visual spatial perception abnormality, A/1</td>
<td>Brain atrophy: Absent  White matter hyperintensity: Absent</td>
</tr>
<tr>
<td>2/F</td>
<td>17/NR</td>
<td>Slow down gaze saccades, A/0</td>
<td>Absent  Absent</td>
</tr>
<tr>
<td>3/M</td>
<td>6/1</td>
<td>VSNGP, spasticity weakness, ataxia, dysarthria, IQ-53, AWA/3</td>
<td>Absent  Absent</td>
</tr>
<tr>
<td>4/M</td>
<td>32/15</td>
<td>VSNGP, speech apraxia, ataxia, dysphagia, AWA/3</td>
<td>Moderate cerebral and cerebellar: Marked  Mild cerebral and cerebellar: Mild</td>
</tr>
<tr>
<td>5/M</td>
<td>22/8</td>
<td>Severe dystonia, anarthria, dysphagia, A with support and mild-to-moderate dementia/3</td>
<td>Mild cerebral: Absent  Mild cerebral: Mild</td>
</tr>
<tr>
<td>6/M</td>
<td>39/18</td>
<td>VSNGP, dysarthria, ataxia, mild dystonia, A with support IQ-68, language, visuomotor deficit/3</td>
<td>Mild cerebral: Absent  Mild cerebral: Mild</td>
</tr>
<tr>
<td>7/M</td>
<td>20/6</td>
<td>VSNGP, moderate dystonia, paranoid delusions, A, mild to moderate dementia/2</td>
<td>Moderate cerebellar: Absent  Moderate cerebellar: Absent</td>
</tr>
<tr>
<td>8/M</td>
<td>25/18</td>
<td>VSNGP, dystonia, dysphagia, ataxia, AWA, IQ-65, deficient language and visuomotor function/3</td>
<td>Absent  Absent</td>
</tr>
<tr>
<td>9/F</td>
<td>20/11</td>
<td>VSNGP, mild dysarthria, perceptual skills/2</td>
<td>Moderate cerebral: Absent  White matter hyperintensity: Absent</td>
</tr>
<tr>
<td>10/F</td>
<td>15/6</td>
<td>Complete quadripleas, ophthalmoparesis responsiveness, NA/4</td>
<td>Moderate cerebral: Moderate  White matter hyperintensity: Marked</td>
</tr>
</tbody>
</table>

A=ambulatory; NA=non-ambulatory; AWA=ambulatory with assistance; NR=not relevant; VSNGP=vertical supranuclear gaze palsy.

### MRI Studies

**Brain MRI of patients with NP-C** were obtained, before the acquisition of the 1H-MRSI data, with a 1.5 Tesla magnet (GE Medical Systems, Milwaukee, WI, USA) with T1 (TR: 416–500 ms; TE 9–16 ms) and T2 weighted (TR 2000–4000 ms; TE 90–108 ms) pulse sequences. The acquired images were reviewed by an experienced neuroradiologist (NJP) in a blind fashion without previous knowledge of the 1H-MRSI and clinical findings. Two variables were examined: the incidence of brain atrophy and the presence and severity of white matter abnormalities.

To assess the presence of atrophy, the bifrontal diameter of the lateral ventricles was measured and compared against the transverse diameter of the skull at the same level as previously described. From these measurements a bifrontal ratio was obtained; a value >33% was considered abnormal. With subjective criteria, the size of the cortical sulci in the cerebral hemispheres and in the cerebellum was also evaluated.

Abnormalities in the white matter were assessed by the presence of abnormal areas of increased signal intensity with the T2 weighted technique. A three grade scale (mild, moderate, or marked) was used to rate brain atrophy and white matter abnormalities.

**1H-MRSI Studies**

The 1H-MRSI studies were performed on the same 1.5 Tesla MR imager equipped with self shielded gradients with a previously described data acquisition procedure and a standard quadrature imaging head coil. Images were obtained at an angle of about +20° from the orbitomeatal line to depict the maximum number of spectroscopic voxels throughout the brain. Phase encoding procedures were used to obtain a 32×32 array of spectra from voxels with a nominal volume of 0.84 ml (7.5 mm×7.5 mm×15 mm) within the selected slices. The 1H-MRSI data acquisition comprised a multiple slice spin echo slice selection with a repetition time (TR) of 2200 ms and a TE of 272 ms. Outer volume signal saturation was used to suppress signals arising from the skull marrow and surface tissues. Four 15 mm thick slices with 2.5 mm interslice spacing were acquired. One patient (10) was studied with an earlier 1H-MRSI technique that allowed acquisition of a single 15 mm spectroscopic slice, which we located at the level of the centrum semiovale.

The raw data from each slice consisted of a set of 804 phase encoded full spin echoes. The phase encodings sample a circular region of the k space centred at the origin. Each echo consists of 256 complex points sampled 1 ms apart (sweep width 1 kHz). The echoes were apodised by multiplying the nth point by the factor:

\[
\sin\left(\pi \frac{n}{128}\right) \text{ for } n<64 \\
1 \text{ for } 64 \leq n \leq 192 \\
\sin\left(\frac{256-n}{128}\right) \text{ for } n>192
\]

The echoes were zero filled to 512 points and Fourier transformed to the frequency domain; the k space at each point in the frequency domain was zero filled to form a 32×32 square matrix (with k=0 at the centre), and the k space domain was apodised by multiplying spectrum l,m (-15<l,m<16) by sin ((l-0.5)/33) sin ((m-0.5)/33) before Fourier transforming to yield a 32×32 array of spectra.

To generate metabolite signal intensity images, the following procedure was used: (a) the magnitude for each spectrum was computed; (b) an automated peak picking program was used to identify the Cho, Cre, NA, and Lac peaks; (c) the peak identification was reviewed and manually changed when the automatic procedure had failed; and (d) spectra from voxels contaminated by fat were zeroed out. After the peaks in all the spectra were properly identified, metabolite values were assessed for each pixel by summing the magnitude spectrum over a frequency band of width 6 Hz (0.1 ppm) centred at each peak. Magnitude values were integrated to produce four 32×32 arrays showing spatial variation of the strength of each signal in each of the selected slices.

The 3 mm T1 and T2 weighted MRIs were used to identify the spectroscopic voxels encompassing defined neuroanatomical structures within the brain. Regions of interest (ROIs, fig 1), containing an integral number of 0.84 ml spectroscopic voxels, were identified from the frontal cortex, temporal cortex, occipital cortex, parietal cortex, cingulate gyrus, centrum semiovale, thalamus, and caudate, according to the following criteria: (a) the spectroscopic voxels should fit entirely within...
Figure 1  Location of the regions of interest (ROIs) and representative spectra in a control. The ROIs were selected from the frontal cortex (FC), temporal cortex (TC), occipital cortex (OC), parietal cortex (PC), cingulate gyrus (CG), centrum semiovale (CSO), thalamus (TH), and caudate (CD). Cho=choline; Cre=creatine; NA=N-acetylaspartate.
Table 2  Abnormal ^1^H-MRSI and clinical rating scale scores (CRSS) findings in patients with Niemann-Pick disease type C (NP-C) and controls

<table>
<thead>
<tr>
<th>NPC</th>
<th>CRSS</th>
<th>FC</th>
<th>TC</th>
<th>OC</th>
<th>PC</th>
<th>CG</th>
<th>CSO</th>
<th>TH</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA/Cre</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2.22↓</td>
<td>NS</td>
<td>NS</td>
<td>—</td>
<td>NS</td>
<td>1.72↓</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>1.64↓</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
<td>1.65↑</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1.73↓</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>—</td>
<td>2.22↓</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>1.63↓</td>
<td>1.83↓</td>
<td>NS</td>
<td>NS</td>
<td>1.50↓</td>
<td>1.54↑</td>
<td>2.03↓</td>
<td>1.28↑</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>1.58↓</td>
<td>1.85↓</td>
<td>NS</td>
<td>NS</td>
<td>1.96↑</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>1.63↓</td>
<td>2.104</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>1.60↓</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>2.18↓</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
<td>1.08↓</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>3.13↑</td>
<td>—</td>
<td>—</td>
<td>NS</td>
<td>—</td>
<td>—</td>
<td>NS</td>
<td>—</td>
</tr>
</tbody>
</table>
| Controls  | Mean (SD) | (2.83 (0.30), (2.65 (0.17), (2.59 (0.43), (2.52 (0.25), (2.39 (0.21), (2.81 (0.26), (2.54 (0.22), (2.53 (0.23)
| Cho/Cre   | Range | (2.55–3.70), (2.20–4.40), (1.50–3.10), (1.50–3.10), (1.65–2.84), (2.11–3.79), (2.58–4.12), (1.98–3.31), (1.68–2.87)
| NA/Cre    |      |     |     |     |     |     |     |     |     |
| 1         | 1    | NS  | NS  | NS  | NS  | NS  | 1.87↑ | NS  | NS  |
| 2         | 0    | NS  | NS  | NS  | NS  | —   | NS  | NS  | NS  |
| 3         | 3    | 1.80↑ | NS  | NS  | NS  | —   | 2.03↑ | NS  | NS  |
| 4         | 3    | 1.79↑ | NS  | NS  | NS  | NS  | NS  | NS  | —   |
| 5         | 3    | 1.73↑ | 1.60↑ | NS  | NS  | 1.85↑ | 1.75↑ | —   | —   |
| 6         | 3    | 1.64↑ | NS  | NS  | NS  | NS  | 1.99↑ | —   | —   |
| 7         | 2    | NS  | NS  | NS  | NS  | NS  | NS  | NS  | —   |
| 8         | 3    | 1.82↑ | —   | NS  | —   | NS  | 2.09↑ | NS  | NS  |
| 9         | 2    | 1.64↑ | —   | NS  | NS  | —   | 2.28↑ | NS  | NS  |
| 10        | 4    | 2.15↑ | —   | —   | NS  | —   | 2.49↑ | —   | —   |
| Controls  | Mean (SD) | (1.08 (0.22), (1.11 (0.18), (0.95 (0.12), (1.20 (0.24), (1.09 (0.17), (1.24 (0.20), (1.24 (0.20), (1.32 (0.30)
| Range     | (0.86–1.50), (0.81–1.57), (0.61–1.29), (1.01–1.72), (0.82–1.81), (1.05–1.69), (1.06–1.67), (1.12–1.75)

For definition of abnormal ^1^H-MRSI values and abbreviations see methods.

FC=frontal cortex; TC=temporal cortex; OC=occipital cortex; PC=parietal cortex; CG=cingulate gyrus; CSO=centrum semiovale; TH=thalamus; CD=caudate.

Proton magnetic resonance spectroscopic imaging in Niemann-Pick disease

Table 2 shows the abnormal ^1^H-MRSI and clinical rating scale scores (CRSS) findings in patients with Niemann-Pick disease type C (NP-C) and controls. The table presents the mean (SD) of the abnormal metabolism ratios for each ROI and each patient. The table includes the following ROIs:

- Frontal cortex (FC)
- Temporal cortex (TC)
- Occipital cortex (OC)
- Parietal cortex (PC)
- Cingulate gyrus (CG)
- Centrum semiovale (CSO)
- Thalamus (TH)
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Figure 2  Two sections of the $^1$H-MRSI and corresponding MRI of (A) a control and (B) a patient with NP-C (S). The MRI slice is 3 mm thick and corresponds to the centre of the 15 mm thick $^1$H-MRSI slice. Cho=choline; Cre=creatinine; NA=N-acetyl aspartate. $^1$H-MRSI data are displayed with a colour scale which depicts the strongest signal integral with red and the weakest with dark blue. The $^1$H-MRSI data are displayed at their nominal voxel in plane resolution (7.5 mm×7.5 mm). Colour images are scaled to the highest value of one the three metabolite signal intensities for each $^1$H-MRSI, so that the pattern of regional distribution of metabolite signal intensities within the same slice can be compared between subjects, although colour intensity from the same anatomical location cannot be compared between subjects.
Proton magnetic resonance spectroscopic imaging in Niemann-Pick disease

In patients with Niemann-Pick disease (NP-C), there were 1H-MRSI abnormalities. In two of the three patients with normal MRI, there were 1H-MRSI abnormalities.

Five of the 10 patients showed evidence of cerebral atrophy (table 1). In four of them, the lateral ventricles were enlarged and the cortical sulci were slightly widened, whereas in the fifth patient, who was less severely affected, brain atrophy was documented by ventricular enlargement. White matter abnormalities were found in five patients; four of them also had evidence of brain atrophy. In two of these patients, there was marked white matter involvement, whereas in the remaining three, involvement was mild. The periventricular and deep white matter structures were more severely affected with the subcortical regions being relatively spared. In four of the five patients (4, 5, 7, and 10) with white matter abnormalities, the central semiovale spectroscopic data partially included the affected white matter.

Significant correlations were found between clinical staging scale scores and NA/Cre in the frontal cortex ($r=−0.91; p<0.0002$) and caudate ($r=−0.97; p<0.005$) and Cho/Cre in the frontal cortex ($r=0.87; p<0.001$); percentage of abnormal ROIs for NA/Cre ($r=0.78; p<0.006$), percentage of abnormal ROIs for Cho/Cre ($r=0.76; p<0.01$); and brain atrophy ($r=0.72; p<0.02$).

**Discussion**

The clinical range of NP-C is heterogeneous, and two clinical subgroups with five stages of severity within each group have been differentiated. Histological brain abnormalities include storage material in ballooned neurons and axons, axonal spheroids, neuronal and axonal loss, and to a minor extent, astroglisis. Neuronal ballooning is widespread, but is particularly evident in the basal ganglia, brain stem, and spinal cord. Neurofibrillary tangles, not associated with $β$-amyloid deposits, have been found in the cerebral cortex as well as in the basal ganglia, thalamus, and hypothalamus. N-acetyl aspartate is inferred to be neuron specific because it is absent in both mature glial cell cultures and tumours of glial cell origin. Also, immunofluorescence studies have shown that fluorescent anti-NA antibodies colocalise with antibodies against neuron specific proteins. Recent experimental and clinical evidence suggests that NA may also be a marker of neuronal dysfunction. The present multislice 1H-MRSI study showed a diffuse pattern of neuronal involvement in patients with NP-C as indicated both by a significant reduction of NA/Cre (as group differences) in the frontal cortex, parietal cortex, centrum semiovale, and caudate and by the abnormal values in each patient. 1H-MRSI findings are consistent with the diffuse involvement of the CNS reported in previous neuropathological studies. In particular, the frequent presence of spectroscopic abnormalities in the frontal cortex in our patients parallels the predominant frontal lobe involvement that is found in postmortem analysis of NP-C brains. The topographical heterogeneity of our 1H-MRSI findings is also consistent with the diversified clinical presentation of patients with NP-C.

The Cho peak reflects total brain choline stores, with major contributions from free choline, glycerophosphocholine, and phosphocholine. Increased Cho signal has been attributed to myelin breakdown as found in multiple sclerosis, some childhood white matter diseases, and increased turnover of membrane constituents, as found in brain tumours. Higher concentrations of Cho are also found in astrocyte preparations. Therefore, we suggest that the significant Cho/Cre increase found in the frontal cortex and centrum semiovale of patients with NP-C may be regarded as an in vivo correlate of demyelination and astroglisis.

Methods of obtaining absolute measures of signal intensity are not yet fully developed for 1H-MRSI techniques. Because additional time-consuming scans are required, no effort was made in the present study to attain absolute signal levels. In such instances, the Cre signal is often used as a normalising factor to enable comparison between different brain regions and different subjects. The brain Cre MR signal has been studied in detail by Petroff et al. The molecules (creatinine and phosphocreatine) which generate the Cre signal are widely distributed throughout the brain at a concentration of 7−11 mmol/kg wet weight. The total creatine plus phosphocreatine pool remains stable under a wide variety of abnormal metabolic and physiological conditions. Creatine and phosphocreatine are present in grey matter and white matter at about equal concentrations. For these reasons, the Cre signal was used as a normalising factor for our analysis. Despite these attributes, Cre is generally the smallest signal in the voxel spectrum. Accordingly, it is influenced to a greater extent proportionally by the random noise and artifacts which may be present in the spectrum. These factors are likely to be responsible for the apparent regional variation in Cre signal which appears in fig 1.

The MRI features of patients with NP-C have not been extensively described. Our MRI findings suggest that cerebral and cerebellar atrophy and white matter abnormalities, although non-specific, are often present in NP-C. The significant correlation between brain atrophy and clinical score scales increases the value of MRI in evaluating patients with NP-C.

Significant correlations were found between the clinical stage and decreased NA/Cre in the frontal cortex and caudate, increased Cho/Cre in the frontal cortex, and the percentage of abnormal ROIs for both NA/Cre and Cho/Cre. The limited number of significant correlations
found between clinical rating scale scores and metabolite ratios may be due to the few patients and the negative effect of the undetected spectroscopic voxels in several ROIs. Nevertheless, these results support the usefulness of 1H-MRSI in differentiating among patients with different degrees of severity of clinical abnormalities. In particular, with both the degree of abnormality of NA/Cr and Cho/Cr and the topographical distribution of these abnormalities, 1H-MRSI is likely to become a sensitive tool to evaluate brain involvement in NP-C, and possibly other neurodegenerative diseases.

To our knowledge, there is only one previous 1H-MRS study of one patient with NP-C.44 Proton spectra, acquired from a single subventricular volume of interest containing some grey but mostly white matter, showed normal Cho/Cr and NA/Cr and the presence of an abnormal lipid peak (at TE of 136 ms). Treatment with cholesterol lowering agents caused the disappearance of the lipid peak at 13 and 19 months. Our results are not consistent with previous findings.45 We found regionally reduced NA/Cr and increased Cho/Cr but no abnormal lipid peaks in any of the ROIs of our patients. This lack of an abnormal lipid peak may be due to the different TE (272 ms) used in the present study, which is less sensitive for detecting peaks from free lipids. Indeed, at TE of 272 ms, no lipid peak was evident.46 We suggest that these discrepancies reflect the advantages of multislice 1H-MRSI that permits a more detailed approach to studying diffuse CNS disorders.

The inclusion criteria used in the present study led to the exclusion of several spectroscopic voxels, and in some ROIs, no spectroscopic data could be collected at all. This was due to a combination of two limiting factors. Firstly, the size of the anatomical structure influences the number of spectroscopic voxels that could be selected, which resulted in only limited information from small but important structures (the caudate). Therefore, we were unable to explore all the structures (the posterior fossa structures) could be a sensitive tool to evaluate brain involvement in NP-C, and possibly other neurodegenerative diseases. Moreover, 1H-MRSI is a useful non-invasive and objective method in the clinical evaluation of patients with NP-C, and may find application in therapeutic trials directed at the primary metabolic defect in this disease.

We thank CTW Moonen and JH Duyn for making the 1H-MRSI sequence available. We also appreciate the skilful editing of DG Schoenberg.

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