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Proton MR spectroscopy features of normal appearing white matter in neurofibromatosis type 1

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Abstract

To determine whether differences exist between neurofibromatosis type 1 (NF1) patients with or without focal lesions and healthy normal volunteers in the metabolite ratios of normal appearing white matter, 27 patients with NF1 (with parenchymal lesion, MR positive, n: 17; without parenchymal lesions, MR negative, n: 10) and 20 healthy volunteers underwent MRI and short TE (31 ms) proton MR spectroscopy (MRS). In 17 patients with parenchymal lesions, 61 focal lesions were detected by MRI. MRS was performed from normal appearing frontal and posterior parietal white matter (FWM and PWM) in NF1 and from control groups. NAA/Cr, Cho/Cr and MI/Cr ratios were calculated. Significant increase in Cho/Cr and MI/Cr ratios were found in FWM and PWM in MR negative and positive groups when compared to control group. NAA/Cr ratio in MR positive group was significantly decreased in FWM compared to control group. There were no significant differences between FWM and PWM in all metabolite ratios of MR negative group. MI/Cr ratio in MR positive group was significantly elevated in PWM compared to FWM. Metabolite changes detected by MRS could indicate demyelination and gliosis in normal appearing white matter in all NF1 patients, and additionally neuroaxonal damage in the FWM of NF1 patients with focal lesions. For that reason, in the clinical evaluation and follow-up of these patients MRS features of normal appearing white matter should be considered in addition to focal lesions.

Keywords: Neurofibromatosis type 1; Magnetic resonance spectroscopy; White matter

1. Introduction

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is a member of neurocutaneous syndrome. It is also the most frequent autosomal dominant genetic disease in humans, inherited by a gene located in chromosome 17, affecting one in 3000 to 4000 individuals, regardless of race, ethnic origin, or sex [1–4].

Parenchymal lesions, whether benign or malignant, all appear as focal areas of increased signal intensity on T_2-weighted images, and are common feature of this disease. Globus pallidum, brainstem, thalamus, hypothalamus, cerebellum and subcortical white matter are the most commonly involved sites [1,5–9].

MRS is a non-invasive imaging modality that can provide information on neuronal/axonal viability, cellular energetics, and cellular membrane status [10] It could give neurochemical information about white matter changes in NF1.

Although some of the investigators reported MRS characteristics of normal appearing brain tissues, their findings are about that of basal ganglia or findings of a very limited number of cases [11,12]. In the literature search, no studies could be found investigating the differences between normal appearing white matter of NF1 patients and white matter of normal healthy controls.

Our aims in this study were to determine; the differences in the metabolite ratios of normal appearing white matter between NF1 patients, with or without parenchymal lesions, and healthy normals.

2. Materials and methods

A total of 27 consecutive patients (14 females, 13 males, age range: 4–61 years, mean age: 21.7 ± 14.5) who were

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referred to our neuroradiology department and had the diagnosis of NF1 based on standard clinical criteria [13,14] and 20 healthy volunteers (7 females, 13 males, age range: 7–39 years, mean age: 16.2 ± 10.1) were included in this prospective study. Informed consents were obtained from all patients or parents of juvenile patients, and healthy controls. None of the patients and controls was sedated. The MRI examination consisted of routine imaging and single voxel spectroscopy.

MRI was performed on a 1.5-T system (Philips, Gyroscan Intera Master, Netherlands). T1 weighted images (TR: 560, TE: 15) were obtained in the axial and sagittal planes (with 5 mm- thick slices). T2 weighted images (TR: 4530, TE: 100) were obtained in the axial and coronal planes. Additionally, axial and coronal gadolinium enhanced images were acquired.

Single voxel spectroscopy (SVS) was performed in all patients by using a point-resolved spectroscopy sequence (PRESS) (TR: 2000/TE: 31 ms) with 256 averages; voxel sizes of 15 × 15 × 15 mm were used. Voxels were placed in FWM and PWM. Since focal lesions develop from white matter [4,15,16], voxels were placed in FWM and PWM in order to determine whether there are metabolic changes in white matter even though normal appearance on MRI or not. In the placement of the voxels, contamination by gray matter and CSF was avoided. Due to the increased signal/noise ratio of short TE, and the visualization of additional compounds like myo-inositol seen by short TE, the short TE PRESS was chosen as the primary pulse sequence. Prior to MR spectroscopy, shimming was performed to optimize field homogeneity and water suppression was optimized using automated routines. The water signal was suppressed by a chemical-shift selective saturation pulse. A spectral sweep width of 1000 Hz was used with data size of 1024 points. All data postprocessing was performed with software provided by the manufacturer (MMR 5461 1 H spectroscopy 1.5 T package). The magnitude spectra were processed automatically using baseline correction and curve-fitting procedures to determine the resonance areas of N-acetylaspartate (NAA), creatinine (Cr), choline (Cho) and myo-inositol (MI). Resonances were assigned as follows: NAA, 2.0 ppm; Cr, 3.02 ppm; Cho, 3.2 ppm; MI, 3.56 ppm. Peak area metabolite ratios (NAA/Cr, Cho/Cr, and MI/Cr) were calculated. For each patient, two authors assessed whether the spectra were diagnostic.

All statistical analyses were performed using a commercially available SPSS release 10.0 software package (SPSS Inc., Chicago, IL). The results are presented as mean ± standard deviation in order to facilitate comprehension of the tables. Measurements in all groups showed normal distribution by Shapiro-Wilks method ($p > 0.05$). One Way ANOVA test was utilized for the general comparison of metabolite ratios of groups. Tukey HSD test was used for the comparison of MRS metabolite ratios between the controls and the patients with NF1. Unpaired *t* test was utilized for the assessment of difference in metabolite ratios between FWM and PWM in NF1 patients. A *p* value below 0.05 was considered statistically significant.

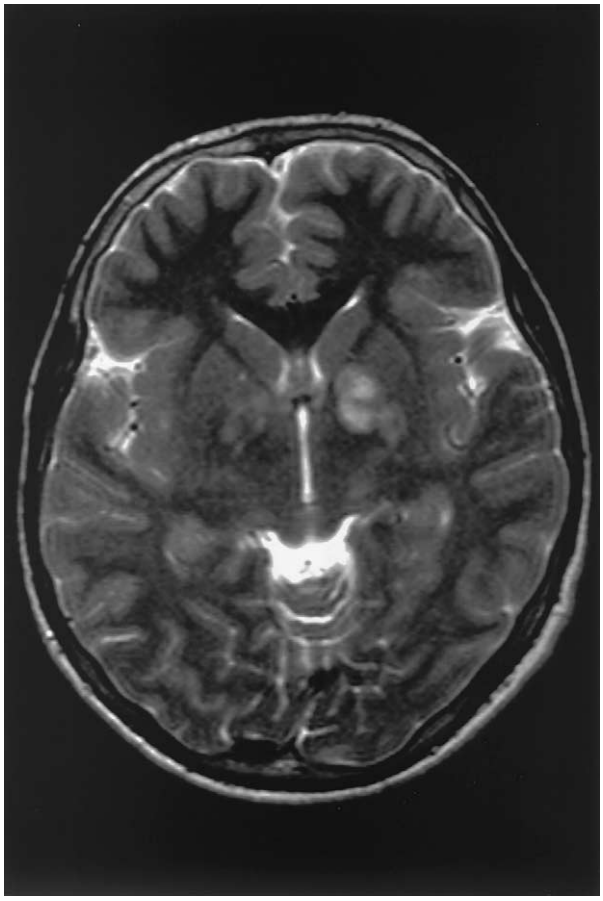

Fig. 1. Axial T2 weighted image (4530/100) shows focal lesions in bilateral globus pallidum and right hippocampus.

3. Results

There was a significant difference in age between MR positive and negative groups. The mean age of MR negative group was significantly higher than that of MR positive group.

Parenchymal lesions were identified in 17 (9 females, 8 males, age range: 4–36, mean age: 13.1 ± 5.2 years) our of 27 patients with NF1. In the remaining 10 (5 females, 5 males, age range: 8–61, mean age: 33.4 ± 13.8) no parenchymal lesions were identified. With MRI a total of 61 focal lesions were found in the cerebellar white matter (n: 13), globus pallidum (n: 18), midbrain (n: 10), thalamus (n: 10), hippocampus (n: 7), and pons (n: 3) (Fig. 1).

There was no significant difference between MR negative and control groups in NAA/Cr ratio obtained from FWM and PWM (p: 0.2). NAA/Cr ratio in MR positive group was significantly decreased in FWM compared to control group (Fig. 2) (p: 0.03). The Cho/Cr and MI/Cr ratios of the NF1 patients (both MR positive and negative

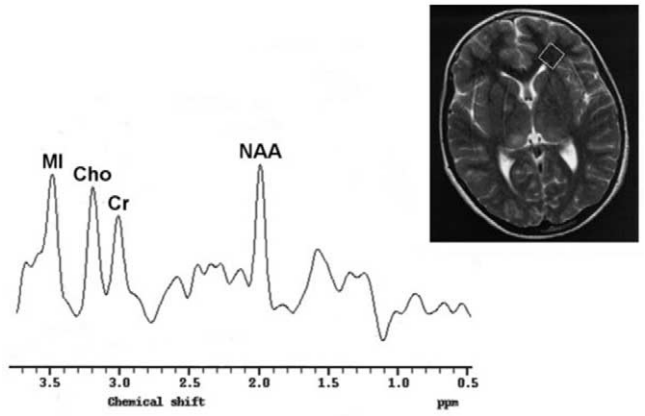

Fig. 2. An 8-year-old female with focal lesions in bilateral thalamus and right globus pallidum. MR spectrum obtained from normal appearing frontal white matter shows decreased NAA/Cr and increased Cho/Cr and MI/Cr.

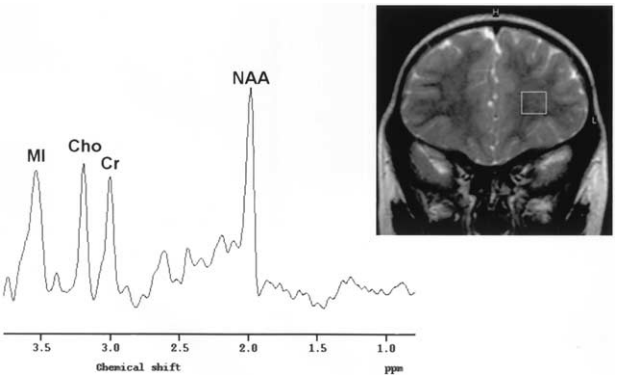

Fig. 4. A 26-year-old female patient without parenchymal lesion. MR spectrum obtained from normal appearing frontal white matter shows normal NAA/Cr and increased Cho/Cr and MI/Cr.

ones) were significantly higher in both FWM and PWM when compared to control group ($p > 0.05$) (Fig. 3). In the MR negative group, there were no significant differences between FWM and PWM in all metabolite ratios (Fig. 4, 5). But in the MR positive group, only the MI/Cr ratio was significantly different between FWM and PWM (1.07 ± 0.18 and 1.33 ± 0.28 respectively). Table 1 shows the mean metabolite ratios in each of the three groups.

4. Discussion

NF1 is the most common phakomatosis, having an autosomal dominant inheritance. The modification in genes causes variable activity of neurofibromin and oligodendrocytic myelin glycoprotein [4].

The parenchymal brain involvement in this disease is focal that appears as hamartomas and gliomas. Traditionally hamartomas regarded as areas of heterotopias, which include gliosis, low-grade astrocytomas, atypical glial infiltrates, foci of microcalcifications, and spongiform or vacuolar change in myelin [5,17–22]. Edematous changes and vacuolization of myelin, secondary to metabolite changes within the brain lead to variations in imaging appearances of lesions which may also depend on the anatomic location itself. It is probable that metabolic changes precede the changes seen on MRI [12].

Asymptomatic lesions are not generally seen in adults with NF1 and spontaneous regression, often in the second decade, has been reported [15,23,24]. The ages of the patients without focal lesions were significantly higher than patients with focal lesions in our study which is concordant with the literature.

MRS is being used for the study of biochemical behavior of demyelinating disorders in vivo [10]. It is possible to detect metabolite changes in the normal appearing white matter by MRS. The issue of metabolite ratios of asymptomatic brain lesions in NF1 patients is debatable. Castillo et al. [5] reported normal intervening brain and no significant differences in metabolites in the normal appearing brain in NF1 patients with and without focal lesions when compared with healthy volunteers. On the other hand, Jones

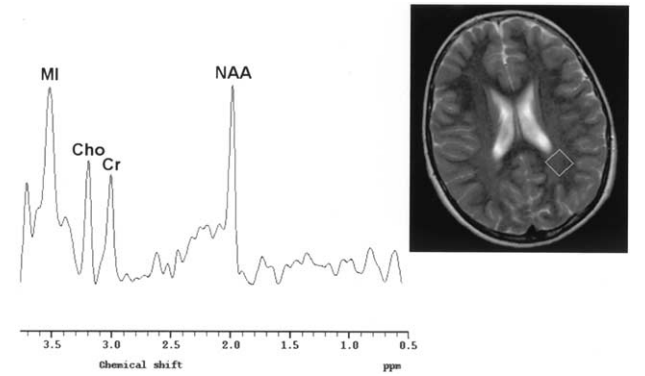

Fig. 3. An 11-year-old female with focal lesions in bilateral globus pallidum. MR spectrum obtained from normal appearing posterior parietal white matter shows increased Cho/Cr and MI/Cr.

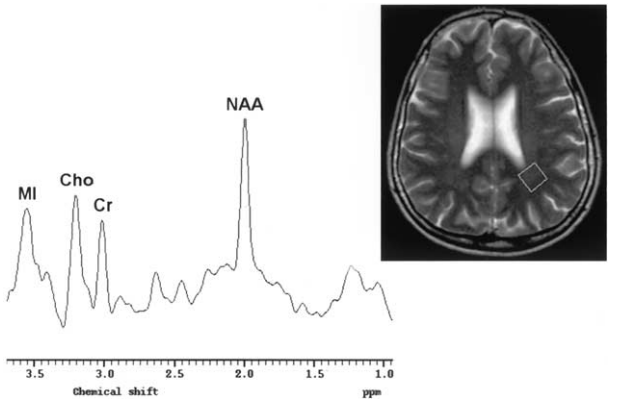

Fig. 5. A 14-year-old female without parenchymal lesion. MR spectrum obtained from normal appearing posterior parietal white matter shows normal NAA/Cr and increased Cho/Cr and MI/Cr.

Table 1
Spectroscopy findings obtained from normal appearing parietal white matter in NF1 patients

	FWM			PWM		
Metabolite ratios	MR Positive (n = 17)	MR Negative (n = 10)	Control (n = 20)	MR Positive (n = 17)	MR Negative (n = 10)	Control (n = 20)
NAA/Cr	1.52 ± 0.24*	1.58 ± 0.27	1.74 ± 0.24	1.57 ± 0.17	1.56 ± 0.24	1.67 ± 0.10
Cho/Cr	1.14 ± 0.13*	1.16 ± 0.31*	0.75 ± 0.16	1.09 ± 0.14*	1.07 ± 0.26*	0.75 ± 0.18
MI/Cr	1.07 ± 0.18*	1.13 ± 0.23*	0.69 ± 0.14	1.33 ± 0.28*	1.01 ± 0.18*	0.68 ± 0.13

* $p < 0.05$ compared with control group.
FWM: Frontal white matter
PWM: Parietal white matter

et al. [12] reported abnormal metabolic changes in the corresponding area of normal appearing brain on MRI in a patient who had hamartoma on the previous MRI examination performed one year ago. Based on this finding, they concluded that metabolic changes in corresponding area of normal brain could be due to residual lesions. With MRS, we have found metabolic changes in the normal appearing white matter in NF1 patients with or without focal lesions (Fig. 6A, B).

The decrease in NAA/Cr ratio may indicate neuroaxonal damage or deficient neuronal formation in white matter [10]. The finding of significant decrease in NAA/Cr ratio from normal appearing FWM of MR positive patients and no difference in NAA/Cr ratio in MR negative group, when compared to control group, could indicate neuroaxonal damage in FWM of NF1 patients with focal lesions and conversely no neuroaxonal damage in patients without focal lesions in our study. For that reason, it may be speculated that neuroaxonal damage in white matter could regress similar to the regression of focal lesions after second decade.

The increased Cho/Cr and MI/Cr levels, which could indicate increased membrane turnover, and myelin breakdown and astrocytosis respectively, might correspond to glial cell proliferation [10]. The significant increases in Cho/Cr and MI/Cr ratios, both in FWM and PWM, observed in our study could be an indication of demyelination and gliosis. Additionally, the increase in MI/Cr ratio was higher in PWM in both groups. Thus, the degree of gliosis might be prominent in PWM.

The presence of metabolic changes in the normal appearing white matter in addition to parenchymal focal lesions in NF1, could suggest a similar pathology in these brain regions [4,11,12]. Since NF1 is a genetic disorder involving a gene on the long arm of chromosome 17 that causes changes in cells of neural crest origin [4], it is reasonable to expect disorders in myelination beginning from birth. The degree of disorder might be independent of MRI appearance in NF1, i.e., although the brain is affected, MRI appearance may be normal. Therefore, MRS should also be utilized in the delineation of brain involvement of NF1 patients.

5. Conclusion

We have found metabolic changes in the normal appearing white matter of all NF1 patients both with and without brain parenchymal lesions. These changes in metabolite ratios could indicate demyelination and gliosis in all NF1

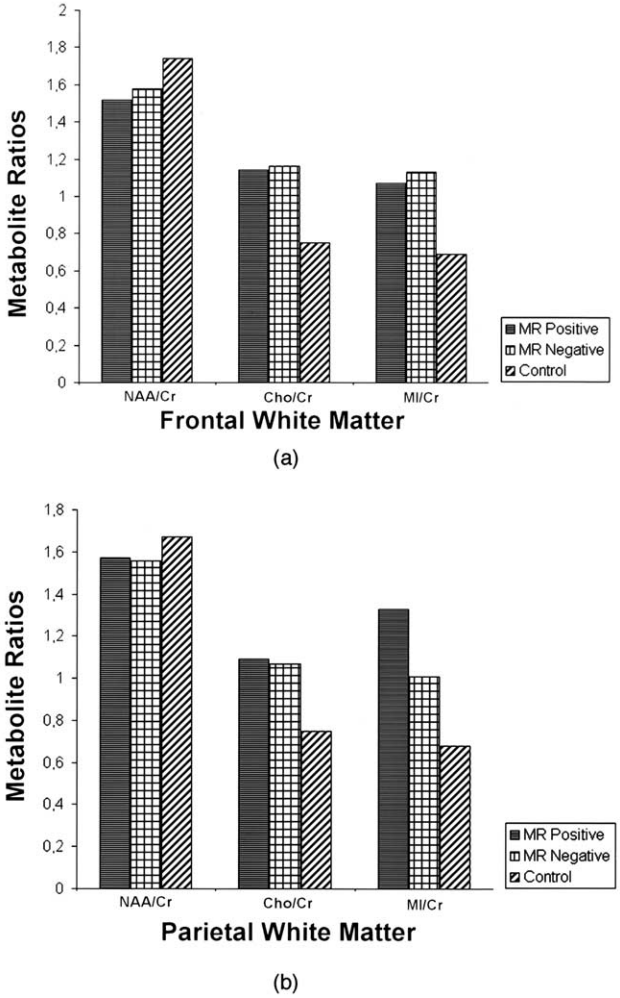

Fig. 6. Mean Cho/Cr and MI/Cr ratios obtained from frontal (A) and parietal (B) white matter of NF1 patients are higher than healthy control subjects. Additionally, NAA/Cr ratio of frontal white matter is significantly decreased in MR positive group.

patients, and neuroaxonal damage in the FWM of NF1 patients with focal lesions. For that reason, MRS features of normal appearing white matter should be evaluated together with focal parenchymal lesions.

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