

Single-voxel Proton MR Spectroscopy of the Basal Ganglia in Patients with Neurofibromatosis Type 1¹

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Purpose : To demonstrate the proton MR spectroscopic characteristics of non-neoplastic focal basal ganglia lesions with high signal intensity on long TR MR images in patients with neurofibromatosis type 1(NF-1), and to compare them with those of normal-appearing basal ganglia in patients without focal lesions.

Materials and Methods : Single-voxel proton MR spectroscopy was performed in six patients with NF-1 from two families(three with and three without non-neoplastic focal brain lesions). All six individual spectra were obtained from basal ganglia with voxel sizes of about $1 \times 1 \times 1$ cm, three from focal pallidal lesions in patients with focal lesions and three from normal-appearing basal ganglia in patients without focal lesions. Spectra were acquired using a 1.5T clinical MR imager and stimulated echo acquisition mode sequence, with the following parameters : 30 ms of echo time, 13.7 ms of mixing time, and 2560 ms of repetition time. Zero and first-order phase correction was performed.

Results : N-acetyl aspartate(NAA)/creatine(Cr) ratios were similar between focal basal ganglia lesions and normal-appearing basal ganglia, though the former showed slightly lower choline(Cho)/Cr ratios and slightly higher NAA/Cho ratios than the latter. Relatively enhanced resonances around 3.75 ppm, assigned as glutamate/glutamine, were observed in the spectra of three focal lesions. Lipid resonances around slightly different positions were observed in all six patients, regardless of the presence or absence of focal lesions.

Conclusion : Slightly decreased Cho levels and relatively enhanced glutamate/glutamine resonances are thought to characterize the focal basal ganglia lesions of NF-1. Different mobile lipids appear to be present in the basal ganglia of NF-1 patients, regardless of the presence of focal lesions.

Index words : Brain, metabolism
Brain, MR
Magnetic resonance(MR), spectroscopy
Neurofibromatosis

Neurofibromatosis type 1(NF-1) or von Recklinghausen's disease is the most common phacomatosis,

with a prevalence of about one in 3000 births. It is transmitted as an autosomal dominant trait in approximately one half of cases, but spontaneous mutations involving the long arm of chromosome 17 are known to be responsible for the remainder(1). The most common intracranial lesions reported in up to 80% of patients with NF-1 are focal areas of high signal intensity on long repetition time(TR) magnetic resonance(MR) images, and are commonly demonstrated in the basal ganglia, especially the globus pallidus, brain stem,

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internal capsule, cerebellar white matter, dentate nucleus, and cerebral white matter(2–5). These lesions are generally not associated with vasogenic edema, mass effect, hemorrhage or contrast enhancement, but unusual lesions in the globus pallidus may reveal a mild mass effect or hyperintensity on T1-weighted images (5–8).

The purpose of our study was to determine the proton MR spectroscopic characteristics of non-neoplastic focal basal ganglia lesions in patients with NF-1 using stimulated echo acquisition mode (STEAM) sequence with small voxel sizes of about 1×1×1 cm, and to compare them with those of normal-appearing basal ganglia in patients with no focal lesions.

Materials & Methods

Six patients from two families(two girls and their father from one family, and two boys and their father from another family ; patient age range, 10–52 years; mean age, 24 years) were diagnosed as NF-1 on the basis of the criteria of the National Institute of Health (NIH) Consensus Development Conference. Three of the six patients showed typical multifocal brain

parenchymal lesions on one or both sides of the basal ganglia, thalamus, internal capsule, cerebral peduncles and dentate nucleus, but in the remaining three the brain appeared normal on MR images. The six basal ganglia lesions (bilateral abnormalities in three patients with focal brain lesions) measured between 0.9 and 1.5 cm in their greatest dimension.

Normal variations are known to be present in metabolite concentrations at different anatomic sites, and to improve the reliability of sampling for single-voxel proton MR spectroscopy all six individual samples were thus obtained from the same site. Three spectra (patient age range, 10–13 years; mean age, 11 years) were obtained from the focal lesions of basal ganglia and three (patient age range, 16–52 years; mean age, 37 years) from the regions of basal ganglia of normal appearance in which MR images did not reveal focal lesions. In patients with bilateral basal ganglia lesions, the larger one was selected for sampling. Spectral voxel was selected graphically from axial T2-weighted scout images with a voxel size of about 1×1×1 cm(Fig. 1A). In the case of a small lesion measuring about 0.9 cm in its greatest dimension, an even smaller voxel size was selected ; this was so as to minimize the contamination

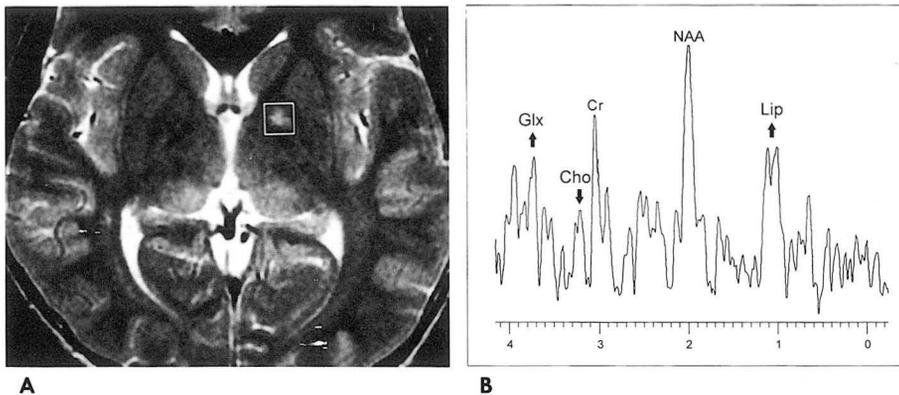


Fig. 1. A 13-year-old male NF-1 patient with focal brain lesions on MR images.

A. Axial T2-weighted scout image shows the location of MR spectroscopic single-voxel (about 1×1×1 cm) at the left pallidal lesion. There also showed right pallidal lesion at the lower level(not shown). Note associated bilateral thalamic lesions at the pulvinars.

B. Proton MR spectra show slight decrease of Cho level at 3.22 ppm, relative enhancement of the glutamate/glutamine(Glx) resonances around 3.75 ppm, and observable lipid resonances around 1.05 ppm.

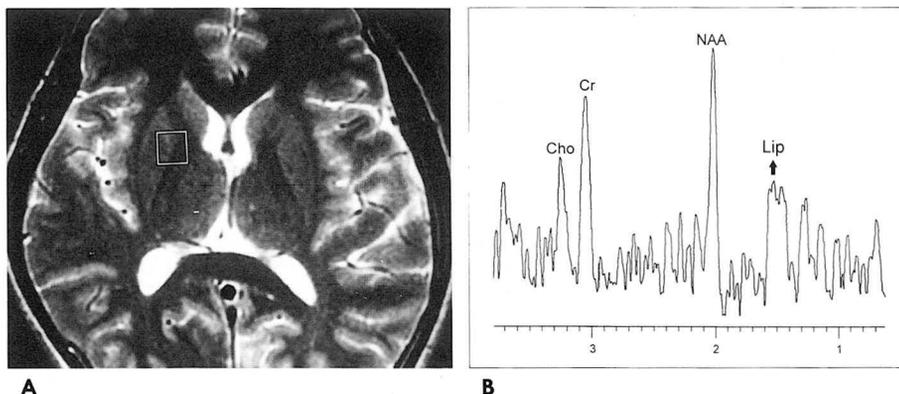


Fig. 2. A 42-year-old male NF-1 patient without focal brain lesions.

A. Axial T2-weighted scout image shows the location of MR spectroscopic single-voxel (about 1×1×1 cm) at the normal-appearing right basal ganglia.

B. Proton MR spectra show observable lipid resonances around 1.5 ppm without particular alteration of the NAA and Cho levels.

of surrounding normal brain. In cases in which brain appeared normal on MR images, we centered the voxel to the basal ganglia (Fig. 2A). Shimming of selected voxel was performed until a water line width of 3 Hz was obtained. Water suppression was achieved by the prior application of chemical-shift selective (CHESS) three orthogonal radiofrequency pulses. All proton spectra were acquired using a 1.5 T GE Signa Horizon clinical MR imager and STEAM sequence for localization, with the following parameters: 30 ms of echo time, 13.7 ms of mixing time, and 2560 ms of repetition time. Spectral width was 2000 Hz, and was stored in 2048 data points. The typical average number of scans was 128-256. Raw data were zero-filled to 4096 and exponentially apodized with 1.5 Hz line broadening, and subsequently Fourier-transformed. Zero and first-order phase correction was performed, though there was no baseline correction, further smoothing or resolution enhancement.

Results

NAA/Cr, Cho/Cr, and NAA/Cho ratios of the three basal ganglia lesions were 1.07 ± 0.10 , 0.46 ± 0.10 , and 2.46 ± 0.72 , respectively, whereas these ratios in the three regions in which basal ganglia appeared normal, with no focal lesions, were 1.08 ± 0.08 , 0.73 ± 0.08 , and 1.48 ± 0.08 , respectively (Table 1). Focal lesions showed slightly lower Cho/Cr ratios and slightly higher NAA/Cho ratios than brain regions of normal appearance, but NAA/Cr ratios were similar. Analysis of proton MR spectra observed from focal basal ganglia lesions therefore showed no distinctive change in NAA levels but slightly lower Cho levels than those observed in basal ganglia of normal appearance.

Relatively enhanced resonances of around 3.75

Table 1. Metabolic Ratios Between Focal Basal Ganglia Lesions and Normal-appearing Basal Ganglia in Patients with NF-1

	NAA/Cr	Cho/Cr	NAA/Cho
Basal ganglia lesions			
Case 1.11/F	1.01	0.58	1.75
Case 2.10/F	1.19	0.38	3.18
Case 3.13/M	1.01	0.42	2.44
mean \pm SD	1.07 ± 0.10	0.46 ± 0.10	2.46 ± 0.72
Normal-appearing B.G			
Case 4.16/M	1.02	0.65	1.57
Case 5.42/M	1.05	0.73	1.43
Case 6.52/M	1.17	0.81	1.44
mean \pm SD	1.08 ± 0.08	0.73 ± 0.08	1.48 ± 0.08

ppm, assigned as glutamate/glutamine, were observed in the spectra of three focal lesions (Fig. 1B). Lipid resonances around slightly different positions were observed in all six patients with NF-1, regardless of the presence or absence of focal lesions (Fig. 1B, 2B).

Discussion

Patients with NF-1 exhibit a wide variety of neoplastic and non-neoplastic intracranial lesions (1). The most common abnormality demonstrated by neuro-imaging studies is non-neoplastic high-signal-intensity foci in the basal ganglia, especially in the globus pallidus, brain stem, internal capsule, cerebellar white matter, dentate nucleus, and cerebral white matter, as seen on long TR MR images (2-5).

Because no correlation has been established between pathologic and radiologic findings, the high-signal-intensity foci seen on long TR MR images have confusingly been described as hamartomas (5), heterotopias (4, 6), gliosis (6), low grade tumors (3), or disordered myelination (8). Follow-up MR imaging studies demonstrated critical evidence of temporal evolution of the lesions, and this transient nature with spontaneous regression would thus deny the possibility of developmental abnormalities such as hamartoma, heterotopia, or neoplastic proliferation (8, 9). The fact that the lesions seen on MR images were found only in children aged less than 13 (mean age, 11 years), but not in older children or adults (mean age, 37 years) supports the hypothesis of evolution of focal brain lesions in patients with NF-1. A recent histopathologic study by Di Paolo et al (10) suggested that hyperintense foci on T2-weighted images were related to spongiform myelinopathy or vacuolar change (vacuoles ranging from 5 to 100 μ m in diameter) of myelin which appeared to constitute the predominant pathologic change. There was no evidence of inflammatory reaction or demyelination. They believed that water within the vacuoles was responsible for the occurrence of high signal intensity on T2-weighted images, and that isointensity rather than hypointensity, as seen on T1-weighted images, was due to partial volume averaging of water within small vacuoles and intervening tissue. Microcalcifications and perivascular schwannosis seen in the globus pallidus might account for the unusual hyperintensity seen on T1-weighted images.

Using large voxel sizes measuring $2 \times 2 \times 2$ cm to $3 \times 3 \times 3$ cm, Castillo et al (11) reported proton MR spectroscopic characteristics of the brain in patients with NF-1 and showed that focal lesions had proton spectroscopic patterns similar to those of normal brain; this might,

we think, influence their results, derived as they were from partial volume averaging of normal surrounding brain within the volume sampled. The long-echo-time point resolved spectroscopy (PRESS) sequence they employed is subject to limitation when used to detect resonances from a coupled spin system such as glutamate, glutamine or inositol. We used the STEAM sequence to reveal any subtle changes in more metabolites that have short decay times.

In our antegrade study, all samples for single-voxel proton MR spectroscopy were obtained from the same anatomic sites; this was because metabolite concentrations at different anatomic sites are known to vary (12). Basal ganglia were selected for sampling because they have been reported to be the most frequent site of focal lesions, which are larger than those found elsewhere. So as to include as much of focal basal ganglionic lesions or regions of normal-appearing basal ganglia in patients without focal lesions as possible, while minimizing partial volume averaging, optimal sizes and locations of voxels were chosen.

Our proton MR spectroscopic study of the brain in patients with NF-1 revealed that NAA levels observed in focal basal ganglia lesions were not significantly different from those in normal-appearing basal ganglia without focal lesions or from those previously reported in normal volunteers. NAA is mostly found in neuronal cells and some neuroglial precursors such as 0-2A progenitor cell line, and is thus accepted as a neuronal marker. Normal levels of NAA in focal brain parenchymal lesions in NF-1 suggest that there is no particular loss or damage of neuronal cells and/or axonal processes of the lesions, and this would explain the transient nature of the lesion and its spontaneous regression without residual abnormal signal on follow-up MR images. Proton MR spectroscopy is therefore a useful diagnostic tool for the differentiation of a focal lesion from a glioma, another common CNS lesion in patients with NF-1 (11).

Cho levels appeared to be slightly lower in focal NF-1-type brain lesions. The *in vivo* Cho signal consists of various compounds such as choline, phosphocholine, glycerophosphocholine, acetylcholine and betaine, all of which are components of phospholipid metabolism and constituents of cell membranes in the brain. Thus, decreased Cho signal intensity in focal lesions may reflect some change other than demyelination or inflammation in cell membrane metabolism. The relationship between reduced cerebral Cho concentration and focal brain lesions in NF-1 remains to be established.

Relatively enhanced resonances of around 3.75 ppm, assigned as glutamate/glutamine, were observed

in focal basal ganglia lesions of NF-1, but not in the spectra of normal-appearing basal ganglia. In addition, lipids resonating around slightly different positions were observed in all six patients, and this may represent the presence of different mobile lipids in both focal lesions and regions of normal-appearing brain without focal lesions. Changes in glutamate/glutamine and lipid metabolism of the brain in patients with NF-1 have not been demonstrated by previous proton spectroscopic studies; this is because the researchers involved used the PRESS sequence, which is inherently insensitive to glutamate/glutamine and lipid (11). In man, *in vivo* spectroscopic studies of cerebral glutamate/glutamine concentrations have been performed mainly in chronic hepatic encephalopathy patients, in whom it was postulated that glutamine acted as an osmolyte (13). The cause of increased glutamate/glutamine levels only in focal basal ganglia lesions and the appearance of lipid resonances regardless of the presence or absence of focal lesions in patients with NF-1 is unclear and requires further investigation.

In summary, the spectra of presumptive non-neoplastic focal basal ganglia lesions in patients with NF-1 are characterized by slightly decreased levels of Cho and relatively enhanced glutamate/glutamine resonances without particular changes in NAA levels.

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신경섬유종증 1형 환자에서 기저핵의 단일 화적소 양성자 자기공명분광소견¹

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목 적 : 신경섬유종증 1형 환자에서 긴 반복시간 자기공명영상에 고신호강도로 보이는 기저핵의 비종양성 국소병변의 양성자 자기공명분광검사상 특징을 찾아보고, 국소 뇌병변이 없는 신경섬유종증 1형 환자에서 정상으로 보이는 기저핵의 자기공명분광검사 결과와 비교하고자 하였다.

대상 및 방법 : 2가족 6명의 신경섬유종증 1형 환자에서 단일 화적소 양성자 자기공명분광검사를 실시하였고, 이중 3명은 비종양성 국소병변이 있었고 3명은 없었다. 6개의 모든 표본은 약 1×1×1cm 크기의 화적소를 사용하여 기저핵에서 얻었고, 이중 3개는 국소 뇌병변이 기저핵에 있었던 환자의 담창구 병변에서 그리고 나머지 3개는 국소 뇌병변이 없었던 환자의 정상으로 보이는 기저핵에서 얻었다. 1.5 Tesla 자기공명영상장치를 사용하였고, 30msec의 에코시간, 13.7msec의 혼합시간 그리고 2560msec의 반복시간으로 자극에코획득방식을 이용하여 스펙트럼을 얻었다. 영점 그리고 일차 위상수정을 실시하였다.

결 과 : N-acetyl aspartate(NAA)/creatine(Cr) 비는 기저핵의 국소병변과 정상으로 보이는 기저핵에서 비슷하였으나, 전자가 후자보다 choline(Cho)/Cr 비가 조금 낮고 NAA/Cho 비는 조금 높았다. Glutamate/glutamine에 해당하는 3.75ppm 근처에서 비교적 증가된 공명이 3예의 국소병변 스펙트럼에서 관찰되었고, 서로 약간 다른 위치에서 공명하는 지방은 국소병변의 동반 유무와 관계없이 6예 모두에서 관찰되었다.

결 론 : 약간 감소된 Cho치 그리고 비교적 증가된 Glutamate/Glutamine 공명이 신경섬유종증 1형에서 보이는 기저핵의 국소병변의 특징으로 생각된다. 그리고 상이한 유동성 지방들이 국소병변의 유무에 관계없이 NF-1 환자의 기저핵에 존재하는 것으로 생각된다.

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