Hybrid Two-Dimensional Proton Spectroscopic Imaging of Pediatric Brain: Clinical Application

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Purpose : To introduce and demonstrate the advantages of the new hybrid two-dimensional (2D) proton spectroscopic imaging (SI) over the single voxel spectroscopy (SVS) and conventional 2D SI in the clinical application of spectroscopy for pediatric cerebral disease.

Materials and Methods : Eighty-one hybrid 2D proton spectroscopic imaging was performed in 79 children (36 normal infants and children, 10 with hypoxic-ischemic injury, 20 with toxic-metabolic encephalopathy, seven with brain tumor, three with meningoencephalitis, one with neurofibromatosis, one with Sturge-Weber syndrome and one with lissencephaly) ranging in age from the third day of life to 15 years. In adult volunteers (n=5), all three techniques including hybrid 2D proton SI, SVS using PRESS sequence, and conventional 2D proton SI were performed. Both hybrid 2D proton SI and SVS using PRESS sequence were performed in clinical cases (n=12). All measurements were performed with a 1.5-T scanner using standard head quadrature coil. The 16×16 phase encoding steps were set on variable field of view (FOV) depending on the size of the brain. The hybrid volume of interest inside FOV was set as $75 \times 75 \times 15$ mm^3 or smaller to get rid of unwanted fat signal. Point-resolved spectroscopy (TR/TE=1,500 msec/135 or 270 msec) was employed with standard chemical shift selective saturation (CHESS) pulses for water suppression. The acquisition time and spectral quality of hybrid 2D proton SI were compared with those of SVS and conventional 2D proton SI.

Results : The hybrid 2D proton SI was successfully conducted upon all patients. The 2D spectral data acquisition time was less than 6 minutes, while the data acquistion time of SVS was 4.3 minutes. This was short enough for pediatric application. The spectra acquired with hybrid 2D proton SI showed nearly the same sensitivity and spectral resolution with SVS. The spectral quality of hybrid 2D proton SI was, on the other hand, far better than that of conventional 2D proton SI. The other advantage of hybrid 2D proton SI was that the extent of metabolic abnormalities could be evaluated through the characteristics of the relative levels of the three metabolites, i.e., N-acetylaspartate, choline, and creatine.

Conclusion : The hybrid 2D proton SI can be successfully employed for the evaluation of the metabolic abnormalities in the various pathologic conditions of pediatric brain without penalty in acquisition time and spectral quality when compared to SVS. The extent of metabolic abnormalities, which cannot be obtained with SVS technique, also can be evaluated with hybrid 2D proton SI.

Index words : MR Spectroscopy, Brain, Children

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Introduction

Currently, two localization schemes are established for in vivo proton magnetic resonance spectroscopy (MRS) of the human brain (1, 2): single voxel spectroscopy (SVS) and spectroscopic imaging (SI). The SVS technique is generally considered to provide the optimal spectral resolution. On the other hand, SI technique provides the simultaneous acquisition of multiple spectra from adjacent locations without penalty in acquisition time. This feature of the SI methods is especially desired in pediatric applications where magnetic resonance (MR) imaging does not reveal a well-delineated region of interest for SVS. In the conventional 2D SI, the subcutaneous fat severely contaminates the spectrum at nearby voxels and degrades overall quality of the MRS data (3). With hybrid 2D SI technique, which preselects a large volume of brain inside field of view (FOV), contamination from unwanted subcutaneous fat signal can be avoided (4).

In this study, we introduced hybrid 2D SI technique in pediatric brain, and demonstrated the advantage of this new spectroscopic technique in clinical application.

Materials and Methods

Subjects

Over a twenty-month period from August 1998 to April 2000, 81 hybrid 2D proton MR spectroscopic studies were performed in 79 children.

1. Volunteers

Five adult volunteers (four males and one female; mean age, 34 years; range, 25–40 years) underwent SVS, conventional 2D proton SI, and hybrid 2D proton SI to compare the spectral quality and acquisition time of individual MRS study. They have no clinical evidences of neurological abnormalities or abnormal MR findings. Informed consent was obtained in all volunteers prior to MR spectroscopic study.

2. Patient Groups

1) Patient group without any neurologic sign

Thirty-six children (23 boys and 13 girls, mean age: 3 years 10 months, age range: the third day of life to 15 years) underwent hybrid 2D proton SI using point-resolved spectroscopy (PRESS) sequence (TR/TE = 1,500 msec/135 or 270 msec). Included in this group were as follows: 17 leukemic patients (prior to the initiation of anti-leukemic treatment and who have no neurological abnormalities or abnormal MR findings), 14 neonates with a history of mild perinatal asphyxia, but without neurologic signs, who later have normal neurologic development, two with convulsion which resolved on its own, and normal findings on MR imaging and eletroencephalographic examination, one patient had abdominal neuroblastoma with calvarial metastasis, one patient with mutism, one with mild developmental delay, but with normal MR findings.

In addition, SVS also was performed in 4 children using PRESS sequence.

2) Patient group with neurologic abnormalities

Forty-five hybrid 2D proton spectroscopic imaging was performed in the 43 children (23 boys and 20 girls, age ranged from 3 days of life to 15 years with mean age of 4 years 8 months) with a variety of neurologic disorders including toxic-metabolic disorders (n = 20), hypoxic-ischemic injury (n = 10), brain tumor (n = 7), meningoencephalitis (n = 3), neurofibromatosis (n = 1), Sturge-Weber syndrome (n = 1) and lissencephaly (n = 1).

SVS also was performed in 8 children using PRESS sequence.

Magnetic Resonance Spectroscopic Study

All patients were examined with MR spectroscopy in conjunction with MR imaging of the brain under a 1.5-T scanner (Siemens Vision Plus, Erlangen, Germany) using standard head quadrature coil.

Informed consent of the parents was obtained in all cases. Permission for this study was granted by the joint ethical committee of the department of radiology and pediatrics at our institution. Infants and young children received oral or anal chloral hydrate at a dose of 75–100 mg/kg for sedation. Vital signs including pulse rate and arterial oxygen saturation were continuously monitored using oxymeter during the examination of neonates and infants.

For hybrid 2D proton SI, the 16×16 phase encoding steps were set on FOV to prevent wrap around artifact. The hybrid volume of interest (VOI) inside FOV was

set as 75×75×15 mm^3 or smaller (Figs. 1B-1D). This combination yields good localization and excellent rejection of unwanted subcutaneous fat signal. In the patient group without neurologic signs, hybrid 2D proton SI was performed at the level just superior to the lateral ventricles which allowed inclusion of major portion of deep white matter. In the patient group with various neurologic abnormalities, the volume of interest of hybrid 2D proton SI included area of maximum signal intensity abnormality on MR imaging. The PRESS pulse sequence was employed with standard chemical-shift-selective saturation (CHESS) pulses for water suppression. The following spectroscopic parameters were used for acquisition of MR spectra: repetition time = 1,500 msec, echo time = 135 or 270 msec, and NEX = 1. For long-echo

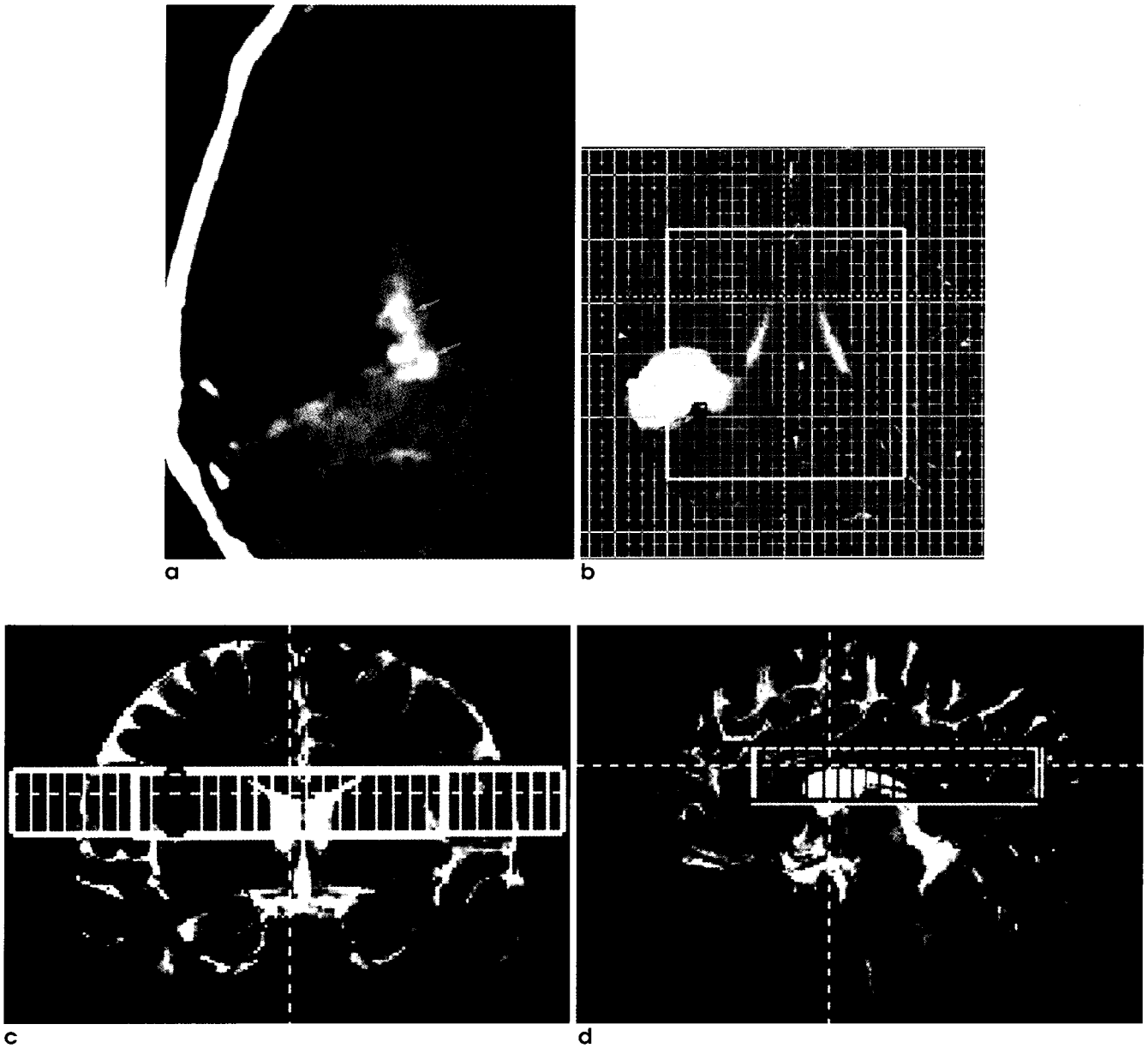
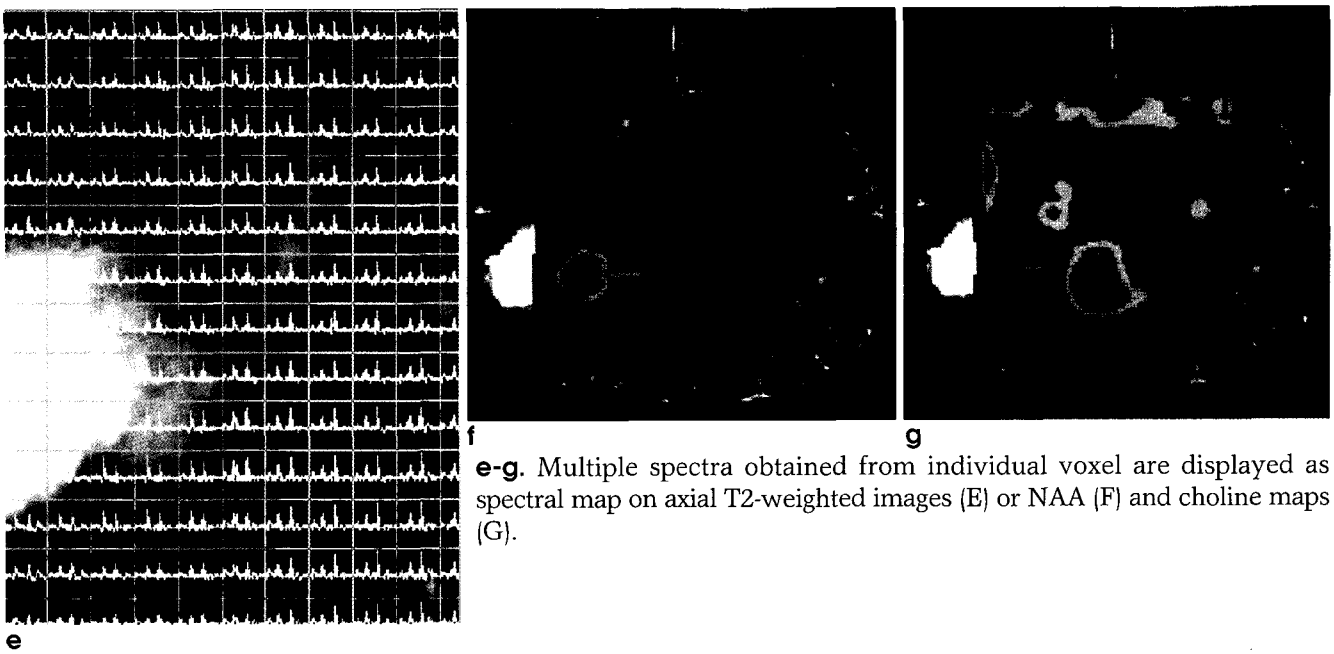


Fig. 1. Localization scheme of hybrid 2D proton SI in 13-year-old boy with recurrent glioblastoma multiforme.
a. Gadolinium-enhanced T1-weighted spin-echo image (TR/TE=665/14) demonstrates enhancing recurrent tumor (arrows) at the periphery of the cystic lesion in the right parietal region. **b.** To prevent contamination from subcutaneous fat, hybrid volume of interest (VOI) is selected within the field of view (FOV) on axial T2-weighted image. The hybrid VOI is 7.5 cm×7.5 cm along the x-, and y-directions. **c, and d.** Hybrid VOI along z-direction is 1.5 cm on coronal (C) and sagittal (D) localization images.



e-g. Multiple spectra obtained from individual voxel are displayed as spectral map on axial T2-weighted images (E) or NAA (F) and choline maps (G).

acquisition, we use PRESS with an echo time of 270 msec to enhance the sensitivity for lactate detection in newborn with suspected hypoxic-ischemic injury. Hybrid SI raw data were then postprocessed using CSIFT software (SUN SPARC 20, Numaris 3) with or without k-space zero filling. Either 2–4 Hz Lorentzian or Gaussian filter was employed for apodization. The areas of three major peaks including N-acetylaspartate (NAA), creatine (Cr), and choline (Cho) were measured using Levenberg-Marquart algorithm. The processed proton spectra were then displayed as either spectral map on axial T1- or T2-weighted image (Fig. 1E) or single spectrum on each voxel. The major metabolites were also displayed as NAA, Cr, and Cho maps (Figs. 1F, 1G).

SVS using PRESS sequences were performed on 4–8 ml of volume of interest centered in the parietooccipital white matter adjacent to the lateral ventricle.

The spectral quality and acquisition time of each pulse sequence were compared (Fig. 2).

Spectral Analysis

Two radiologists (SWY and SKL) and one physicist (YC), who were blinded to the clinical or MR imaging findings, independently evaluated the MR spectra. Major metabolites, i.e., NAA, Cho, Cr and lactate if present, were included in spectral analysis. The quality of spectrum was visually evaluated in regard of the signal to noise ratio (SNR) or spectral resolution and stability of the baseline. If necessary, the metabolite ratios among the metabolites were also calculated. The agreement about results was induced by the consensus of two radiologists and one physicist.

Results

Acquisition Time

The Hybrid 2D proton SI was successfully conducted upon all patients. The 2D spectral data acquisition time was less than 6 minutes, which was similar to that required for SVS. The data acquisition time of single-voxel PRESS with TR/NEX = 2000 msec/128 was 4.3 minutes. This was short enough for the application in infant and young children, where the patients were usually under sedation.

Spectral Quality

In all volunteers (n = 5) and clinical cases (n = 12) in whom both hybrid 2D proton SI and SVS using PRESS sequence were performed, the spectra acquired with hybrid 2D proton SI showed virtually the same sensitivity and spectral quality with SVS (Fig. 2A, B). The spectral quality of hybrid 2D proton SI was, on the other hand, far better than that of conventional 2D proton SI in all adult volunteers (n = 5) (Fig. 2C, D). This clearly demonstrates that the concept of

pointspread function (3) in the conventional 2D proton SI results in the contamination of several voxels near subcutaneous fat. The spectrum obtained by conventional 2D proton SI demonstrated severe fluctuation of baseline (Fig. 2D).

The MR spectra of white matter in volunteers and the patients group without neurologic sign were dominated by three prominent peaks from methyl groups: NAA at 2 ppm, Cr at 3 ppm, and Cho at 3.2 ppm.

Small lactate peak just above the noise level of the spectra was noted with PRESS sequence (1,500 msec/270 msec) in four of 12 neonates who were determined to have normal neurologic development at follow-up neurologic examinations.

Extent of Metabolic Abnormalities

The advantage of hybrid 2D SI was that the extent of metabolic abnormalities could be seen through the characteristics of the relative levels of the three metabolites (i.e., NAA, Cr and Cho) and lactate (Figs. 1E). Metabolite map clearly demonstrated the extent of metabolic abnormality (Figs. 1F, 1G, 3D). The extent of metabolically abnormal areas on the hybrid 2D proton SI correlated well with the abnormalities on MR images in all cases except hypertensive encephalopathy (n=3), treatment-related leukoencephalopathy (n=3), Wilson's disease (n=1), and end-stage periventricular leukomalacia (n=1) after the progression of disease has been stopped. In these patients, no significant spectral difference was noted between areas showing normal and abnormal MR imaging findings on both SVS and hybrid 2D proton SI.

Discussion

MR spectroscopy functions as a further diagnostic tool for noninvasive assessment of brain metabolism

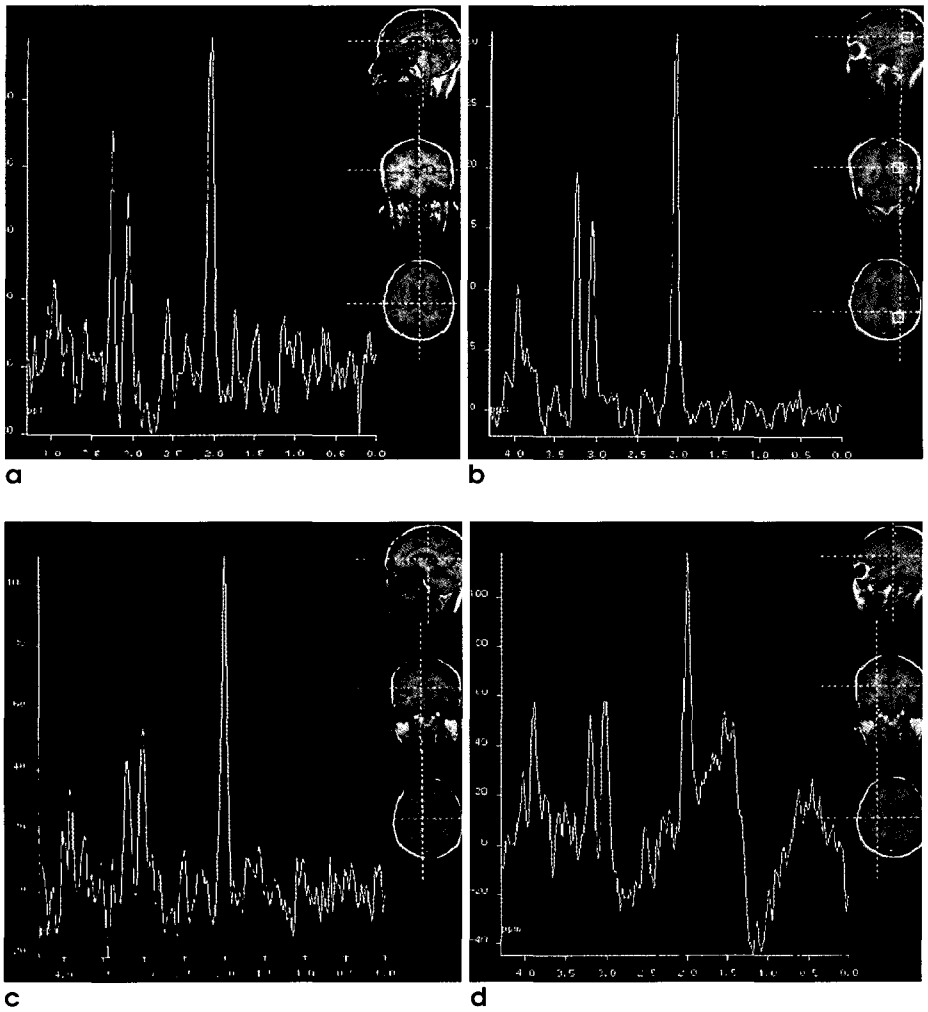


Fig. 2. 38-year-old volunteer with normal spectroscopic findings.
a, b. The spectrum obtained by hybrid 2D proton SI (A) shows nearly same spectral qulaity as that obtained by single voxel proton spectroscopy (B) at the same site. **c, d.** The spectral quality of hybrid 2D proton SI (C) is better than that of conventional 2D proton SI (D) in that the baseline is stable and the fluctuation of the spectrum is absent.

(5). Progress in localization techniques has allowed the application of volume-sensitive proton MR spectroscopy in a clinical environment (6, 7). Currently, two localization schemes are established for in vivo proton MR spectroscopy of the human brain (1, 2): SVS and SI. The SVS is one of the most widely used technique and generally considered to provide the optimal spectral quality. The limitation of SVS, however, is that metabolite levels are measured in a single volume, thus, spatial distribution of metabolites cannot be measured with this technique. On the other hand, SI technique provides the simultaneous acquisition of multiple spectra from adjacent locations, thus, the spatial distribution of metabolites (NAA, Cho, Cr, and lactate, for example) is measured over a predetermined VOI. In conventional 2D proton SI, the FOV inevitably contains subcutaneous fat, and the spectra obtained from the voxels, which are contaminated by subcutaneous fat, affect the spectra of nearby voxels by the "pointspread function", a characteristic of Fourier transform, thus degrade overall quality of the MRS data (3). To obtain spectra from a large FOV in conventional 2D SI, high magnetic field homogeneity should be maintained, and this is technically difficult. Thus, high spectral quality cannot be obtained with conventional 2D SI. Hybrid 2D SI technique for human brain metabolism is based on preselection of a VOI within the brain, to reduce the undesirable resonances of water and lipid originating from areas outside the VOI. The selected VOI can be divided by 16 or 32 along the x- or y-direction by using phase encoding gradient and MR spectrum can be

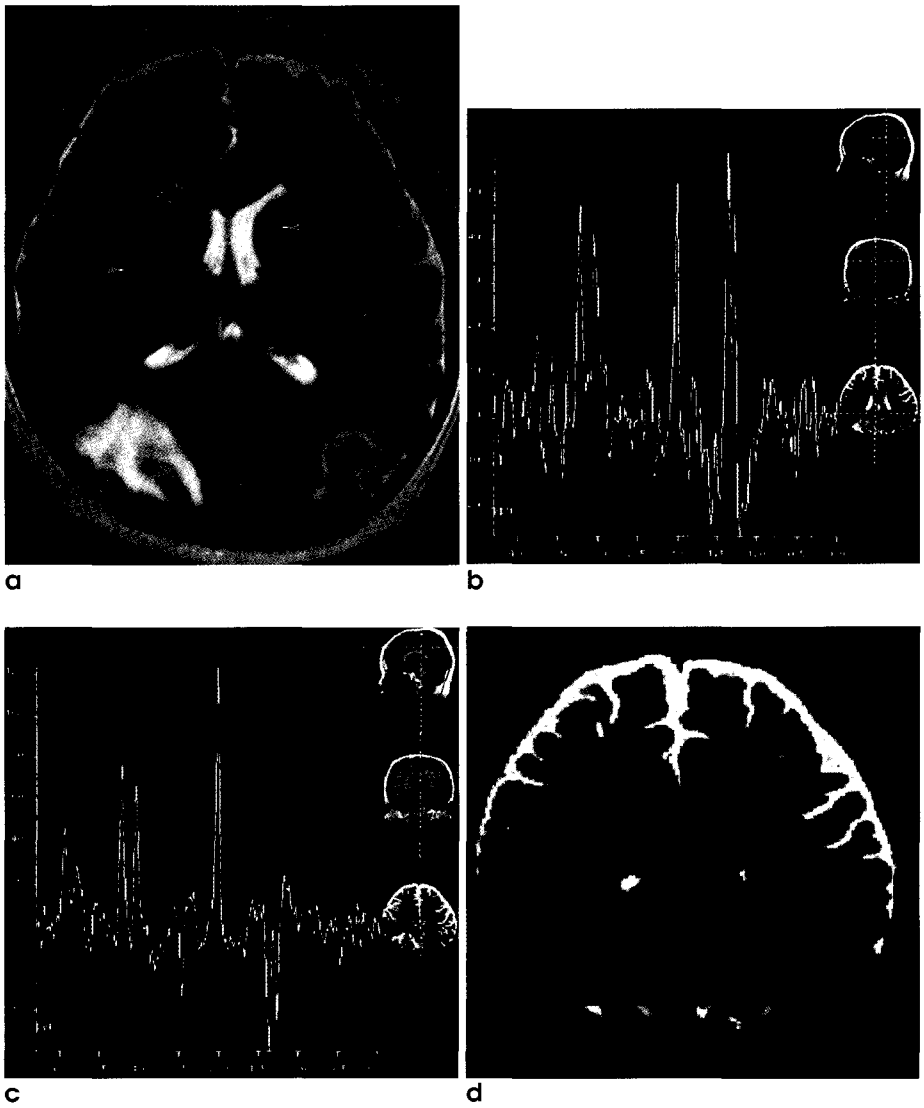


Fig. 3. 8-year-old boy with hypertensive encepyhalopathy.
a. T2-weighted SE image (3,300/95) demonstrates high signal intensity lesions in the basal ganglia (arrowheads) and parieto-occipital regions (arrows) bilaterally. **b.** MR spectrum obtained by hybrid 2D proton SI using PRESS sequence (TR/TE = 1,500 msec/270 msec) demonstrates high lactate peak at 1.33 ppm, but nearly normal NAA, creatine and choline peak. **c.** Lactate peak is inverted on spectrum obtained with TE of 130 msec. **d.** Lactate map demonstrates the extent of metabolic abnormality (arrows) comprehensively.

obtained from individual voxel. Thus, the spectrum from individual voxel is compatible with the spectrum obtained by single voxel spectroscopy. These properties of hybrid 2D proton CSI can be used for the establishment of the normal spectra according to the anatomical structures of the brain. The establishment of normal MR spectrum is important in that it can be used as a reference for various neurologic abnormalities. In addition, the extent of metabolic abnormalities, and the extent of various pathologic conditions can be assessed with hybrid 2D proton SI. These features of the hybrid 2D proton SI are especially desired in pediatric applications where MRI does not reveal a well-delineated region of interest for SVS. For example, misinterpretation from erroneous selection of VOI, which occasionally may occur with SVS, can be avoided by investigating the adjacent areas simultaneously with hybrid 2D proton SI. Thus, acquisition of spectra from the larger areas of the brain with hybrid 2D proton SI may increase the overall sensitivity and specificity of in vivo MRS. Furthermore, hybrid 2D proton SI may allow the discrimination of the border between the normal and abnormal areas, which is especially important for the spectroscopic examimation of the brain tumor.

The 2D spectral data acquisition time was less than 6 minutes, while that of single-voxel PRESS with TR / NEX = 2000 msec/128 was 4.3 minutes. Because there is no penalty in acquisition time as compared with SVS, hybrid 2D proton SI is particularly suitable for the assessment of diffuse or multifocal lesions of the brain in infants and young children where sedation is inevitable. In some of infants and young children included in this study (n = 31), SVS using PRESS sequence could be performed in addition to hybrid 2D proton CSI using PRESS sequence during a single sedation.

In our study, hybrid 2D proton SI using PRESS sequence was successfully performed in all cases. Furthermore, despite of multi-voxel technique covering large areas of the brain, the spectral quality of hybrid 2D proton SI is as good as single voxel technique using the same pulse sequence in all volunteers (n = 5) and clinical cases (n = 12) in whom both techniques were performed.

It is important to note that the signal intensity of each metabolite depends on the particular repetition time and echo time used in the pulse sequence. With PRESS sequence using long echo time, the major metabolites including NAA, Cho, and Cr can be evaluated.

Lactate has a detectable methyl group. It appears as a doublet at 1.3 ppm if the concentration is considerably above the physiologic level of 1–2 mmol (8). We found small lactate peaks just above the noise level of the spectra with PRESS sequence in four out of 12 neonates who were determined to have normal neurologic development at clinical follow-up. Small lactate peak in neonatal period has been reported in the literature (9). Thus, the small lactate peak seen very early in the neonatal period may be nonspecific and not necessarily indicative of abnormal metabolic state.

In some cases, despite of signal intensity alterations on MR imaging, hybrid 2D proton MR spectroscopic studies showed little or no change in metabolite ratios. This was true in our cases with end-stage periventricular leukomalacia, late stage of treatmentrelated leukoencephalopathy, hypertensive encephalopathy, and Wilson' s disease after the progression of diseases has been stopped. SVS also was performed in these patients and failed to demonstrate metabolic abnormalities. This imaging-spectroscopic discrepancy has also been reported in previous in vivo proton MR spectroscopic studies (9–11). Although, not included in this study, we have experienced a case with treatment-related leukoencephalopathy which demonstrated marked decrease in NAA/Cr ratio and high lactate peak at acute stage. These results did suggest that a decrease in NAA/Cr may accompany the early stages after high-dose chemotherapy at a time of maximal white matter change and, unlike MR imaging findings, may return to normal. These findings, however, require further verification.

In conclusion, the hybrid 2D proton SI can be successfully employed in the evaluation of the metabolic abnormalities in the various pathologic conditions of pediatric brain without penalty in acquisition time and spectral quality when compared to SVS. The other advantage of hybrid 2D proton SI is that the extent of metabolic abnormalities, which could not be obtained with SVS, can also be evaluated.

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소아 뇌에서의 혼성 이차원 양성자 자기공명분광법의 임상적 응용

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목적: 소아 뇌 질환에서의 자기공명분광법의 임상적 적용에 있어서 단일화적소 양성자 자기공명분광법과 고식적 이차원 양성자 자기공명분광법에 비해 혼성 이차원 양성자 자기공명분광법이 가지는 장점에 대하여 알아보고자 하였다.
대상 및 방법: 생후 3일에서 15세까지의 79명의 소아 (정상 소아 36명, 저산소성-허혈성 뇌 손상 10명, 대사성 질환 20명, 뇌막염-뇌염 3명, 뇌종양 7명, 신경섬유종증 1명, Sturge-Weber 증후군 1명, lissencephaly 1명)를 대상으로 81회의 혼성 이차원 양성자 자기공명분광검사를 시행하였다. 성인자원자(n=5)에서 단일화적소 양성자 자기공명분광법, 고식적 이차원 양성자 자기공명분광법, 그리고 혼성 이차원 양성자 자기공명분광법 모두를 실시하였고, 환아군 중 일부(n=12)에서 PRESS기법을 이용한 단일화적소 분광법과 혼성 이차원 양성자 자기공명 분광법을 함께 시행하였다. 1.5-T 초전도영상장치 하에서 standard head quatrature coil을 이용하여 양성자 자기공명분광을 얻었다. Phase encoding step은 16×16으로 하였고, FOV는 환자 뇌의 크기에 따라 다양하게 하였으며, FOV 내의 혼성 관심 체적 (hybrid VOI)은 75×75×15 mm^3 또는 그 이하로 함으로써 원하지 않는 지방에 의한 신호를 없애도록 하였다. PRESS기법 (TR/TE=1,500 msec/135 또는 270 msec)을 적용하였고, 물에 의한 신호를 억제하기 위하여 chemical shift selective saturation pulse를 사용하였다. 혼성 이차원 양성자 자기공명분광검사의 획득시간(data acquistion time)과 분광의 질(spectral quality)을 단일화적소 양성자 자기공명분광법과 고식적이차원양성자 자기공명분광법의 그것과 비교하였다.
결과: 혼성 이차원 양성자 자기공명분광법은 79명의 소아 전 예에서 성공적으로 시행되었다. 단일화적소 양성자 자기공명분광법의 획득시간은 4.3분인 반면에, 혼성 이차원 양성자 자기공명분광법의 획득시간(data acquition time)은 6분 미만으로, 이는 소아의 뇌영상용으로 쓰기에 충분히 짧은 소요시간이었다. 혼성 이차원 양성자 자기공명분광법에 의한 분광은 단일화적소 자기공명분광법에 의한 분광과 거의 비슷한 민감도와 분광분해능을 나타내었으며, 반면에 고식적인 이차원 양성자 자기공명분광법에 의한 분광보다는 훨씬 우수하였다. 뿐만 아니라 혼성 이차원 양성자 자기공명분광법은 N-acetylaspartate, creatine 및 choline 등 3가지 주요 뇌 대사물질의 상대적인 비를 통하여 뇌의 대사 이상의 범위를 잘 평가할 수 있었다.
결론: 혼성 이차원 양성자 자기공명분광법은 소아 중추신경계의 다양한 질병에 대한 대사 이상을 평가하는데 있어서, 소요 시간이나 분광의 질을 단일화적소 양성자 자기공명분광법과 비슷하게 유지하면서 성공적으로 적용될 수 있었다. 또한 단일화적소 양성자자기공명분광법으로는 얻을 수 없는, 대사 이상의 범위를 평가하는데 유용할 것으로 생각된다.

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