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Potential of proton magnetic resonance spectroscopy in the evaluation of patients with tethered cord syndrome following surgery

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Object. Spinal cord dysfunction is associated with an altered neuronal metabolism. The objective of this study is two-fold: 1) to compare pre- and postoperative levels of cerebrospinal fluid (CSF) metabolites in patients with spinal dysraphism and in control patients by performing proton magnetic resonance spectroscopy; and 2) to evaluate the use of magnetic resonance (MR) spectroscopy in the assessment of surgical outcomes in patients with spinal dysraphism.

Methods. The study group population was composed of patients with meningomyeloceles, lipomeningomyeloceles with tethered cord syndrome, and tethered fatty fila. All patients underwent preoperative clinical and neuroimaging (ultrasonography or MR imaging) examinations and MR spectroscopy analysis of metabolites in their CSF. Excision of the neural placode and detethering of a low-lying cord were performed with or without laminectomy. Two months postoperatively, the investigations were repeated. A comparison of pre- and postoperative CSF metabolites was performed using the Wilcoxon signed-rank test and nonparametric tests. Probability values less than 0.05 were considered significant.

High levels of lactate (Lac), alanine (Ala), acetate, glycerophosphorylcholine, and choline were observed in the CSF of patients with spinal dysraphism before surgery; after surgery these levels normalized to those observed in control patients. Patients in whom cord retethering occurred could be identified by increased concentrations of Ala and Lac.

Conclusions. The results highlight the potential of MR spectroscopy as a promising tool in the assessment of surgical outcomes in patients with spinal dysraphism.

Key Words • spinal dysraphism • tethered cord syndrome • cerebrospinal fluid • detethering surgery • magnetic resonance spectroscopy • pediatric neurosurgery

Tethering of the spinal cord and neurological dysfunction in patients with spina bifida still remain areas of concern. The cord may be tethered when associated with pathological conditions such as MMC; LMMC; intraspinal lesions including lipoma, dermoid cyst, osseous spur (diastematomyelia), tight terminal filum, and arachnoiditis; and postoperative adhesions (also known as retethering).[19] Stretching of the cord during pelvic or cervical flexion, growth and development, and a change in the curvature of the vertebral column may lead to intermittent but chronic repetitive ischemia or to progressive ischemia with ensuing spinal cord dysfunction.[19] A general neurological examination, nerve conduction studies, monitoring of somatosensory evoked potentials, electrocystography and electrohysterography, and neuroimaging studies (ultrasonography, computed tomography, MR imaging, and MR myelography) have been used to assess spinal cord dysfunction in patients with TCS. Nevertheless, these diagnostic modalities are inadequate in providing a clear assessment of the underlying spinal dysfunction, and they fail to address the issue of reversible and preventable causes of dysfunction.[8,14,20]

There are reports that considerable recovery in motor and sensory functions occurs after surgery (detethering, kyphectomy, and excision of an intraspinal lipoma, dermoid cyst, or spur), indicating that some cases of spinal dysfunction are preventable or reversible.[7,13,19,23,28,29] Spinal cord dysfunction directly affects neuronal metabolism and changes the local milieu of CSF in the spinal column.[2,25,30] Several investigators have found altered levels of metabolites, neurotransmitters, and free radicals in the CSF in the presence of several systemic[2,17,21,22,25] and local disorders affecting the spinal cord,[6,11,16,26,30] and have reported their findings to aid our understanding of neuronal dysfunction.

Proton MR spectroscopy of CSF enables quantification

Abbreviations used in this paper: Ace = acetate; Ala = alanine; Cho = choline; Cr = creatine; CSF = cerebrospinal fluid; Glu = glucose; GPC = glycerophosphorylcholine; Lac = lactate; LMMC = lipomeningomyelocele; MMC = meningomyelocele; MR = magnetic resonance; NMR = nuclear MR; PCr = phosphocreatine; TCS = tethered cord syndrome; TSP = 3-trimethylsilyl-2,2,3,3-tetradeuterosodium propionate; ^{1}H-MR = proton MR.

of metabolites including products of anaerobic metabolism, cell membrane damage, and lipid peroxidation.[5,6,16,27,30] Recently, we reported the metabolite profile of CSF in patients with spina bifida, particularly those with MMC and retethering, and observed a state involving nerve ischemia, anaerobic metabolism, and disruption of neuronal membranes.[18] The objective of this study is twofold: 1) to quantify pre- and postoperative levels of CSF metabolites in patients with spinal dysraphism to understand the effects detethering and retethering of the cord and excision of the neural placode have on the metabolic profile of CSF; and 2) to examine the potential of MR spectroscopy in the assessment of surgical outcomes in patients with spinal dysraphism.

Clinical Material and Methods

Patient Population

Sixteen infants and children with spinal dysraphism who presented to the Department of Pediatric Surgery, All India Institute of Medical Sciences, between January 2000 and December 2002 were recruited into this study. For each patient their age and sex, the nature of the defect, findings of ultrasonography or MR imaging of the spine, the degree of neurological deficit, and intraoperative findings were evaluated, and these details have been published earlier.[18] The 16 patients in this series were treated with oral decongestants and none received shunts. All data in these patients were evaluated carefully to see if there were any intrapartum or postpartum events, such as birth asphyxia or intraventricular hemorrhage, and no such events occurred in any of these patients.

We recently reported on the biochemical characterization of CSF in the same patients with spinal dysraphism by using ^{1}H-MR spectroscopy.[18] Data from that report (preoperative groups) are included to provide a comparison between the preoperative and postoperative status of CSF metabolites. In the present paper, we report findings following laminectomy or excision of the lesion or detethering of the cord in these patients (postoperative groups). Their CSF was analyzed using the method outlined in our earlier study.[18] Details on the patients are given in the following subsections.

Preoperative Groups

Spinal Dysraphism. This group consisted of six patients (four patients with an MMC and two with an LMMC); the mean age in this group was 24.6 ± 13.3 days (range 8–40 days) and the male/female ratio was 4:2.[18] All patients exhibited some degree of neurological deficit during the clinical examination performed at presentation. Tethering of the cord, a low-lying cord, or a second lesion was observed in all patients.

Retethering of the Cord. This group was composed of 10 children who had undergone surgery at an earlier time, but retethering occurred.[18] Among these, two patients had a tethered low-lying fatty filum, four had an MMC with a tethered cord, and four had an LMMC with a low-lying cord. The mean age of patients in this group was 23.9 ± 7.6 months and the male/female ratio was 6:4.

Postoperative Groups

Postoperative Spinal Dysraphism. All patients with spinal dysraphism underwent excision, laminectomy, and detethering with or without excision of a second lesion by the same surgeon. At the time of this study, the mean age of patients in this group was 84.6 ± 13.3 days and the male/female ratio remained 4:2. Two to three months after surgery, all patients underwent both clinical and neuroimaging examinations. In none of them was there any neuroimaging evidence of retethering or a second lesion or a deterioration in their neurological symptoms. Subsequently, MR spectroscopy was used to assess their CSF metabolites.

Detethering. This group comprised six patients who had signs of retethering (two patients with a tethered low-lying fatty filum and four with an MMC and a tethered cord) after having undergone laminectomy and detethering at our institution. Two months postoperatively, MR spectroscopy was performed to examine the patients' CSF. After surgery two patients exhibited some recovery from their neurological symptoms, whereas four did not show any appreciable improvement; the latter patients also had urological symptoms, and those symptoms as well as their neurological symptoms remained stable. The concentrations of CSF metabolites in these patients were determined using MR spectroscopy.

Control Group. Ten age-matched children formed the control group.[18] These children underwent lumbar puncture at the Department of Pediatric Medicine at our institute for suspected meningitis, but the results of the cytological and biochemical examinations did not confirm the diagnosis.

Exclusion Criterion and Approval of the Study

Three children in the control (one child) and patient (two children) groups who experienced accidental bleeding during the collection of CSF were excluded from the study. Our institutional ethical committee approved the study.

Processing of CSF

Samples of CSF were collected in clean glass vials. The samples were immediately frozen in liquid nitrogen, transported in a liquid nitrogen container, and stored at −35°C. Magnetic resonance spectra were acquired within 2 days of sample collection. Before the MR spectroscopy experiments, the samples were thawed and 60 μl of deuterium oxide (D_2O; Aldrich Company, Inc., Milwaukee, IL) containing 0.5 mmol/L of TSP (E. Merck, Darmstadt, Germany) was added to 540 μl of the native CSF sample. The resulting solution was transferred to a 5-mm NMR tube and experiments were performed immediately (within ~10 minutes). The samples were immediately subjected to an MR spectroscopy analysis to avoid any alterations in metabolite levels.[18]

Proton MR Spectroscopy

Proton spectra were acquired at a frequency of 400.13 MHz by using an NMR spectrometer (DRX-400; Bruker, Switzerland) equipped with a broadband inverse probe. The one-dimensional ^{1}H-MR spectra were acquired using a single pulse with the following parameters: pulse width 90°, number of data points 32K, spectral width 5000 Hz, number of images 32 to 48, and relaxation delay 14 seconds. A 0.3-Hz line broadening was applied before Fourier transformation. The intensity of various metabolites' resonances was measured with reference to the TSP resonance.

Quantification of Metabolites

Quantitative data were obtained by calculating metabolite concentrations in millimoles per liter from the area of their corresponding resonance(s) with respect to the area of TSP resonance after correction for the number of protons.[18,24] Two of the authors (U.S. and N.R.J.), who were unaware of the patients' diagnoses, performed the characterization and quantification of the metabolites.

Statistical Analysis

Data were analyzed using a statistical software program (SPSS version 11.5 for Windows; SPSS, Inc., Chicago, IL). Concentrations of the various metabolites were expressed as mean values ± standard deviations. A one-way analysis of variance and a post hoc least statistical difference test were used to assess differences between groups. A comparison of pre- and postoperative values of all the metabolites in the MMC group and the tethering group were conducted by performing the Wilcoxon signed-rank test and the nonparametric tests. Probability values less than 0.05 were considered significant.

Results

Figure 1 shows expanded regions of ^{1}H-MR spectra recorded from CSF obtained in a patient in the control group and a patient with spinal dysraphism (MMC). Resonances corresponding to Lac, Ala, Ace, GPC, and Cho were observed in the spectra. Elevated levels of several metabolites were noted in patients in the MMC group compared with those examined in the control group (Fig. 1). Resonances due to GPC and Cho were not observed in control patients (Fig. 1 *lower*). Figure 2 shows the comparison of typical ^{1}H-MR spectra of CSF obtained before and after surgery in a patient suffering with MMC. Significant reductions in the Lac, Ala, Ace, GPC, and phosphorylcholine resonances were observed after surgery (Fig. 2). In patients who presented with cord retethering and worsening of their neurological, orthopedic, and urological symptoms, there was neuroimaging evidence of tethering to the scar site, kyphosis, and an intraspinal second lesion. Of these 10 patients, six underwent detethering at our institute and were assigned to the detethering group. Spectra obtained from the CSF of one such patient with retethering before and after detethering are shown in Fig. 3. The concentrations of various metabolites observed in these patients were calculated and compared with earlier data obtained in the control group and with data obtained before surgery.[18] These are presented in Table 1 along with associated probability values.

Higher levels of Lac were observed in patients with spinal dysraphism and retethering than in those in the control group.[18] Following surgery, concentrations of Lac decreased in comparison with preoperative values and were similar to those of the control group (Table 1). A similar change was observed for Ala and Ace, whose levels were significantly higher preoperatively in patients with spinal dysraphism than in controls and whose levels decreased following surgery (Table 1).

The concentrations of Cr/PCr were similar in the pre- and postoperative groups. Cerebrospinal fluid from the control

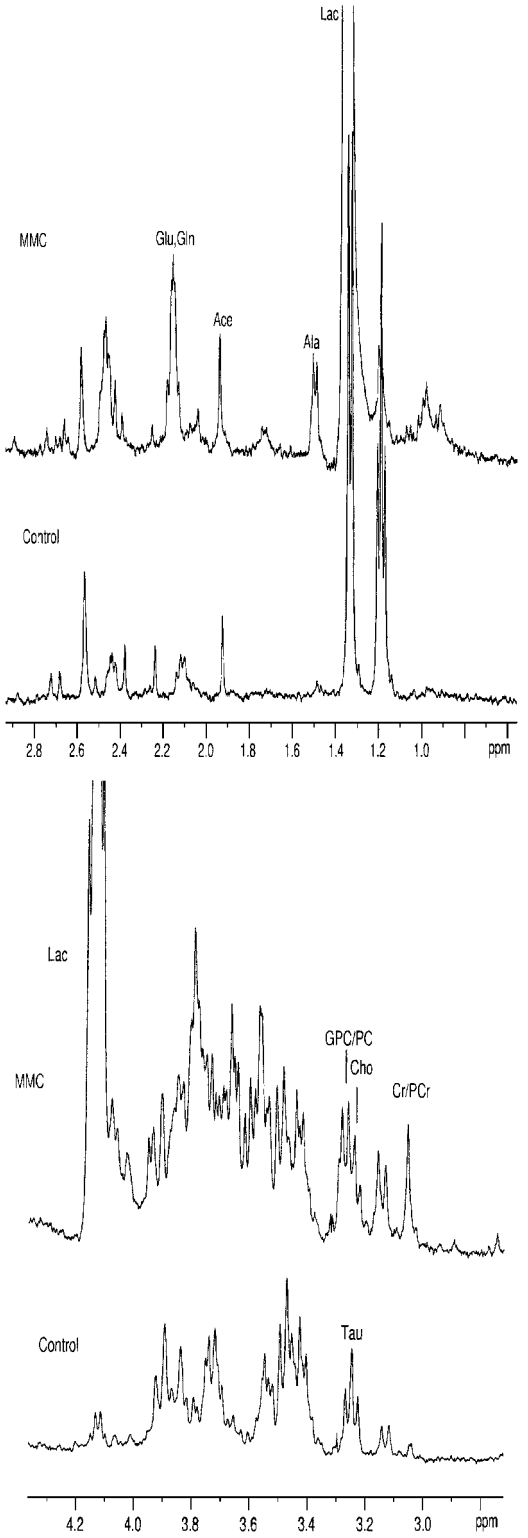

FIG. 1. *Upper:* Expanded region (0.6–2.9 ppm) of ^{1}H-MR spectra in CSF samples from a patient in the control group and a patient with an MMC at 298K data points. The samples contain 10% D_2O and 0.5 mM TSP. *Lower:* Expanded region (2.8–4.3 ppm) of the ^{1}H-MR spectra in CSF samples from a patient in the control group and a patient with an MMC at 298K data points. The samples contain 10% D_2O and 0.5 mM TSP. Gln = glutamine; PC = phosphorylcholine; ppm = parts per million; Tau = taurine.

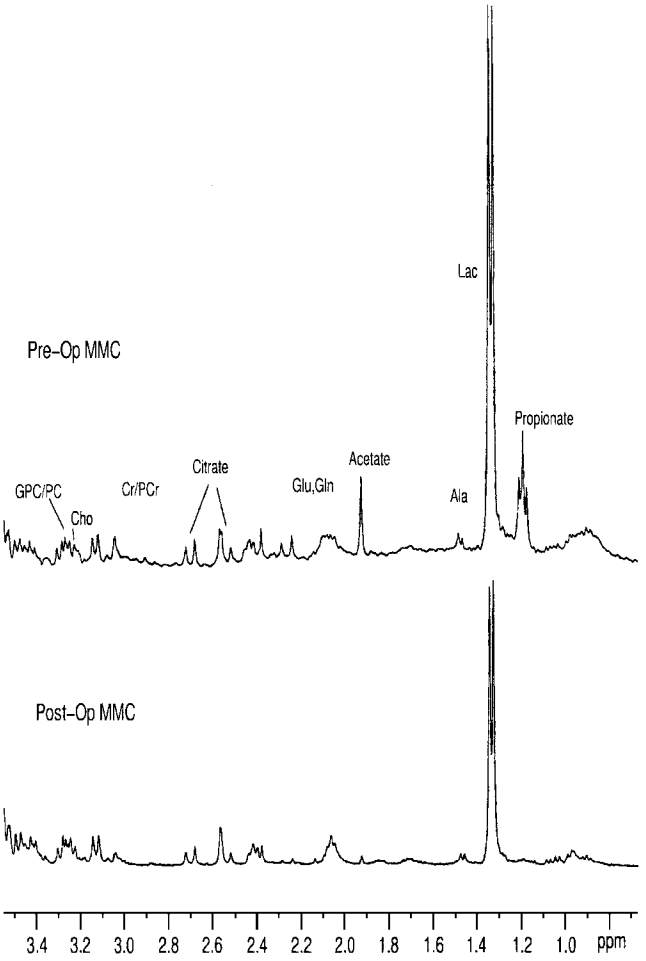

FIG. 2. Expanded region (0.8–3.5 ppm) of ^{1}H-MR spectra in CSF samples from a patient with an MMC at 298K data points, obtained before (Pre-Op MMC) and after (Post-Op MMC) surgery. The samples contain 10% D_2O and 0.5 mM TSP.

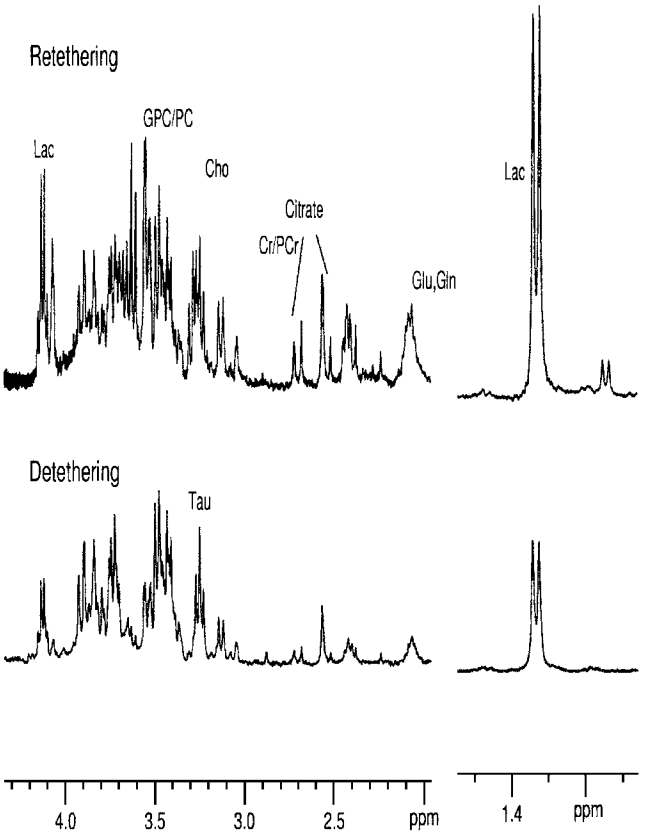

FIG. 3. Expanded regions (1.1–1.5 ppm and 2.4–4.5 ppm) of ^{1}H-MR spectra in CSF samples from a patient with retethering at 298K data points, obtained before and after surgical detethering. The samples contain 10% D_2O and 0.5 mM TSP.

group did not display any resonance corresponding to Cho and GPC. High levels of these metabolites were observed in patients before surgery; however, these levels were significantly decreased postoperatively (Table 1). The concentrations of Glu in the control group was similar to those in the other patient groups (Table 1).

Discussion

We recently reported metabolic differences observed in the CSF of patients with spinal dysraphism and the CSF of control patients.[18] In the present study we investigated surgical outcomes in patients with TCS, adding another dimension to the diagnostic application of NMR studies to medicine. The results indicate significant metabolic changes in the CSF of patients with spinal dysraphism compared with data in control patients, and these changes were found to be reversed after surgical detethering of the cord.

Patients with spinal dysraphism were found to have significant increases in the concentrations of Lac, Ace, and Ala compared with patients in the control group.[17] The elevated levels of these metabolites suggest an increased anaerobic or impaired oxidative metabolism that may contribute to cord dysfunction in these patients.[15] Anaerobic metabolism due to tissue anoxia has been reported to increase levels of Lac and Ace in the CSF.[11,27] A similar increase has also been documented in CSF removed from a cat spinal cord following trauma.[3] The relationship between the severity of neuronal dysfunction and the degree of impairment in the oxidative metabolism has been reported.[19,28] Mechanical tension within the cord and decreased blood flow due to stretching results in nerve ischemia and impairment of Glu metabolism.[28,29] Yamada and colleagues[28,29] showed a state of mitochondrial anoxia within the conus in patients with TCS. The severity of neuronal dysfunction corresponds to the degree of impairment in the oxidative metabolism.[19,28]

Following surgery (detethering and/or excision of the lesion that causes tethering of the cord), significant reductions in the concentrations of Lac, Ace, and Ala were observed in these patients, indicating that the anaerobic process due to nerve anoxia can be reversed by surgery. An increase in blood flow and a postoperative improvement in the patient's neurological status lend credence to our findings.[19,28,29] Caution, however, should be exercised in interpreting concentrations of metabolites such as Lac, which may change as a result of degradation on exposure of the CSF samples to room temperature during processing or because of anaerobic metabolic activity.[12] No change in concentrations were observed for Ala, Ace, and Glu, however.[12] In our study,

TABLE 1

*Concentrations of metabolites in the different spina bifida groups and the control group and probability values of comparisons between groups**

Groups	Concentration of Metabolite (mmol/L) & p Value						
	Lac	Ala	Ace	Cr/PCr	Cho	GPC	Glc
control (10 patients)†	2.09 ± 0.54	0.05 ± 0.05	0.26 ± 0.32	0.06 ± 0.14	ND	ND	2.46 ± 0.76
spinal dysraphism (6 patients)†	26.23 ± 20.86	1.23 ± 0.54	1.25 ± 1.09	0.16 ± 0.06	0.17 ± 0.07	0.18 ± 0.07	2.17 ± 0.61
postop spinal dysraphism (6 patients)	4.31 ± 0.95	0.32 ± 0.15	0.17 ± 0.05	0.13 ± 0.18	0.05 ± 0.04	0.05 ± 0.02	1.74 ± 0.92
retethering (10 patients)†	10.85 ± 3.91	0.31 ± 0.18	0.99 ± 0.37	0.06 ± 0.02	0.14 ± 0.18	0.16 ± 0.21	1.94 ± 0.77
detethering (6 patients)	2.96 ± 0.42	0.07 ± 0.08	0.31 ± 0.12	0.11 ± 0.16	0.15 ± 0.03	0.04 ± 0.05	1.94 ± 0.21
p values between spina bifida & control groups‡							
control vs preop spinal dysraphism	<0.001	<0.001	0.001	0.104	0.002	0.002	0.42
control vs postop spinal dysraphism	0.60	0.04	0.73	0.36	0.42	0.47	0.05
control vs preop retethering	0.02	0.02	0.003	0.05	0.003	0.001	0.1
control vs postop detethering	0.84	0.85	0.88	0.06	0.77	0.51	0.15
postop spinal dysraphism vs preop spinal dysraphism	<0.001	<0.001	0.001	0.52	0.03	0.02	0.29
postop spinal dysraphism vs detethering	0.78	0.09	0.66	0.83	0.65	0.96	0.63
retethering vs detethering	0.07	0.07	0.01	0.49	0.02	0.02	0.99
retethering vs spinal dysraphism	0.001	<0.001	0.34	0.09	0.63	0.71	0.51

* ND = not detected.
† Data published by Pal, et al.
‡ Statistical analyses included analysis of variance and post hoc least statistical difference tests.

CSF samples were snap-frozen in liquid nitrogen and stored at −35°C; they were not exposed to room temperature and, therefore, we attribute differences observed in concentrations of metabolites between the spinal dysraphism group and the control group to changes in metabolism due to the patients' pathological conditions.[18]

Hydrocephalus develops in approximately 85 to 90% of individuals with spina bifida and this is managed by placing a shunt to drain excess CSF from the brain to the abdomen, where the fluid can be absorbed by the body. Although a shunt generally works well, it may stop working due to obstruction by brain tissue, fluid, bacteria, or blood, or because of a mechanical failure or disconnection. Shunt blockade and hydrocephalus may also influence the levels of CSF metabolites. Jones and associates[9] demonstrated early changes in cell membrane compounds in untreated hydrocephalic rats, followed later by a decrease in energy metabolites and, finally, changes in amino acid/neurotransmitter levels. The degree of reversibility of these changes depends on the duration of the hydrocephalus.[10] In a recent study of clinical hydrocephalus conducted by Braun, et al.,[4] however, ^{1}H-MR spectroscopy could not detect abnormalities in levels of cerebral metabolites. These conflicting findings suggest the need for additional research to evaluate changes in the levels of CSF metabolites in the presence of hydrocephalus and shunt blockade. In addition, such studies may produce findings that improve our understanding of the mechanisms involved, which in turn may lead to the development of new approaches for treatment of children with spina bifida.

None of the patients included in our study underwent shunt placement. In our institute a shunt is usually not placed until the patient is between 6 and 12 months of age to avoid damage to the fragile growing brain caused by shunt malfunction or shunt-related infection. The patients described in this report were treated with oral decongestants. Their patient records were carefully evaluated to see if there were any intrapartum or postpartum events, such as birth asphyxia or intraventricular hemorrhage, and no such events occurred. In addition there was no evidence of increased intracranial pressure. The CSF metabolites were quantified in the same children before and after the surgery; hence, each patient served as his or her own control for the postoperative levels. In our study, differences between pre- and postoperative metabolite levels in CSF could therefore be attributed to detethering of the cord.

In patients with spinal dysraphism the Cho and GPC levels were raised, whereas in the control group these metabolites were not detected.[18] Given that the levels of Cho and GPC decreased significantly after surgery, it is evident that a significant portion of this dysfunction can be reversed, or progression of neuronal membrane disruption can be halted by surgery. Disruption of the integrity of the neuronal cell membrane has been associated with increased CSF levels of Cho and GPC.[27] This suggests that several factors (for example, stretching and compression) may be responsible for the disruption of neuronal integrity of the cord in the setting of TCS. No significant difference was found in the concentrations of Cr/PCr metabolites between the control and spinal dysraphism groups in our study. However, a decrease in creatinine kinase expression following traumatic injury to the spinal cord has been documented in the literature.[1] No significant change in the levels of Glu in patients with spinal dysraphism was observed when compared with controls. The Glu level in CSF reflects the status of blood sugar in the patients. Although we did not correlate patients' blood sugar with that observed in CSF, the comparable values of CSF Glu among the control and spinal dysraphism groups (no statistical difference in mean values) suggest that there was no element of central nervous system infection or other systemic hypermetabolic state to confound our results. Based on this metabolic evidence, one may conclude that the MR spectra reflected changes due to the disease process and not due to surgery. The improvement in the neurometabolism following detethering of the

cord may not have translated into clinical improvement in more than 67% of cases because of a permanent loss in neuronal function due to several factors.

Postoperative imaging changes following the correction of spinal dysraphism are complex and scarring is commonly seen. Nevertheless, it is not appropriate to infer that all scarring seen postoperatively is synonymous with tethering. The criteria used to distinguish scarring at the site of surgery and tethering of the cord are well documented:[15] 1) posterior adherence of the cord to the scarred tissue, and 2) the presence of decreased flow in spinal vessels on Doppler ultrasound studies. However, these criteria are not adequate to diagnose spinal tethering until the patient displays a deterioration in neurological signs. In such cases MR spectroscopy may have the potential to detect retethering of the cord. If spectral characteristics are similar to those of controls, then they may indicate adequate detethering with normalization of spinal cord metabolism. If the follow-up spectra demonstrate metabolite levels that indicate tethering, however, an opportunity is offered to make an early decision whether to detether the cord again, long before irreversible neurological deficits can occur.

Routine lumbar puncture is not the preferred choice; nevertheless, our data suggest a role for NMR imaging in the investigation of metabolic derangements in the CSF. In vivo MR spectroscopy may be the best alternative to lumbar puncture. Currently, however, several technical limitations are involved in performing such studies.

In the present study only patients with spinal dysraphism were investigated. Similar findings may be seen even after the correction of disc prolapse or nerve root decompression. It would be useful to study CSF in patients with tethered cord who are asymptomatic postoperatively; this would highlight the possible use of this method in the prognostication of postoperative outcomes following detethering. Finally, in the future this novel approach may lead to broader studies of a vast range of other spinal disorders.

Conclusions

The results reported here indicate that deranged neuronal metabolism leads to alteration in the levels of various metabolites in the local milieu of spinal cord CSF in patients with spinal dysraphism. The levels of Lac, Ala, Ace, Cho, and GPC in CSF were significantly higher in patients with spinal dysraphism than in controls. This suggests that a significant component of anaerobic metabolism and cell membrane damage contributes to neuronal dysfunction in patients with spinal dysraphism. Following surgery, the levels of these metabolites are comparable to those in control patients, indicating considerable recovery of neuronal metabolism and neurovascular physiology following surgery.

In addition our results indicate that retethering, if diagnosed early and corrective surgery is performed, may reinstate normal biochemical processes and neurological functions or prevent further deterioration. The persistence of a deranged metabolism after surgery may be indicative of the presence of untreatable lesions in the spinal cord. With respect to this, an MR spectroscopy analysis of CSF would provide several possible biochemical markers and quantitative parameters that can be used to postulate a prognosis with some objectivity. Finally, the study demonstrates the potential of ^{1}H-MR spectroscopy, which may be used as an adjunct to the investigative armamentarium in the evaluation of patients' spinal dysraphism.

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