Single Voxel Proton MR Spectroscopy Methods and Applications in Neuropediatrics

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SUMMARY – The purpose of this contribution is to introduce quantitative single voxel proton MR spectroscopy of the human brain as an easy-to-use method for a noninvasive assessment of cellular composition and metabolism and to demonstrate its clinical potential in the field of neuropediatrics.

The chosen approach transforms fully relaxed (TR = 6000 ms) short echo time (TE = 20 ms) proton MR spectra (STEAM localization sequence) into absolute metabolite concentrations by automatically fitting the raw data with a library of model spectra comprising all metabolites at known concentration (LCModel). The procedure includes total N-acetylaspartyl compounds as a marker for viable neuroaxonal tissue and myo-inositol as a purely glial constituent as well as total creatine, choline-containing compounds, glutamate and glutamine, and lactate.

Extensive studies of brain disorders in childhood suggest the use of proton MRS as a promising tool for an in vivo histopathologic characterization of brain tissue. Typical metabolite patterns are observed for pathologic processes such as lactic acidosis, loss of functioning neurons, astrocytosis, myelin breakdown, or loss of oligodendrocytes. Examples deal with the diagnostic workup of enzyme deficiencies, demyelinating white matter diseases, and focal brain lesions.

Spettroscopia protonica con risonanza magnetica Metodi e applicazioni in neuropediatria

SOMMARIO – *Scopo di questo contributo è quello di introdurre l'analisi quantitativa degli spettri RM acquisiti a livello cerebrale come metodo di semplice utilizzo per la determinazione non invasiva della composizione cellulare e del metabolismo e per dimostrare il potenziale clinico di questo metodo nel campo della neuro-pediatria.*

L'approccio scelto trasforma spettri completamente rilassati (TR = 6s), acquisiti a tempi di eco brevi (TE = 20 ms) con la sequenza STEAM, in concentrazioni assolute dei metaboliti mediante "fitting" automatico dei dati con una libreria di spettri-modello contenenti tutti i metaboliti a concentrazioni note (LC-Model). Questa procedura include i composti del N-acetilaspartato come marker del tessuto neuro-assonale, il mio-inositolo come marker della glia così come la creatina totale, i composti della colina, il glutammato, la glutammina e l'acido lattico.

Studi estensivi su malattie neurologiche nei bambini hanno mostrato come la risonanza magnetica spettroscopica sia uno strumento molto promettente per la caratterizzazione istopatologica del tessuto cerebrale. Spettri caratteristici sono stati osservati per processi patologici quali l'acidosi lattica, la perdita di neuroni, l'astrocitosi, la rottura delle catene mieliniche o la perdita di oligodendrociti. Gli esempi di applicazioni della spettroscopia riportati nel testo riguardano il deficit di enzimi, le malattie demielinizzanti della materia bianca e le lesioni cerebrali focali.

Introduction

Complementing ongoing advances in magnetic resonance imaging (MRI) of the human brain that extend anatomic studies to functional assessments, magnetic resonance spectroscopy (MRS) has technically matured and successfully been applied to a wide variety of cerebral abnormalities in children and adults. For recent overviews see [1,2] and references cited therein. The approach provides noninvasive insights into the neurochemistry of normal and pathologic states of the central nervous system that reflect both tissue composition and cellular metabolism.

At present, the experimental optimization of localized proton MRS and the availability of suitable evaluation strategies lead to a steady increase of MRS examinations covering a wide range of brain disorders. Reliable interpretations are based on determinations of absolute metabolite concentrations that exclude effects from T1 and T2 relaxation and translate spectroscopic observations into true biochemical quantities.

Absolute metabolite concentrations are considered beneficial because they:

– facilitate clinical evaluations in individual patients relative to data from age-matched controls that account for interindividual variabilities;

– avoid relative comparisons of (T1- or T2-weighted) resonance intensity ratios as a potential confound in the interpretation of the data;

– do not rely on intrasubject comparisons with normal-appearing control regions which may also be affected, e.g. in temporal lobe epilepsy;

– allow for intraindividual follow-up studies over several years.

Using this methodology we have extensively studied brain disorders in childhood since 1989. Pertinent findings have been related to clinical symptoms, to disease progression, and to histopathologic classifications. Altogether, the growing knowledge in this field suggests the use of proton MRS as a limited though often conclusive method for *in vivo* histopathologic characterizations of brain tissue. Altered concentration patterns of multiple metabolites including neuroaxonal and glial markers allow the identification of pathologic processes such as loss of functioning neurons, astrocytosis, myelin breakdown, loss of oligodendrocytes, or lactic acidosis.

In fact, regardless of the underlying pathology the two most prominent and frequent alterations in brain tissue that give rise to MRS-detectable metabolite changes are damage to or loss of neuroaxonal tissue and the occurrence of glial proliferation. Using *N*-acetylaspartate and N-acetylaspartylglutamate (tNAA) and (myo)-inositol (Ins) as respective cellular markers [3,4], any reduction of neuroaxonal cells manifests itself as reduced t-NAA and glutamate (Glu), whereas growth of glial cells (mainly astrocytes) leads to increased Ins and glutamine (Gln) and/or increased choline-containing compounds (Cho, mainly oligodendrocytes). As a constituent of both glial and neuronal cells creatine and phosphocreatine (tCr) may be reduced or enhanced depending on the relative importance of the two aforementioned processes. Strong variability is observed for lactate (Lac) which often reflects the anerobic metabolism of infiltrating macrophages and only rarely indicates mitochondrial dysfunction.

In this contribution we first describe our method for quantitative single voxel proton MR spectroscopy and then demonstrate its clinical potential in neuropediatrics. Selected examples deal with the evaluation of enzyme deficiencies, white matter diseases associated with dysmyelination and hypomyelination, and focal brain lesions.

Methods

All patients underwent proton MRS as part of their diagnostic workup. Before each examination informed written consent was obtained from the parents. Proton MRS studies of children were approved by the institutional review board.

MRI/MRS examinations were performed at 2.0 T (Magnetom Vision, Siemens, Erlangen, Germany) using either the standard imaging head coil or – for children under 20 kg bodyweight – the extremity coil. Children younger than six years were sedated with chloral hydrate and monitored by pulse oximetry.

Single voxel proton MR spectroscopy

Meaningful insights into the chemistry of the intact human brain require spatial discrimination of MRS responses. Two different concepts have been proposed that either emphasize spatial (imaging) or biochemical resolution (spectroscopy). In contrast to chemical shift imaging, single voxel MRS techniques attempt to restrict the excitation to a pre-defined volume-of-interest (VOI). They acquire a spatially localized time-domain signal from the VOI which directly results in an uncompromised frequency spectrum by a simple Fourier transformation.

In general, single voxel MR spectra reveal a much more detailed metabolic picture of selected foci than metabolite maps. Specific advantages are the excellent spectral resolution and water suppression, the short measurement times of about 5

min, and the possibility to use long repetition times that avoid the need for T1 corrections. This is of particular importance for studies of patients as T1 relaxation times of pathologic tissues are usually unknown.

The two major techniques for single voxel proton MRS are PRESS [5,6] and STEAM [7]. Here, we have exclusively used STEAM sequences because the technique provides optimum conditions for MRS acquisitions at short echo times TE which minimize signal losses due to T2 relaxation, spin-coupling modulation, and multiple-quantum interferences. In this study we have empoyed TR = 6000 ms, TE = 20 ms, and TM = 10 ms (30 ms in some older spectra) with 64 accumulations that lead to measuring times of 6.5 min per spectrum. Water suppression was achieved by means of three successive chemical-shift-selective (CHESS) pulses of 60 Hz bandwidth (i.e., affecting pm 0.35 ppm around the water resonance) and associated spoiler gradients [8]. Technical details of the water-suppressed STEAM sequence have been described elsewhere [9,10]. For a comparison of MRS localization strategies see [11].

Volumes-of-interest were selected from three sets of orthogonal T1-weighted images (3D FLASH, TR/TE = 15/4 ms, flip angle 20 circ) and transverse T2-weighted images (FSE, TR/TE = 2625/98 ms, flip angles 90/120 circ). Typically, several MR spectra (4 - 12.5 mL VOI) in standardized locations in paramedian parietal (frontal) gray matter, parieto-occipital (frontal) white matter, basal ganglia or thalamus, and cerebellum were acquired within an examination time of 1 - 1.5 hours. Focal lesions in mixed gray/white matter volumes also required a suitable control region such as a homologue area of the contralateral hemisphere.

Quantitation of absolute metabolite concentrations

Spectral evaluation was accomplished with use of LCModel (S.W. Provencher, Göttingen, Germany) which represents a user-independent fitting routine. It is based on a library of calibrated model spectra of individual metabolites with known absolute concentrations [12]. Concentrations are expressed in mM, i.e. mmole per liter VOI, and obtained without further corrections for cerebrospinal fluid and residual T2 attenuation. The approach takes advantage of a nearly model-free constrained regularization method and incorporates prior knowledge by fitting metabolite reference spectra. Taking differences in rf coil loading into account (e.g., due to different head sizes), the procedure results in absolute metabolite concentrations that are largely independent of instru-

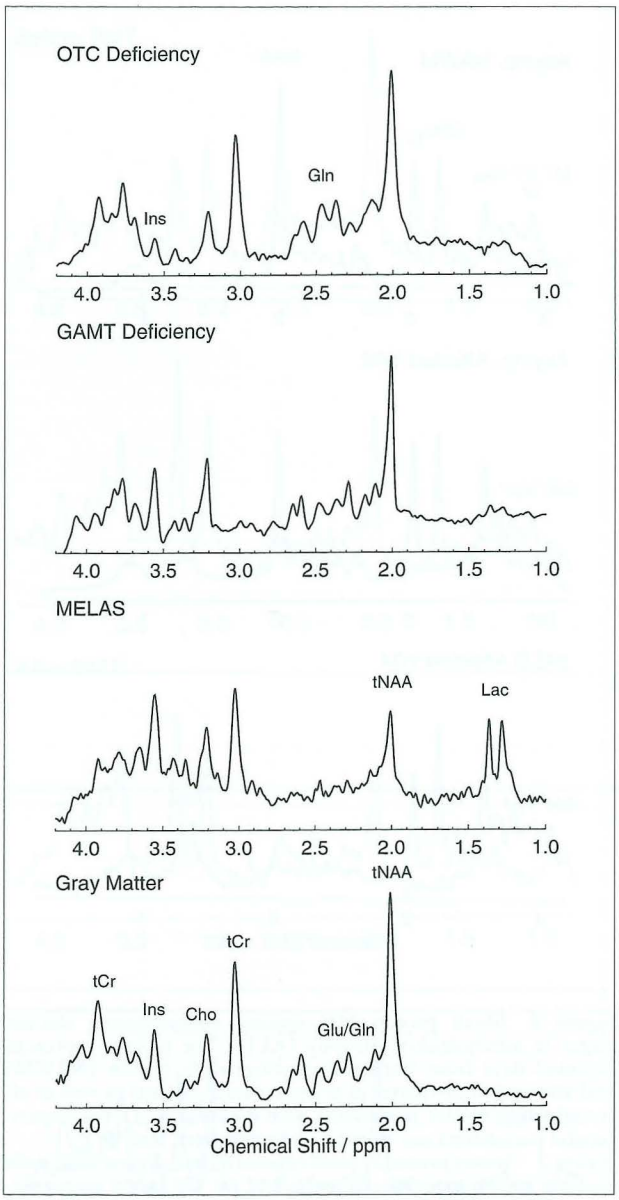

Figure 1 Proton MR spectra of parieto-occipital gray matter (2.0 T, STEAM, TR = 6000 ms, TE = 20 ms, TM = 10 ms, 64 accumulations, same scale) of a healthy control comprising N-acetylaspartate and N-acetylaspartylglutamate (tNAA), glutamate (Glu) and glutamine (Gln), creatine and phosphocreatine (tCr), choline-containing compounds (Cho), and (myo)-inositol (Ins) in comparison with a 10-year-old girl with MELAS (myoclonic epilepsy with lactic acidosis and stroke-like episodes), a 2-year-old boy with GAMT (guanidinoacetate methyltransferase) deficiency, and a 17-year-old girl with OTC (ornithine transcarbamylase) deficiency.

Figura 1 Spettro protonico della materia grigia parieto-occipitale (2,0 T, STEAM, TR = 6000 ms, TE = 20 ms, TM = 10 ms, 64 acquisizioni, stessa scala) di un soggetto di controllo sano che mostra i picchi del N-acetylaspartato e del N-acetylaspartylglutammato (tNAA), del glutammato (Glu) e della glutammina (Gln), della creatina e fosfocreatina (tCr), dei composti della colina (Cho) e del myo-inositolo (Ins) confrontato con lo spettro di una bambina di 10 anni con MELAS (myoclonic epilepsy with lactic acidosis and stroke-like episodes), con quello di un bambino di due anni con deficit di GAMT (guanidinoacetate methyltransferase) e con quello di una ragazza di 17 anni con deficit di OTC (ornithine transcarbamylase).

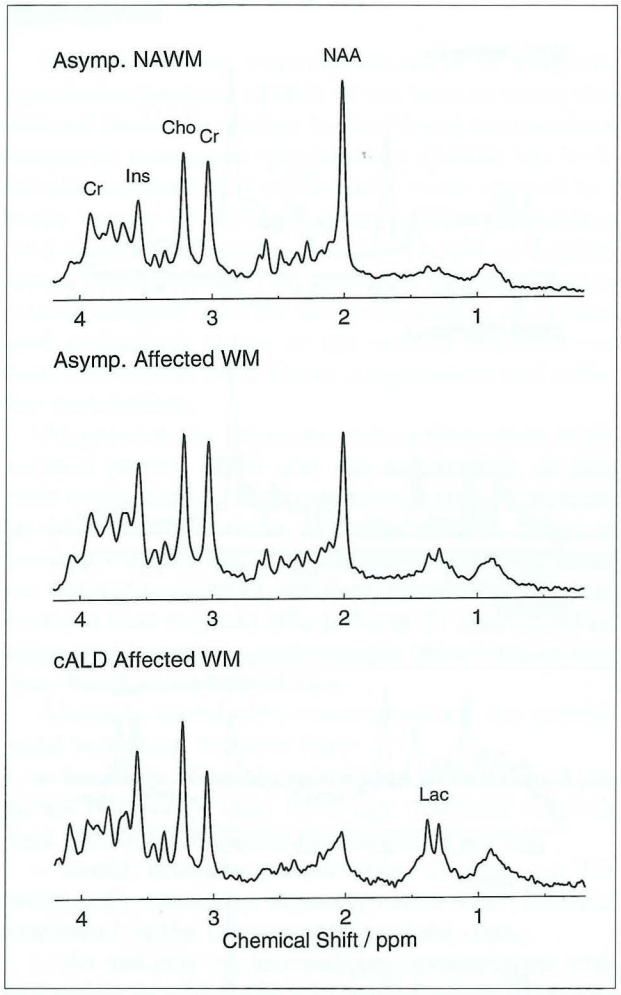

Figure 2 Mean proton MR spectra characterizing disease stages in adrenoleukodystrophy (ALD). The spectra represent summed data from normal-appearing white matter (NAWM) and affected white matter in asymptomatic patients as well as affected white matter in patients with cerebral ALD. For experimental parameters see figure 1. Adapted from Ref 19.
Figura 2 Spettri protonici medi caratterizzanti diversi stadi della malattia nella adrenoleucodistrofia (ALD). Gli spettri rappresentano dati ottenuti dalla sostanza bianca in soggetti apparentemente normali (NAWM), in pazienti asintomatici e in pazienti con ALD cerebrale. Per i parametri sperimentali vedere figura 1. Adattato dalla ref. 19.

mental inadequacies with only a minimum number of assumptions (e.g., no lineshape and baseline assumptions). The approach may be referred to as an absolute reference method [13].

It should be emphasized that metabolic assessments and clinical decisions were exclusively based on quantitative spectroscopic data obtained by the aforementioned automated and user-independent analysis. Extensive investigations of regional age dependencies of cerebral metabolites in human brain [10,14,15] provided age-matched controls for the evaluation of abnormal metabolite concentrations. If suitable data for a particular brain region was not available, the results were compared with an individual control region. The qualitative presentation of manually processed proton MR spectra in this article only serves for easy visual inspection.

Results and Discussion

To demonstrate the clinical value of single voxel proton MRS we have selected examples from three different categories of brain disorders in childhood. The first part comprises metabolic disorders caused by specific enzyme deficiencies, the second part describes neurodegenerative diseases in white matter that are related to either dysmyelination or hypomyelination, and the last part presents MRS contributions to the differential diagnosis of focal lesions, in particular of tumours, that remained undetermined by MRI.

Metabolic disorders

Figure 1 compares three proton MR~spectra of gray matter in patients with different enzyme deficiencies with gray matter of a normal control. All spectra are processed and scaled in proportion.

MELAS (myoclonic epilepsy with lactic acidosis and stroke-like episodes) is a mitochondrial disturbance causing acute and chronic lesions mainly in the occipital lobe. They are characterized by strongly elevated concentrations of Lac and glucose (at 3.43 ppm) as well as severely reduced concentrations of tNAA, Glu, and tCr [16]. These findings are consistent with a reduced capacity of the mitochondrial oxidative energy metabolism resulting from impaired respiratory chain function and further indicate damage or loss of viable neuroaxonal tissue. In contrast, glial cell populations, in particular astrocytes, seem to remain unaffected as evidenced by unchanged concentrations of Ins.

Deficiency of guanidinoacetate methyltransferase (GAMT) was first identified by proton (and phosphorus) MRS in a 2-year-old boy with extrapyramidal movement disorder [17]. This novel inborn error of metabolism causes a generalized depletion of brain tCr concentrations that is partially reversible after oral supplementation of creatine-monohydrate [18]. Phosphorus MRS revealed no detectable phosphocreatine before Cr substitution and a significant increase afterwards. Partial restoration of cerebral tCr levels was accompanied by an improvement of the patient's neurologic symptoms.

Patients with a deficiency of the urea cycle enzyme ornithine transcarbamylase (OTC) suffer

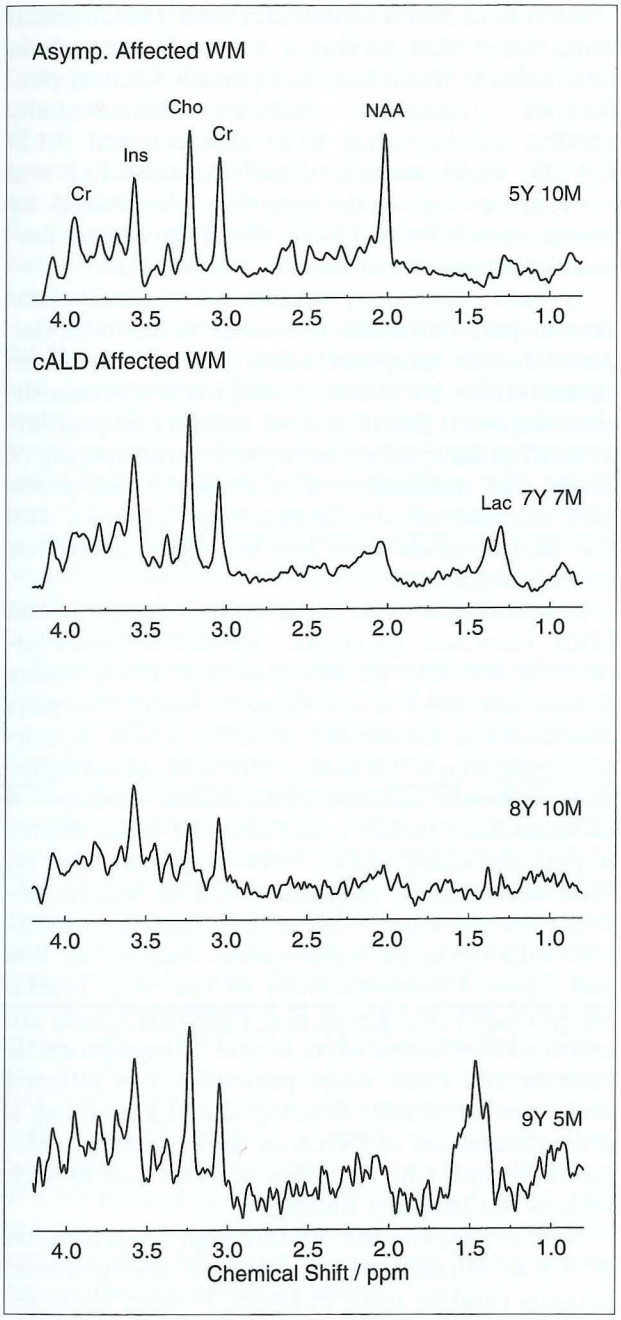

Figure 3 Follow-up proton MR spectra of right parieto-occipital white matter of a patient with ALD at the age of 5Y 10M (TR = 3000 ms, 12 ml), 7Y 7M (TR = 3000 ms, 8 ml), 8Y 10M (TR = 6000 ms, 8 ml), and 9Y 5M (TR = 6000, 4.1 ml). For other parameters see figure 1. Adapted from Ref 19.

Figura 3 Spettri protonici di controllo della sostanza bianca parieto-occipitale destra in un paziente con ALD all'età di 5 anni e 10 mesi (TR = 3000 ms, 12 mL), 7 anni e 7 mesi (TR = 3000 ms, 8 mL), 8 anni e 10 mesi (TR = 6000 ms, 8 mL), e 9 anni e 5 mesi (TR = 6000 ms, 4,1 mL). Per gli altri parametri vedere figura 1. Adattato dalla ref. 19.

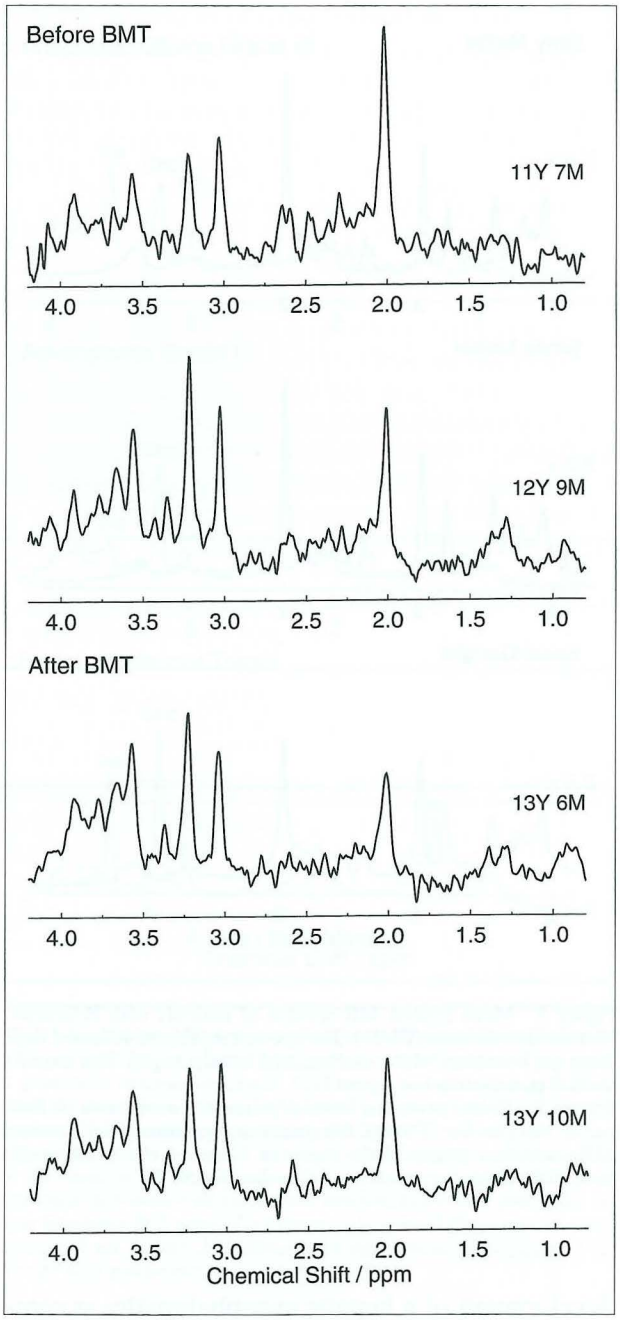

Figure 4 Follow-up proton MR spectra of right parieto-occipital white matter (4.1 ml) of a patient with ALD before and after bone marrow transplantation (BMT) at the age of 13Y 1M. For experimental parameters see figure 1. Adapted from Ref 19.

Figura 4 Spettri protonici di controllo della sostanza bianca parieto-occipitale destra (4,1 mL) in un paziente con ALD prima e dopo trapianto del midollo (BMT, bone marrow transplantation) all'età di 13 anni e 1 mese. Per i parametri sperimentali vedere figura 1. Adattato dalla ref. 19.

from a metabolic disturbance of liver function that leads to elevated blood ammonia. The observed alterations of the cerebral metabolism originate from the uptake of excess blood ammonia by astrocytes that are rich in glutamine synthetase and therefore accumulate Gln from Glu and ammonia. This process also leads to a down-regulation of the osmolyte Ins. Both events are indicators for the

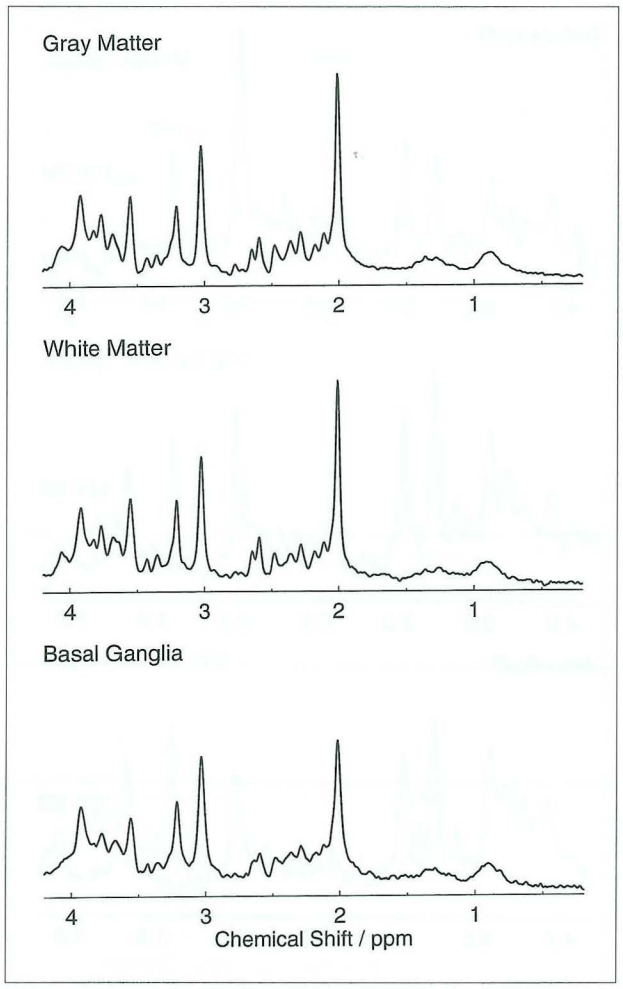

Figure 5 Mean proton MR spectra of patients with Pelizaeus-Merzbacher disease (PMD). The spectra represent summed data from gray matter, white matter, and basal ganglia. For experimental parameters see figure 1.
Figura 5 Spettri protonici medi di pazienti con malattia di Pelizaeus-Merzbacher (PMD). Gli spettri rappresentano dati ottenuti dalla sostanza grigia, dalla sostanza bianca e dai nuclei della base. Per i parametri sperimentali vedere figura 1.

development of a hepatic encephalopathy as commonly found in patients with impaired liver function due to liver cirrhosis.

Adrenoleukodystrophy: demyelination

Whereas demyelination refers to a breakdown of structurally and biochemically normal myelin as in multiple sclerosis, dysmyelination in adrenoleukodystrophy (ALD) denotes a breakdown of structurally and biochemically abnormal and/or instable myelin. Hypomyelination in Pelizaeus-Merzbacher disease (PMD) indicates a disturbance and delay in the formation of normal myelin (see next section).

ALD is an X-linked disorder with a biochemical disturbance that increases the very long chain fatty acids in fibroblasts and plasma. Clinical phenotypes comprise adrenomyeloneuropathy (AMN) as the adult form and cerebral ALD (cALD) which manifests itself between five and 12 years of age with symptoms dominated by ataxia, spasticity, deafness, visual problems, personality changes, and mental deterioration.

Typically, pathology reveals severe demyelination in periventricular locations of the occipital, parietal, and temporal lobes. These lesions are characterized by three histologically distinguishable stages: (i) destruction of myelin and proliferation of sudanophilic macrophages with sparing of axons, (ii) myelinated and demyelinated axons with an associated inflammatory response, and (iii) dense gliosis with loss of oligodendrocytes, myelin, and axons.

In accordance with these classifications proton MRS identifies metabolic abnormalities of increasing severity in white matter. Using mean spectra averaged across subjects, figure 2 depicts characteristic metabolite patterns found in normal-appearing white matter (NAWM) of asymptomatic patients, affected white matter (lesions) of asymptomatic patients, and affected white matter of patients with cALD [19]. NAWM unsuspicious on MRI shows mildly reduced tNAA as well as elevated Ins and Cho. These observations are consistent with moderate neuroaxonal damage or loss and signs of demyelination in line with myelin phospholipid changes in glia. Pertinent trends are enforced in affected white matter of asymptomatic patients and much more pronounced in affected white matter of fully developed cALD yielding a severe reduction of tNAA as well as strongly elevated Ins and Cho. Increase of brain Lac in such regions is a frequent finding.

Noteworthy, the remarkably high concentration of tCr in affected white matter of asymptomatic patients (middle trace in figure 2) most likely reflects the increase in glial cells with disease progression (very high Ins) in the presence of only mild neuroaxonal disturbances in beginning lesions (mildly reduced tNAA). As both glial and neuronal cells contain tCr, its overall concentration may be transiently elevated. With the development of advanced lesions in cALD, tCr is decreased as a result of the marked loss of axons. Obviously, these observations preclude the use of tCr as a "stable" reference in proton MRS studies of ALD.

Figure 3 shows follow-up spectra (same VOI) of an individual patient over a period of four years [19]. In line with his clinical deterioration during disease progression, they demonstrate consecutive

stages of metabolic affection starting from moderate abnormalities in a still asymptomatic state (compare middle trace of figure 2) to the development of a burnt-out zone containing mostly glial fibrils and astrocytes. The corresponding spectra reveal largely reduced concentrations of all metabolites (8Y 10M) or a metabolic pattern reflecting only glial cells (9Y 5M) indicating sequential dysmyelination, structural disintegration of neuroaxonal tissue, and gliosis.

A major purpose of proton MRS studies of ALD is to unravel early markers for disease onset and progression. Thus, monitoring of asymptomatic ALD patients and detecting metabolite alterations before the onset of neurologic symptoms could help to identify those patients who might benefit from bone marrow transplantation (BMT) as the only therapeutic option. BMT has been reported to stabilize the disease when applied in an early phase, but may lead to clinical deterioration in advanced stages.

Figure 4 compares proton MR spectra of a patient before and after BMT [19]. The boy underwent his first MRS examination at the age of 8Y 6M indicating no metabolic alterations. Three years later, neuropsychologic tests and MRI still showed no abnormalities, whereas MRS revealed mildly elevated Ins in parieto-occipital white matter (11Y 7M). Rapid progression occurred as indicated by more pronounced metabolic changes only one year later (12Y 9M). The onset of neurologic symptoms led to the decision of BMT which was successfully performed at the age of 13Y 1M. Five months after BMT (13Y 6M) the metabolic alterations remained unchanged, but nine months after BMT (13Y 10M) proton MRS suggested stabilization or even partial reversal of degenerative processes (arrested demyelination), i.e. a decrease of Cho toward normal levels in two frontal and two parieto-occipital white matter regions and an increase of tNAA in one frontal and both parieto-occipital white matter locations.

Although long-term monitoring of many patients has to clarify to which degree a stabilizing metabolism correlates with a stable clinical condition, proton MRS turns out to be suitable for a follow-up of asymptomatic patients with ALD during stable and "silent" stages of the disease. It shows great potential for an early detection of disease progression and is expected to significantly contribute to patient management in ALD.

Pelizaeus-Merzbacher disease: hypomyelination

The classical X-linked type of Pelizaeus-Merzbacher disease (PMD) is caused by a genetic defect that precludes the formation of proteolipid-

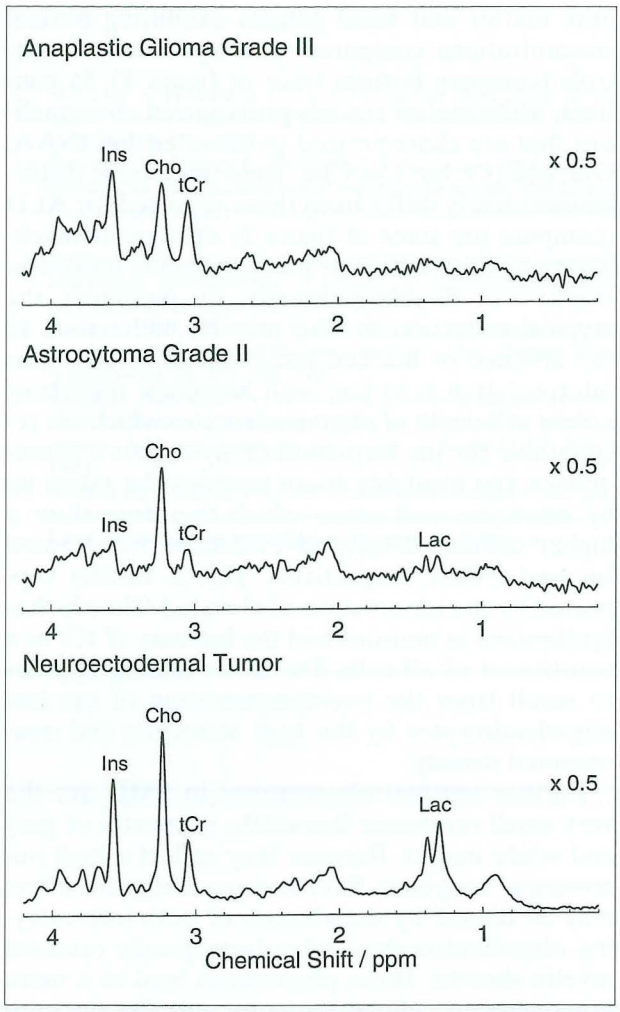

Figure 6 Proton MR spectra of a grade III anaplastic glioma in a 13-year-old boy, a grade II astrocytoma in a 6-year-old girl, and a primitive neuroectodermal tumour in a 1-year-old girl. The spectral intensities are scaled down by a factor of 2 relative to figures 1-5. For other parameters see figure 1.

Figure 6 Spettri protonici di un glioma anaplastico di grado III in un ragazzo di 13 anni, di un astrocitoma di grado II in una bambina di 6 anni e di un tumore neuroectodermale primitivo in una bambina di 1 anno. Le intensità dei picchi degli spettri sono scalate di un fattore 2 relativamente agli spettri delle figure 1-5. Per gli altri parametri vedere la figura 1.

protein as one of the major myelin proteins. It results in a disturbance of myelin formation with hypotonia, nystagmus, ataxia, and spasticity as clinical symptoms. As a prominent finding in MRI, the arrest of brain myelination during early development yields almost no distinction between gray matter and non-myelinated white matter in T1-weighted images, whereas T2-weighted images show white matter hyperintensities.

Figure 5 depicts mean proton MR spectra of gray matter, white matter, and basal ganglia in PMD patients [20]. As a distinct feature, and in parallel to the MRI findings, the metabolite profiles in gray and white matter are virtually identical with

gray matter and basal ganglia exhibiting normal concentrations compared with age-matched controls (compare bottom trace of figure 1). In contrast, white matter reveals pronounced abnormalities that are characterized by elevated Ins, tNAA, Glu, and tCr, but low Cho. These metabolic disturbances clearly differ from those reported for ALD (compare top trace of figure 2) or other demyelinating disorders such as metachromatic leukodystrophy [21] or Krabbe's disease [1]. In particular, the atypical reduction of Cho may be understood as the absence or marked reduction of myelin. This interpretation is in line with histologic reports of severe cell death of oligodendrocytes which are responsable for the formation of myelin. As a consequence, the available space seems to be taken up by astrocytes and axons which therefore show a higher cellular density as evidenced by elevated Ins and tNAA, respectively. This is further supported by the observation of elevated Glu which is synthesized in neurons and the increase of tCr as a constituent of all cells. The latter finding appears to result from the overcompensation of the lost oligodendrocytes by the high astrocytic and neuroaxonal density.

Further unusual observations in PMD are the very small resonance linewidths in spectra of gray and white matter. Because they reflect a high microscopic magnetic field homogeneity, the effect may be caused by the absence of both iron-carrying oligodendrocytes and anisotropically oriented myelin sheaths. These phenomena lead to a more homogeneous cellular structure and less susceptibility differences than obtained for normal white matter.

Altogether, proton MRS of PMD yields a distinct metabolic pattern with no similarities to other leukodystrophies. In contrast to dysmyelination and neuroaxonal loss, the high concentration of tNAA points to the preservation of intact neuroaxonal tissue components, and the low Cho level seems to represent a specific feature reflecting damage or loss of oligodendrocytes. In other words, the MRS-detectable correlates of hypomyelination clearly differ from those observed for other myelin disorders.

Differential diagnosis of focal brain lesions

Despite considerable progress in neuroimaging, differential diagnosis of brain tumours and other focal lesions often poses problems. Because of its access to a metabolic characterization of brain tissue, proton MRS may improve this situation in children with suspect MRI findings. Pertinent attempts seek to exploit the characteristic metabolite alterations that have been reported for the majority of intracranial tumours, i.e. reduced content or even lack of neuroaxonal tissue and proliferation of glial cells. Accordingly, the proton MR spectra of most primary brain tumours exhibit low tNAA levels as well as elevated Ins and/or Cho concentrations and eventual Lac. Conversely, gliosis causes elevated Ins and/or Cho but only mild or no reduction of tNAA and no Lac.

Typical findings for brain tumours are demonstrated in figure 6 depicting MR spectra of a high grade anaplastic glioma, a grade II astrocytoma, and a primitive neuroectodermal tumour, respectively. In a recent study of 17 children with unclear lesions [22], proton MRS correctly identified 14/17 cases, failed in 1/17 cases, and was not informative in 2/17 cases as evidenced by subsequent histologic examination. One false positive tumour diagnosis was a case of severe reactive gliosis mimicking a typical tumour spectrum. The two inconclusive cases comprised an astrocytoma with moderately elevated Ins but reduced Cho and a patient with an abscess leading to a marked reduction of all metabolites but very strong contributions from mobile lipids. Such promising results underline that quantitative single voxel proton MRS bears considerable clinical value for a presurgical characterization of focal brain lesions with unknown dignity.

Conclusions

In summary, the ease of use and the growing understanding of its results moves single voxel proton MRS of the human brain toward a tool for (in vivo) histopathology. As such it improves and extends the diagnostic potential of MRI and may gain significant impact on patient management.

However, instead of using ratios of T1- and/or T2-weighted resonance intensities, proton MRS should be based on multi-metabolite patterns of absolute metabolite concentrations and compared with regional control values from large groups of age-matched healthy subjects.

Methodologic quality, absolute quantitation, proper controls, and care in the interpretation of the data will be mandatory in its further application to brain disorders in childhood and beyond.

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