Spectroscopy 16 (2002) 297–306
IOS Press

The role of clinical *in vivo* 1H-MR spectroscopy in the evaluation of epilepsies

T. Hammen [a,*], H. Stefan [a] and B. Tomandl [b]
[a] *Clinics of Neurology Center Epilepsy, University of Erlangen-Nürnberg, P.O. Box 3520, D-91023 Erlangen, Germany*
[b] *Department of Neuroradiology, Clinics of Neurosurgery University of Erlangen Nürnberg, P.O. Box 3520, D-91023 Erlangen, Germany*

Abstract. 1H-MRS which is a noninvasive method in detecting various brain metabolites containing N-acetylaspartat (NAA), cholin (Cho), creatin (Cr) GABA and glutamat has become a diagnostic tool for assessing a number of diseases of the central nervous system particularly including epilepsies and brain tumours. 1H-MRS plays an increasing role in the evaluation of epilepsies and their treatment schedules today. NAA is accepted as a marker of neuronal/axonal density and viability. It's detailed physiological role is yet unknown. A loss or decrease of NAA is seen in diseases which are associated with loss of neurons or axonal degeneration. GABA, glutamate and glutamin (Glx) probably define the epileptic focus in biochemical terms. 1H-MRS implies high sensitivity and validity in focus localization in patients with temporal lobe epilepsies (TLE) compared to established methods like video EEG, MR-volumetry and SPECT. In patients with intractable mesial TLE who were scheduled for surgery NAA/Cr or NAA/Cr + Cho asymmetry indexes of the hippocampal formation were created and compared to healty controls. The results were related to the mentioned already established localization techniques. Most authors which investigated this topic likewise found that 1H-MRS is highly concordant to EEG and MRI-Vol findings. Recent studies show that 1H-MRS besides it's capability to lateralize the epileptic focus is able to distinguish between mesial and lateral TLE. In addition to it's sensitivity in focus lateralization 1H-MRS contains a predictability concerning the evaluation of postoperative outcome in patients with intractable TLE. Most studies reveal that changes contralateral to the epileptogenic focus or bilateral changes in metabolite spectra of 1H-MRS are associated with a poor whereas homolateral alterations to the focus reveal a good postoperative seizure outcome. The evaluation of anticonvulsive drugs by 1H-MRS is the topic of various recent studies in which human brain GABA levels are investigated by 1-HMRS under the influence of antiepileptic drugs mainly including vigabatrin and topiramat. The effect of antiepileptic drugs and their influence on seizure inhibitoring brain metabolites was investigated and the authors were able to create responder profiles by correlating the mentioned metabolites in a long-term study. They verified an increase of GABA within the beginning of antiepileptic treatment and an increase of homocarnosine, a GABA metabolite, in long term treatment (2–3 months) in the responder group.

1. Metabolites examined in neurospectroscopy and their clinical significance

N-acetyl-aspartat (NAA)

The N-acetyl methyl(CH_3) group of NAA provides a prominent peak at 2.02 ppm and is the dominant peak in normal adult brain spectra. Today NAA is accepted as a marker of neuronal/axonal density and viability. It s detailed physiological role is yet unknown. A loss or decrease of NAA is seen in diseases which are associated with loss of neurons or axonal degeneration. For that reason destructive or infitrating diseases associated with a neuronal degeneration or loss lead to a reduction of the NAA peak.

Choline (Ch)

Choline gives a strong peak at 3.2 ppm. Phosphorylcholine and glycerophosphorylcholine are the main parts which contribute to the choline resonance peak. Choline is bound to cell membranes, myelin and

*Corresponding author. Supported by Wilhelm Sander foundation.

complex brain lipids. An increased cholin signal may reflect an increased membrane synthesis and and is thought to reflect a myelin breakdown and increased cell density and gliosis. In adult brain increased choline peaks are associated with Alzheimers disease, chronic hypoxia, postliver transplantant, epilepsy and tumorous mass lesions (gliome I–IV) while a decrease is seen in hepatic encephalopathy.

Creatine + phosphocreatine (Cr)

The major peak at 3.02 ppm results from the CH_3 group of creatine and phosphocreatine and is referred to as total Cr. Total Cr is used as an internal reference in reporting relative concentrations of other brain metabolites because it's considered to be a relative stable compound.

Increased signals can be correlated with trauma and a decrease correlates with hypoxia, stroke, tumour and gliosis.

Lactate (Lac)

The lactate peak when present provides it s signal at 1.33 ppm and rises above the baseline at a TE of 272 ms and becomes inverted at a TE of 135 ms. Having a concentration about 1 mM, Lac is not detected in brain tissue under normal conditions. It increases under failed oxidative metabolism or increased glycolysis. Lactate can be detected in patients with stroke, brain tumours, hypoxia, anoxia and mitochondrial encephalopathies. It's increased in the epileptogenic regions postictal.

Gammaaminobutyric acid (GABA)

GABA shows peaks at 1.9 and 2.3 ppm from protons in the β- and α-CH_2 group and at 3.00 ppm from the gamma-CH_2 group which is usually hidden by the Cr peak. GABA represents the most important inhibitory neurotransmitter. Short echotimes are needed to generate the peak which is sensitive to artifacts due to lipids and macromolecules.

Glutamate and glutamine (Glx)

Is a excitatory neurotransmitter which needs short echo times as GABA as well, high levels of Glx are markers of epileptogenic processes. The methylene groups shows peaks in the 2.0–2.45 ppm range and 3.6–3.8 ppm.

GABA and glutamate probably define the epileptic focus in biochemical terms.

2. *In vivo* 1H-MRS as a method of focus localization in patients with TLE

Many studies have been carried out to evaluate 1H-MRS as a method of epileptic focus localisation and tried to rank it's sensitivity, validity and reliability by comparison with established methods like EEG as the goldstandard, MRI-Vol, FDG-PET and SPECT. Hugg et al. who were one of the first authors who investigated this problem detected a significant asymmetry in the intensity of the NAA left/right metabolite ratios in hippocampal formations in all patients on the side of the EEG seizure foci [1]. The affected hippocampi showed $21 \pm 5\%$ lower NAA signals compared to the contralateral hippocampal formation in which no epileptogenic activity was found by EEG investigations. MRI investigations which included volumetric measurements and T2 signal density resulted in correct localisation in 7 of 8 patients. Tc-SPECT findings of reduced perfusion interictally resulted in correct localisation in 2 of 5 cases. Most of the studies dealing with the topic demonstrate comparable results as mentioned above and demonstrate a decrease in NAA combined with increased Cr and Cho signals in the affected temporal lobe of patients with intractable TLE. In general the results can be distinguished into three groups: The first group of authors, which is the biggest group demonstrate a decrease of NAA/Cr or NAA/Cho + Cr ratio [2,7,8], the second group reports single reduced concentration of NAA without significant changes in

the levels of Cr and Cho [1] in the affected temporal lobe. Single increases of Cho and Cr have been reported as well in fiew cases [7]. The different results probably base on different techniques on one hand and the inhomogeinity of the group of patients with TLE including hippocampal sclerotic alterations and MRI neg. groups. Kuzniecky et al. investigated the validity of 1H-MRS in lateralizing the pathologic metabolite variations in the hippocampal area of 30 consecutive preoperative patients with mesial temporal lobe epilepsy (MTLE) who showed pathologic confirmation of mesial temporal sclerosis [5]. Patients with other pathologic malformation or with dual pathology were excluded. MR-volumetry correctly lateralised the side of surgery in 93% of patients and 1H-MRS did so in 97% compared to EEG localization. Incorrect lateralization occured by volumetry in two patients, by 1H-MRS in one patient. Concordance between the described MRI modalities was 73%. No correlation was found between the degree of hippocampal volume loss and the degree of metabolic disturbance in 1H-MRS. Comparable results were described by Cendes et al. who investigated 100 consecutive patients with intractable MTLE [3]. An asymmetry index for NAA/Cr values of temporal lobes was calculated in each case and compared among patients and with 21 healthy controls. The results of 1H-MRS were related to the focus localization of extensive EEG investigation. The authors likewise found that the EEG, 1H-MRS and MRI Vol findings were highly concordant. The 1H-MRS was abnormal in 99 of 100 patients showing bilateral affection in 54%. A correct lateralization was performed in 86% of patients using 1H-MRS alone. MRI-Vol was abnormal in 86 of 98 patients with bilateral affection in 28%. Correct lateralisation was obtained in 83% using MRI-Vol alone and in 90% using the mentioned methods in combination (vs 93% lateralization by EEG). Beyond it's sensitivity in lateralizating single foci 1H-MRS is a sensible method to detect bilateral affections which might be underdiagnosed in conventional MRI. In general the degree of asymmetry in NAA/Cr ratios correlated with the degree of one sidedness of EEG abnormalities. The metabolite asymmetry ratios of 1H-MRS were less pronounced in patients with more frequent bilateral (ictal and interictal) EEG abnormalities compared with patients who showed a higher degree of more unilateral EEG abnormalities. These results support the fact that 1H-MRS is a valid method in focus localization in patients with TLE. The authors found a correlation between the volume loss in MRI-Vol and reduced NAA/Cr ratios which supports the hypothesis that reduced NAA/Cr ratios is associated with neuronal loss in hippocampal structures. In contrast to this point of view 12 patients with normal MRIV showed pathologic metabolitealterations in 1H-MRSI, a fact that points out that the evaluation of metabolitespectra is more complex, a topic which will be discussed beneath.

Knowlton et al. included FDG-PET investigations to compare the method with 1H-MRS in focus localization in TLE patients with no lesional MRI findings [10]. He compared the results to EEG findings, hippocampal volumes of MRI and metabolite ratios of 1H-MRS which were performed in the mid and posterior hippocampus of 23 patients. Criteria for best lateralisation was determined for each modality in accordance with ictal EEG. PET had a concordance of 87% without dicordant results, MRVol showed a 65% and 1H-MRS showed a 61% concordance to EEG focus-localisation. In patients with hippocampal atrophy PET was sensitive in 75% and 1H-MRSI in 50%. The combination of 1H-MRS and MRI-Vol showed a comparable lateralization sensitivity than FDG-PET. Bilateral abnormalities were detected in 17% with volumetric studies and in 33% in 1H-MRS using metabolic ratio or NAA concentrations. The authors came to the conclusion that both FDG-PET and 1H-MRS are suitable methods for lateralizing epileptic foci in patients in which MRI shows no lesional damage. FDG-PET shows the highest significance because of the higher recall ratio in detecting the foci.

In general the data support that 1H-MRS is a useful and sufficient noninvasive tool to localize epileptogenic foci in patients with temporal lobe epilepsia (TLE) with high degree of validity. After one got aware that 1H-MRS is a useful tool in lateralising the hemisphere of the focus the question arised whether

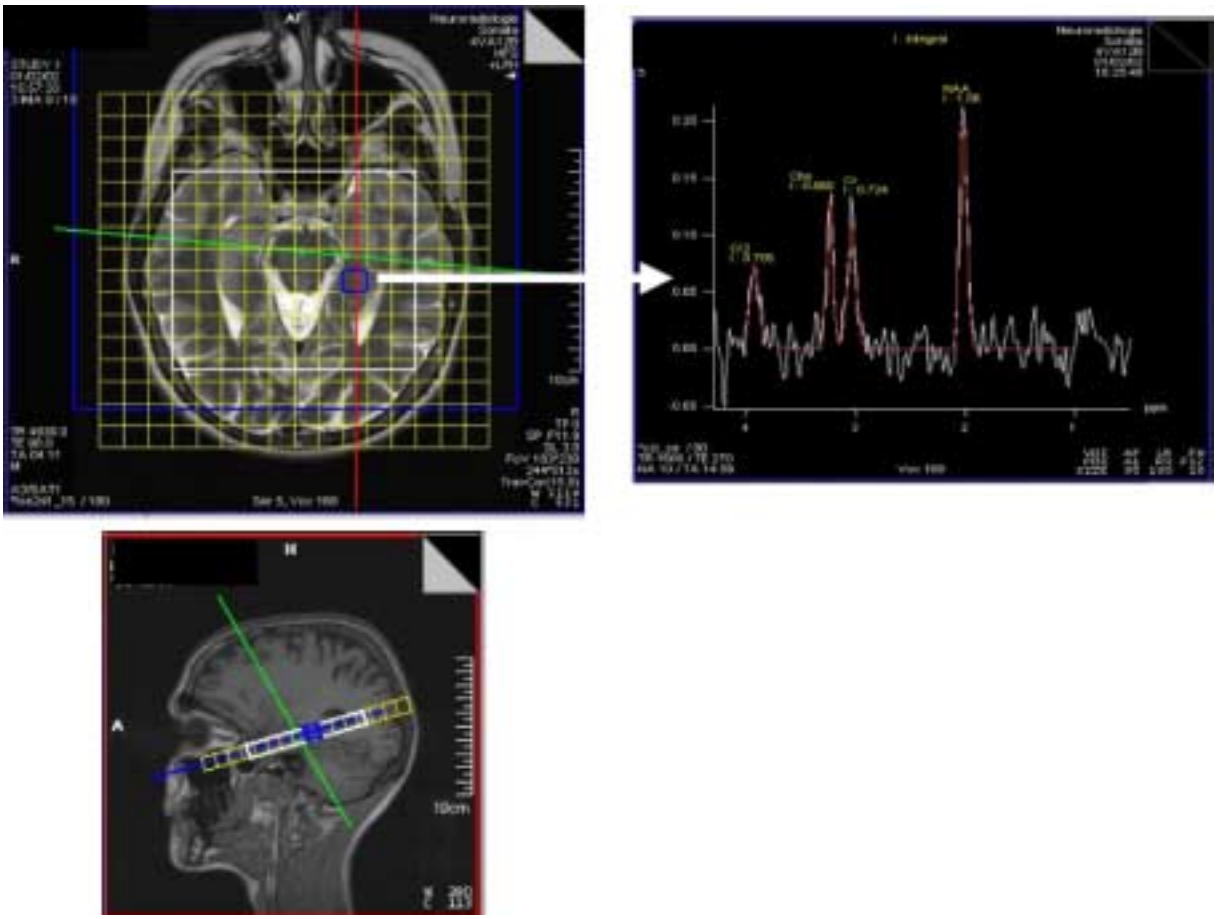

Fig. 1. Positioning of the CSI-grid in temporomesial structures covering the hippocampal formation in patients with TLE.

the method is able to distinguish mesial from lateral foci in the temporal lobe and to differentiate mesial (MBTLE) from lateral, neocortical TLE (NCTLE) in MR nonlesional patients. Recent studies give strong evidence that metabolic differences between mesial and lateral TLE in hippocampal regions exist and that 1H-MRS is likely to be a reliable diagnostic tool in separating them [12]. The authors investigated NAA in the hippocampal formation of neocortical and mesial TLE. The results were compared to controls. The authors detected that hippocampal NAA was able to discriminate the mentioned different TLE's. The patients with mesial TLE showed a significant marked reduction of NAA in the hippocampal formation compared to controls. In the neocortical TLE group NAA was neither reduced in the ipsilateral- nor in the contralateral hippocampus. These results are in common to our findings which demonstrate a significant asymmetry of metabolite ratios in hippocampal structures as well. We showed that the metabolite alterations in hippocampal formations were more severe in patients with mesiobasal focus compared to the lateral, neocortical TLE group which were not associated with predominant 1H-MRS-pathologies. The results support the thesis that the absence of spectroscopic differences in the hippocampus of temporal neocortical epilepsies may help to distinguish those from mesiotemporal lobe epilepsies.

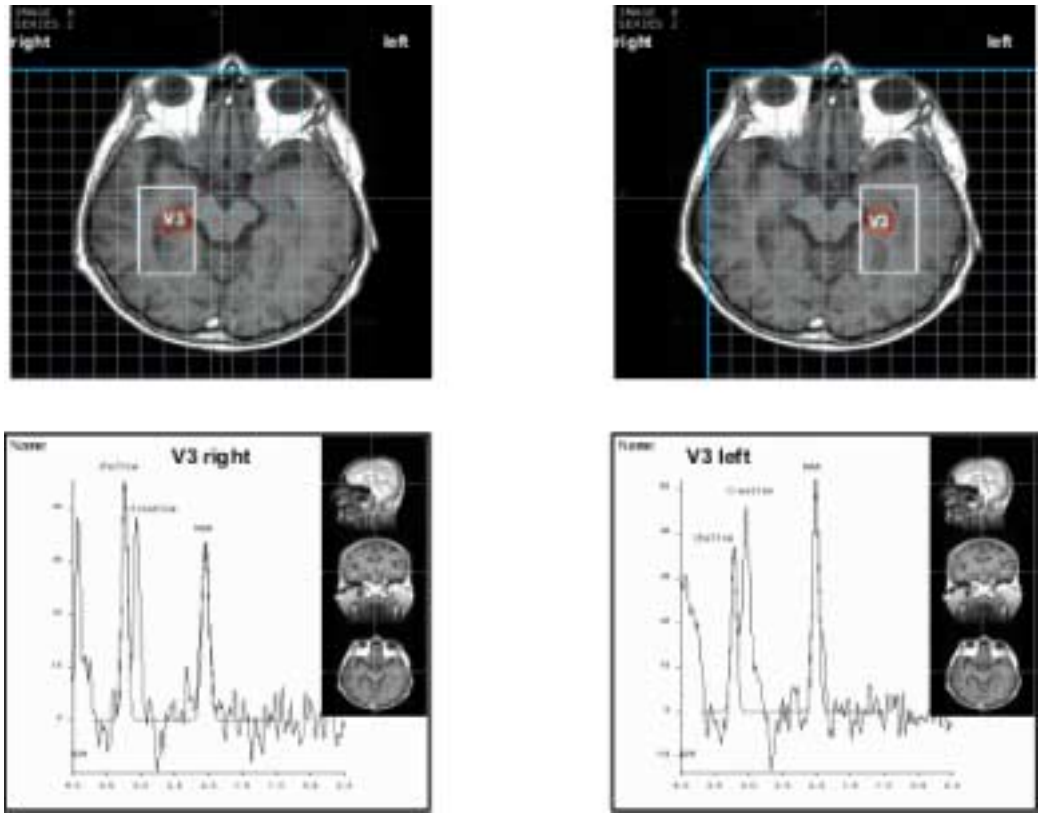

Fig. 2. Spectra of a patient with cryptogenic temporal lobe epilepsy and unilateral pathological spectra on the right side presenting a reduced NAA/Cho ratio.

3. The predictability of 1H-MRS concerning the evaluation of postoperative outcome in patients with intractable TLE

The studies mentioned above confirm the role of 1H-MRS as a noninvasive diagnostic tool in epileptic focus localisation. In a second step the question whether different distributions of metabolite-spectra alterations are correlated with postoperative outcome was investigated. The studies which were carried out in our institute reveal the following results: Stefan et al. and Eberhardt et al. evaluated the significance of preoperative bilateral CSI changes for the prognosis of postoperative seizure outcome [17–19]. CSI multivoxel spectroscopy was performed in 26 consecutive TLE patients scheduled for epilepsy surgery. Discriminant analysis of ipsilateral and contralateral CSI was performed. The volume of interest included voxels which covered hippocampal and parahippocampal structures. The NAA/Cho ratios were determined from the described voxels and compared to results of the contralateral hemisphere and to normal controls. The authors could verify that contralateral metabolic changes are able to predict postoperative seizure outcome in TLE patients. The results indicated that contralateral changes in 1H-MRS are a good predictor for poor seizure outcome whereby 92.3% of patients who became seizure free postoperatively had no severe bilateral metabolic deviations and showed unilateral metabolite alterations which were classiefied correctly with the mentioned method.

Comparable results have been reported by Kuzniecky et al. and Li et al. [6,21]. Kuzniecky et al. investigated the metabolite alterations by chemical shift imaging (CSI) preoperatively in 40 consecutive

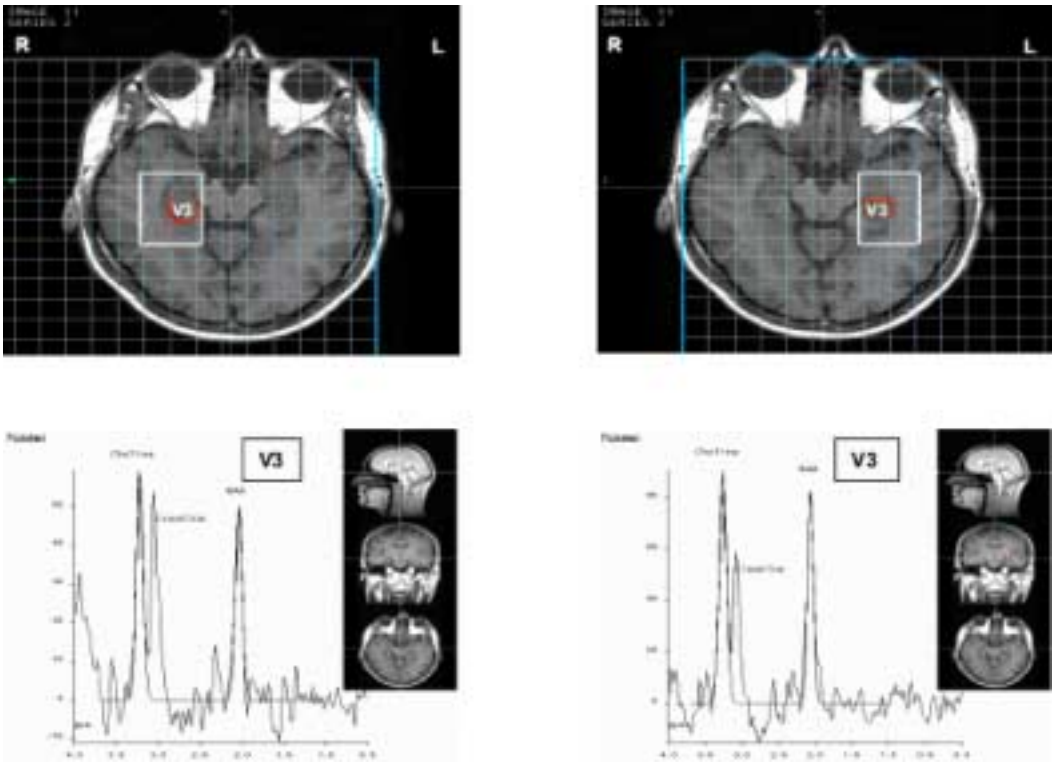

Fig. 3. Spectra of a patient with cryptogenic temporal lobe epilepsy and bilateral pathological spectra.

patients with intractable TLE who were scheduled for temporal lobe surgery. The postoperative outcome at a mean of 24 months was classified as seizure free or not seizure free. As described in our article bad postoperative outcome was associated with metabolite alterations contralateral to the epiletic focus or bitemporal abnormalities of 1H-MRS spectra. The authors correlated a bad postoperative results with either preoperative elevations in the Cr/NAA ratio in the contralateral, nonoperated temporal lobe or in case of bilateral abnormalities with the presence of Cr/NAA ratio above 1.21 contralateral to the proposed surgery. Li et al. investigated the surgical outcome in patients with intractable TLE and bilateral hippocampal atrophy defined by volumetric measurements [21]. The ratio of NAA/Cr was determined in 21 patients for mid and posterior temporal lobe regions by 1H-MRS in both hemispheres. An asymmetry index was determined. Engel classification was used to assess surgical outcome with respect to seizure control. All patients were operated on the side of maximal EEG lateralization. The study including patients with TLE and bilateral hippocampal atrophy showed the same results as mentioned above. An absence of contralateral NAA/Cr reduction in the posterior temporal region revealed a favorable surgical outcome. The authors additively analyzed the relative asymmetry ratio NAA/Cr of midtemporal regions. A regression correlations analysis showed significant linear correlation between the degree of asymmetry and surgical outcome. The greater the asymmetry the better the outcome.

The results show that nuclear MRS is able to predict postoperative seizure outcome in which monolateral abnormalities which are located ipsilateral to the epileptogenic focus determined by EEG stand for a good prognostic outcome whereas contralateral or even bilateral abnormal spectra are associated with a bad postoperative outcome.

4. Proton MR-spectroscopy in the evaluation of conservative treatment schedules in epilepsies

1H-MRS in the evaluation of anticonvulsive drugs has been the topic of various studies. Petroff et al. has carried out multiple studies which investigated human brain GABA levels under the influence of vigabatrin therapy [22]. Vigabatrin increases the level of brain GABA by irreversibly inhibiting GABA transaminase. *In vivo* single voxel spectroscopy with short echo times was carried out in the occipital lobe before and 2 hours after Vigabatrin intake. The GABA peak increased by more than 40% 2 hours after intake of a single dosis of Vigabatrin (50 mg/kg/day). The authors monitored the GABA levels under the mentioned Vigabatrin intake and discovered a further increase the next day. Levels of GABA declined gradually from day 5 to day 8. The study support that vigabatrin promptly offers protection against further seizures by elevating GABA levels. The authors additively investigated an increase of homocarnosine levels (a dipeptide of GABA) which is thought to be an inhibitory neuromodulator as well [23]. Daily low dose medicamentation of Vigabatrin (2 g) increased both metabolites GABA and homocarnosine while larger doses of Vigabatrin (4 g) further increased homocarnosine but changed GABA levels minimally. In general seizure control improved with increasing homocarnosine and GABA concentrations. The authors were able to get an insight into the responder profiles of patients treated with Vigabatrin at this point. They discovered that improved seizure control under Vigabatrin therapy was associated with higher mean homocarnosine levels in responders compared to lower mean levels of the non-responder group. Responders and non-responders did not differ in the mean GABA-level. To summarize the effects of Vigabatrin the study reveal that GABA levels rise within the first hours and days under Vigabatrin therapy, in the later time period of medication (after 2–3 months) homocarnosine levels rises more gradually than GABA levels. Increased homocarnosine levels are likely to represent long term protection. Mueller et al. investigated responder profiles in patients who were treated by Vigabatrin by analyzing GABA + (including homocarnosine and macromolecules) to a Cr ratio (GABA+/Cr) [23]. The GABA+/Cr ratio was measured in the epileptogenic and nonepileptogenic hemisphere in a volume of 8 cm^3 by single voxel spectroscopy. Measurements were performed before and after a titration period of 1 month. A third meaurement followed a maintenance period of 3 months. The authors were able to correlate responder groups depending on the therapeutic efficacy of VGB to changes in the GABA+/Cr signal. The non responders which showed no increase in seizure reduction under the treatment of Vigabatrin showed no significant change in the GABA+/Cr signal compared to baseline during the treatment. The full responders had a significant increase of the GABA+/Cr signal during the whole treatment phase and a lower ipsilateral level at baseline before antiepileptic medication. The partial responders also showed lowered ipsilateral GABA+/Cr signals before antiepileptic treatment. The GABA+/Cr ratio increased at the beginning of the treatment and decreased when seizures under antiepileptic treatment started again. Recent studies try to include other antiepileptic drugs in the investigation of their influence on seizure inhibitoring brain metabolites. Petroff et al. investigated the influence of Topiramate on GABA, homocarnosine and pyrrolodinone two metabolites of GABA with antiepileptic action [24]. *In vivo* measurements of the mentioned metabolites in twelve patients with refractory complex partial seizures were carried out. Topiramate increased mean brain GABA, homocarnosine and pyrrolidinone concentrations in all patients. The increased levels could contribute to the potent antiepileptic actions of Topiramate.

At last if we try to integrate 1H-MRS in the diagnostic procedure and evaluation of epilepsies or any neurological diseases we have to ask ourselves what do abnormal spectra in 1H-MRS stand for? Do they reflect an irreversible tissue degeneration or a reversible neuronal dysfunction? The high concordance between abnormal spectra in 1H-MRS and atrophic alterations in MRI-Vol in epileptogenic foci was

interpreted in the way that the metabolite alterations may reflect a neuronal loss or damage in the hemisphere of the seizure focus. This result has been supported by early pathologic studies. Already before 1H-MRS investigations were performed neuropathological studies of the epileptogenic foci determined by EEG investigations were carried out with particular reference to TLE [11]. The authors discovered an extensive neuronal loss and reactive astrocytosis in the affected hippocampal structure and in the adjacent temporal lobe. The reduced NAA levels of 1H-MRS in previous studies were thought to represent a neuronal loss, the increased cholin and creatin signals were related to reactive astrocytosis and gliosis. A lot of current studies strongly suggest that the mentioned topic is more complex and hides a variety of histopathological and pathobiochemical aspects still unknown. Recent studies which are mentioned in the following tried to give new insight into the question what do abnormal 1H-MRS spectra stand for and tried to investigate whether 1H-MRS is able to give any additive information on the etiology of epilepsies. Recent studies of Cendes et al. and Kuzniecky et al. support the view that the spectra of 1H-MRS cover a more complex pathology than it was thought in the beginning [21,22]. Cendes et al. performed 1H-MRS in patients with TLE before and after surgical treatment in order to investigate wheter postoperative changes were correlated with surgical outcome. The authors investigated NAA/Cr ratios and discovered that the NAA/Cr ratio was abnormally low preoperatively in at least one temporal lobe in all patients examined. Reduced ipsilateral NAA/Cr ratios were associated with a good postoperative outcome, while bilateral changes revealed a bad postoperative outcome. The interesting point in the studies of Cendes et al. is the fact that reduced NAA/Cr ratio increased to normal range postoperatively in all patients who became seizure free. In contrast the mentioned ratios did not change in patients who continued to have seizures after surgery. The authors concluded that postoperative reversible NAA (and Cr) abnormalities in TLE do not solely result from neuronal loss and gliosis but represent at least in part dynamic markers of local and remote physiologic dysfunction associated with ongoing seizures. In order to get more insight into the question wheter abnormal metabolic spectra in 1H-MRS reflect neuronal dysfunction or cell loss Kuzniecky et al. investigated whether metabolic changes detected by 1H-MRS correlate to hippocampal cell loss in TLE [22]. The authors investigated 33 patients with intractable mesial temporal lobe epilepsy who were undergoing surgery. Quantitative hippocampal MR imaging volumetry and 1H-MRS imaging was performed in all patients. The studies were carried out at a 4.1 T whole body imaging spectroscopy, the region of interest included the midbrain, the hippocampus and portions of the temporal lobe. Postoperative quantitative hippocampal cell counts were carried out by obtaining a neuronal glial ratio of the cornu ammonis and fascia dentata of the hippocampus which was correlated to pathologic specimens of age matched autopsy control case hippocampi. As described by Babb et al. and Corsellis et al. [23,24] hippocampal sclerosis (HS) is characterized by neuronal cell loss and astrogliosis in the cornu ammonis (CA) with relative sparing of the CA2-sector and the fascia dentata. In MRI HS shows an atrophy and a hyperintensive signal intensity in T2 weighted scans. The atrophy found in MRI-Vol were related to the hippocampal cell losss in the CA regions. Up to now it was hypothesed that decreased NAA are related to neuronal cell loss and increased Cho and Cr is related to gliosis. In the mentioned study Kuzniecky et al. verified the facts that HS is associated with a significant lower neuronal–glial ratio of the patient group compared to the control group in the cornu ammonis region. Correlations of hippocampal volumes with the cornu ammonis and neuronal–glial ratios revealed a significant interdependence. So far the results are in common to prior investigations. An interesting point of this study includes the comparison of 1H-MRS results to the mentioned histopathological results with special intention to neuronal–glial ratios. If NAA, Cho and Cr peaks of nucleus MR spectroscopy represent neuronal cell loss there should be a positive significant correlation between the histopathological grading and the quantitative metabolite abnormalities of Cr- and NAA compound ratios within the investigated hippocampal structure. The study of Kuzniecky

et al. showed no significant correlation between the cornu ammonis- or fascia dentata neuronal–glial ratios and the corresponding hippocampal Cr/NAA compound ratio. These findings support the concept that the results of 1H-MRS and the hippocampal volume loss detected by MRI-Vol do not necessarily have the same neuropathologic basis. Altered metabolic spectra of *in vivo* 1H-MRS are not inevitably connected to temporal gliosis or sclerosis. These findings and the normalisation of neuronal metabolic dysfunction after surgery for TLE as described by Cendes et al. suggest that metabolic alterations of 1H-MRS do not reflect neuronal cell loss in any case but are rather correlated to neuronal dysfunction.

The role of 1H-MRS in the investigation of neurological diseases like epilepsy depends on the solution of the main problems in nuclear magnetic resonance spectroscopy of today which should be the topic of further technical investigations and developments. The main problems concern the impaired quality especially of spectra with short echo-times by lipid and water artifacts. Lipid signals interfere the CSI spectra especially when using short echo times in regions with neighbouring fat tissue (subcutaneous or temporobasal fat inclusion of bony structures of the skull base). The problems will potentially be solved by improving lipid suppression by advanced filters (outer volume suppression) or special editing pulses which separates the fat signal from the spectra. The further development of an outer volume suppression includes a suppression of signals sources which are not located in the Volume of interest (VOI). This technique could contribute to an increased spectra quality especially in cortex-, and temporobasal located regions. An improved automated shimming method and a further development of special shim coils will increase the magnet field homogeneity and lead to a better spectral quality and spectral resolution. Full brain coverage will probably be obtained with multislice studies, or 3D acquisition using echo planar multivoxel techniques. Because of the non-invasiveness of the method there is no interference with pathology and can be used for evaluating the progression of pathological alterations in epilepsy. As a non-invasive tool the method contributes to a better understanding of dynamic aspects, plasticity and brain function during the course of epilepsy and changes during therapy. If the method will overcome the mentioned problems, MR-spectroscopy becomes more user friendly and if totally automated and robust data processing software is available the method becomes more established for clinical use and a growing future of nuclear magnetic resonance spectroscopy as a single and a coregestrative method is possible.

References

[1] Jw. Hugg, K.D. Laxter, G.B. Matson, A.A. Maudsley and W.M. Weiner, Neuron loss localises human focal epilepsy by in vivo proton MR spectroscopic imaging, *Ann. Neurol.* **34** (1993), 788–794.
[2] F. Cendes, F. Andermann, M.C. Preul and D.L. Arnold, Lateralization of temporal lobe epilepsy based on regional metabolic abnormalities in proton magnetic resonance spectroscopic images, *Ann. Neurol.* **35**(2) (1994), 211–216.
[3] F. Cendes, Z. Caramano, F. Andermann, F. Dubeau and D.L. Arnold, Proton magnetic resonance spectroscopic imaging and magnetic resonance imaging volumetry in the lateraliszation of temporal lobe epilepsy: a series of 100 patients, *Ann. Neurolog.* **42** (1997), 737–746.
[4] A. Conelly, G.D. Jackson, J.S. Duncan, M.D. King and D.G. Gadian, Magnetic resonance spectroscopy in temporal lobe epilepsy, *Neurology* **44** (1994), 1411–1417.
[5] R. Kuzniezky, J.W. Hugg, H. Hetherington, E. Butterworth, E. Bilir, E. Faught and F. Gilliam, Relative utility of 1H spectroscopic imaging and hippocampal volumetry in the lateralization of mesial temporal lobe epilepsy, *Neurology* **51**(1) (1998), 66–71.
[6] R. Kuzniecky, J.W. Hugg, H. Hetherington and F. Gilliam, Predictive value of 1H-MRSI for outcome in temporal lobectomy, *Neurology* **53**(4) (1999) 694–708.
[7] D.F. Gadian, A. Conelly, J.S. Duncan et al., H-magnetic resonance spectroscopy in the investigation of intractable epilepsy, *Acta Neurol. Scand.* **152**(Suppl.) (1994), 116–121.
[8] J.H. Cross, A. Connelly, G.D. Jackson, C.L. Johnson, G.R. Neville and D.G. Gadian, Proton magnetic resonance spectroscopy in children with temporal lobe epilepsy, *Ann. Neurol.* **39** (1996), 107–113.

[9] I. Constandinitis, J.A. Malko, S.B. Petermann et al., Evaluation of 1H magnetic resonance spectroscopic imaging as a diagnostic tool for the lateralization of epileptogenic seizure foci, *Br. J. Radiol.* **69**(817) (1996), 15–24.
[10] R.C. Knowlton, K.D. Laxer, G. Ende et al., Presurgical multimodality neuroimaging in electroencephalographic lateralized temporal lobe epilepsy, *Ann. Neurol.* **42** (1997), 829–837.
[11] J.H. Margerison and J.A.N. Corsellis, Epilepsy and the temporal lobes. A clinical, electroencephalographic and neuropathologic study of the brain in epilepsy with particular reference to the temporal lobes, *Brain* **89** (1966), 499.
[12] P. Vermathen, G. Ende, K.D. Laxer, R.C. Knowlton, G.B. Matson and M.W. Weiner, Hippocampal N-acetylaspartate in neocortical epilepsy and mesial temporal lobe epilepsy, *Ann. Neurol.* **42**(2) (1997), 194–199.
[13] F. Cendes, F. Andermann and D.L. Arnold, Normalization of neuronal metabolic dysfunction after surgery for temporal lobe epilepsy. Evidence from proton MR spectroscopic imaging, *Neurology* **49**(6) (1997), 1525–1533.
[14] R. Kuzniecky, Ch. Palmer, J. Hugg and R. Knowlton, Magnetic resonance spectroscopic imaging in TLE: Neuronal dysfunction or cell loss, *Arch. Neurol.* **58** (2001), 2048–2053.
[15] T.L. Babb, Pathological substrates of epilepsy, in: E. Wylie et al. eds, *The Treatment of Epilepsy: Principles and Practice*, Lea and Febiger, Philadelphia, PA, 1993, pp. 55–70. A.N. Corsellis, The incidence of Ammons Horn sclerosis, *Brain* **80** (1957), 193–203.
[16] W. Van Paesschen, S. Sisodiya and A. Conelly, Quantitative hippocampal MRI and intractable temporal lobe epilepsy, *Neurology* **45** (1995) 2233–2240.
[17] K.E. Eberhardt, H. Stefan, M., B.F. Tomandl et al., The significance of bilateral CSI changes for the postoperative outcome in temporal lobe epilepsy, *Journal of Computer Assisted Tomography* **24**(6), 919–926.
[18] H. Stefan, E. Pauli, K.E. Eberhardt, I. Schafer, P. Hopp and W.J. Huk, MR-Spektroskopie, T2 relaxometry and postoperative prognosis in cryptogenic temporal lobe epilepsy, *Nervenarzt* **71**(4) (2001), 282–287.
[19] H. Stefan, K.E. Eberhardt, M. Huk et al., Diagnostic imaging in refractory temporal lobe epilepsy. A comparison of MR volumetry and multivoxel-MR-spectroscopy for assessment of postoperative prognosis, *Nervenarzt* **72**(2) (2001), 103–105.
[20] R. Kuzniezky, J. Hugg, H. Hetherington, R. Martin, E. Faught, R. Morawetz and F. Gilliam, Predictive value of 1H-MRSI for outcome in temporal lobectomy, *Neurology* **53**(4) (1999), 694–698.
[21] L.M. Li, F. Cendes, S.B. Antel, F. Andermann, W. Serles, F. Dubeau, A. Olivier and D.L. Arnold, Prognostic value of proton magnetic resonance spectroscopic imaging for surgical outcome in patients with intractable temporal lobe epilpesy and bilateral hippocampal atrophy, *Ann. Neurol.* **47**(2) (2000), 195–200.
[22] O.A. Petroff, D.L. Rothmann, K.L. Behar, T.L. Collins and R.H. Mattson, Human brain GABA levels rise rapidly after initation of vigabatrin therapy, *Neurology* **47**(6) (1996), 1567–1571.
[23] O.A. Petroff, R.H. Mattson, K.L. Behar, F. Hyder and D.L. Rothmann, Vigabatrin increases human brain homocarnosine and improves seizure control, *Ann. Neurol.* **44**(6) (1996), 948–952.
[24] S.G. Mueller, O.M. Weber, C.O. Duc, B. Weber, D. Meier W. Russ, P. Boesiger and H.G. Wieser, Effects of Vigabatrin on brain GABA+/Cr signals in patients with epilepsy monitored by 1H-NMR-spectroscopy: responder charachteristics, *Epilepsia* **42**(1) (2001), 29–40.
[25] O.A. Petroff, F. Hyder, R.H. Mattson and D.L. Rothman, Topiramate increases brain GABA, homocarnosine, and pyrrolidinone in patients with epilepsy, *Neurology* **52**(3) (1999), 473–478.