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ORIGINAL RESEARCH

Extent of Preoperative Abnormalities and Focus Lateralization Predict Postoperative Normalization of Contralateral 1H-Magnetic Resonance Spectroscopy Metabolite Levels in Patients with Temporal Lobe Epilepsy

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BACKGROUND AND PURPOSE: Magnetic resonance (MR) spectroscopy can be used to determine the side of seizure onset in patients with temporal lobe epilepsy. Some patients with abnormal MR spectroscopy findings also have contralateral abnormalities, which in some cases have been reported to normalize after temporal lobe resection. With the aim of better understanding the mechanisms underlying abnormal MR spectroscopy findings, the current study was performed to define patient features that would predict this postoperative normalization.

METHODS: Fifteen patients with temporal lobe epilepsy were subjected to preoperative and postoperative 1H-MR spectroscopy investigations, and the preoperative and postoperative metabolite levels in the contralateral hippocampus and contralateral lateral temporal lobe (CLTL) were determined.

RESULTS: In the CLTL, postoperative normalization was more pronounced for patients showing extensive preoperative ipsilateral and contralateral abnormalities on MR spectroscopy. A second factor that influenced the degree to which the metabolite levels changed postoperatively was the focus lateralization. Surgery tended to have a more pronounced effect on the contralateral metabolite levels in patients with a right temporal focus, whereas in patients with left temporal foci, postoperative metabolite levels were virtually unchanged. In the contralateral hippocampal region, neither preoperative abnormalities nor focus side was related to postoperative normalization.

CONCLUSIONS: We have thus identified 2 different factors (widespread preoperative MR spectroscopy abnormalities and right-sided focus) that predict postoperative normalization of contralateral MR spectroscopy abnormalities. We suggest that both factors indicate a more generalized epileptic disease (ie, that the patients in whom the MR spectroscopy abnormalities normalize are recovering from a more severe impairment).

Magnetic resonance (MR) spectroscopy (both single-voxel and MR spectroscopy imaging techniques) has been used in several studies of epileptic patients, in particular in patients with temporal lobe epilepsy. Correct lateralization of the abnormal findings to the side of seizure onset has been found in between 55% and 95% of patients who showed positive MR imaging findings and/or were seizure-free after temporal lobe resection.[1-8]

Of the patients with abnormal MR spectroscopy findings, up to 50% also have contralateral abnormalities, mostly in the hippocampus, in both adult and pediatric series.[2,3,9] There are reports[10-12] that the abnormal values in the contralateral temporal lobe may improve after temporal lobe resection and that a good surgical outcome may be obtained also in cases with bilateral abnormal findings.[13] These results would thus suggest that contralaterally abnormal values are mainly functional and thus possibly reversible.[14,15] On the other hand, contralaterally abnormal metabolite levels have sometimes been shown to relate to less favorable postoperative outcome,[11] and abnormal values may also remain in cases with good seizure control.[16,17] Together, these results indicate that contralateral metabolite abnormalities are partially functional and reversible but that they may also, to a certain extent, reflect underlying tissue damage that remains unchanged by the intervention.

The purpose of the current study was to try to gain further knowledge on these issues by trying to identify specific groups of patients with a temporal lobe focus in whom such contralateral postoperative improvement would occur. Our hypothesis was that the degree of preoperative MR spectroscopy abnormality and focus side would both have an influence on the postoperative MR spectroscopy normalization.

Patients and Methods

Fifteen patients with partial complex seizures of temporal lobe origin were investigated. In 12 patients, MR imaging showed hippocampal sclerosis (5 left- and 7 right-sided), in 6 cases combined with temporal lobe atrophy on the same side. Two patients showed right hippocampal atrophy; in 1 patient, this was associated with a discrete atrophy of the right temporal and frontal lobes and in the other case with postoperative changes, it was due to a previous intervention (resection of an arteriovenous malformation) in the right temporal lobe. In the remaining patient, results of MR imaging were normal. All patients had been subject to temporal lobe resection and had been seizure free

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Clinical information for patients

Patient	MRI	Preop Spectroscopy (months)	Postop Spectroscopy (months)	Surgery	Postop Seizure Free (months)
1	Right hippocampal sclerosis	4	3	Right T	16
2	Right hippocampal sclerosis	7	4	Right T	3
3	Right hippocampal atrophy, discrete atrophy Right T and F	2	5	Right T	24
4	Right hippocampal sclerosis	5	3	Right T	40
5	Left hippocampal sclerosis + T atrophy	4	3	Left T	6
6	Postoperative changes	11	3	Right T	18
7	Left hippocampal sclerosis + T atrophy	5	9	Left T	3
8	Left hippocampal sclerosis + T atrophy	3	3	Left T	19
9	Left hippocampal sclerosis + T atrophy	2	3	Left T	28
10	Left hippocampal sclerosis	4	3	Left T	15
11	Right hippocampal sclerosis	5	3	Right T	12
12	Right hippocampal sclerosis + T atrophy	6	3	Right T	31
13	Right hippocampal sclerosis + T atrophy	6	4	Right T	16
14	N	3	9	Right T	3
15	Right hippocampal sclerosis	5	3	Right T	3

Note:—T indicates temporal lobe; F, frontal lobe; N, normal

for 3–40 months (median, 16) after surgery. Clinical information about the patients is given in Table 1.

Each patient was subject to 1 preoperative and 1 postoperative proton MR spectroscopy (1H-MR spectroscopy). The preoperative investigation was performed between 2 and 11 months (median, 5 months) preoperatively, and the postoperative investigation between 3 and 9 months (median, 3 months) after surgery.

The spectroscopy was performed using a 1.5T Eclipse system (Marconi/Philips Medical Systems, Cleveland, Ohio) with a standard head coil. The 1H-MR spectroscopy measurements consisted of long-echo-time double spin-echo point-resolved spectroscopy sequences (repetition time/echo time/number of averages, 1600 ms/288 ms/256) centered preoperatively on 4 regions of interest (ROIs): the hippocampi (voxel volume, 4.6 mL) and the temporal lobes (voxel volume, 9.4 mL). The temporal lobe voxel was centered on the superior and middle temporal sulcus, at the midportion of the temporal lobe, because of shimming issues and to avoid contamination from subcutaneous fat. The ratio of gray versus white matter in a voxel was, on the average, 55%:45%. The data reduction was performed with the use of SAGE spectroscopy analysis software (General Electric Medical Systems, Fremont, Calif) and consisted of low-frequency filtering, 4-Hz exponential apodization, zero filling, and Fourier transform. Unsuppressed water signal intensity was used for baseline correction because of eddy currents and automatic phase correction. The peak amplitudes were derived after fitting of the spectra using the Levenberg-Marquardt algorithm of the SAGE program. The metabolites assessed were the choline-containing compounds (Cho), creatine and phosphocreatine (Cr), and *N*-acetylaspartate (NAA). To obtain normative values for the different metabolite levels, 20 healthy subjects younger than the age of 42 years were also investigated.

The preoperative and postoperative spectra in the temporal lobe and the hippocampus contralateral to the resection were compared for their NAA, Cr, and Cho content. Decreased NAA is considered to reflect neuronal loss or dysfunction, whereas increased Cho or Cr indicates gliotic changes.[18,19] Therefore, the intensity ratio NAA/(Cho+Cr) (henceforth referred to as IR) was used as an index for spectral abnormality. In this study, a relative increase of this ratio from the preoperative to the postoperative investigation was thus considered to reflect postoperative metabolite normalization. The degree of postoperative normalization was then related to 2 different factors, the extent of preoperative ipsilateral and contralateral abnormalities on MR spectroscopy and the side of the epileptic focus. Nonparametric statistics were applied, including the Mann-Whitney *U* test or the Wilcoxon matched-pairs test. $P < .05$ was considered a statistically significant difference.

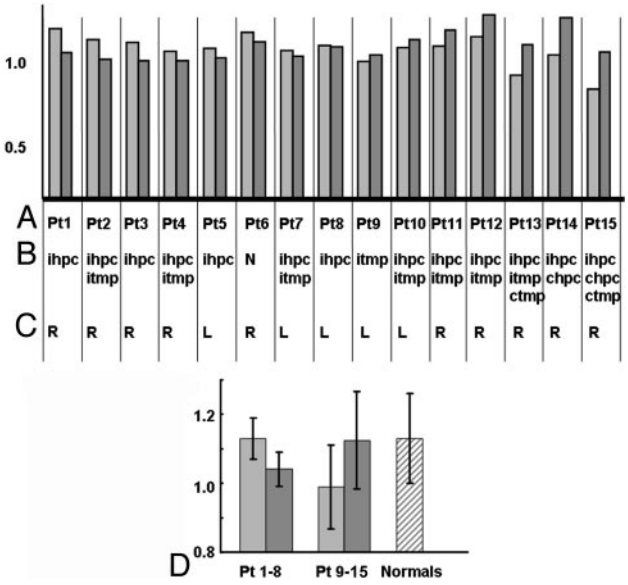

Fig 1. NAA/(Cho+Cr) ratios in the contralateral neocortical temporal region and their relation to different patient parameters. *Light gray bars*, Preoperative values; *dark gray bars*, postoperative values. *A*, Patient number; *B*, preoperative MR spectroscopy abnormalities; *N* = normal, *ihpc* = ipsilateral hippocampus, *itmp* = ipsilateral temporal lobe, *chpc* = contralateral hippocampus, and *ctmp* = contralateral temporal lobe. *C*, Lobe with epileptic focus (*L* = left, *R* = right). *D*, Means and SDs of MR spectroscopy values in patients with decreasing (*Pt 1–8*) and increasing (*Pt 9–15*) postoperative MR spectroscopy values and in healthy subjects. In the patients in whom the MR spectroscopy values normalize (*Pt 9–15*), it does so from an abnormally low value ($P = .03$), whereas in the cases where the values decrease (*Pt 1–8*), they still always stay within the normal range as determined from the results in the healthy subjects.

Results

The main results of the study are shown in Fig 1.

Importance of Preoperative MR Spectroscopy Abnormalities. Before surgery, the IR was significantly lower on the

side ipsilateral to the focus compared with contralateral, both for the hippocampal ROI ($P = .000002$) and the neocortical ROI ($P = .01$). The degree of preoperative MR spectroscopy abnormality in the 4 regions (ipsilateral hippocampus, ipsilateral temporal, contralateral hippocampus, and contralateral temporal) was assessed in each patient, and compared with the preoperative/postoperative normalization of IR in the contralateral lateral temporal lobe (CLTL). As a lower limit for normality, the mean value of the 20 healthy subjects minus 2 SD was used. There was a significant relation between the number of preoperatively abnormal regions (2–3 versus 0–1 regions) and the degree of postoperative normalization in the CLTL ($P = .02$). Thus, 6 of the 7 patients in whom the IR increased postoperatively showed preoperatively abnormal MR spectroscopy values in 2 or more of the 4 regions. Furthermore, in the 3 patients with the most pronounced preoperative/postoperative normalization, the preoperative abnormal MR spectroscopy values also included the contralateral side. Of the 8 patients in whom the IR did not improve from the preoperative to the postoperative investigation, only 3 showed preoperative abnormalities in more than 1 region. The results thus show that patients in whom the metabolic levels normalize postoperatively tend to have more extensive preoperative MR spectroscopy abnormalities.

Differences between Left and Right Temporal Epileptic Foci. The side of the epileptic focus was compared with the preoperative/postoperative difference in IR in the CLTL. Patients with a right temporal focus showed more pronounced preoperative/postoperative differences (increase or decrease in IR) compared with those with a left temporal focus ($P = .0006$). All 5 patients in whom the most significant increase in IR (and thus metabolite normalization) was obtained had a right temporal focus. On the other hand, the 4 cases in which the IR decreased the most also had a right temporal focus. The results indicate that the operation has a stronger impact on the metabolite levels in right temporal cases, either as a normalization or the opposite, whereas in left temporal cases surgery tends to have little effect on contralateral metabolite levels.

All the results presented here concern the preoperative/postoperative changes in the CLTL. For the contralateral hippocampus, the preoperative/postoperative metabolite normalization related neither to preoperative MR spectroscopy abnormalities nor to focus side. Analysis of other metabolite ratios (NAA/Cho, NAA/Cr) gave results in the same direction as the NAA/(Cho+Cr) ratio, but the results were less significant.

Discussion

The results of this study indicate 2 different features of the epileptic disease that are associated with postoperative MR spectroscopy normalization on the contralateral side. One of these, widespread MR spectroscopy abnormalities, may be associated with a more generalized epileptic disease. We would like to argue that the same is true for the second factor, a right-sided epileptic focus.

The first question that has to be addressed concerns the extent to which contralateral abnormal MR spectroscopy findings are functional and reversible[14,15] and to what extent they actually reflect neuronal damage.[11,16,17] In our study, the contralateral neocortical metabolite normalization was more pronounced in patients with extended preoperative MR spectroscopy abnormalities and most pronounced in cases where the preoperative abnormal MR spectroscopy values also included the contralateral side. This result rather supports the hypothesis of a mainly functional mechanism. In other words, if the abnormalities are mainly functional, normalization will be expected to be more pronounced in patients who are recovering from a more unbalanced state. The results thus illustrate how the epileptic lobe exercises a negative influence on the contralateral side and how this negative influence can be reversed by resection of the epileptic cortex. In this way, the results are also in line with the notion of epileptiform activity as distributed epileptic networks rather than discrete foci.

The second result of this study concerns the relation between postoperative normalization of the metabolites and the side of the epileptic focus. Postoperative changes in metabolite levels were most pronounced in patients with a right temporal focus, whereas in the patients with left temporal foci, the operation had limited effect on the contralateral metabolite levels. These findings indicate stronger pathophysiologic connections between the 2 temporal lobes in patients with right temporal foci, and are in line with other reports indicating that right temporal epilepsy might be a more diffuse or generalized disease. Examples of such findings are a higher tendency for contralateral temporal lobe MR spectroscopy abnormalities in right temporal lobe epilepsy,[20] worse performances by right temporal lobe patients on several psychosocial parameters,[21] and a stronger tendency for altered left hippocampal volumes in patients with a right focus than vice versa in patients with a left focus.[21]

In almost half of the patients in this study, the contralateral IR actually decreased from the preoperative to the postoperative investigation. As already discussed, these patients generally had limited preoperative MR spectroscopy abnormalities, which indicates a relatively localized and less diffuse disease. In some patients, the decrease in IR was quite small and might be explained by the inaccuracy of the measurements. In some patients, however, the decrease was rather pronounced. Why the contralateral IR would tend to decrease postoperatively in some patients with restricted foci, and whether this has any functional significance, is not clear, and the issue needs to be further investigated. It should be noted, however, that the values, even in the more pronounced cases, never decreased below the normal limits, as determined from the results in the healthy subjects (Fig 1).

Our results hold only for the lateral temporal lobe, not for the hippocampus; the reason for this is also not clear. If the factors indicated by this study also affect the recovery of the hippocampus, different explanations may be found for this not appearing in our results. One reason may be the relatively small volume in our hippocampal ROI (around half of that of the neocortical ROI). Another possible explanation might be the relatively short time between surgery and postoperative investigation (median, 3 months). According to Serles et al,[11] the time period required to achieve a 50% increase in metabolite level would be approximately 6 months.

The results of the present study may have different diagnostic and clinical implications. First, the results confirm the findings from previous studies[10-13] that an abnormal preoperative contralateral temporal MR spectroscopy result is not by

itself an indication of contralateral temporal malfunction. Second, the finding that normalization of the MR spectroscopy results is more pronounced in right-sided compared with left-sided patients adds to the results of previous studies indicating that right-sided temporal lobe epilepsy should be a more bilateral disease than previously appreciated. If it can be established that left- and right-temporal-lobe epilepsy are actually to some extent different diseases with different effects on other brain areas, this might be important for patient preoperative counseling and would require earlier surgery in right-temporal-lobe epilepsy to minimize remote effects from the right-sided focus.

Conclusion

We have been able to identify 2 different factors (widespread MR spectroscopy abnormalities and right-sided focus) that predict postoperative normalization of contralateral MR spectroscopy abnormalities. We suggest that both factors are indicators of a more generalized epileptic disease and that this degree of generalization of the disease is the main factor determining the presence and extent of contralateral metabolite normalization.

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