Multimodal MRI reveals secondarily generalized seizure related microstructural brain tissue abnormalities at 1.5 T

J. F. Jansen[1], M. E. Kooi[1], M. C. Vlooswijk[2], H. J. Majoie[2], R. P. Reijs[2], P. A. Hofman[1], K. Nicolay[3], M. C. de Krom[2], A. P. Aldenkamp[2], and W. H. Backes[1]

[1]Department of Radiology, Maastricht University Hospital, Maastricht, Netherlands, [2]Department of Neurology, Maastricht University Hospital, Maastricht, Netherlands, [3]Biomedical NMR, Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, Netherlands

Introduction

In patients with persistent seizures, cognitive impairments are the most common comorbid disorder [1]. Especially, patients who have suffered a high number of secondarily generalized tonic-clonic seizures (SGTCS) frequently show cognitive decline [2]. It is yet unclear whether a higher number of SGTCS is associated with tissue changes in the brain. In this study we investigated whether a high number of SGTCS accumulated over life is associated with microstructural and/or metabolic changes in brain tissue characteristics in the temporal and frontal lobes, as determined by multimodal quantitative MR.

Material and Methods

Patients The study population included 16 patients with localization-related epilepsy (10 women and 6 men; mean age 40 years; range 21-59). Patients were divided into two groups, one group with less than 20 SGTCS (n=8), and one group with more than 20 SGTCS (n=8). Various patient data were collected (Table 1).

MRI Whole cerebrum imaging was performed with a clinical 1.5 T MRI system (Philips Intera, Philips Medical Systems), which was equipped with a standard quadrupolar head receiver coil. The protocol included a 3D T1-weighted fast field-echo sequence [TR 11 ms, TE 3.5 ms, flip angle 90°, matrix 256×256, 150 contiguous slices, 3.5×3.5×3.5 mm^3 sized voxels], a dual-echo turbo spin echo sequence (TSE-Dual) [TR 5211 ms, TE 11.9 ms/80 ms, matrix 256×256, FOV 204×112 mm^3], a DW multi-shot echo-planar imaging (EPI) sequence [EPI-factor 31, b-values 0/400/800/1200 s/mm^2, 3 orthogonal diffusion sensitizing directions, TR 2 cardiac cycles, TE 76 ms, matrix 128×128, FOV 230×230 mm^2], and a turbo spectroscopic sequence [turbo factor 3, 1 slice, 24×24 voxels per slice, FOV = 230×230 mm^2, slice thickness = 20 mm, TR = 2.5 s, TE = 272 ms, a nominal voxel size of 1.84 ml, localization PRESS, water suppression CHESS].

Analysis All images were co-registrated and spatially normalized to Talairach space. A percentile volume CSF map was created by attributing to each pixel a CSF percentage (λ_{CSF}) on a scale of 0-100%, based on their T2 relaxation times calculated from the dual-echo images. Tissue was segmented from CSF by incorporating the cut-off $\lambda_{CSF} \leq 5\%$. Maps of the apparent diffusion coefficient (ADC) were calculated by second order polynomial fitting of the direction averaged logarithmic signal intensities versus b-values. T2 maps were calculated on a pixel-by-pixel basis using the logarithm of the ratio of signal intensities at the two TE's. Mean metabolite ratios NAA/(Cr+Cho) maps were obtained through Gaussian fitting (using the CSX software), and all voxels with a NAA peak linewidth >2 and <9 Hz were included for analysis. Analysis for the T2, ADC, and NAA/(Cr+Cho) maps was performed in predefined regions in the frontal and temporal lobes. For T2 and ADC, grey matter (containing neurons) and white matter (containing axons) were analyzed separately, using specific maps obtained from segmentation of T1-weighted images (SPM2). Multiple end point testing was controlled for by first combining λCSF, grey matter T2, and grey matter ADC values (all effected by water changes) per region. For each region, differences between the two patient groups for the combined MRI measures were tested using the ordinary least squares test of O-Brien and Läuter [3]. Statistical significance was calculated with two-tailed Student's t tests with Hochberg correction for multiple comparisons. Additionally, separate tissue T2, λCSF, ADC values, and spectroscopic data of the two groups were compared using two-tailed Student's t tests ($p < 0.05$).

Results

The ordinary least squares test revealed statistically significant SGTCS-related MRI alterations for the combined regional MRI values in both left and right frontal lobe, but not in the temporal lobe. In the right frontal lobe, a significantly decreased (-25%, $p<0.05$) T2 relaxation time for grey matter and cerebrospinal fluid (-22%, $p<0.05$) content was observed. Decreased ADC values in both white (-14%, $p<0.05$) and grey matter (-13%, $p<0.05$) of the left frontal lobe were observed (Fig 1&2). Furthermore, a significant decrease in ADC (-14%, $p<0.05$) was noticed for the grey matter of the right frontal lobe. No significant differences in NAA/(Cho+tCr) concentrations were detected between two groups. Results are summarized in Table 1.

		<20 SGTCS Mean (SEM)		>20 SGTCS Mean (SEM)
Clinical parameters				
	Total number of SGTCS	6 (2) †		62 (22)
	Partial seizure frequency	47 (37)		14 (9)
	Age	46 (5)		35 (5)
	Epilepsy duration	21 (6)		16 (4)
	Drug load	1.1 (0.3) †		2.5 (0.4)
	*IQ**	116 (5) †		94 (7)
Regions	*Quantity*			
left frontal				
	T2 WM	130 (13)		102 (5)
	T2 GM	155 (14)		120 (6)
	λ_{CSF}	17.4 (1.2)	‡	14.1 (1.3)
	ADC WM	1287 (67) †		1106 (48)
	ADC GM	1408 (59) †		1228 (41)
	NAA/(Cho+tCr)	0.52 (0.03)		0.55 (0.02)
right frontal				
	T2 WM	135 (14)		103 (5)
	T2 GM	160 (16) †		120 (5)
	λ_{CSF}	16.5 (1.2) †	‡	12.9 (1.1)
	ADC WM	1257 (68)		1077 (55)
	ADC GM	1372 (62) †		1181 (43)
	NAA/(Cho+tCr)	0.50 (0.04)		0.55 (0.03)
left temporal				
	T2 WM	101 (5)		92 (2)
	T2 GM	112 (6)		102 (2)
	λ_{CSF}	11.3 (0.7)		9.5 (0.5)
	ADC WM	1140 (70)		1005 (34)
	ADC GM	1205 (76)		1080 (51)
	NAA/(Cho+tCr)	0.55 (0.04)		0.65 (0.02)
right temporal				
	T2 WM	108 (6)		97 (3)
	T2 GM	122 (6)		109 (4)
	λ_{CSF}	12.5 (0.9)		10.0 (1.1)
	ADC WM	1172 (71)		1077 (41)
	ADC GM	1244 (76)		1144 (56)
	NAA/(Cho+tCr)	0.52 (0.04)		0.63 (0.03)

Table 1: Clinical and quantitative MRI results in patients with less than 20 SGTCS and patients with more than 20 SGTCS. † 2-tailed $P<0.05$, ‡ 2-tailed $P<0.05$ ordinary least squares test, Hochberg correction

Discussion

Chronic neuronal damage due to seizures is often associated with increased water content, leading to increased pericortical CSF fractions, and T2 and ADC values [4]. We, however, very consistently observed the opposite effect: a high number of SGTCS was associated with decreased T2, ADC, and fractional CSF values. A possible explanation for this apparent discrepancy is that most clinical quantitative MRI epilepsy studies were focused on detecting abnormalities at or near the epileptic focus. Our method was primarily aimed at detecting general abnormalities remote from the seizure focus, therefore different mechanisms may be underlying these abnormalities. In a recent diffusion tensor imaging study of patients with medial temporal lobe epilepsy and hippocampal sclerosis, Thivard et al [5] also observed decreased ADC values in a region distant from the epileptic focus, e.g. the contralateral amygdala and hippocampal region. It was hypothesized that the observed abnormalities would be related to neuronal dysfunction, rather than neuronal loss. The effect of SGTCS on altered MRI characteristics was more pronounced in the grey matter than the white matter. Apparently, neurons (predominantly present in grey matter) are more sensitive to SGTCS-related damage than axons (predominantly present in white matter). The signal transduction properties of axons might be more robust and less prone to increased neurotransmitter traffic than the signal reception properties of neurons.

Conclusion

In the present study, frontal, but not temporal, MRI abnormalities were found to be related to SGTCS. These findings suggest that SGTCS are associated with substantial changes in microstructural brain tissue characteristics within the frontal lobes (in line with the cognitive problems). Future studies on cognitive abilities in chronic epilepsy should reckon with the observation that cerebral tissue abnormalities, which can be detected by quantitative MR techniques, may be a relevant factor.

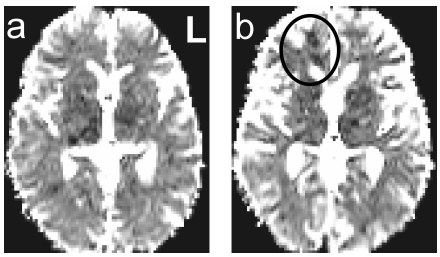

Figure 2. ADC-maps of (**A**) a patient with 6 SGTCS and (**B**) with 96 SGTCS. The circle in (**B**) indicates a hypointense prefrontal region in the ADC. Both patients had a right temporal epileptic focus. No right frontal abnormalities were observed on the conventional MRI.

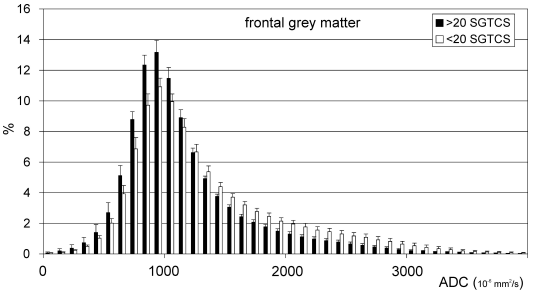

Figure 1. Average histogram distribution plots of ADC values within the right frontal grey matter. Error bars display standard error of the mean.

References

[1] Thompson PJ, Epilepsia 1992;33 S6:18-20, [2] Dodrill CB, Epilepsia 1986;27 S2:64-76, [3] Läuter J. Biometrics 1996;52:964-970, [4] Hugg JW, Neurology 1999;53(1):173-176, [5] Thivard L, Neuroimage 2005;28(3):682-690.