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Quantitative diffusion tensor imaging in herpes simplex virus encephalitis

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Diffusion-weighted imaging (DWI) has been employed in many brain pathologies, but with few studies only and heterogeneous results in herpes simplex virus encephalitis (HSVE). Diffusion tensor imaging (DTI) in comparison to DWI yields additional directional diffusion data, adding information and enabling a more differentiated description of brain pathologies. The authors addressed the question whether tissue changes as identified on T2-weighted magnetic resonance imaging (MRI) could be further characterized by DTI, in particular whether different forms of edema may occur in HSVE. Six patients with HSVE confirmed by positive polymerase chain reaction (PCR) from cerebrospinal fluid (CSF) samples were studied. Patients were examined with MRI including DTI in the early stage of the infection. Conventional MRI– and DTI-derived parameter maps were analyzed for signal change qualitatively and by region-of-interest (ROI) analysis of the affected brain parenchyma. All patients showed typical clinical characteristics of HSVE and lesions in the mediobasal temporal structures and insula. In two cases hemorrhagic inflammatory tissue changes were found. DTI analysis showed slightly reduced mean diffusivity (MD) and increased fractional anisotropy (FA) values in the earliest phase. Patients scanned at day 14 or later had lesions with increased MD and reduced FA in accordance with inflammatory vasogenic edema. This study confirms signal change consistent with the presence of inflammatory vasogenic edema in HSVE as the most prominent DTI finding. In the early stage slight reductions of MD may be found, which might be due to a specific mechanism of viral infection. *Journal of NeuroVirology* (2007) **13,** 426–432.

Keywords: diffusion-weighted imaging; edema; herpes simplex virus encephalitis; MRI

Introduction

Herpes simplex virus encephalitis (HSVE) is the single most frequent sporadic viral encephalitis diagnosed in children and adults. Due to the heterogeneous and nonspecific clinical presentation, occasionally with only subtle neuropsychological symptoms, early diagnosis can be challenging, but is important to ensure early treatment with virustatic agents (Skoldenberg *et al*, 1984; Whitley *et al*, 1986). The diagnostic gold standard is the detection of HSV DNA in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR). However, frequently a lumbar puncture is considered only after magnetic resonance imaging (MRI) points to possible HSVE demonstrating a pattern of T2-hyperintense cortical lesions in the mediobasal temporal lobe and/or insula. Diffusion-weighted imaging (DWI) studies in HSVE mainly consist of well-documented cases (Table 1) and the DWI findings show some heterogeneity. Several authors reported hyperintense DWI abnormalities (Kuker *et al*, 2004; Ohta *et al*, 1999) in an early phase of the disease, in some cases

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Table 1 Review of the literature

	Number of patients	*Time from symptom onset to MRI*	*Localization of DWI findings*	*DWI/ADC findings*
Duckworth *et al*, 2005	1	24 h	Temporal lobe, insular region	DWI ↑, ADC ↓
Küker *et al*, 2004	3	40–96 h	Temporal lobe, insular region, Cingulum	DWI ↑, no ADC
Heiner and Demaerel, 2003	1	≤24 h	Temporal lobe, cingulum, frontal cortex	DWI ↑, ADC ↓
McCabe *et al*, 2003	1	48 h	Temporal lobe, insular region	DWI ↑, ADC ↓
Sämann *et al*, 2003	1	8 weeks	Cingulum, trigonum	ADC ↑
Sener, 2001	5	Not indicated	Temporal lobe, insular region, thalamus	DWI ↑, ADC ↓ ADC ↑
Ohta *et al*, 1999	1	Unclear (on admission)	Temporal lobe, insular region	DWI ↑, no ADC

Note. Listed are articles on DWI findings in HSVE, number of patients examined, locations of DWI findings, and nature of DWI/ADC changes.

along with reduced values of the apparent diffusion coefficient (ADC) (Duckworth *et al*, 2005; Heiner and Demaerel, 2003; McCabe *et al*, 2003; Sener, 2001). Similar findings are well known to occur in acute cerebral ischemia (Fisher *et al*, 1995; Sartor and Heiland, 1997) as a consequence of cytotoxic edema (Ebisu *et al*, 1993; Sevick *et al*, 1992). On the other hand, there are reports on increased ADC values in HSVE as well (Samann *et al*, 2003; Sener, 2001), indicating vasogenic or extracellular edema (Ebisu *et al*, 1993; Schwartz *et al*, 1998).

Diffusion tensor imaging (DTI) allows the investigation of brain tissue with regard to its histological organization and directionality (anisotropy) based on the estimation of the full diffusion tensor and by calculation of derived metrics, mainly fractional anisotropy (Le Bihan *et al*, 2001). DTI has already been applied in many neurological disorders and has been shown to be sensitive to even minor tissue changes not yet visible on conventional MR images (Horsfield and Jones, 2002). We used DTI in a series of six patients with HSVE who were studied at different time points in the early phase of the disease with the aim to more exactly classify tissue changes and their course.

Results

All patients presented with fever and mild to severe cognitive symptoms. Four patients (3, 4, 5, and 6) presented with either complex partial seizure (CPS) or electroencephalographic (EEG) findings suggestive of epileptogenic foci, or both. In 2/6 patients EEG showed either generalized or focal slowing.

Conventional MRI

In all patients MRI showed typical changes suggestive of encephalitis, i.e., cortical areas with a hyperintense T2-signal and mild to moderate swelling in the mediobasal temporal lobe, predominantly in the anterior hippocampal formation, the adjacent white matter, and insular region (Table 2). Two patients showed concomitant chronic pathology: Patient 1 had a chronic ischemic lesion in the left (ipsilateral to HSVE pathology) paraventricular white matter. Patient 2 had parenchymal defects on the contralateral side due to a previous HSVE episode. Patients 3 to 6 did not show signs of previous or acute pathology other than encephalitis. In patients 4 and 6 areas of subtle hyperintensity on T1 images, indicative of subacute hemorrhage were seen in temporal and insular regions. In patient 4 there was also a subtle enhancement after administration of contrast agent in the aforementioned areas.

DWI and DTI

We analyzed regions of interest (ROIs) in all patients from two anatomical regions with abnormal signal (mediobasal temporal cortex, insular region) and determined MD and FA values.

Areas of reduced MD were found within the temporal lobe of patient 1 examined on day 5 (see Figure 1). On follow-up imaging 8 days later, the MD reduction had completely resolved (not shown). Of the remaining five patients, three showed clearly elevated MD values in either one or both anatomical areas (Figures 2 and 3). On DWI hyperintense lesions were regularly seen and corresponded to hyperintense changes of the T2 signal. These combinations of MD elevation and T2 prolongation are usually referred to as "T2-shine through."

A slight increase of FA was found within the gray matter of the temporal lobe in patient 1, whereas it was reduced or unchanged in the remaining patients. MD values (10^{-5} s/mm^2) for the contralateral hemisphere were 917.18 (±53.85) for the temporomedial

Table 2 Patient data

Patient	*Age, sex*	*Initial clinical presentation*	*CSF findings*	*EEG findings/seizures*	*Neuropsychological findings*	*Predominant location of T2 abnormalities*	*Timing of DTI*
1	59, M	Dysphasia, confusional state	112 cells HSV-PCR +	Left temporal slowing/—	Mild cognitive impairment, MMSE 21	Left	Day 5 (DWI follow up on day 12)
2	36, M	Headache, fever, severe confusional state	301 cells HSV-PCR +	Generalized slowing/—	Severe cognitive impairment, amnestic syndrome, MMSE 16	Right	Day 6
3	63, F	Fever, confusional state	HSV-PCR +	Left temporo-central focal slowing/complex-partial seizure on day 10	Severe cognitive impairment amnestic syndrome, MMSE 10	left	Day 12
4	70, F	Fever, somnolent state	84 cells HSV-PCR +	Right temporal rhythmic sharp waves/complex-partial seizure on day 17	Severe cognitive impairment, MMSE 12	Right	Day 14
5	74, F	Fever, headache, confusional state	48 cells HSV-PCR +	Right temporal rhythmic sharp waves/−	Mild cognitive impairment, MMSE 21	Right	Day 18
6	16, M	Single generalized seizure, fever, headache	70 cells HSV-PCR +	Right temporal rhythmic sharp waves/−	Mild cognitive impairment amnestic syndrome, MMSE 19	Right	Day 30

Note. Overview of the clinical data including CSF and EEG findings as well as timing of the DTI examinations.

cortex and 830.49 (±37.96) for the insular region. FA values for the contralateral hemisphere were 0.19 (±0.05) and 0.26 (±0.03) for the analogous regions, respectively. Figure 2 also gives a graphical summary of the DTI measurements.

Discussion

In this study we investigated DWI and DTI in patients with HSVE. Our findings largely confirm and extend the findings from previously reported cases. All patients showed typical anatomical involvement of the medial temporal lobe and insular region. Conventional MRI showed mainly cortical T2 hyperintensity and tissue swelling, minimal, if any, contrast enhancement, and indications of a slight hemorrhagic tissue component in two patients. In light of these rather typical findings of HSVE we consider the DWI and DTI results in further detail. They are of particular interest as they point to a potential temporal evolution of the lesions.

All patients were investigated in an acute early phase of HSVE; however, not all at the same time point after symptom onset but with variable intervals since their first symptoms. As demonstrated in Table 3 and Figure 4, MD values develop over time. In the earliest phase MD may be slightly reduced, somewhat similar to the situation in cerebral ischemia but less pronounced and without the subsequent development of pannecrosis in the affected area. In later stages there is an elevation of MD and tissue swelling indicating inflammatory edema. A typical condition leading to vasogenic edema is an increased

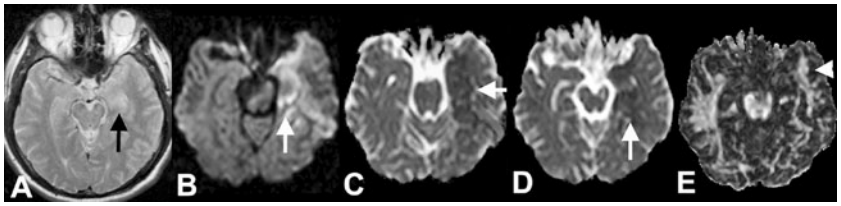

Figure 1 MR images of patient 1 examined on day 5. The T2-weighted (**A**), as well as the DW image (**B**) demonstrates hyperintense signal and cortical swelling in the medial left temporal lobe (*arrows*). The MD images (**C** and **D**) show a reduced signal (i.e., ADC reduction; *arrows*) in the corresponding location, while there is no visible reduction of the FA (**E**, *white arrowhead*).

Table 3 MRI, DWI, and DTI findings

	Uncus					*Insular region*				
Patient	*T2*	*Hemo/ Gad*	*DWI*	*MD/ADC*	*FA*	*T2*	*Hemo/Gad*	*DWI*	*MD/ADC*	*FA*
1	↑	0	↑	↓ 19.5%	↑ 5%	↑	0	↗#	↑ 15%	↓ 30%
2§	↑	0	↗	↑ 8%	↓ 15%	↔	0	↔	↔ (2%)	↗ (6%)
3	↑	0	↗	↓ 5%	↑ 8%	↗	0	↗#	↑ 3%	↔ 3%
4	↑	+/0	↑#	↑ 25%	↓ 20%	↑	+/(+)	↑#	↑ 29%	↓ 35%
5	↑	0	↑#	↑ 30%	↓ 18%	↑	0	↑#	↑ 18%	↓ 29%
6	↑	+/0	↑#	↑ 16%	↓ 30%	↔	0	↔	↔ (1%)	↔ (0%)

↑increased; ↗ slightly increased; ↓ decreased: ↘ slightly decreased; ↔ no difference.
Values given are differences between the affected and unaffected hemisphere as percentage of the latter value. Hemo = signs of hemorrhage; Gad = enhancement after administration of gadolinium (0 = no, + = yes). # = T2 shine-through. §= patient 2 had severe parenchymal defects on the contralateral side due to recurrent former HSVE, the corresponding mean values of the unaffected hemispheres of the remaining five patients were used for comparison.

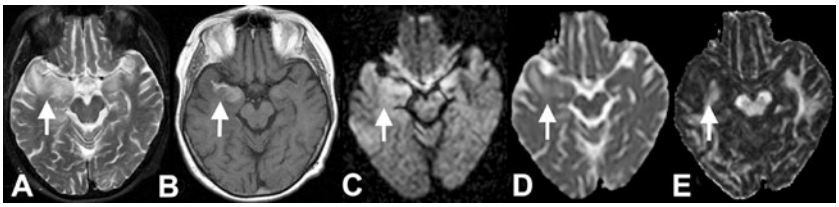

Figure 2 MR images of the temporal region of patient 4 examined on day 14. T2- (**A**) and T1- (**B**) weighted, as well as DW (**C**) images demonstrate hyperintense signal in the anterior temporal lobe on the right side (*arrows*). Whereas hyperintensity on the T1-weighted image is due to subacute hemorrhage, on the T2-weighted and DW images it indicates edema. Corresponding hyperintensity on the MD image (**D**, *arrow*) identifies the edema as extracellular. Note visibly reduced FA (**E**, *arrow*) in the corresponding area in comparison to the contralateral side.

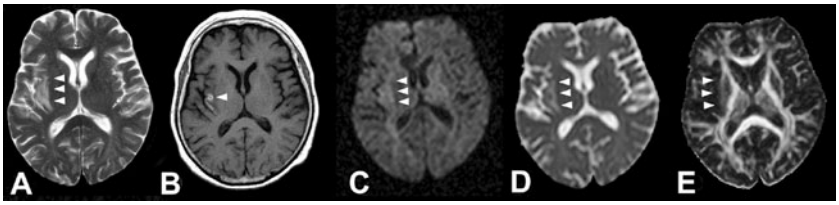

Figure 3 MR images of the insular region of patient 4 examined on day 14. The T2-weighted image (**A**, *arrowheads*) shows hyperintense edema of the insular cortex and subjacent white matter. Therein is a hyperintense spot on the T1-weighted image (**B**, *arrowhead*) again indicating subacute hemorrhage and after administration of contrast agent there was a subtle enhancement (not shown). Edema is seen as hyperintensity on the DW image (**C**, *arrowheads*) as well and is recognized as extracellular edema since the MD image (**D**) shows the corresponding area as hyperintense, too. On the FA image (**E**), reduced anisotropy of the external capsule (*arrowheads*) in comparison to the contralateral side is obvious.

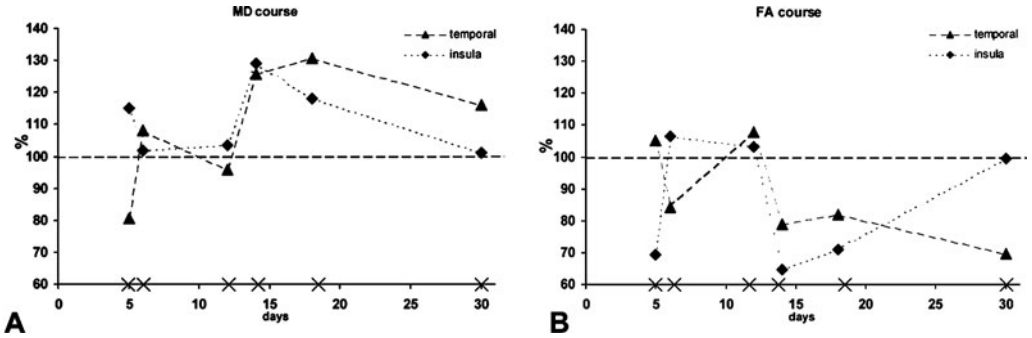

Figure 4 Course of MD (**A**) and FA (**B**) in the medial temporal lobe and the insular region. Relative values of MD and FA are plotted for each patient with respect to the time point of the examination during the individual disease course. Both curves of the MD course show a sigma-like shape, with reduced values in the early disease, followed by a plateau of more or less unchanged MD values in the subacute phase and a steep rise in the further course, whereas the FA values show an antidromic course. Crosses on the *x*-axis mark the time point of examination for the particular patients.

permeability of the blood-brain barrier (BBB), which, in HSVE, is also indicated by the evidence of an intrathecal antibody production against the herpes simplex virus (Meziere *et al*, 1988).

The potential reasons for a reduction of MD are less clear. In patient 1 (Figure 1), and, less pronounced, in patient 3, both investigated in an early stage (days 5 and 12, respectively), there was a combination of reduced MD along with increased FA values. This is consistent with the literature, where DWI hyperintensities and ADC reductions are reported to even precede findings on conventional MR imaging (Duckworth *et al*, 2005; Heiner and Demaerel, 2003; Kuker *et al*, 2004; McCabe *et al*, 2003; Ohta *et al*, 1999; Sener, 2001). Similar findings are reported for acute ischemia (Armitage *et al*, 1998; Yang *et al*, 1999), where it is considered, that cell swelling due to cytotoxic edema narrows the extracellular space and thereby increase its tortuosity and anisotropy. Experimental work points to a potential different mechanism: Herpes simplex virus 1 has been shown be able to enter neurons followed by replication of its components thereby affecting neuronal integrity (Cunningham *et al*, 2006; Meyding-Lamade *et al*, 1999). Because several studies, experimental ones (O'Shea *et al*, 2000; Shepherd *et al*, 2003; Verheul *et al*, 1994) as well as in humans (Darquie *et al*, 2001; Righini *et al*, 2005), suggest a relationship between the ADC and cell size also for minor changes, a slightly increased FA in HSVE could be considered as an indicator of cellular swelling due to viral intrusion and replication. Another potential mechanism might be mitochondrial dysfunction due to aggressive inflammatory mediators.

Another explanation of MD reductions in HSVE are postictal changes (Szabo *et al*, 2005), but there was no evidence for ictal activity in patient 1, who showed the most pronounced MD reductions. Patient 3 had suffered from CPS 2 days prior to the DTI examination, thus postictal changes cannot be ruled out completely.

When considering all patients the findings suggest an evolution of MD and FA values over time (see Figure 4). After an inital reduction of the MD pronounced vasogenic edema formation sets in and MD values are elevated. Neuropsychological impairment is a typical presenting feature in HSVE matching the frontal and temporal location of the pathology. In both, early lesions with reduced MD and in later stages, when MD was elevated, cognitive impairment was found. When considering the direction and amplitude of MD and FA changes there was no obvious relationship with cognitive impairment: in two patients cognitive impairment was mild in the presence of MD changes in both directions.

In order to improve our understanding of the pathophysiology of cerebral viral infections future studies should aim at more frequent DWI and DTI examinations to further characterize lesion evolution. However in HSVE, which shows much more heterogeneity of the clinical presentation and individual disease course than, e.g., in acute stroke, it will remain difficult to create a homogeneous sample of patients. In order to substantiate our findings further longitudinal studies demonstrating the dynamic nature of diffusion changes in HSV may be useful.

Our findings suggest a typical sequence of different forms of edema as indicated by DWI and DTI parameters in the predominantly affected brain tissue of acute and subacute HSVE patients.

Materials and methods

Patients

Between September 2003 and April 2005 we examined six consecutive HSVE patients: three men, three women, 16 to 74 years of age, presenting with acute or subacute symptoms of HSVE encephalitis, mainly fever, cognitive impairment, and seizures. The diagnosis was confirmed in all cases by positive PCR from CSF. The onset of symptoms was determined from information provided by family members and family physicians. DTI was performed at different time points of the individual disease course, ranging from 5 to 30 days after the first recorded symptoms. Clinical data as well as EEG and neuropsychological findings are summarized in Table 2. The study was approved by the local ethics committee and all patients or their responsible relatives gave written informed consent.

DTI protocol

Imaging was performed on a 1.5-T whole-body scanner (Symphony; Siemens, Erlangen, Germany) with a maximum gradient strength of 30 mT/m, 240 μs rise time, and 125 T/m/s slew rate using a circular polarized head coil.

Diffusion tensor imaging consisted of a double spin-echo–echo planar imaging (DSE-EPI) sequence, 19 to 20 contiguous slices of 6 mm thickness without gap for whole-brain coverage (TR/TE 7200/106, field-of-view 240 mm, matrix 96 $\times$ 96) were acquired.

Diffusion gradients were applied in six noncollinear directions with a b value of 1000 and one image without diffusion weighting (b = 0) was acquired. To increase the signal-to-noise ratio (SNR) we used eight averages. Total acquisition time for diffusion imaging was 7 min 28 s. All patients also underwent conventional MR imaging including isotropic DWI, T2/FLAIR, and T1 images before and after administration of gadolinium for diagnostic purpose.

MRI data analysis

The diffusion tensor was calculated for each voxel, diagonalized to yield eigenvectors and -values and values of mean diffusivity (MD), according to the trace of the diffusion tensor (**D**) and fractional anisotropy (FA) for each voxel according to the

method described by Basser et al. (Basser *et al*, 1994; Pierpaoli *et al*, 1996), using a MatLab-based in-facility software. Two experienced neuroradiologists (M.H. and C.H.) used a standardized reporting scheme for conventional MRI (T2, FLAIR, T1 ± contrast agent) and analyzed DW images ($b = 1000$ mm/s^2) and MD and FA maps separately on a consensus basis. After identification of abnormal brain tissue areas on conventional MRI, these regions were further investigated with region of interest (ROI) analysis on MD and FA maps. Identical ROIs were placed in areas of abnormal signal as identified on T2-weighted images and on contralateral corresponding normal appearing brain tissue. MD and anisotropy values as listed in Table 3 are expressed as arithmetic mean ± standard deviation; differences between the affected and normal tissue are given as percentage change in comparison to normal tissue.

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