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A study on viral CNS inflammation beyond herpes encephalitis

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Abstract The early diagnosis of herpes simplex virus encephalitis (HSVE) enables induction of antiviral therapy in this potentially life-threatening disease. The study aimed to determine clinical findings including cerebrospinal fluid (CSF) data and MRI imaging in HSVE patients and to identify features distinguishing HSVE from encephalitis of other viral etiologies. We retrospectively reviewed consecutive patients who were diagnosed with viral encephalitis between 2000 and 2014 at the University Hospital Halle. Forty-nine patients with viral encephalitis were identified. A viral etiology could be confirmed by PCR or antibody testing in 22/49 (44.9 %) of patients (15 (30.6 %) HSV, 5 (10.2 %) VZV, 2 (4.1 %) EBV). In HSVE, typical findings were focal slowing in electroencephalophy (EEG) (80 %, $p = 0.021$) and presence of cortical (86.7 %, $p = 0.030$) lesions in MRI. Restricted diffusion was particularly helpful in detection of early signal abnormalities in HSVE ($p = 0.014$). In 27/49 (55.1 %) of patients, no causative agent could be elucidated. In these patients, 15/27 (55.6 %) experienced a rather "benign" disease course with no MRI pathology despite initially HSVE mimicking clinical picture. However, CSF was significantly different showing a higher amount of granulocytes and activated lymphocytes. The remaining 12/27 (44.4 %) patients developed MRI changes consistent with encephalitis, in 4 of these patients, disease course was fatal. Beside PCR-based serology as standard procedure, MRI including diffusion-weighted images and EEG represent additional tools in early HSVE diagnosis. CSF cytology might be particularly supportive in differentiating likely benign forms of encephalitis.

Keywords Viral encephalitis · Herpes simplex virus · Varizella zoster virus · CSF · Diffusion-weighted MRI

Introduction

Viruses account for approximately 50–70 % of confirmed and probable causes of encephalitis. The most frequent viral causes comprise enteroviruses, HSV (herpes simplex virus) 1, and varicella zoster virus (VZV) as well as adenovirus (Frantzidou et al. 2008; George et al. 2014; Grahn and Studahl 2015; Koskiniemi et al. 2001; Long 2011; Vora et al. 2014). In contrast, immunocompromised patients typically present with cytomegalovirus (CMV), Epstein-Barr virus (EBV), or human herpes virus (HHV) 6 or 7 infection of the brain. Twenty percent of subjects with infectious-like clinical presentation were shown to have CNS bacterial infections or infections due to spirochetes, parasites, or fungi (Solomon et al. 2012). However, in several studies, no etiology could be found in more than 50–60 % of encephalitis cases (Long 2011). Thus, failure to identify the pathogen does not rule out e.g., viral encephalitis.

Herpes simplex encephalitis (HSVE) accounts for about 20 % of all cases of sporadic encephalitis (Kennedy and Steiner 2013). In 90 %, HSVE is caused by HSV-1, whereas HSV 2 leads to disseminated infection especially in

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immunocompromised individuals and neonates (Solomon et al. 2012). The diagnosis is based on typical cerebrospinal fluid (CSF) and MRI findings and also on clinical, serological, and EEG parameters (Steiner et al. 2010). HSVE is common and potentially fatal sporadic encephalitis when treatment with antiviral drugs (acyclovir) is missed or significantly delayed (Raschilas et al. 2002; Solomon et al. 2012).

Recently, we had the impression that encephalitis cases are present with features resembling HSVE, but without serological or PCR findings supporting an HSVE diagnosis. Therefore, we investigated our cases with probable or definite viral encephalitis, in order to determine clinical, CSF, and MRI findings to identify potential features distinguishing HSVE from encephalitis of other viral etiologies.

Material and methods

We performed a retrospective study of patients who had been treated with confirmed or probable viral encephalitis at the University Hospital Halle between January 2000 and November 2014. All patients were admitted through the emergency department or directly to the neurological intensive care unit (ICU) after transfer from another hospital. Clinical data were collected on case record forms.

In-and exclusion criteria

Inclusion criteria Diagnosis of viral encephalitis was established according to the criteria of the International Encephalitis Consortium; new onset of altered mental state or personality change lasting more than 24 h and 2 or more of the following parameters: fever > 38.5 °Celsius (C) rectal within 72 h before or after presentation, brain imaging consistent with encephalitis, new onset of seizure including EEG abnormalities not fully attributable to a preexisting seizure disorder, and/or focal neurological deficit, CSF pleocytosis/inflammatory syndrome (white cell count (WCC) >5/μl), EEG consistent with encephalopathy (focal or generalized slowing), and new MRI lesion(s) of brain parenchyma suggestive of encephalitis (Venkatesan et al. 2013). In this patient group, CSF-positive viral PCR testing or specific antibody synthesis was shown.

Probable virus encephalitis was diagnosed in those patients who fulfilled the criteria mentioned above but no causative virus could be identified.

Exclusion criteria Patients with toxic, septic or metabolic encephalopathy, antibody-mediated encephalitis, postinfectious encephalitis (e.g., acute disseminated encephalomyelitis or Bickerstaff's), and patients suffering from purely vascular or paraneoplastic diseases of the brain as well as migraine were excluded.

Clinical data recording

Demographic and clinical characteristics on admission, throughout hospitalization and discharge, were documented. These included sex, age, duration and features of clinical symptoms before admission to hospital, neurological findings (level of consciousness, cognitive impairment, paresis, speech disorder, seizures, and meningism), history of new onset of headache, vomiting, history of preceding infection and fever, potential immunocompromised state.

Laboratory data on admission included blood tests (leucocytes, CRP, procalcitonin) and initial CSF data (white cell count (WCC), protein and albumin levels, CSF cytology, glucose and lactate levels, intrathecal synthesis parameters for IgM, IgG, and IgA, presence of oligoclonal bands). CSF PCR tests were promptly initiated including HSV, VZV, CMV, EBV, enterovirus, adenovirus, measles, mumps and rubella virus, FSME (tick borne encephalitis virus), RSV including influenza A and B, HHV 6, and HHV 7. CSF criteria were recorded on the day of admission and during follow-up within 24–72 h. In formerly negative cases, PCR was repeated. Serological investigations in blood and CSF for the viruses given above on day of admission and 14 days later as well as HIV testing were added. Brain biopsy was documented if performed.

Electroencephalography (EEG) recording and neuroimaging with 1.5 T magnetic resonance imaging (MRI) were performed within 48 h after admission to our hospital. For data analysis, MRI scans were re-evaluated by an experienced neuroradiologist blinded to clinical data. The following MRI sequences were included in the analysis: FLAIR, T2-weighted images, diffusion-weighted images (DWI), and contrast enhanced T1-weighted images.

Data on initial therapy, duration of therapy, outcome at discharge, and clinical complications of therapy were collected as well. All patients with suspected viral encephalitis were started on aciclovir, which was discontinued after negative HSV PCR when typical MRI changes were missing or clinical remission was obvious. Thus, in patients presenting with clinical hints for HSV (temporal MRI lesions, temporal EEG slowing, aphasia, and paresis) HSV PCR was repeated, and even in negative cases, aciclovir application was prolonged for at least 10 days.

Statistical procedures

All analyses were performed with SPSS 22. Fisher's exact test was performed for categorical variables to compare different patient groups including *Z* test for particular subgroup analysis. Quantitative parameters were compared using non-parametric tests (Kruskal-Wallis test (KWT) with Mann-Whitney test post hoc (*U* test). Bonferroni correction was

neither used for post hoc analyses nor for subgroup analyses, in order to keep false negative results low (Perneger 1998).

Results

A total of 49 patients were included in this study (Table 1). A viral etiology was confirmed in 22/49 (44.9 %) of the patients. HSV infection was found in 15 patients (30.6 %), VZV in 5 patients (10.2 %), and EBV in 2 patients (4.1 %). Clinical findings of patients with confirmed and probable virus encephalitis are summarized in Table 1. Twelve patients with probable virus encephalitis showed MRI findings consistent with encephalitis, 15 patients showed normal MRI scan.

Patients with confirmed herpes virus encephalitis: HSV, VZV, and EBV

Clinical admission status Clinical data are shown in Table 1. Main symptoms in patients with HSV encephalitis (HSVE) were altered mental state (73.3 %), seizures (66.7 %), aphasia (53.3 %), paresis (46.7 %), and a reduced level of consciousness (46.7 %). Paresis was accompanied by aphasia in 30 %, by seizures in 60 % of the patients. Fifty percent of febrile patients presented with both paresis and seizure; in 70 % of this subgroup aphasia occurred. One patient with EBV (67 years old patient with multiple myeloma, immunocompromised due to chemotherapy with high-dose melphalan) simultaneously suffered from CSF-PCR confirmed CMV infection. She initially presented with tetraparesis, cerebellar ataxia, and cognitive impairment, later she rapidly became soporous.

Duration of symptoms prior to admission The mean time interval between onset of HSVE symptoms and hospital admission was 2.7 days with a standard deviation of (SD) ± 1.5. In VZV encephalitis (VZVE), a longer mean prodromal phase of 8.8 days (SD ± 11.1) was observed.

Signs of systemic inflammation (Tables 1 and 2) Together, 66.7 % of HSV patients initially presented with rectal temperature above 38.5 °C. However, rectal temperatures above 39 °C were measured in only 33.3 % of HSVE patients. A subgroup of 20 % of HSVE patients did not show relevant signs of systemic inflammatory involvement, neither fever or elevated WCC or CRP, respectively (Table 2). Febrile temperatures were completely absent in VZVE patients.

CSF results In HSVE patients as shown in Table 2, mean CSF WCC values on admission were 126/μl (SD ± 186, range 2–645/μl, median 25/μl), mean CSF protein levels were 803 mg/l (SD ± 692, range 250–2940 mg/l, median 532 mg/l), mean albumin quotient 14.7×10^{-3} (SD ± 12, range $4.1–49 \times 10^{-3}$, median 9.7×10^{-3}). Cytology patterns were dominated by lymphocytes in 85.7 % of cases, while in one patient it switched from an initial dominance of granulocytes to a lymphocyte predominant pattern on the next day. On admission, the CSF WCC tended to be higher in VZVE (mean 348/μl, SD ± 349, range 2–867/μl, median 235/μl) as compared with HSVE, and the blood CSF barrier displayed a massive disruption in VZVE patients with a mean protein of 4772 mg/l (SD ± 4251, range 374–9994 mg/l, median 98 mg/l), and mean albumin quotient of 104.5×10^{-3} (SD ± 98.7×10^{-3}, range 7–209×10^{-3}, median 98×10^{-3} mg/l). For both, WCC and CSF protein values, the differences between HSVE and VZVE did not reach statistical significance (Table 2). However, CSF lactate was significantly higher in VZVE (*U* test, *p* 0.037). In two HSVE patients with repetitively negative HSV, PCR serological diagnosis was based on specific intrathecal antibody synthesis.

EEG As shown in Table 2 EEG revealed focal slowing in 80 % of the HSVE patients in contrast to only 20 % of VZV patients (*z* test $p < 0.05$).

Outcome at discharge In HSVE, 26.7 % of the patients recovered completely (Table 3), 73.3 % showed mild to moderate disability including aphasia and altered mental state in 40 %. Outcome in VZVE was similar. In HSVE and VZVE patients, no deaths occurred.

MRI findings Radiological features of all confirmed herpes virus encephalitis groups are shown in Table 4. Eighty percent of HSVE patients but only 2 out of 5 VZVE patients (40 %) showed abnormal MRI findings consistent with encephalitis on T2-weighted images (*z* test, $p < 0.05$). In VZVE patients, MRI revealed entirely normal findings in 3 patients (imaging done 1 and 6 days after first presentation of symptoms). Significantly more HSVE patients (90 %) showed diffusion restriction on DWI (diffusion-weighted imaging) whereas none of the VZV patients did (*z* test, $p < 0.05$). HSVE patients showed bilateral lesions in 53.3 % and a tendency to focal oedema in 66.7 %. In HSVE, a predominant involvement of the temporal lobe (86.7 %, $p < 0.05$ *z* test compared with VZVE) was found affecting especially cortical gray matter in inferotemporal (46.7 %), mesiotemporal (40 %), and insula (46.7 %) areas with widespread planar lesion pattern (80 %, *z* test, $p < 0.05$). A tendency to hemorrhagic cortical transformation was observed in 33.3 % of HSVE. In VZVE, gray matter lesions including the frontal cortex, cerebellum, and lamina quadrigemina were found in 3 patients, while no changes have been identified in the white matter.

Triple constellation of systemic inflammation, meningitis (in CSF), and radiological sign of encephalitis in MRI at presentation in HSVE patients As depicted in Table 2, 12 out of 15 HSVE patients (75 %) presented with systemic

Table 1 Clinical data: medical history, admission, therapy

	Confirmed herpes virus group encephalitis			Probable viral encephalitis of unknown cause		Fisher's exact test (FT), KWT, *U* test (UT) *p* value
	HSV $n = 15$	VZV $n = 5$	EBV $n = 2$ pat 1/pat 2	MRI pathologic $n = 12$	MRI normal $n = 15$	
Mean age (SD), sex (m:f)	45.4 (19), 9:6	$64.8\ (14.9)_{a,}$ 3:2	67;38 0:2	50.4 (17.3), 7:5	$42.8\ (18.3)_{b}$, 9:6	KWT *p* 0.090, UT (a, b) 0.024
Medical history						
Immunosuppression, %	0_{a}	$2\ (40)_{b}$	Yes/no	1 (8.3)	1 (6.7)	FT *p* 0.062
Mean time to hospitalization, days (SD)	$2.7\ (1.5)_{a}$ CI 1.84–3.5	8.8 (11.1) CI 0–22.6	n.a./8	$7.9\ (7.2)_{b}$ CI 3.3–12.5	$2.6\ (1.7)_{c}$ CI 1.6–3.6	KWT *p* 0.05, UT (a, b) *p* 0.021, UT (b, c) *p* 0.018
Mean hospital stay, days (SD)	$22.6\ (8.8)_{a}$ CI 17.7–27.5	$31.2\ (17.7)_{d}$ CI 9.3–53.1	65/30	$32.5\ (9.6)_{b}$ CI 26.1–39	$13.2\ (6.4)_{c}$ CI 9.5–16.9	KWT 0.000, UT (a, b) *p* 0.015, UT (a, c) *p* 0.001, UT (d, c) *p* 0.004, UT (b, c) *p* 0.000
Clinical data on admission						
Somnolence	7 (46.7)	2 (40)	Artificially ventilated due to sopor/somnolent	6 (50.0)	5 (33.3)	n.s.
Sopor	3 (20)	0_{a}		$6\ (50.0)_{b}$	$0_{a,\ c}$	FT *p* 0.005
Coma	1 (6.7)	1 (20)		1 (8.3)	0	n.s.
Artificial ventilation	$3\ (20)_{a}$	1 (20)		$7\ (58.3)_{b}$	$1\ (6.7)_{a}$	FT *p* 0.022
Paresis	$7\ (46.7)_{a}$	1 (20)	Yes/no	5 (41.7)	$2\ (13.3)_{b}$	FT *p* 0.207
Altered mental state	11 (73.3)	5 (100)	n.a./yes	10 (83.3)	9 (60.0)	n.s.
Aphasia	8 (53.3)	1 (20)	n.a./no	5 (41.7)	3 (20.0)	n.s.
Meningeal irritation	6 (40)	2 (40)	No/yes	4 (33.3)	5 (33.3)	n.s.
Headache	7 (46.7)	3 (60)	No/yes	7 (58.3)	12 (80.0)	n.s.
Vomiting	4 (26.7)	0	No/no	2 (16.7)	3 (20.0)	n.s.
Seizure	10 (66.7)	1 (20)	No/no	5 (41.7)	5 (33.3)	n.s.
Focal EEG slowing	$12\ (80)_{a}$	$1\ (20)_{b}$	No/yes	$3/8\ (30.0)_{b}$	$5/13\ (38.5)_{b}$	FT *p* 0.021
Rectal temperature >38.5 °C (%)	$10\ (66.7)_{a}$	0_{b}	No/yes	4 (36.4)	7 (46.7)	FT *p* 0.068
Mean rectal temperature, (SD)	38.6 (1.1) CI 38–39.2	37.8 (0.3) CI 37–38.2	36.5/39.0	38.3 (1.1) CI 37.6–39	38.2 (0.9) CI 37.7–38.7	n.s.
Therapy						
Antibiotics (%)	$7\ (46.7)_{a}$	4 (80)	1	$11\ (91.7)_{b}$	9 (60)	
Antivirals (%)	15 (100), Aciclovir	5 (100), Aciclovir,	Gangciclovir and foscavir (1); aciclovir (2)	12 (100), Aciclovir	15 (100), Aciclovir	
Steroids (%)	5 (33.3)	0_{c}	Yes/no	$8\ (66.7)_{b}$	$2\ (13.3)_{a,\ c}$	

KWT Kruskal-Wallis test; *U*-test; Mann-Whitney test (UT; in brakes: subgroups compared); *SD* standard deviation; *CI* confidence interval, *n.s.* not significant, *n.a.* not applicable, Fisher's exact test run for comparison of 4 groups (HSV, VZV, probable encephalitis with and without MRI pathology), including *z* test run for comparison of individual subgroups with each other (subgroups indicated by different subscripted letters (a, b, c) significantly differ from each other, p value < 0.05), EBV patients not included in testing

Table 2 Blood and CSF parameters

	Confirmed herpes virus encephalitis			Probable viral encephalitis of unknown cause		Fisher's exact test (FT), KWT, *U* test (UT) *p* value
	HSV *n* = 15	VZV *n* = 5	EBV *n* = 2 pat 1/pat 2	MRI pathologic *n* = 12	MRI normal *n* = 15	
Blood tests on admission						
Mean leucocytes, WCC in 10^3/μl, (SD)	10 (3.2) CI 8.2–11.7	9.2 (4.1) CI 4.2–14.3	6.3/ 6.0	10.7 (6.7) CI 5.9–15.5	10.9 (3.3) CI 9.2–12.8	n.s.
WCC (10^3/μl) <11/<15/>15	11/2/2	4/0/1	2/0/0	8/1/1	9/4/2	
Mean CRP in mg/l, (SD)	15.2 (24.0) CI 1.9–28.5	21 (21.9) CI 0–48.2	<5/<5	13.7 (10) CI 6.6–20.8	48.3 (102.6) CI 0–110	
Presence of systemic signs of inflammation						
Fever−, CRP/WCC−	3 $(20)_a$	4 $(80)_b$	Yes/no	5 (45.5)	4 $(26.7)_a$	FT n.s.
CSF WCC in patients with fever−, CRP/WCC−	25/2/25	2/114/ 522/867	–	1/9/28/ 118/444	26/52/329/ 333	*p* 0.212
Pos. DWI in patients with fever−, CRP/WCC−	2/2	0/2	n.d.	3/5	0/4	
Fever+, CRP/WCC−	7 (46.7)	0	No/yes	4 (36.4)	3 (20)	
CRP or WCC+, fever−	2 (13.3)	0	No/no	0	4 (26.7)	
CRP/WCC+, fever+	3 (20)	0	No/no	0	4 (26.7)	
CSF on admission						
PCR positive	13/15 (86.7 %)	3/5 2/5 VZV ab	2/2	0/12	0/15	
Mean CSF WCC d1 in /μl, (SD)	126 (186), CI 22.7–229	348 (348.9)$_c$ CI 0–781.2	2; 276	63.9 (126.2)$_a$ CI 0–144.1	144.3 (151.4)$_b$ CI 60.5–228.2	KWT *p* 0.109 UT (a, b) *p* 0.043 UT (a, c) *p* 0.078
CSF WCC d1 (/μl) <10/<30/<100/<200/>200	4/5/1/1/4	1/0/0/1/3		6/3/0/2/1	2/3/4/1/5	
Mean CSF protein in mg/l, (SD)	803 (692) CI 420–1187	4772 (4251) CI 0–10,051	850/ 981	1212 (1204) CI 447–1977	925.7 (342.9) 735.8–1115.6	n.s.
Mean Q albumin in $\times 1/10^3$, (SD)	14.7 (12.0) CI 7.6–20.9	104.5 (98.7) CI 0–227	6.5/ 15.5	21.5 (19.0) 8.7–34.2	15.2 (7.6) 10.9–19.4	n.s.
Mean lactate in mmol/l, (SD)	2.7 $(1.3)_a$ CI 2.0–3.5	3.9 $(1.2)_b$ CI 2.4–5.3	2.67/3.3	3.5 (2.3) CI 1.9–5.2	2.4 $(0.8)_c$ CI 1.9–2.9	KWT *p* 0.138, UT (a, b) *p* 0.037, UT (b, c) *p* 0.027
CSF cytology						
Mean fraction of granulocytes in % (SD)	4.1 $(7.7)_a$ CI 0–8.5	1 (2) CI 0–4.2	12/0	11.8 (27.8) CI 0–31.7	34.4 $(37.8)_b$ CI 10.4–58.5	KWT *p* 0.090, UT (a, b) 0.024
CSF pattern dominated by granulocytes, *N* (%)	1 $(7.1)_a$	0	0	1 $(10.0)_a$	6 $(50)_b$	FT *p* 0.060
CSF pattern dominated by lymphocytes, *N* (%)	12 $(85.7)_a$	4/4 (100 %)	2	9 $(90.0)_a$	6 $(50)_b$	
Presence of activated lymphocytes in CSF, *N* (%)	7/14 $(50)_a$	4/4 (100)	0/1	6/11 $(54.5)_a$	11/12 $(91.7)_b$	FT *p* 0.045

Glucose ratio normal in all groups. Fisher's exact test run for comparison of 4 groups (HSV, VZV, probable encephalitis with and without MRI pathology), including *z* test run for comparison of subgroups (subscripted letters indicate a *p* value < 0.05), EBV patients not included in testing

n.d. not done, *N* number of patients, *ab* antibody, *n.s.* not significant

Table 3 Clinical outcome at discharge

	Confirmed herpes virus encephalitis			Probable viral encephalitis of unknown cause		Fisher's exact test, KWT, *U* test *p* value
	HSV $n=15$	VZV $n=5$	EBV pat 1/pat 2	MRI pathologic $n=12$	MRI normal $n=15$	
Outcome at discharge						
Complete remission (%)	4 $(26.7)_a$	1 $(20)_a$	−/no	0_a	11 $(73.3)_b$	FT $p<0.001$
Mild–moderate disability (%)	11 $(73.3)_a$	4 $(80)_a$	−/yes	6 (50.0)	3 $(20.0)_b$	
Severe disability (%)	0	0	−/no	2 (16.7)	1 (6.7)	
Death (%)	0_a	0	Yes/no	4 $(33.3)_b$	0_a	
Aphasia at discharge (%)	6 $(40)_a$	0	−/no	0_b	0_b	FT p 0.006
Paralysis at discharge (%)	0_a	1 (20)	−/no	3 $(37.5)_b$	0_a	FT p 0.008
Altered mental state (%)	6 $(40)_a$	2 (40)	−/yes	6 $(75)_b$	4 $(26.7)_a$	FT p 0.178

Fisher's exact test run for comparison of 4 groups (HSV, VZV, probable encephalitis with and without MRI pathology), including *z* test run for comparison of subgroups (subscripted letters indicate a *p* value < 0.05), EBV patients not included in testing

inflammatory signs including fever and/or blood changes (CRP or WCC elevation); but only 3 patients out of the 12 patients (20 %) presented with fever and blood changes. Four out of 15 (26.7 %) HSVE patients showed even normal or minor abnormal CSF constellations (CSF WCC <10/μl and albumin quotient $<10\times10^{-3}$) at initial presentation. In all of these patients, MRI was positive including DWI. In one HSVE patient with normal MRI findings including DWI, focal EEG slowing indicated possible HSVE diagnosis.

Patients with probable viral encephalitis and pathological MRI

A group of 12 patients has been diagnosed with probable viral encephalitis of unknown etiology but with MRI lesions consistent with encephalitis (Table 1). These patients presented with somnolence (50.0 %), sopor (50.0 %), and altered mental state (83 %). Prodromal phase was significantly longer in comparison to HSVE patients (*U* test, *p* 0.021, Table 1). Seven patients (58.3 %) were artificially ventilated on admission (*z* test, $p<0.05$).

In this group of patients, the mean CSF WCC seemed to be lower (64/ μl, SD ± 126, range 0.3–444/μl, median 11.5/μl) than in the other encephalitis groups (Table 2). Of note, 45.5 % of these patients presented neither with fever nor with relevant signs of inflammatory blood parameters (CRP, WCC), Table 2. Disease course appeared predominately unfavorable and longstanding in comparison to HSVE. Thus, 33.3 % of the patients in this group died (Fishers and *z* test, $p<0.05$) and 16.7 % were severely disabled ($p<0.001$) including paralysis on discharge in 37.5 % of the patients (Fisher's test *p* 0.008, z test $p<0.05$).

MRI showed predominantly temporal gray matter pathology as depicted in Table 4. There was a tendency for parietal (25 %) but also for thalamic lesions (33.3 %) in the MRI compared with HSVE patients. In addition, in 75 % of patients, MRI lesions displayed a multifocal type of lesion pattern (only in 26.7 % in HSVE). Whereas in HSVE, a combined pattern of cortical and white matter lesions was observed in 53.3 % of the cases, in patients with probable viral encephalitis with MRI pathology, this was rarely seen (8.3 %, *z* test, $p<0.05$).

Special cases Three patients (aged 26, 40, 42 years) presented with sopor after prodromal phase of unspecific fatigue lasting about several weeks. Initial CSF was normal, later a disruption of blood brain barrier developed together with edematous lesions in cerebral cortical areas, basal ganglia, and thalamus on MRI. The outcome was deleterious. Brain biopsy, which was done in 2 patients, revealed unspecific findings with tissue oedema, necrosis, glial activation, and unspecific glial activation predominantly in gray matter. The cause of encephalitis has never been elucidated.

Patients with probable viral encephalitis and normal MRI

Another 15 patients with inflammatory CSF syndromes presented with acute focal neurological signs but normal MRI including DWI. As depicted in Table 2, these patients showed neither signs of substantial systemic inflammation nor metabolic disarrangement. Within this group, 60 % of the patients presented with altered mental state, headache in 80 %, and meningeal irritation was present in 33.3 % of the cases (Table 1). Time to hospitalization from onset of symptoms was similarly short like in HSVE (mean 2.6 days, SD ± 1.7). This group of patients recovered significantly faster than all other groups described (mean 13.2 days, SD ± 6.4, *U* test $p<0.005$, Table 1) correlating with rapid CSF improvement in the lumbar re-puncture within 2 days. Together, 73.3 % of these patients experienced a complete clinical remission within a few days (*z* test $p<0.05$, Table 3).

Whereas initial CSF WCC and blood-CSF-barrier function were comparable to HSVE patients (Table 2), granulocyte predominance in CSF was seen in 50 % of these patients on admission and only in 7.1 % in patients with HSVE. Correspondingly,

Table 4 MRI findings

	Confirmed herpes virus group encephalitis			Probable viral encephalitis of unknown cause and MRI pathology, $n = 12$	Fisher's exact test
	HSV $n = 15$	VZV $n = 5$	EBV pat 1/pat 2*		
T2 abnormalities suspicious for encephalitis (%)	12 (80.0)$_a$	2 (40)$_b$	Yes	10 (83.3)	n.s.
DWI image done	10/15	3/5	No/yes	12/12	
Restricted diffusion (%)	9/10 (90)$_a$	0/3$_b$	−/no	6/12 (50)$_b$	0.014
Cortical lesion (%)	13 (86.7)$_a$	2 (40)$_b$	No	7 (58.3)	0.030
Nuclear lesion (%)	2 (13.3)	1 (20)	No	2 (16.7)	n.s.
Gray matter (%)	13 (86.7)	3 (60)	No	9 (75.0)	n.s.
White matter (%)	8 (53.3)$_a$	0$_b$	Yes	4 (33.3)	n.s.
Cortex and white matter (%)	8 (53.3)$_a$	0$_b$	No	1 (8.3)$_b$	0.004
Gray and white matter (%)	8 (53.3)$_a$	0$_b$	No	3 (25)	0.030
Lesion localisation					
Temporal (%)	13 (86.7)$_a$	0$_b$	Yes	9 (75.0)$_a$	0.064
Inferotemporal (%)	7 (46.7)	0	No	2 (16.7)	0.025
Mesiotemporal (%)	6 (40)	0	No	1 (8.3)	0.028
Insula (%)	7 (46.7)	0	No	5 (41.7)	n.s.
Parietal (%)	0$_a$	0	Yes	3 (25.0)$_b$	n.s.
Frontal (%)	5 (33.3)	2 (40)	Yes	5 (41.7)	n.s.
Occipital (%)	2 (13.3)	0	Yes	2 (16.7)	n.s.
Thalamus (%)	2 (13.3)	0	No	4 (33.3)	n.s.
Hypothalamus (%)	0	0	No	2 (16.7)	n.s.
Brainstem (%)	0	1 (20)	No	1 (8.3)	n.s.
Cerebellum (%)	1 (6.7)	1 (20)	No	1 (6.7)	n.s.
Lesion bilateral (%)	8 (53.3)	1 (20)	Yes	6 (50)	n.s.
Lesion focal (%)	4 (26.7)$_a$	2 (40)	No	9 (75.0)$_b$	0.045
Lesion widespread planar (%)	12 (80)$_a$	0$_b$	Yes	5 (41.7)$_b$	0.007
Lesion confluent (%)	4 (26.7)	0	Yes	0	0.029
Hemorrhage (%)	5 (33.3)	0	No	1 (8.3)	0.066
Oedema (%)	10 (66.7)	2 (40)	No	6 (50)	n.s.
Parenchymal contrast enhancement (%)	2 (13.3)	0	No	5 (41.7)	n.s.
Meningeal contrast enhancement (%)	2 (13.3)	2 (40)	No	1 (8.3)	n.s.

Fisher's exact test run for comparison of 4 groups (HSV, VZV, probable encephalitis with and without MRI pathology), including z test run for comparison of subgroups (subscripted letters indicate a p value < 0.05), EBV patients not included in testing

n.s. not significant

*MRI in patient 2 with EBV was normal

initial fraction of granulocytes in CSF in this rather "benign" form of encephalitis was significantly higher (mean 34.4 %, ±SD 37.8) than in HSVE (mean 4.1 %, SD ± 7.7, U test p 0.024). In addition, 91.7 % of patients showed activated CSF lymphocytes in initial CSF what was significantly higher than in HSVE patients (50 %) (z test, $p < 0.05$, Table 2).

Discussion

Viruses are the most common infectious cause of encephalitis. In our study, we could identify viral causes of encephalitis in 44.9 % of patients. This result is slightly lower than previously reported where in approximately 60 % of patients evidence for a viral pathogenesis could be detected (Singh et al. 2015). One reason might be the retrospective nature of this study and the long collection period with different available diagnostic tools.

Patients with confirmed herpes virus encephalitis: HSV, VZV, EBV

Clinical data in HSVE and VZVE patients

HSVE In accordance with previous studies, the clinical findings of HSVE patients such as presence of altered mental state

(63–83 %), aphasia (57–67 %), seizures (42–63 %), coma (3–24 %), headache (42–70 %), and meningeal signs (32 %) are comparable (Sili et al. 2014). The subacute symptom onset in the HSVE group was also in line with previously reported data from Sili et al. (mean 2.3 days, SD ± 2.6, range 1–20 days) (Sili et al. 2014). Focal EEG slowing was present in 80 % in our study which compares to 81–88 % in other studies (Granerod et al. 2010; Sili et al. 2014) and therefore underlines the importance of EEG as a diagnostic tool to help in distinguishing HSVE from other etiologies. Indeed, 33.3 % of HSVE patients presented with rectal temperature below 38.5 °C, a finding that has been reported in 19–24 % of patients (Granerod et al. 2010; Sili et al. 2014). Only one-third of HSVE patients presented with fever above 39 °C in our study which is in contrast to a reported incidence of 76–92 % in other studies (Granerod et al. 2010; Sili et al. 2014). Consistent with previous findings, WCC and CRP values confirmed only marginal elevation (Sili et al. 2014). These findings show the possibility of different clinical presentation of patients with HSVE and emphasize the awareness of potential different clinical scenarios.

VZVE Our data confirm that VZVE primarily affects older and immunosuppressed patients (Granerod et al. 2010). Furthermore, clinical presentation of VZVE is rather subacute and shows lower frequency of temporal EEG slowing or seizures in comparison to HSVE (Grahn and Studahl 2015). VZV CNS infection-related vasculopathy may lead to acute stroke accompanied by cerebellitis and retinal necrosis, abnormalities of cranial nerves and cervical myelon. Patients in our study presented with optic neuritis and cerebellar gait imbalance, another patient developed cervical myelitis, all patients suffered from altered mental state. No patient developed a typical rash, that may be absent in 37–55 % of VZVE patients (De Broucker et al. 2012). In contrast to previous reports, when fever was present at initial presentation in 50–90 % (De Broucker et al. 2012; Granerod et al. 2010), all our patients were afebrile.

Treatment and outcomes at discharge in HSVE and VZVE All patients with HSVE and VZVE were treated with aciclovir for at least 14 days (Table 1). Outcome in both entities has been previously discussed to be similar (Raschilas et al. 2002; Sonneville et al. 2015) and is often characterized by neuropsychological deficits (Grahn and Studahl 2015) which is in accordance with our findings. In contrast with previously reported fatality rates of 7–35 % in HSVE and of 20 % in VZVE (Grahn and Studahl 2015; Granerod et al. 2010; Sili et al. 2014; Singh et al. 2016), the outcome in our study was more favorable as none of our patients died.

CSF pathology in HSVE and VZVE patients

Our data on CSF parameters (e.g., WCC, CSF cytology patterns, and median protein concentrations) are in line with previously reported data (Granerod et al. 2010; Sili et al. 2014). Important to acknowledge, in 3 (20 %) patients, CSF was completely normal on admission while later HSV PCR revealed a positive result. In fact, 5 % of HSVE patients may present with initial normal CSF findings (Jakob et al. 2012). However, according to previous data, specific CSF HSV antibody detection was seen around day 10 of the disease (Domingues et al. 1998).

It is well established that CSF in viral encephalitis typically shows an initially mixed or then lymphocyte pleocytosis of 10–200 cells/μl (or more) and an elevated protein content of 0.5–1 g/l or more. The diagnostic mainstay remains detection of viral antigen by PCR within the first week of illness even after the patient is on acyclovir treatment (Lakeman and Whitley 1995). In our study, positive CSF PCR for both entities was less than reported in the literature (HSVE: 86.7 8 %, VZVE 60 %). As reported by Steiner et al., the diagnostic sensitivity for HSV CSF PCR are 96 % and for VCV CSF PCR 80 % (Steiner et al. 2012). Of note, a negative HSV PCR within the first 3 days of HSVE should be recognized as a potential pitfall (Steiner et al. 2010).

In contrast, detection of VZV antibodies in CSF appears to have greater sensitivity than detection of viral DNA (Gilden et al. 2009).

In our small 5 VZVE patient series, CSF WCC and protein values were much higher than reported by others (Granerod et al. 2010). However, there are notes on a few VZV encephalitis cases with CSF WCC up to 1240 Mpt/l and CSF protein of 3900 mg/l showing normal MRI (De Broucker et al. 2012).

MRI imaging

In our study, no clear correlation between appearance of MRI lesions and neurological outcome could be detected, which is supported also by other study results (De Broucker et al. 2012).

HSVE MRI findings in the present investigation are consistent with previous studies showing typical temporal MRI pathology in 86–100 % of HSVE cases (Domingues et al. 1998; Granerod et al. 2010; Sheybani et al. 2013; Sili et al. 2014). As well, involvement of the basal ganglia, thalamus, and (orbital) frontal lobe may appear; our series changes were even bilateral in 53 % of patients (Chow et al. 2015; Domingues et al. 1998; Oyanguren et al. 2013; Sili et al. 2014). Our study suggests the superiority of DWI to conventional T2- or FLAIR-weighted MRI in detection of early signal abnormalities in HSVE (Renard et al. 2015). Restricted diffusion imaging represents the acute initial phase of cytotoxic edema in

encephalitis (Maschke et al. 2004; Tsuchiya et al. 1999). There are a few case reports available reporting about the distinct value of DWI as the key to the diagnosis (Kiroglu et al. 2006; Kuker et al. 2004; McCabe et al. 2003; Sawlani 2009). This may be of particular importance especially in cases with initial normal CSF and missing systemic inflammatory signs. Nevertheless, MRI may even be repeatedly negative in PCR-based HSVE (Hollinger et al. 2000; Sheybani et al. 2013) even when DWI imaging was performed (Oyanguren et al. 2013). In our study, 2/15 HSV patients remained negative in MRI imaging including DWI in one patient (done on second day after onset of symptoms).

Forty-eight hours after onset of symptoms T2-weighted images seem to be reliable in detecting typical HSVE changes as well (Maschke et al. 2004).

VZVE Pathophysiology of VZVE has been proposed to be predominantly vasculopathic rather than demyelinating or infectious (Gilden et al. 2009). MRI typically demonstrates ischaemic changes involving cortical and deep gray-white matter and may include changes in the cerebellum and cervical medulla as well (Grahn and Studahl 2015). In our quantitatively limited study, MRI showed pathologic lesions on T2-weighted images in 2 patients. One patient presented with involvement of the lamina quadrigemina and of the cerebellar peduncle and another patient with frontal cortical lesions different from a typical ischaemic type of pattern. However, pure small-artery involvement has been described in 37 % of patients with VZV infection of the brain (Nagel et al. 2008). There was no bleeding complication as reported by others (Gilden et al. 2009). In 2 of our 5 patients, MRI was completely inconspicuous as also described in 35–57 % of the cases by others (De Broucker et al. 2012; Grahn and Studahl 2015; Granerod et al. 2010). Of note, DWI scan was negative in all 3 patients in whom DWI scan was performed including those with positive T2-weighted lesions.

EBVE Two patients were diagnosed as EBVE based on PCR. The typical radiological pattern of EBVE involves the basal ganglia and thalamus as well as the cerebellum being accompanied by a strong contrast enhancement (Venkatesan et al. 2013). One patient presented with temporary periventricular occipital subcortical lesions, the other had normal MRI including DWI. Both phenomena are known in EBVE (Bulakbasi and Kocaoglu 2008).

Patients with probable viral encephalitis and pathological MRI

In comparison to HSVE, except for a lower frequency of focal EEG slowing and seizures, no clinical or neither CSF nor MRI discriminating factors could be found in this group. In a distinct number of patients, clinical disease features, MRI, and CSF findings of these patients were quite similar to HSVE. However, PCR and serologic testing did not confirm HSVE.

Obviously, outcome in this group was significantly worse compared to HSVE patients leading to death in 16.7 % of patients or severe disability in a third of patients. Three young patients died due to progressive cerebral oedema predominantly involving cortical and thalamic gray matter. Thalamic involvement has been described in HSVE as well, but also in arbovirus (eastern equine encephalitis), influenza, West Nile, EBV, and variegated squirrel bornavirus infections (Hoffmann et al. 2015; Renard et al. 2015; Stretz and Finelli 2015). Taking into account, the geographic region, the medical history and course of disease, and the viruses mentioned above are rather unlikely to be causative in our patients. However, the rather poor outcome in this group of patients for whom a cause could not be identified underlines the importance of further research to elucidate the nature and the pathogen of this aggressive and detrimental disease.

Patients with probable viral encephalitis and normal MRI

In our study, in 15/49 (30.6 %) of patients with encephalitis no causative pathogen could be detected even in repetitive investigations. Aciclovir treatment in these patients had been stopped after negative HSV PCR results or missing pathologic features in MRI correlating with significant clinical and CSF improvement within 2 days. In regard to clinical outcome, 73.3 % of patients recovered completely and 20 % were only moderately affected. In particular in this patient group, the presence of focal signs like EEG slowing (38.5 %) or the de novo onset of seizures (33.3 %) correlated with rather short onset of symptoms (mean 2.6 days) but did not allow to distinguish these cases from those with potentially life-threatening HSVE. In the emergency situation, a fast decision is necessary. Indicative signs could rather be the initial CSF data showing significantly more often a granulocytic pattern or a higher amount of activated lymphocytes. However, it must be recognized that HSV infection may be masked by normal initial CSF including DNA PCR, dominating granulocytes, absence of systemic inflammatory signs and in exceptional cases also with normal MRI findings.

Clinical signs mimicking encephalitis can appear due to infectious causes like bartonella hensela or influenca virus, which are known to be symptomatic for several days, yet without CSF pleocytosis (Bloch and Glaser 2007; van Zeijl et al. 2005). Further, MRI imaging has been reported to be unremarkable in cerebral infections like CMV, non-polio enterovirus (Coxsackie, E 71), EBV, and rarely in HSV, as well as in VZV and adenovirus (Akyldz et al. 2008; Grahn and Studahl 2015). Adenovirus usually leads to respiratory infections, conjunctivitis, or gastroenteritis in immunocompetent hosts (especially in children) and represents a rare and mild cause of encephalitis leading usually to complete recovery

(Dubberke et al. 2006). However, all these viruses might mimic the clinical picture initially resembling HSVE, which therefore needs to be ruled out.

In conclusion, here, we demonstrated that a considerable part of patients with encephalitis of probable viral origin present with a relatively malign disease course with features similar to HSVE. Furthermore, beside typical herpes encephalitis such as HSVE, VZVE, and EBVE, a patient group with rather "benign" encephalitis and missing MRI pathology seems to exist. For distinguishing these groups, the CSF cytology patterns might be a helpful diagnostic tool. In regard to brain MRI, we strengthen with our results the hypothesis that DWI is particularly helpful in detection of early signal abnormalities in HSVE in order to accelerate the diagnosis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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