Eur Arch Psychiatr Neurol Sci (1987) 236:372–378

European Archives of Psychiatry and Neurological Sciences

Non-Herpes Simplex Encephalitis is Early Exclusion of Herpes Simplex Etiology Possible?

V. Schuchardt[1] and H. Buchner[2]

[1] Abteilung für Neurologie der Rheinischen Landesklinik Bonn, Kaiser-Karl-Ring 20, D-5300 Bonn 1,
[2] Abteilung für Neurologie der Medizinischen Fakultät der Rheinisch-Westfälischen Technischen Hochschule Aachen, D-5100 Aachen, Federal Republic of Germany

Summary. Since effective antiviral treatment is available for herpes simplex encephalitis (HSE), early diagnosis or exclusion of herpes simplex etiology is essential for prognosis. In a retrospective study of 25 cases of acute viral encephalitis not caused by herpes simplex virus (non-HSE), we investigated whether HSE can be excluded in the early phase before serological evidence is present. Using clinical means, history, investigations of CSF (protein, cells), EEG, and CCT, HSE could not be excluded with reliability. This is because clinical signs and laboratory results are not pathognomonic for any form of viral encephalitis, even if periodic activity in EEG and temporal attenuation in CCT are more frequent in HSE than in other forms of encephalitis. Therefore, in all cases of severe encephalitis, acyclovir therapy should be initiated early.

Key words: Viral encephalitis – Herpes simplex virus encephalitis – Differential diagnosis of viral encephalitis

Introduction

Early exclusion or diagnosis of herpes simplex etiology is of great importance in acute viral encephalitis, since effective treatment of herpes simplex encephalitis (HSE) has been established [28, 34, 35, 36, 38]. For viral encephalitis of other origins, except varicella zoster encephalitis, specific therapy is not available. The incidence of HSE is believed to be about 2 cases per million inhabitants per year [28], and HSE represents only 2% to 19% of all cases of encephalitis [27]. The frequency of encephalitis caused by other viruses or encephalitis with no detected pathogen (non-HSE) is much higher. In the present retrospective study, our aim was to investigate, if HSE can be excluded early by clinical means in encephalitis of non-HSE outcome.

Patients and methods

Patients with clinical evidence of acute viral encephalitis in whom herpes simplex etiology was excluded serologically were involved in the study. Inclusion criteria were signs and symptoms of acute inflammatory encephalopathy: fever, meningism, CSF changes, altered personality, impairment of consciousness, epileptic seizures, and/or other neurological findings. Not included were persons in whom herpes simplex etiology was not excluded ($n = 1$) and those with isolated dysfunction of the cerebellum or brainstem (brainstem encephalitis) without other evidence of cerebral affection. Patients were treated in Bonn ($n = 17$) and Aachen ($n = 8$) between 1980 and June 1986.

Extensive serological investigations[1] were performed on CSF and serum for herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus, tick-borne encephalitis virus, adenovirus, enterovirus, rubella virus, measles virus, mumps virus and additionally for ornithosis, mycoplasma pneumoniae, neurosyphilis, and borreliosis if possible. Recently HIV was investigated in a few patients.

Antiviral treatment was administered for 2 to 12 days in patients with suspected HSE using vidarabine 15 mg/kg body weight daily or acyclovir 10 mg/kg body weight every 8 h.

Case reports

Case 1

This 16-year-old girl had suffered from headaches and sore throat for 7 days, and was admitted following an epilectic seizure. Her temperature was 38.3°C and we found tonsillitis but no enlarged lymphnodes. There was neck-stiffness and moderate clouding of consciousness. The CSF contained 36 mononuclear cells/mm^3, with 67 mg/dl protein. On the 1st day, EEG was severely slowed, and there was a non-specific left-sided frontotemporal focus on the 4th day; CCT was unchanged. Because of the focus in EEG, HSE was considered, and the patient received acyclovir for 5 days. She recovered quickly and left hospital after 24 days. Serum IgM against EBV was positive and EBV encephalitis was diagnosed.

Case 2

This 62-year-old lady had been bitten by ticks 4 weeks prior to admission and had suffered from headaches, visual disturbances, and fever for 9 days before she entered hospital.

Offprint requests to: V. Schuchardt

[1] We wish to thank Prof. Dr. med. K. P. Schaal, Director of the Institute of Medical Microbiology, University Bonn, and Prof. Dr. Dr. G. Gillissen, Head of the Department of Medical Microbiology of the Rheinisch Westfälische Technische Hochschule Aachen

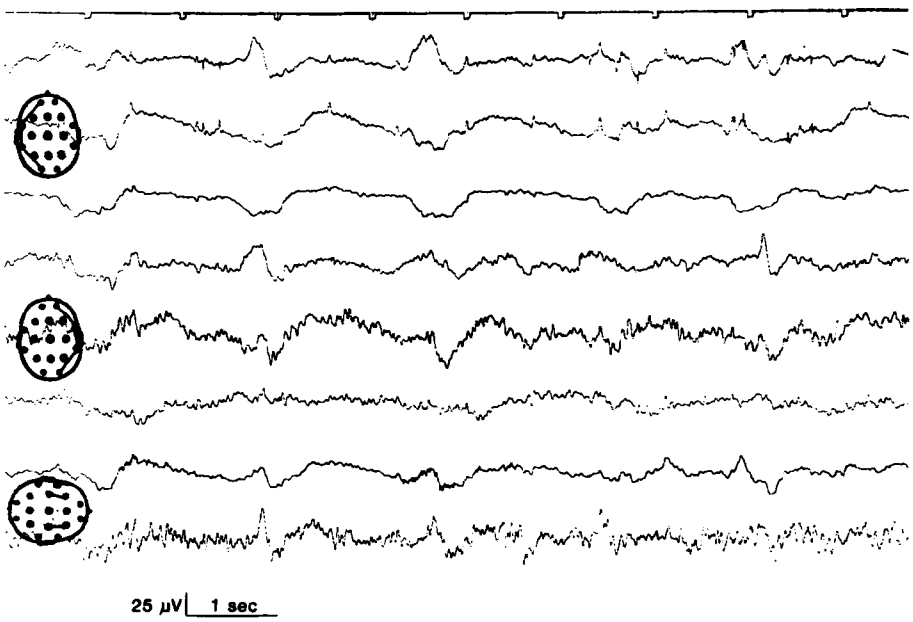

Fig. 1. VZV encephalitis, EEG on 6th day

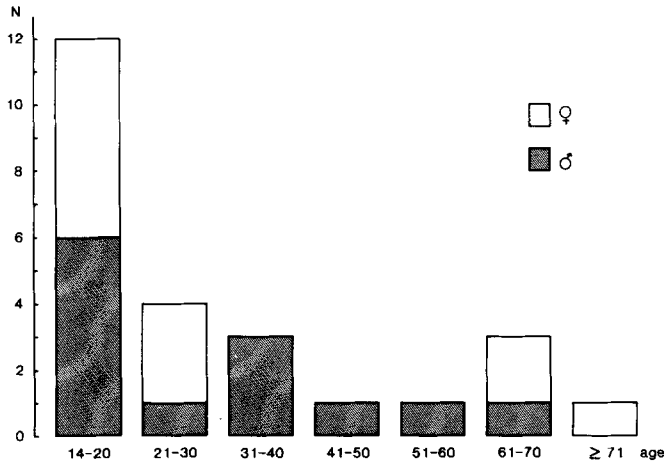

Fig. 2. Age distribution in 25 patients with acute viral encephalitis (non-herpes simplex encephalitis, non-HSE)

Fever was high, her consciousness clouded, and because of right temporal EEG finding, HSE had been assumed. Therefore the patient was transferred to our hospital on the 6th day of encephalitis. She was unconscious, neck-stiffness was absent, but she displayed extensor spasms of her right arm and her right leg. The CSF contained 54 cells/mm^3, 50% lymphocytes, and 50% polymorphs. This finding and the EEG, flattended on the left side with bilateral periodic activity, enhanced the suspicion of HSE. Therefore, acyclovir therapy was started at once (Fig. 1). CCT showed a small focal attenuation of the right central region (Fig. 3a). The patient was unconscious for 14 days and had to be intubated and mechanically ventilated for 38 days, she received intensive care for 70 days. Epileptic fits of her left leg appeared on the 7th day of treatment, and on regaining consciousness, there was severe paresis of all four limbs. Whether it was due to myelitis or to polyneuritis could not be determined. For a long time she was confused, and on the 106th day after the onset of encephalitis, she died from acute pulmonary embolism. A postmortem was not allowed. The etiology of the encephalitis remained unknown, extensive serological investigations including HSV, VZV, and tick-borne encephalitis virus were negative.

Results

We report on 25 patients, 12 female, 13 male, aged 14 to 74 years with a medium age of 30.9 years, 12 patients were 20 years or younger (Fig. 2). There was a peak of admission in the months of August ($n = 7$) and September ($n = 4$).

Etiology

Etiology was clear in 9 cases, in 16 cases it remained undetected (Table 1). We established a diagnosis of EBV encephalitis in 3 patients, measles virus encephalitis in 3, VZV encephalitis in 2, and rubella virus encephalitis in 1. In 6 of these 9 patients, the etiological diagnosis was first established by clinical features and later confirmed serologically. In 2 other cases the diagnosis was made on clinical grounds alone: in one because of typical measles exanthema, and in the other because of characteristic zoster. Only in 1 case of measles encephalitis, was the etiological diagnosis established serologically alone. In 16 patients, in spite of extensive serological investigations, no viral pathogen could be found, and diagnoses of acute viral encephalitis were made because of typical clinical features. In all patients, herpes simplex etiology was excluded by serological means. Serological diagnosis was established for measles virus by complement fixing reaction (CFR) in CSF, for VZV by CFR in CSF and serum, for EBV by immunofluorescence detection of specific IgM antibodies in CSF, and for rubella virus by detection of specific IgM by an enzyme-linked immunosorbent assay in CSF.

Clinical Features

Prodromal symptoms were reported by 20 patients, mostly fever, headaches, and vomiting (Table 2). Indeed, most of the

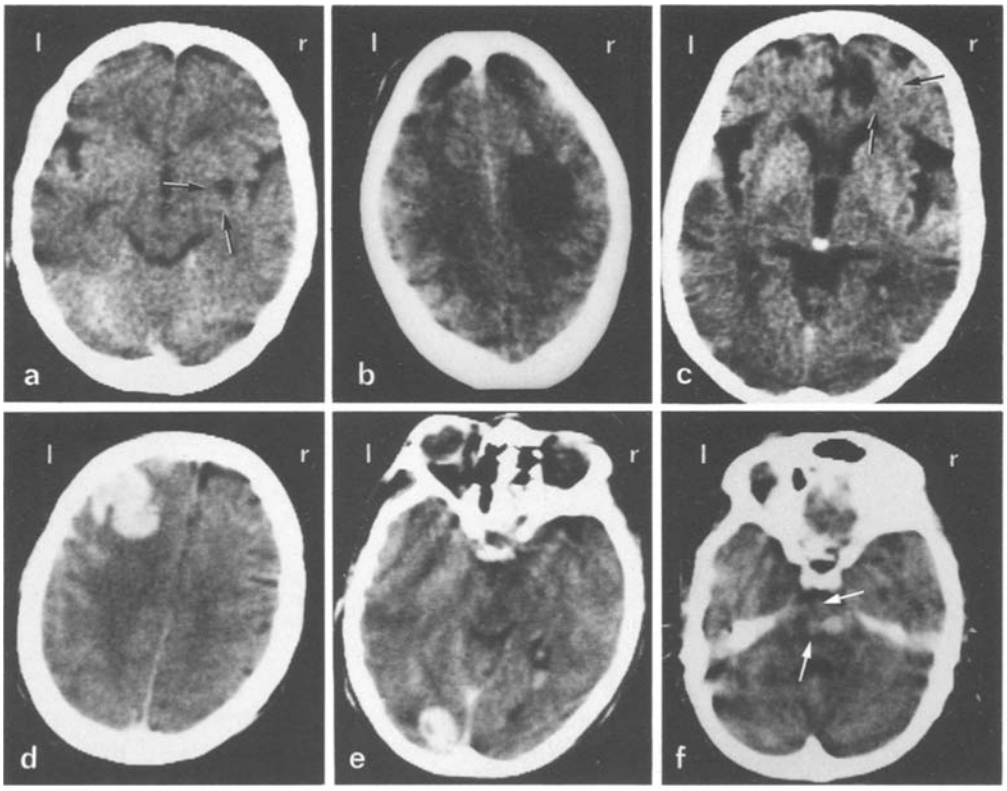

Fig. 3a–f. CCT in acute viral encephalitis (non-HSE). **a** 62-year-old woman, undetected pathogen, **b** 30-year-old woman, measles virus encephalitis, **c** 54-year-old man, undetected pathogen, **d–f** 74-year-old women, VZV encephalitis

Table 1. Etiology, clinical course, outcome

Etiology	*n*	Medium age in years	Clinical course			Outcome				
			I	II	III	Rec.	I	II	III	+
Epstein-Barr virus (EBV)	3	16	1	1	1	2	1	–	–	–
Measles virus	3	17	1	1	1	1	2	–	–	–
Varicella zoster virus (VZV)	2	70	–	–	2	–	–	1	–	1
Rubella virus	1	19	–	1	–	1	–	–	–	–
Not detected	16	32.0	1	8	7	8	5	2	–	1
Σ	25	30.9	3	11	11	12	8	3	–	2

Clinical course:
I = light course, treatment on general ward
II = moderate, treatment on intensive care unit
III = severe, artificial ventilation

Outcome:
Rec. = recovered
I = mildly handicapped
II = moderate sequelae
III = severely handicapped
+ = deceased

patients had fever some time during their illness (18/25), leukocytosis was less frequent (9/25). Two patients had typical measles exanthema, 1 typical rubella exanthema, 2 patients had segmental zoster appearing later. Initially infectious mononucleosis was diagnosed in 3 patients. One patient suffered from myocarditis during the illness, another from mild hepatitis (non-A non-B), another from pancreatitis, and in 1 patient a complicating typical infectious mononucleosis appeared later on in rubella encephalitis. During acyclovir therapy, 2 patients suffered from renal failure, 1 of them needing dialysis.

The first clinical signs of encephalitis were frequently epileptic seizures and focal neurological signs. Less frequent were acute psychosis, disturbance of consciousness, and meningism (Table 2). At the height of the illness, 12 patients displayed focal neurological signs; 7 were comatous. In 4 patients with undetected pathogen, tetraparesis ($n = 3$) and transverse myelitis ($n = 1$) appeared later on during the course of the illness on the 5th, 7th, 8th, and 19th days, respectively. Immunological mechanisms might be assumed. All but 3 patients with mild courses were treated with intensive care ($n = 22$), and 11 of them needed artificial ventilation; 2 patients died: a 62-year-old women from pulmonary embolism on the 106th day after incomplete recovery, and a 74-year-old women on the 48th day from brainstem hermorrhage and central circulatory failure.

The onset of the illness was acute in all cases. The maximum stage was reached in 12 patients within 24 h, in 10 within 7 days, and within 10 to 20 days for the 4 others. The maximum stage lasted less than 1 week in 18 persons, 1–2 weeks in 4, and more than 2 weeks in the other 3. The whole illness was the shortest in a case of rubella virus encephalitis

Table 2. Clinical findings

	n	Remarks
Prodromi		
None	5	1 case of measles encephalitis included
Fever	7	–
Headaches	6	–
Tonsillitis	5	3 cases of EBV encephalitis included
Common cold	4	–
Exanthema	5	Measles virus encephalitis $n = 2$, rubella virus $n = 1$, VZV encephalitis $n = 2$
Diarrhea	2	–
Restlessness	2	–
Vertigo, vomiting	6	–
Zoster	2	–
Tick bite	1	Tick-borne encephalitis excluded
First Clinical Sign		
Epileptic seizure	10	
Acute focal neurological sign	7	
Acute psychosis	3	
Disturbance of consciousness	2	
Meningism	3	
Neurological signs in maximum stage		
Isolated meningism/ pleocytosis[a]	8	
Epileptic seizures	13	generalized 10 focal 5
Hemiparesis	6	
Tetraparesis	6	
Aphasia	3	
Myoclonic jerks/hyperkinesia	6	
Cranial nerve impairment	3	
Vestibular syndrome	1	
Cerebellar syndrome	1	
Psychopathology		
Unchanged	2	
Disturbed consciousness	16	
Coma	7	
Psychosis	9	

[a] Besides seizures and psychopathological signs

(6 days), quite short in EBV encephalitis (medium duration 20 days), and in cases of measles encephalitis (medium duration 23 days). The disease duration was long in encephalitis with undetected pathogen (medium duration 51 days), and in 1 case of VZV encephalitis (48 days). In 1 patient, the total duration was not known.

Investigations

CSF. The CSF was examined in all patients, and was normal in 4 out of 25. The most common pathological finding was pleocytosis between 9 and 750 cells/mm^3 ($n = 20$). In 19 of these patients pleocytosis was mononuclear, and in 1 there were 50% lymphocytes and 50% polymorphonuclear cells. In 1 patient, there was isolated elevation of CSF protein without pleocytosis (Table 3).

Table 3. Investigations

	n
CSF ($n = 25$)	
Unchanged	4
Isolated pleocytosis	3
Pleocytosis and elevated protein	17
Isolated elevation of protein	1
EEG ($n = 25$)	
Unchanged	3
General slowing	21
Temporal alteration	13
Bilateral occipital changing	1
Frontal intermittent rhythmic delta activity	4
CCT ($n = 23$)	
Unchanged	15
Diffuse swelling	4
Focal changes	5
Temporal attenuation	0

EEG. The EEG was completely normal in 3 patients, in 22 it was altered. Mostly we found bilateral slowing of background activity ($n = 21$). In 4, slowing was the only pathological finding, whereas in 13 patients slowing was combined with focal temporal alteration, and in 1 slowing was combined with bilateral occipital delta activity. Three patients showed slowing and frontal intermittent rhythmic delta activity (FIRDA), and 1 more isolated FIRDA with no slowing. The temporal alterations correlated with hemiparesis, aphasia, or focal fits in 10 patients. Focal alteration was homolateral to hemiparesis in 1 patient, and in 2 instances no clinical finding correlated with the temporal focus. The degree of slowing did not significantly correlate with the degree of impairment of consciousness (Table 3).

CCT. In 23 patients CCT was performed, it was normal in 15, although 6 of them were severely ill needing artificial ventilation. General swelling was the only finding in 3 patients, 1 more showed swelling and a localized attenuation in the right temporal lobe. In 3 patients we found a single localized alteration (twice central, once frontal) without swelling, and in another patient, there were three localized findings at once (frontal right, occipital left, pons). In 6 instances, normal or changed CCT was not to be related to clinical findings.

Antiviral Treatment

Antiviral treatment was performed in 12 patients because of assumed HSE. In 1983 2 patients received adenine arabinoside. From 1984 on, 10 persons were treated with acyclovir. Additionally, 1 patient received beta-interferon. During acyclovir therapy, 2 patients developed reversible renal failure, 1 of them needing hemodialysis.

Outcome

The outcome was good in 20 patients: 12 recovered completely, 8 left hospital with mild sequelae, 1 of them had only moderately slowed EEG showing FIRDA; 3 more patients were moderately handicapped. There was no patient with severe sequelae like apallic syndrome. Two patients died, one

from brainstem hemorrhage and another from pulmonary embolism.

Discussion

In every case of acute encephalitis, the possibility of herpes simplex etiology has to be considered, as with this pathogen antiviral treatment will be effective if started early. Is clinical diagnosis possible during the first days of infection before serological results are available?

Clinical Findings

The syndrome of acute viral encephalitis is characterized by rapid onset and progression of diffuse, localized, or multifocal cerebral involvement. Clinical courses vary from a mild illness of short duration to a fulminant disorder leading to coma and death [18, 30]. In our series, only 3 courses were mild and patients were treated on the general ward. The other 22 courses were severe and 11 of the patients had to be intubated and artificially ventilated (Table 1).

Non-specific prodromal symptoms, indicating viral infection, are common [13, 17] and were reported by 20 patients of our series. In a few cases, concomitant or preceding general findings may indicate the etiological agent. In 8 patients (of 9 with diagnosed pathogen) etiology was suspected: because of features of infectious mononucleosis ($n = 3$), typical segmental, later generalized zoster ($n = 2$), rubella exanthema ($n = 1$), and measles exanthema ($n = 2$). In 6 of them, serological results sustained the clinical diagnosis; in the remaining 2, no other virus was found. On the other hand, absent clinical signs do not exclude these pathogens. Measles virus encephalitis may occur without exanthema, as we have seen in the case of a 19-year-old girl with serologically proved measles virus encephalitis. VZV encephalitis may occur without exanthema, too [21]; and EBV encephalitis may precede the clinical signs of infectious mononucleosis [31].

Clinical features of encephalitis are: fever, impaired consciousness, psychosis, and neurological findings like meningism, generalized and focal epileptic seizures, hemi- and tetraparesis, aphasia, cranial nerve impairment. Frequently, encephalitis begins with an epileptic fit or with acute onset of focal neurological deficit. For the diagnosis of viral encephalitis, other diseases imitating the syndrome have to be ruled out: bacterial infection like pyogenic brain abscess, tuberculous meningitis, fungal and parasitic infection, brain tumor, cerebral infarction and hemorrhage, acute multiple sclerosis. In general, the brain as a whole is affected. In particular generalized fits and alteration of consciousness reflect total involvement. But frequently, certain areas are predominantly involved. Cases of strictly isolated brainstem or cerebellar affection may occur [27], but were excluded of our series. In our group of 25 patients, 20 showed predominant involvement of the hemispheres, 3 combined affection of brainstem and hemispheres. In 2 more patients, the cerebellum and brainstem were predominantly involved. But in both slowed EEG and epileptic seizures showed that the whole brain was affected.

The clinical findings were heterogenous in our group, as described by others [13, 28, 30, 36]. The majority of patients displayed various neurological signs, seizures and impairment of consciousness, and/or psychosis. In 13 patients focal neurological signs, often found in HSE were observed: aphasia ($n = 3$), focal epileptic seizures ($n = 5$), hemiparesis ($n = 6$). The clinical findings or severeness of the course did not enable distinction between the different etiological agents – as far as they had been identified.

The signs and symptoms of the patients in our series did not differ from those described by Sköldenberg et al. [28] and Whitley et al. [36] in patients with HSE. These authors did not find significant differences in clinical signs between the patients with HSE and those in whom HSE had been ruled out. It may be assumed that in both studies most patients of the non-HSE/biopsy-negative groups suffered from acute viral encephalitis. Indeed, outcome is much better in patients with non-HSE described here, compaired to patients with HSE. Discrimination between HSE and non-HSE seems impossible by clinical features during the early stage of the illness.

Investigations

For the diagnosis of viral encephalitis, history and clinical features are not sufficient and other findings are necessary.

CSF. The presence of mononuclear pleocytosis and elevated CSF protein is an important diagnostic feature in viral encephalitis [13, 30]. In our series, pleocytosis between 9 and 750 cells/mm^3 was present in 20 patients (Table 3). It was mononuclear in 19, 1 patient with VZV encephalitis showed mixed a lymphocytic-polymorphonuclear population. Besides a raised blood cell count in CSF, protein was elevated in 17 persons. In 1 case there was elevated protein without pleocytosis. In 4 patients however, CSF was unchanged, a finding not uncommon in encephalitis [13, 18, 30]. Normal CSF findings do not exclude the diagnosis of viral encephalitis. In HSE, CSF with white cells and protein is not pathognomonic, and even in a few cases of HSE, CSF can be completely normal [3, 26, 28, 36]. In some cases, polymorphonuclear cells may dominate initially [3], a finding that is not exclusive for HSE, but which is also found in very early stages of viral encephalitis and viral meningitis. CSF investigations for white blood cells and protein are of no help in discriminating HSE from non-HSE at the beginning of the disease.

EEG. The EEG is of considerable value in diagnosing viral encephalitis and in estimating its acuity and course. General slowing is as common a finding as a non-specific one [13, 14, 20, 22, 30], and was observed in 21 of 25 patients, with FIRDA seen in 4 (Table 3). The EEG was normal in 4 other patients, a finding not contradictory to the diagnosis of viral encephalitis. Focal findings are frequent, too. In 7 patients, temporal focus was one of the findings leading to the suspicion of HSE (Table 3).

In HSE, besides disorganization of background activity, EEG may show characteristic unilateral or bilateral periodic complexes, strongly indicative for HSE. They may appear as early as on the 2nd day [32], but mostly are observed between the 4th and 8th days [11, 12, 16]. There are however some problems in diagnosing HSE by EEG: findings indicating HSE are found only in about 65% of all cases of HSE [36], and if they are absent, HSE is not excluded. In the early phase of HSE, focal findings are mostly non-specific [12], and focal periodic activity may appear as late as on the 24th or 30th day [5, 11, 15, 36]. But periodic complexes are not specific for HSE. In one patient with VZV encephalitis we observed bilat-

eral periodic activity (Fig. 1), and in a large number of inflammatory and non-inflammatory diseases of the brain, periodic complexes may appear [6, 10, 20, 23, 25].

To summarize, EEG is indicative of HSE, if there is localized periodic activity, but other diseases of the brain are possible, too. If EEG lacks this finding, HSE is not excluded.

CCT. In our experience, CCT does not reflect the patient's clinical condition in acute viral encephalitis (non-HSE): CCT was normal in 15 out of 23 patients, 6 of them were severely ill. In 6 instances, normal or changed CCT was contradictory to clinical findings (Table 3). In HSE, the most characteristic finding is an unilateral low absorption lesion in the medial temporal and/or insula cortex. But that is seen only in 50% to 55% of all patients at some time during HSE [28]. In 5 of our patients with non-HSE, localized lesions could have been compatible with the diagnosis of HSE (Fig. 3). In encephalitis, CCT, if changed, will not discriminate sufficiently between HSE and non-HSE. Perhaps new neurodiagnostic techniques will provide more and earlier information.

Serological Results. Viral etiology was assumed in all patients because of clinical findings and investigations described. In all 25 cases, herpes simplex etiology was excluded by serological means. In 7 cases, the pathogen was revealed serologically, but results were mostly available too late for the decision on antiviral treatment. As in other series [9, 13, 18, 30], no viruses were found in a large percentage (16 of 25 patients). The predominant aim of serological investigations is to diagnose HSE where the treatment of choice is acyclovir [28, 37, 38]. There are reports that VZV encephalitis can also be treated with vidarabine and acyclovir successfully [4, 33]. But serological evidence is not available in the early phase of the illness, when the decision on antiviral treatment or not is necessary [1, 13, 28, 30]. In HSE, results are delayed in general to the tertiary phase after the 7th day up to the 10th day after the onset of neurological symptoms. Negative serological evidence indeed does not rule out HSE absolutely nor does unchanged brain biopsy [29, 36, 37]. Therefore we must admit that our series might contain patients with serologically negative HSE.

Brain Biopsy. According to Felgenhauer and Ackermann [7], brain biopsy was not done even when HSE was suspected, because of unnecessary risk, the possibility of false negative results, and because 40% to 60% of patients have diseases other than HSE. Biopsy is to be considered only in a few cases: when there is a cryptic brain tumor which first displays cerebral signs with the advent of an unrelated systemic infection, and when vasculitis starts in the brain or is restricted to the brain [2]. For the decision on acyclovir therapy, we think biopsy is dispensible.

Suspected HSE

Herpes simplex virus encephalitis is suspected in encephalopathy with acute onset, high fever, focal neurological findings like Wernicke's aphasia, seizures, hemiparesis, impairment of consciousness, focal EEG findings. Mostly the mediotemporal region of the brain is predominantly affected, but sometimes, other predilections may occur [27]. In 12 patients, nearly half of our patients with non-HSE, herpes simplex etiology was suspected or at least not ruled out. Suspicion was raised because of focal neurological signs ($n = 8$), focal EEG changings ($n = 7$), and CCT findings ($n = 5$). In 1 patient there was no focal finding, but antiviral therapy was used because of acuity and early coma. Antiviral therapy was administered in 2 patients using vidarabine in 1983, from 1984 on we used acyclovir in 10 patients. It is evident that our inclination to commence treatment has increased since the introduction of acyclovir, as it is said to be less toxic. In our series, 2 patients recovered from renal failure during acyclovir therapy, but one of them needed dialysis. Except for 1 case, beta-interferon therapy was not used. In spite of some optimistic case reports [24], efficacy in encephalitis has not been proved, and side effects from this form of treatment are severe.

Between 1979 and 1986, when the 25 patients with non-HSE were treated, there were 6 patients with serologically proven HSE in our departments (not described in this paper). Their courses were severe without exception, and all were diagnosed early on. But mild forms of HSE have been described, and we do not know how many mild courses may exist and are never diagnosed [8, 19], especially taking into account that serological investigations might be negative in a few cases.

In our experience with 25 cases of acute viral encephalitis not caused by herpes virus and 6 cases of HSE, 18 times HSE was suspected by clinical features, CSF investigation, EEG, and CCT. But HSE was proved serologically only in 6 cases. Indeed no patient who had HSE was missed or supposed to have another form of encephalitis. On the other hand only one-third of patients supposed to suffer from HSE finally had it, two-third suffered from other forms of viral encephalitis. In a much larger series, Whitley et al. [36] described that in only 83% of all patients with HSE had the diagnosis been suspected by clinical techniques except brain biopsy and serological investigation (sensitivity 83%). Of patients with suspected HSE, 64% proved positive (specifity 64%).

We think that with an antiviral treatment of moderate toxicity, bad specificity is not fatal for the patient, but he may profit from high sensitivity.

Resumée

In acute viral encephalitis not caused by HSV, clinical features are heterogenous – as they are in HSE. In non-HSE, all symptoms and signs may occur that are said to be typical of HSE: impairment of consciousness, focal and generalized seizures, focal neurological signs like hemiparesis and aphasia. CSF findings are nonspecific. In EEG, besides disorganisation of background activity, there may be focal temporal findings, and even in a few cases focal periodic complexes. In CCT, circumscribed low absorption lesions are also seen in non-HSE. Therefore history, signs, and results of investigations do not provide enough evidence to exclude HSE in the early phase of the disease. Considering all this, we conclude that from a clinical point of view, a term like non-HSE does not respresent a clinical entity and so is not justified. In our experience, only in a certain number of cases, can the etiological agent be assumed because of associated clinical signs like tonsillitis or exanthema. Serological diagnosis of the etiological agent may be negative. If the serological investigation is positive, results are not available during the early phase of the acute illness.

Therefore, in all cases of severe encephalitis with suspected herpes etiology, antiviral treatment should be started early. If HSE is excluded, the treatment may then be discontinued.

Acknowledgement. The authors thank Mrs. E. Tass, Cologne, and Mrs. S. Löffler for technical assistance.

References

1. Barocka A (1980) Akute virale Meningoencephalitiden. Neurol Psychiatr 6:300–302
2. Booss J, Esiri MM (1986) Viral encephalitis. Blackwell, Oxford
3. Cheesbrough JS, Finch RG, Ward MJ (1985) A case of herpes zoster associated encephalitis with rapid response to acyclovir. Postgrad Med J 61:145–146
4. Christe W, Kölmel HW (1985) Die Behandlung des Zoster mit Aciclovir. Klinikarzt 14:1451–1452
5. Elian M (1975) Herpes simplex encephalitis, prognosis and long-term follow-up. Arch Neurol 32:39–43
6. Felgenhauer K (1982) Differentiation of the humoral immune response in inflammatory diseases of the central nervous system. J Neurol 228:223–237
7. Felgenhauer K, Ackermann R (1985) Early diagnosis and treatment of herpes simplex encephalitis. J Neurol 232:123–124
8. Finke E, Ackermann R, Felgenhauer K (1982) Symptomarme Herpes-simplex-Enzephalitis. Dtsch Med Wochenschr 107:1020–1023
9. Flügel KA (1983) Prognose der Enzephalitiden und Meningitiden. Lebensversicherungsmedizin VII:161–165
10. Greenberg DA, Weinkle DJ, Aminoff MJ (1982) Periodic EEG complexes in infectious mononucleosis encephalitis. J Neurol Neurosurg Psychiatry 45:648–651
11. Griffith JF, Ch'ien LT (1983) Herpes simplex virus encephalitis. Med Clin North Am 67:991–1008
12. Hacke W, Zeumer H (1986) Herpes-simplex-Enzephalitis. Dtsch Med Wochenschr 111:23–25
13. Hilgenstock F (1975) Zur Klinik der akuten Virusenzephalitiden. Fortschr Neurol Psychiatr 43:81–97
14. Ikemura Y, Akena H, Okada A (1984) Postinfektiöse Röteln-Encephalitis. Nervenarzt 55:83–85
15. Illis LJ, Taylor FM (1972) The electroencephalogram in herpes simplex encephalitis. Lancet I:718–722
16. Kaschka WP, Kaschka-Dierich CH (1984) Herpes-simplex-Enzephalitis. Dtsch Med Wochenschr 109:1000–1004
17. Kaschka WP, Kaschka-Dierich CH (1985) Diagnostische Möglichkeiten bei viralen Meningoencephalitiden. Therapiewoche 35:573–581
18. Kennard C, Swash M (1981) Acute viral encephalitis its diagnosis and outcome. Brain 104:129–148
19. Klapper PE, Cleator GM, Logson M (1984) Mild forms of herpes encephalitis. J Neurol Neurosurg Pschiatry 47:1247–1250
20. Lethinen I, Halonen JP (1984) EEG findings in tick-bourne encephalitis. J Neurol Neurosurg Psychiatry 47:500–504
21. Möller A, Ackermann R, Felgenhauer K, Ulm H (1982) Zoster-Enzephalitis ohne Exanthem. Dtsch Med Wochenschr 107:882–825
22. Poburski R, Malin JP (1984) Rötelnencephalitis bei einer Erwachsenen mit ungewöhnlichem Verlauf. Dtsch Med Wochenschr 109:1796–1800
23. Pourmand R, Marchand ON, Cook JA (1984) Perodic lateralized EEG abnormality in a case of Neuro-Bechet syndrome. Clinical Electroencephalogr 15:122–124
24. Prange H, Wissmann H, Ritter G (1982) Schwere Virusencephalitiden: Therapie mit Interferon. In: Mertens HG, Dommasch D (eds) Enzephalitis. Perimed, Erlangen
25. Schear HE (1984) Periodic EEG activity. Clin Electroencephalogr 15:32–39
26. Schlageter N, Jubelt B, Vick NA (1984) Herpes simplex encephalitis without CSF leukocytosis. Arch Neurol 41:1007–1008
27. Schorre W (1979) Die Infektionskrankheiten des Nervensystems. Urban und Schwarzenberg, München
28. Sköldenberg B, Alestig K, Burman L, Forkman A, Lövgren K, Norrby R, Hiernstedt G, Forsgren M, Bergström T, Dahlqvist E, Fryden A, Norlin K, Olding-Stenkvist E, Uhnoo J, de Vahl K Acyclovir versus vidarabine in herpes simplex encephalitis. Lancet II:707–711
29. Sköldenberg B, Forsgren M, Alestig K, Fryden A, Norlin K, Norby R, Olding-Stenkvist E (1985) Design of therapeutic studies in herpes simplex encephalitis. Letter to the editor. Lancet I:285
30. Swash M (1984) Management of acute viral encephalitis. Br J Hosp Med 25: 250–255
31. Todman DH (1983) Encephalitis in infectious mononucleosis. Clin Exp Neurology 19:81–86
32. Upton A, Gumpert J (1970) Electroencephalography in diagnosis of herpes simplex encephalitis. Lancet I:650–652
33. Wees SJ, Madhavan T (1980) Herpes zoster encephalitis: successful therapy with vidarabine. Henry Ford Hosp Med J 28:67–70
34. Whitley RJ, Soong SJ, Dolin R, Galasso GJ, Chien LT, Alford CA, and the NIAID Collaborative Antiviral Study Group (1977) Adenine arabinoside therapy of biopsy-proved herpes simplex encephalitis. N Engl J Med 297:289–294
35. Whitley RJ, Soong SJ, Hirsch MS, Karchmer AW, Dolin R, Galasso G, Dunnick JK, Charles AA, and the NIAID Collaborative Antiviral Study Group (1981) Herpes simplex encephalitis. Vidarabine therapy and diagnostic problems. N Engl J Med 304:313–318
36. Whitley RJ, Soong SJ, Linneman C, Lin C, Pazin G, Alford CA (1982) Herpes-simplex-encephalitis. JAMA 247:317–320
37. Whitley RJ, Soong SJ, Alford CA, Hirsch MS, Schooley R, Oxman MN, Connor JD, Betts R, Dolin R, Reichman RC (1985) Design of therapeutic studies in herpes simplex encephalitis. Lancet I:284–285
38. Whitley RJ, Alford CA, Hirsch MS, Schooley RT, Luby JP, Aoki FY, Hanley D, Nahmias AJ, Soong SJ, and the NIAID Collaborative Antiviral Study Group (1986) Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med 314:144–149

Received March 27, 1987