Case Report

Wien Klin Wochenschr (2005) 117/13–14: 495–499
DOI 10.1007/s00508-005-0324-0

WIENER KLINISCHE WOCHENSCHRIFT
The Middle European Journal of Medicine
Printed in Austria

Herpes simplex virus infection limited to the brainstem

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Received October 11, 2004, accepted after revision December 27, 2004

Hirnstamm-Meningoenzephalitis durch Infektion mit Herpes simplex

Zusammenfassung. Die fokale Menigoenzephalitis wird zumeist durch eine Virusinfektion mit Herpes simplex hervorgerufen. Typischerweise sind Temporal- und Frontallappen befallen. Unbehandelt liegt die Mortalität bei 70%. In seltenen Fällen gibt es aber auch auf den Hirnstamm begrenzte Infektionen. Die PCR-Analyse des Liquors gilt als Goldstandard der Herpes simplex Enzephalitis.

Ein 46-jähriger Mann wurde wegen seit 3 Tagen anhaltender Kopfschmerzen mit Fieber bis 39 °C in das Spital eingeliefert. Die Liquoranalyse war mit einer aseptischen Meningitis kompatibel. Am dritten Tag des Spitalsaufenthaltes klagte der Patient über Doppelbilder, wurde zusätzlich verwirrt; es entwickelte sich eine Blicklähmung. Die Situation verschlechterte sich rasch vom Stupor zum Koma. Eine zweite Liquoranalyse zeigte einen niedrigen Glukosespiegel (1,2 mmol/l); Cefotaxim und Ampicillin wurden empirisch verabreicht. Bakterien- und Pilz-Kulturen aus dem Liquor waren durchwegs negativ. Es konnten Serum-IgG-Antikörper gegen Herpes simplex Virus Typ 1 ohne Nachweis spezifischer intrathekaler Antikörper-Synthese nachgewiesen werden. Die am siebenten Tag der Erkrankung durchgeführte PCR des Liquors war negativ für Herpes simplex Virus Typ 1 und 2. Die Computertomographie des Gehirns zeigte keinen abnormen Befund. Trotz intensivmedizinischer Maßnahmen und massiver antibiotischer Therapie verschlechterte sich der Zustand des Patienten zusehends. Der Patient verstarb schließlich am 11. Tag nach Aufnahme im Spital. Bei der Obduktion wurde eine hämorrhagische und nekrotische Hirnstamm-Meningoenzephalitis gefunden. Durch *In-situ*-Hybridisierung konnte eine Infektion mit Herpes simplex Virus Typ 1 bestätigt werden.

Die unbehandelte Herpes simplex Virus-Enzephalitis hat eine Mortalität von 70%. Die atypische Lokalisation der Infektion (Hirnstamm statt Temporal- oder Frontallappen), sowie die atypische klinische Manifestation können gemeinsam mit negativen radiologischen und mikrobiologischen Testergebnissen die Ursache für eine falsche Diagnose und Behandlung sein. Viele Autoren fordern daher bei allen Patienten mit ungeklärter Enzephalopathie eine empirsche Verabreichung von Acyclovir, da eine Verzögerung der Therapie deletär für den Ausgang der Erkrankung sein kann.

Summary. Focal meningoencephalitis is commonly caused by Herpes simplex virus infection, which typically affects temporal or frontal lobes, and carries a mortality rate of 70% if untreated. On rare occasions, however, the infection is restricted to the brain stem. Polymerase chain reaction analysis of cerebrospinal fluid is the gold standard for the diagnosis of herpes simplex encephalitis.

A 46-year-old male was admitted to the hospital with a three day history of headache and fever up to 39 °C. Cerebrospinal fluid findings were in accordance with aseptic meningitis. On the third hospital day, the patient presented with double vision followed by confusion, and gaze paresis developed. The condition rapidly progressed from stupor to coma. A second examination of cerebrospinal fluid revealed a low glucose level (1.2 mmol/l) and cefotaxime with ampicillin were started empirically. All cerebrospinal fluid specimens were negative for bacteria and fungi. Serum IgG antibodies for herpes simplex virus type 1 were found with no intrathecal specific antibody synthesis. A polymerase chain reaction analysis of cerebrospinal fluid sample performed on the seventh day of his illness was negative for herpes simplex virus 1 and 2. A computer tomography scan of the brain did not show any abnormality. Despite antimicrobial and supportive intensive care, the condition of the patient progressively deteriorated and he died on the 11th day after admission. An autopsy revealed hemorrhagic and necrotic brainstem meningoencephalitis, and herpes simplex virus type 1 infection was confirmed by hybridization *in situ*.

Herpes simplex virus encephalitis carries a mortality rate of 70% if untreated. The atypical location of the

infection, as well as an atypical clinical manifestation with negative radiological and microbiological tests could be the reasons for false diagnoses and mistreatment. Many authors advocate the use of empiric acyclovir in any patients with unexplained encephalopathy, since delay in treatment may greatly affect outcome.

We describe a patient who died due to a herpes simplex virus 1 encephalitis affecting the brainstem, where nucleic acids were found post-mortem by in situ hybridization. On rare occasions, the herpes simplex viral infection as well as clinical manifestations and pathological changes are restricted solely to the brainstem.

Key words: Herpes simplex encephalitis, brainstem, diagnosis.

Introduction

Herpes simplex virus (HSV) infections of the central nervous system (CNS) are among the most severe of all viral infections of the human. Herpes simplex encephalitis (HSE) is estimated to occur in approximately 1/250,000 to 1/500,000 people per year. The family of HSV are ubiquitous human pathogens. Infection is non-seasonal, affects both sexes equally, and can occur at any age. The seropositivity rate for HSV 1 among the adult population is 60–100%. The pathologic hallmark of HSE is hemorrhagic necroses in the medial part of the temporal lobes. In addition, adjacent areas such as the orbital surface of the frontal lobe and cingulate gyrus may be involved.

Patients usually present with fever, mental status changes, sometimes with seizures or other focal neurological signs. Early in the disease, symptoms vary in intensity but then tend to progress rapidly. However, the presentation can also be unremarkable and thus a high index of suspicion is required. Early in the disease a polymerase chain reaction (PCR) analysis of cerebrospinal fluid (CSF) is the most useful diagnostic approach. In patients with biopsy-proven HSE the sensitivity and specificity of PCR for the detection of HSV 1 have been documented as 91% and 92%, respectively [1]. There are some reports of HSE patients in whom PCR testing of CSF for HSV 1 early in the course of infection was negative, while repeated testing of samples obtained a few days later showed positive results [2].

Many infectious and non-infectious diseases can mimic HSE. Biopsy with subsequent hybridization or PCR testing of a bioptic specimen is still the most reliable diagnostic method, while biochemical CSF results, electroencephalogram, computer tomography (CT) and magnetic resonance imaging (MRI) are non-specific. The diagnosis of other treatable causes of encephalitis provides the most compelling support for brain biopsy of patients with a focal encephalopathic process [3]. Mortality in untreated HSE reaches 70% and can be reduced to 20% by the use of acyclovir. Despite adequate treatment, neurological sequelae are still common [1]. On rare occasions HSV 1 infections, as well as the clinical manifestations and pathological changes, are restricted to the brainstem. Diagnosis is usually based on clinical findings, rising titers of anti-viral antibodies and PCR analysis of CSF samples. Here, we report the case of a patient with atypical localization of HSV 1 infection whose classic microbiological tests were negative for HSV.

Case report

A 46-year-old, previously healthy male, suddenly experienced nausea and fever up to 39 °C. On the first day, his general practitioner prescribed paracetamol and amoxicillin, which had no clinical effect. The patient was admitted to the hospital on the fourth day as headache, sore throat and coughing further handicapped him. He denied vomiting, diarrhea, recent respiratory infection, rash, neck stiffness, animal exposure, and regular medication intake, while confirming a regular alcohol intake. On admission he was conscious, oriented in time and space, without neck stiffness or palpable lymph nodes, but he had a high body temperature (39.6 °C). Initial CSF analysis was in accordance with aseptic meningitis (Table 1). Serum serology testing for tick-borne encephalitis (TBE) virus, *Leptospirosis* spp., *Listeria monocytogenes* and *Borrelia burgdorferi* were negative. On the third hospital day he complained of double

Table 1. Summary of laboratory tests and treatment events

Day of illness	CSF						Serum	
	Cell count (cells/ml)		Protein level (g/l)	Glucose (mmol/l) (CSF/serum)	HSV 1/2 PCR	HSV 1 IgM/IgG	HSV 1 IgM/IgG	Treatment event
	WBC RBC	(PMN/L)						
4 th	465 0	(302/163)	0.84	2.9 (0.40)	ND	ND	ND	
7 th	501 1261	(213/288)	2.82	1.2 (0.24)	Neg	Neg/Neg	Neg/Pos	Cefotaxime Ampicillin
10 th	181 101	(11/165)	2.03	3.2 (0.34)	ND	Neg/Neg	Neg/Pos	Antituberculous agents
12 th	592 2219	(80/464)	2.59	4.7 (0.50)	ND	ND	ND	

CSF cerebrospinal fluid; *WBC* white blood cell; *PMN* polymorphonuclear cell; *L* lymphocytes; *RBC* red blood cell; *HSV* herpes simplex virus; *PCR* polymerase chain reaction; ND not done.

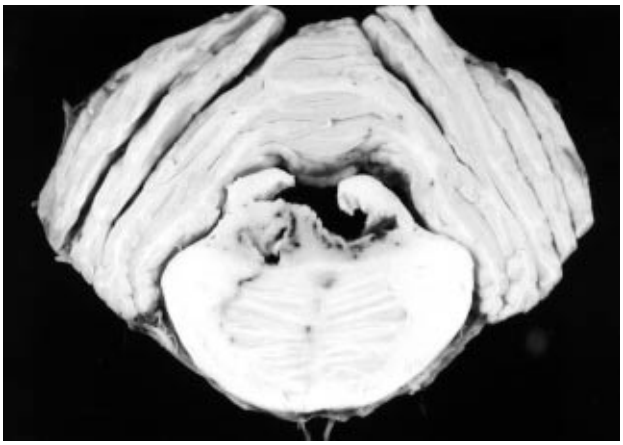

Fig. 1. Tegmentum of the pons is focally necrotic and hemorrhagic

vision and in the next 12 hours he became confused, had difficulties walking, and gaze paresis developed. On the next day his mental status was unchanged, but neck stiffness, vertical nystagmus, convergent strabismus, and peripheral right side facial palsy were present. CSF analysis indicated the possibility of bacterial meningitis (Table 1) and antibiotic treatment with cefotaxime and ampicillin was started. On the evening of the sixth hospital day his mental condition had progressively deteriorated, he became comatose, with no response to deep pain. He went into respiratory failure because of hypoventilation and tracheal intubation with mechanical ventilation was performed.

A CT brain scan on admission and a week later were unremarkable, as were both biochemical and hematological tests. All CSF specimens were negative for bacteria and fungi. Repeated testing for the presence of specific IgM and IgG (enzyme-linked immunoassay) antibodies to *B. burgdorferi*, TBE virus and *Mycoplasma pneumoniae* in serum, as well as for specific IgM and IgG antibodies to *B. burgdorferi* and HSV 1 in CSF were negative, while we found elevated serum IgG titers for HSV 1 and *Chlamydia pneumoniae*. However, no intrathecal HSV 1 antibody synthesis was demonstrated. Breakdown of the blood brain barrier was demonstrated according to the albumin index (0.0323). A CSF sample obtained during the second lumbar puncture was negative for HSV 1/2 by PCR performed at the state laboratory (Real Art HSV1/2 PCR Kit, Artus, Hamburg Germany).

On the basis of clinical manifestations, negative CT brain scan, negative CSF microbiological tests, low CSF glucose concentration and increase of CSF protein level, antituberculous therapy was added. In spite of antimicrobial therapy and supportive intensive care treatment the patient further deteriorated and developed hemodynamic instability, which led to his death on the 11th day after admission.

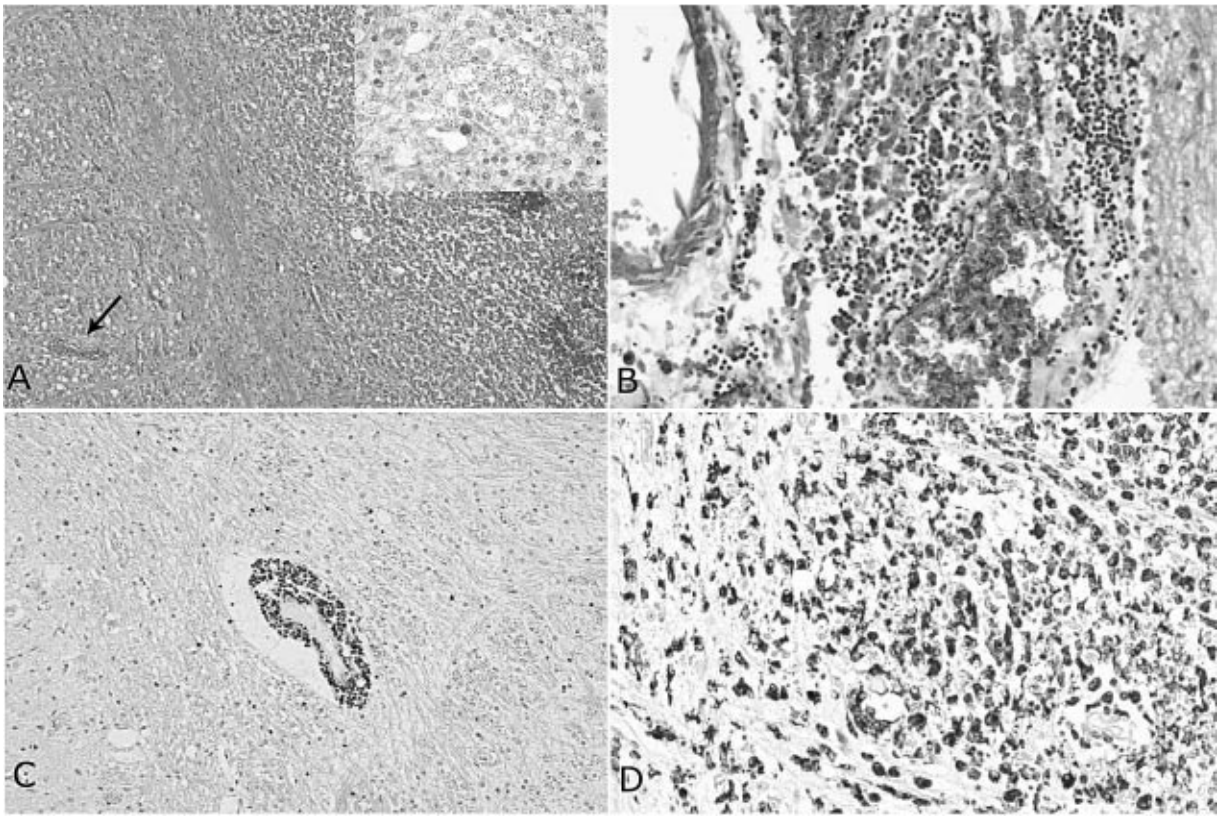

Fig. 2. Microscopic features of the brain stem encephalitis. **A** Perivascular mononuclear cell cuffing (arrow), focal hemorrhage and brain stem necrosis. Inset: the single HSV intranuclear inclusion detected by *in situ* hybridization in an endothelial cell of the brainstem vessel. **B** Numerous macrophages in the necrotic foci. **C** Perivascular cells are mostly T lymphocytes, labeled with anti-CD3 monoclonal antibodies. Rare labeled T lymphocytes are scattered in the brainstem tissue, as well. **D** Numerous macrophages labeled with anti-CD68 in the necrotic area

The autopsy revealed hemorrhagic and necrotic meningoencephalitis restricted to the subependymal tissue of the brainstem (Fig. 1). HSV 1 was detected in the affected brain tissue by hybridization *in situ* (Fig. 2).

Discussion

The clinical hallmark of HSE is the acute onset of fever associated with focal neurological symptoms. Unfortunately, many viral, bacterial and fungal CNS infections as well as non-infectious CNS diseases can mimic HSE. On the other hand, when the clinical presentation and CSF findings are atypical, another diagnosis might be assumed and delay in treatment may greatly affect outcome [1].

Whitley et al. confirmed HSE in only 193 out of 432 (45%) patients who underwent brain biopsy for presumptive HSV CNS infection. Further evaluation revealed a treatable illness such as brain abscess, tuberculosis, cryptococcal infection, and brain tumor in 38 out of 239 (16%) of the remaining patients [3]. The clinical findings of HSE are not sufficiently discriminating to allow a reliable diagnosis even in patients with a standard clinical presentation.

Cranial nerve defects are found in a minority of the patients with HSE. In the study published by Whitley et al. only 32% of patients with biopsy proven HSE had clinical signs associated with cranial nerve involvement [4]. When HSV infection is limited to the brainstem, cranial nerves are usually affected, as we found in our case. However, HSV encephalitis restricted to brainstem is a rare manifestation of HSV CNS infection.

In previous reports on brainstem HSE, the diagnosis was usually based on serum and CSF viral antibody testing or by using the PCR amplification method [5–7]. There are only few reports in which inflammatory response in the brainstem of patients with HSE was confirmed by histopathology and *in situ* hybridization postmortem. However, in these reports pathological changes indicating HSE were not limited to the brain stem, but were found also in the temporal lobe, frontal cortex, cingulate gyrus, occipital lobe or cerebellum [8, 9]. The circumscribed nature of HSV infection limited to the brain stem has been histologically documented in only two cases [10, 11].

Initial examination of the CSF is nearly always abnormal, but laboratory results are non-specific, and differentiation of HSE from other forms of viral encephalitis, as well as from other focal infections and non-infectious processes, is difficult. Patients with a biopsy-proven disease have CSF findings similar to those found in patients with other viral infections of the CNS. Whitley et al. found initial CSF pleocytosis in 97% of 98 patients with biopsy-proven HSE. CSF protein concentration was normal in 18 out of 98 (18%), and CSF red blood cells were present in 84% of HSE patients. In only five of them was hypoglycorrhea found [4]. A low CSF glucose level and a higher CSF protein level as we found in our case, on the other hand, indicate bacterial meningitis. Spanos et al. found a CSF-blood glucose ratio below 0.25 in only 1 of 205 patients (0.5%) with acute viral meningitis, but in 51 of 117 (44%) patients with acute bacterial meningitis (ABM). A CSF protein value greater than 2.2 g/l was the next indicator of ABM. Half of the patients with ABM had CSF greater than 1.72 g/l, and only two patients with acute viral meningitis (1%) had levels in this range [12].

A CT brain scan initially shows low-density areas, with a mass effect localized to the temporal lobe, which can progress to radiolucent and/or hemorrhagic lesions. In the first few days of the disease and in atypical HSE locations, a CT brain scan can be normal, as we found in our case. MRI is superior to CT, and can detect typical lesions earlier.

PCR detection of HSV DNA in the CSF has become the diagnostic procedure of choice. However, we should be aware that when a CSF sample has been obtained early in the course of the disease, PCR results could be negative [2]. In our patient the PCR analysis of the CSF sample was performed on the seventh day after his illness had begun, and the negative result could not be a consequence of a test performed too early. The negative PCR result that was found in the case we report was possibly the result of inhibitors.

In atypical clinical presentations of HSE with nonspecific CT brain scan or MRI, with negative microbiological tests, and in situations when bacterial meningitis is predicted by CSF analysis, the correct diagnosis could be missed. So, many authors advocate the use of empiric intravenous acyclovir (10 mg/kg every eight hours) in any patients with fever, encephalopathy, and/or focal neurological signs, since delay in treatment may greatly affect outcome, and the drug is relatively safe [1, 13]. When diagnosis of HSE is established, the administration of acyclovir should be continued for a period of 10 to 14 days.

This report underlines the importance of considering HSV infection in the differential diagnosis of all patients with unexplained encephalopathy with clinical manifestations of brain stem dysfunctions, even with CSF findings indicating bacterial infection.

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