

Late sequels of Herpes simplex encephalitis

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ABSTRACT - Herpes simplex virus encephalitis (HSVE) is a serious disease associated with high morbidity and mortality. In the last two decades, considerable progress has been made in the diagnosis and treatment of the disease; however, the risk of HSVE and its complications remains high. The predilection sites for the infection are temporal lobes, less frequently frontal lobes. The most common late complications are epilepsy of the complex partial seizure type, behavioral changes, and cognitive impairment. While epilepsy can be successfully treated with good therapeutic outcome, cognitive impairment is permanent in a high proportion of individuals having sustained HSV1 encephalitis. Polymerase chain reaction of viral DNA is a reliable diagnostic assay, while treatment includes acyclovir therapy along with other symptomatic therapeutic procedures. A female patient with late stage HSVE is described in order to illustrate the severe memory and behavioral impairment consequential to HSV infection, to report on diagnostic work-up results, and to point to the role of early diagnosis and treatment of this severe disease.

Key words: herpes virus, encephalitis, cognitive impairment, cognitive function testing, single-photon emission computed tomography

INTRODUCTION

Herpesvirus type 1 (HSV1) belongs to the group of herpesviruses, which also includes varicella-zoster virus and cytomegalovirus (1,2). Animal models used in the studies of the disease pathophysiology suggest that the virus enters the central nervous system *via* peripheral nerves. Temporal lobes are the most common site of infection; extratemporal pathology is found in about 15% of patients, whereas temporal and extratemporal pathology is simultaneously present in about 55% of patients. Herpes simplex virus encephalitis (HSVE) is the

most common non-epidemic encephalitis, with the incidence estimated at 2 million *per year* (3).

DIAGNOSIS

Cerebrospinal fluid polymerase chain reaction for detection of viral DNA (deoxyribonucleic acid).

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Electroencephalogram (EEG) typically shows focal temporal lesions or diffuse slowing down.

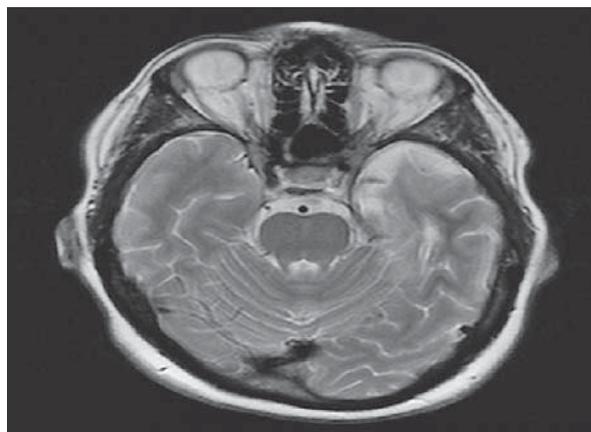
Magnetic resonance imaging (MRI) of the brain typically reveals lesions in the region of temporal lobes, occasionally also hemorrhage and early lesions in the cerebral hemispheric white matter (4-9).

CASE REPORT

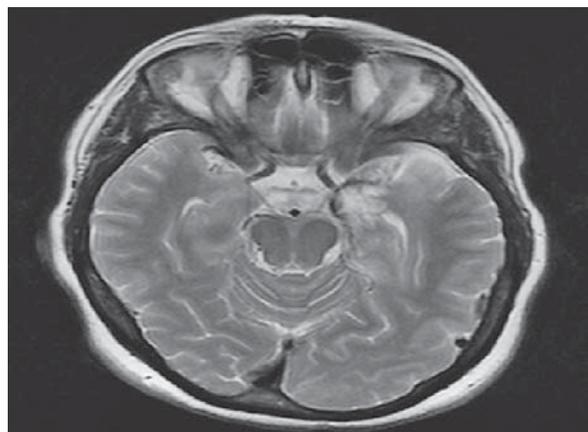
A female patient born in 1972 was diagnosed with HSVE in January 2009.

Personal history: Mother to two children; completed 12-year education with good results. Before HSVE, treated for depression for 3 years; still on occasional psychiatric follow up.

Current disease: Disease onset characterized by nonspecific signs of viral infection. On the second day of disease, the patient developed confusional state and was hospitalized according to the place of residence. On day 4 of disease, transferred to the University Hospital for Infectious Diseases because of deteriorated state of consciousness. On admission, the patient was soporous, with urinary incontinence and without overt motor events on extremities. Diagnostic work-up indicated HSVE. During 46-day hospital stay, the patient's condition gradually improved and her neurologic status was normal at discharge from the hospital. Memory impairment was noted in her letter of discharge. Brain MRI acquired during her hospital stay showed extensive edema of the left temporal lobe, along with lesions of the gray and subcortical white matter, eradicated border between the gray and white mat-

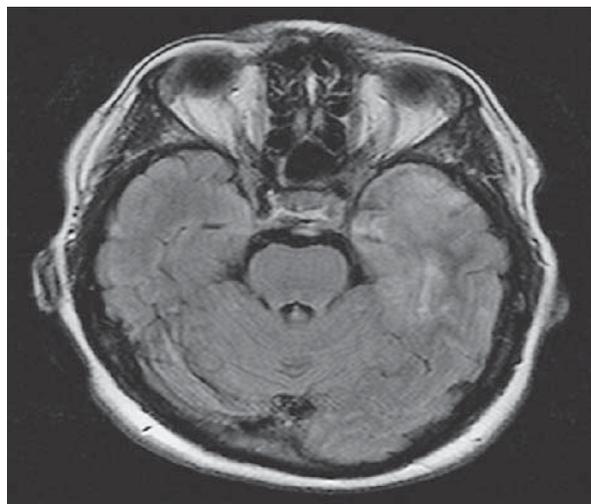


a

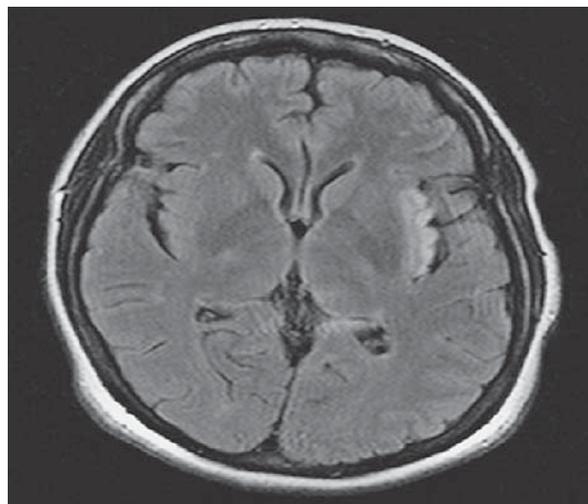


b

Fig. 1. Brain MRI: edema temporobasally on the left (a), with eradicated border between the gray and white matter (b).



a



b

Fig. 2. Brain MRI: extensive lesions in the left temporal lobe (a) and insularly on the left (b).

ter, and identical lesions in the insular region on the left. Upon contrast administration, spotty imbibition of temporal gyrus and insula on the left, with discrete imbibition mediotemporally and leptomeningeal imbibition insularly on the right was observed (Figs. 1 a, b and 2 a, b).

On regular infectological follow up four months later revealed severe memory impairment, therefore the patient was advised to undergo neurological examination. She was examined at general neurology outpatient clinic of the Clinical Department of Neurology, Zagreb University Hospital Center, and scheduled for work-up at Department of Cognitive Function Disorders.

TEST RESULTS:

1) Cognitive function test results:

Mini Mental State Examination (MMSE) 26; corrected for age and education 26 (87%); mMMSE 51 (82%); clock drawing test (CDT) 9; retrograde amnesia for all events occurring in the past 6 years of viral infection; markedly disturbed direct verbal and visual memory; mild disturbance of delayed visual recognition; mood changes.

2) EEG – continuous video-EEG polygraph monitoring: irritative changes temporally on the right.

3) Single-photon emission computed tomography (SPECT) – inhomogeneous and somewhat weaker

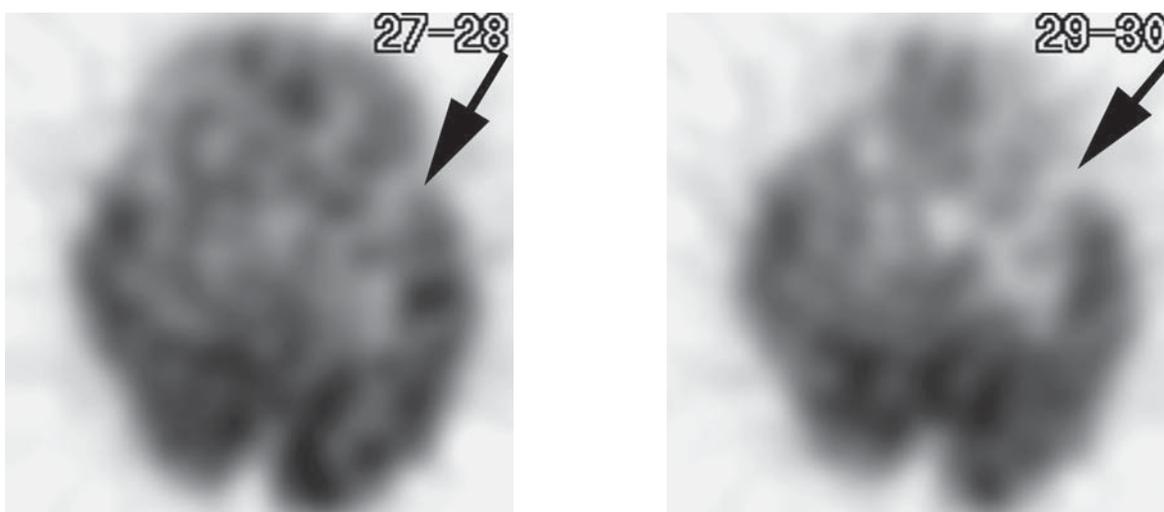


Fig. 3. Single-photon emission computed tomography (scan 27-28; 29-30): mild diffuse cortical global hypoperfusion, severe hypoperfusion temporobasally on the left and hippocampally on the left (arrows).

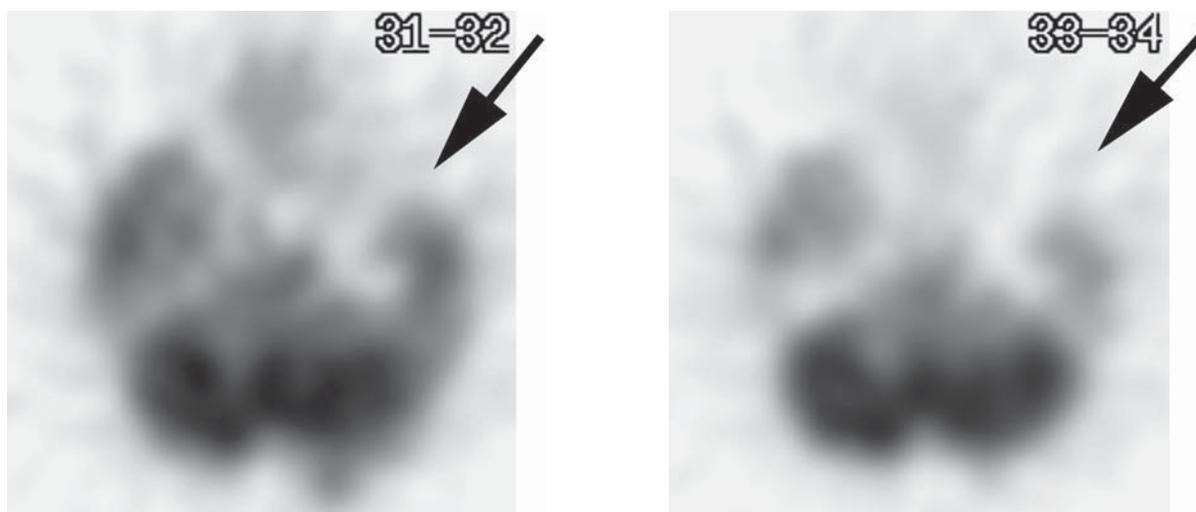


Fig. 4. Single-photon emission computed tomography (scan 31-32; 33-34): extensive hypoperfusion of the left temporal lobe and left hippocampus.

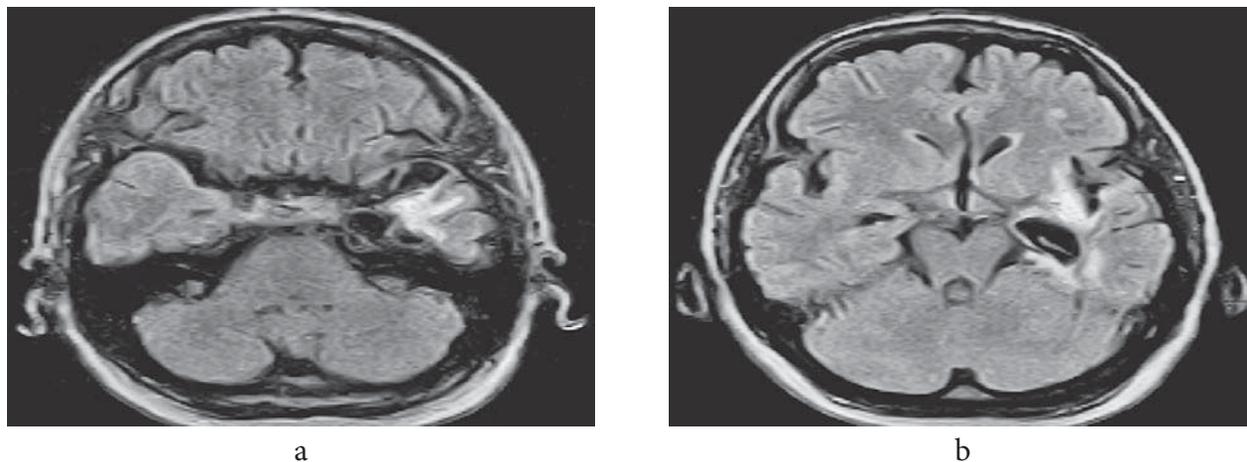


Fig. 5. Brain MRI: extensive gliotic lesions in the region of the left temporal lobe (a) and atrophy of the brain parenchyma (b).

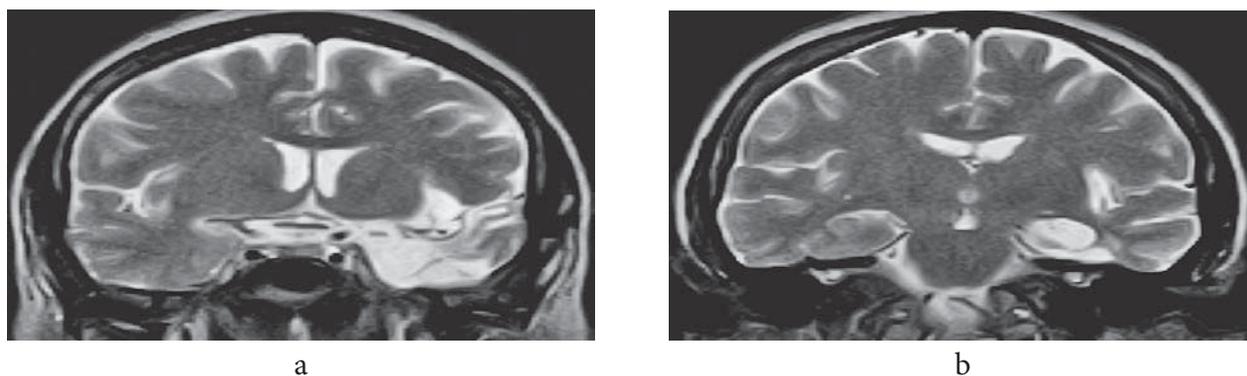


Fig. 6. Brain MRI: T2 weighted coronal sections show extensive gliotic lesions of the left temporal lobe (a) and gliotic lesions in the region of the left hippocampus (b).

radiopharmaceutical accumulation in the cortex; mild, hardly perceivable diffuse cortical hypoperfusion. Areas of severe hypoperfusion pronounced temporobasally on the left, in the hypothalamus projection area in particular (Figs. 3 and 4).

4) Brain MRI – extensive gliotic retraction lesions temporobasally and insularly on the left (Figs. 5 a, b and 6 a, b).

In the first 3-4 months of discharge from the University Hospital for Infectious Diseases, the patient had increased appetite with episodes of binge eating, especially sweet, which resulted in 7 kg weight gain. She exhibited pronounced behavioral and mood changes without any obvious reason, along with verbal and physical aggressiveness and uncontrolled outbursts of rage. She also had increased libido with exaggerated declarations of love toward her husband. Her mood changes and aggressiveness have diminished with time, but abrupt mood changes and intolerance, even occasional aggressiveness, have persisted.

The patient has severely impaired short-term memory, i.e. forgetting what she started doing 3-4 minutes before. She is cooking using recipes, however, unsuccessfully, so other family members had to take over all the housework. She writes messages and notes to herself but regularly forgets them too.

Her retrograde amnesia covers the previous 6 years, since the onset of the disease. She can recollect her attending high school (science school) and working as chemical technician for some time but cannot recollect when she ceased working (after her first childbirth) nor can say anything about her past job. She got married in 2004 but now she does not remember it. She is very close to her husband but she thinks he is her boyfriend. He is the only person she shows emotions to, frequently beyond control, without considering the current environment and situation. She cannot recollect when she gave birth to her children, does not remember their birthdays and other important life events of her children and other family members. She is mother to two children but she is emotionally cold toward

them, almost quite disinterested. She does recognize her children but does not know when they were born nor can remember their major life events. Her husband has noticed that she does not recognize persons from her close environment if she has not met them for a while. She recollects with difficulty the names of famous persons. Clinical examination revealed nominal dysphasia and visual agnosia (inability to recognize familiar objects by sight).

Her family has denied epileptic seizures. During the patient's stay at our Department, no impairments corresponding to complex partial seizures were observed.

In daily life, the patient is heavily dependent on her family's help and surveillance, her husband in particular.

DISCUSSION

The risk of permanent impairment of cognitive functions is 2-4 times greater in HSVE than in encephalitides caused by other neurotrophic viruses. More than half of the individuals having sustained encephalitis can function normally in their environment and resume working after appropriate treatment, whereas others suffer permanent and severe cognitive impairments (10).

This case report is presented to describe late HSVE sequels, since neurological work-up was made one year after the disease, i.e. a period long enough for the patient's condition to be considered definitive. Neurological work-up revealed diffuse cortical hypoperfusion, severe damage to the left temporal lobe, and near-destruction of the left hippocampus.

Brain MRI (SPECT): As the left lobe is dominant in the patient, this destruction has resulted in severe memory loss (retrograde and anterograde amnesia) and behavioral changes with development of visual agnosia and nominal dysphasia (11). Hippocampal destruction has prevented information transfer and short-term to long-term memory transition, with uncontrolled, frequently quite embarrassing emotional reactions (12).

Therapy with acyclovir has proved efficacious in a number of studies; however, treatment should be initiated as early as possible (13). Early treatment is also associated with better recovery of cognitive functions (14). Anticonvulsant therapy is recommended due to the frequent occurrence of symptomatic epileptic seizures, mostly of the com-

plex partial type. Carbamazepine is the drug of choice (15).

Unfortunately, there are no pathognomonic symptoms of HSVE. On the differential diagnosis of confusional states, headaches and subfebrile states with epileptic seizures, HSVE should be taken in consideration because severe and permanent lesions of the brain parenchyma can only be prevented by early therapy introduction. Early diagnosis and therapy means intervention within the first few hours of the onset of infection symptoms.

Bearing in mind that PCR remains positive for 5 days of therapy initiation, there is no fear from false-negative results due to therapy introduction before completion of diagnostic work-up.

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Kasne posljedice encefalitisa uzrokovanog virusom *Herpes simplex*

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SAŽETAK - Encefalitis uzrokovan virusom *Herpes simplex* (HSVE) je teška bolest povezana s visokim morbiditetom i mortalitetom. Posljednjih dvaju desetljeća dijagnostika i liječenje te bolesti znatno su napredovale, ali su još uvijek i rizik i komplikacije encefalitisa uzrokovanog herpesom simpleks vrlo visoki. Predilekcijska mjesta infekcije su temporalni, rjeđe frontalni režnjevi. Najčešće kasne komplikacije su epilepsija tipa kompleksnog parcijalnog tipa, promjene ponašanja i oštećenje spoznaje. Dok se epilepsiju može uspješno liječiti s dobrim terapijskim ishodom, u pojedinaca koji su preboljeli takav virusni encefalitis oštećenje spoznaje je trajno. Pouzdani dijagnostički test je polimerazna lančana reakcija virusnog DNA, a liječenje uključuje terapiju aciklovirom uz druge simptomatske terapijske postupke.

Opisana je bolesnica s HSVE u cilju prikazivanja teškog oštećenja spoznaje i ponašanja kao posljedice infekcije virusom herpesa simpleksa, ukazivanja na dijagnostičke rezultate te naglaska na ulogu rane dijagnostike i liječenja te teške bolesti.

Ključne riječi: herpes virus, encefalitis, oštećenje spoznaje, testovi spoznajne funkcije, single-photon emission kompjutorizirana tomografija