CASE REPORTS

Different courses of herpetic encephalitis as a result of virus reactivation during transient depression of immunological defense – case reports

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SUMMARY

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Herpetic encephalitis is an emerging disease associated with a high mortality rate and significant neurological, neuropsychological and neurobehavioral sequele.
In this paper 4 cases of patients with various courses of herpetic encephalitis are presented.
Based on study we conclude that herpetic encephalitis may start with non characteristic symptoms and different clinical course. In the course of herpetic encephalitis peripheral markers of inflammation may not by present. Not specific beginning of illness may influence a delay in diagnosis, when might cause treatment lag. In each case suspected of encephalitis treatment with the Acyclovir should be administrated. MRI examinations, because of high sensitivity should be used in each case suspected of herpetic encephalitis.

Key words: *herpetic encephalitis, HSV, infectious disease, immunity*

STRESZCZENIE

Odmienne przebiegi opryszczkowego zapalenia mózgu jako wynik reaktywacji wirusa w czasie przejściowej depresji obrony immunologicznej – opisy przypadków

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Opryszczkowe zapalenie mózgu jest ostrą chorobą charakteryzującą się wysoką umieralnością i możliwością rozwoju powikłań neurologicznych, neuropsychologicznych i neurobehawioralnych. W pracy przedstawiono opis 4 pacjentów z opryszczkowym zapaleniem mózgu o różnym przebiegu, jako wynik reaktywacji wirusa podczas spadku odporności. Na podstawie naszych obserwacji wnioskujemy, iż opryszczkowe zapelnie mózgu może mieć nietypowy początek i różnorodny przebieg. W badaniach laboratoryjnych nie muszą występować wykładniki stanu zapalnego. Niespecyficzny początek choroby może wpływać na opóźnienie diagnozy i zastosowania leczenia przyczynowego. Badanie MRI głowy, z uwagi na wysoką czułość powinno być wykonane w każdym przypadku podejrzenia opryszczkowego zapalenia mózgu, a w leczeniu do momentu wykluczenia etiologii opryszczkowej powinien być zastosowany Acyclovir.

Słowa kluczowe: *opryszczkowe zapalenie mózgu, HSV, choroby zakaźne, odporność*

Herpes simplex viruses type 1 and 2 (HSV1 and HSV2) are human neurotropic viruses. They infect posterior nerve roots causing a latent infection of sensory ganglia and may reoccur many years after primary infection.

Although HSV1 and HSV2 cause different diseases and have different molecular structure, they show a few common features which affect the course of a disease. HSV1 causes encephalitis, blindness and disorders of the peripheral nervous system,

whereas HSV2 is a pathogen mostly responsible for encephalomeningitis in neonates and adults, less frequently leading to myelitis and radiculitis [1].

If untreated, herpetic encephalitis is associated with a high mortality rate and significant neurological, neuropsychological and neurobehavioral sequelae, afflicting patients for life. Early diagnosis is critical because treatment with the antiviral drug acyclovir significantly decreases morbidity and mortality.

Infection, spread and reactivation

HSV infects via mucosal surfaces or damaged skin. The primary infection is usually asymptomatic and depends on the immunological status of the host [2].

HSV1 and HSV2 are usually transmitted via different routes. HSV2 causes most cases of genital herpes and is usually transmitted via sexual intercourse whereas HSV1 is typically transmitted during childhood via the orolabial route. Exceptions from this rule are reported in *Nielsen's* et al.[3] and *Tran's* et al. [4]. These authors describe cases of genital herpes caused by HSV1 and persistent oral herpes caused by HSV2.

Recurrent infections are usually caused by endogenic virus reactivation. Infection relapse may be symptomatic or asymptomatic. Asymptomatic reactivation may contribute to the transmission of both types of viruses. It has been proven that asymptomatic shedding may be present in more than 2/3 of seropositive patients [5].

Except for recurrent orolabial and genital diseases, both types of viruses are also responsible for rare diseases such as herpetic meningitis and encephalitis, blindness and infections of newborns [6]. As far as herpetic encephalitis is concerned the neuronal spread of the latent HSV-1 occurs from the peripheral neuron in retrograde pattern to the brain, usually through the trigeminal or olfactory tract while HSV-2 usually infects the central nervous system through hematogenous spread [7].

Neurologic disorders caused by HSV

Herpetic encephalitis is associated with 70% mortality in untreated patients and with up to 30% mortality and a high incidence of severe and permanent neurological sequelae in treated cases. There is a bimodal age distribution of the disease: most patients are either neonates or above 20 years of age with the peak between 60 and 64 years [8].

No relation has been proven between the infection and the season of the year or gender. athogenesis of herpetic encephalitis has not been explained completely so far. The mechanism of the virus penetration to the nervous system may include:

1) reactivation of the virus genome in the trigeminal ganglion, which is a natural reservoir of HSV1
2) in situ reactivation of the latent virus in the central nervous system
3) primary infection of the nervous system

The infection may spread either by the olfactory nerve or by the trigeminal nerve. *Twomey* et al. [9] described viral particles in the olfactory nerve in patients with herpetic encephalitis. The theory of primary nervous system infection has been proved in the study conducted by *Whitley* et al [10].

There are few factors which enable HSV1 virus to penetrate to the central nervous system and to avoid the mechanisms of the immune protection. Experimental studies have proven that the immune system is able to influence the expression of virus genes during the acute phase of infection. Neurons involved in the process show the abnormal expression of MHC antigens, and antigen-related cellular transporter binding proteins, specific for HSV1, lead to the survival of the particles of MHC class I histocompatibility system in the cells, which makes it impossible to avoid a host's immunologic response [11].

Clinical symptoms

Prodromal symptoms such as inflammation of the upper respiratory tract or neurological disorders related to disorders of fronto-temporal lobes, sometimes imitating psychiatric disorders may occur. A patient suspected of HSV neurologic infection shows symptoms of meningitis and encephalitis: headache, neck stiffness, brain disorders with various degrees of altered consciousness and behavioral abnormalities including hallucinations, personality changes or psychotic state. Focal neurological deficits, seizures and myoclonus are often present and reflect the site of infection and inflammation. Personality disorders, confusion and disorientation have been described in 3/4 of patients, epileptic attacks in 1/2 and hemiparesis in 1/3 of patients [12, 13, 14].

Diagnosis

Each patient suspected of herpetic encephalitis should have cerebrospinal fluid examination made immediately. If focal neurologic lesions are present, imaging examinations should be made prior to lumbar puncture [15]. In 95% of patients with herpetic encephalitis, the CSF shows the features of inflammation. It is characterized by moderate pleocytosis with the predominance of mononuclear cells and the presence of erythrocytes due to a haemorrhagic nature of inflammation which affects parenchyma. A moderate rise in the protein concentration is observed in 80% of patients A decrease in the glucose concentration is reported in 5% of patients [16].

Serologic examinations are another important step in setting a proper diagnosis. In the early stage of the primary infection, a titer of antibodies is usually low. Searching for antibodies in the serum is of less importance, especially, in the first few days of infection, due to the lack of antibody production. These examinations have a diagnostic value after 12 days from the onset of the infection or after 10 days from the appearance of neurological symptoms or during convalescence. In latent infection the interpretation of serologic examinations may be difficult, so that only additional examination can assist in diagnosis.

An enzyme-linked immunosorbent assay is used in detection of intrathecal synthesis of immunoglobulin G (IgG) and IgA antibodies to herpes simplex virus (HSV) in patients with HSV encephalitis (HSVE) [17]. The detection of intrathecal antibody synthesis by qualitative methods or the Antibody-Index (AI) is a relevant tool for diagnosis of inflammatory neurological diseases.

PCR from the CSF is another technique used in diagnosis due to its high sensitivity (98%) and specificity (94%). False-positive CSF HSV PCR results are rare when testing is performed in experienced laboratories. Negative CSF HSV PCR results should always be interpreted in the context of the timing of specimen collection and the likelihood of disease. False negative results can be obtained in the first 72 hours of the infection. In this situation, lumbar puncture should be repeated after a few days. The optimal time after which genetic material can be detected by PCR is usually 2-10 days from the onset of the disease [18].

In patients with HSV encephalitis HSV PCR test in CSF after 14 days of Acyclovir treatment will typically give a negative result and a persisting positive PCR should prompt consideration of additional or revised antiviral therapy. It has to be remembered that in many hospitals access to PCR method is limited.

The most valuable diagnostic tool is MRI, which may detect lesions at an early stage. In cases of herpetic encephalitis MRI usually shows abnormalities located in the temporal lobes [19]. Special MRI techniques, including fluid-attenuated inversion recovery and diffusion-weighted imaging, might reveal abnormalities not seen with conventional imaging sequences. Neuroimaging patterns in infants and children differ significantly from those seen in adults and include a higher frequency of extratemporal lesions [9].

Brain CT has no diagnostic value within 4-6 days of the infection. EEG may indicate changes in the fronto-temporal lobes before they can be seen in CT. In EEG, uncharacteristic focal changes can be seen at first. Theta waves and polymorphic delta waves with the frequency of 1.2 sec are observed at the background of the basal activity that is slowed down. Periodically, every 2.4 sec, foci of sharp waves with a low and medium amplitude may show up, usually, in the temporal area or in all leads [20]. Brain biopsy may also be conducted, but only in exceptional cases.

Treatment

In order to stop neurons damaging by the virus activity treatment should be applied as soon as possible. The only medicine used in treatment is Acyclovir [21], which disturbs virus replication via the inhibition of DNA polymerase. In the infected cell, selected phosphorylation of this medicine takes place, which is catalyzed to acyclovir triphosphorane by a virus specific enzyme – tynidin kinase. The false substrate – acyclovir triphosphorate – bound to the virus DNA polymerase – inhibits the virus replication without a side effect on the host's cell replication. The dose usually used is 10mg/kg every 8 h over 10 days. In exceptional situations, treatment may be prolonged to 3 weeks. Control examination of the CSF should be done before making a decision of treatment prolongation.

In herpetic encephalitis, medication of the second choice is phoscarnet [22] and cidofovir – nucleozid analogue, phosphorylated by cell enzymes [23]. Cidofovir should be given once a week because of long T1/2 of cidofovir metabolites. Intracranial hypertension can be reduced by hyperventilation and diuretics (Mannitol in a dose of 0.25-0.5g/kg). The osmolarity of the blood serum should not exceed 320 mosm/l. The liquids administered intravenously should cover for 2/3 of daily requirement, but potential hypovolemia and hypoxia should also be taken into consideration.

In cases of the disease with brain oedema, dexamethasone should be used in a dose of 16-32 mg/d in order to strengthen the anti-oedematous effect. Proper oxygenation and prevention of bedsore, contractures and cornea damage are also important in the treatment, contributing to an increase in the survival rate, but neurological complications of the disease may be severe. Severe complications of the damaged brain tissue such as epilepsia, intellectual defects and severe memory impairment have been described. They frequently constitute a serious problem, despite setting an early diagnosis and proper treatment [24].

In this paper 4 cases of patients with various courses of herpetic encephalitis are presented.

CASE REPORT I

A 71-year-old man, with a history of hypertension was admitted to the Department because of fever

(39°C), headaches and weakness. Five days before hospitalization the patient started treatment with Amoxycylin and antiherpetic drugs.

At admission the patient was in a severe general state, weakened, conscious although with a difficult verbal contact. All meningeal signs (full neck stiffness, *Kernig's* sign and *Brudzinski's* sign) were present. The CSF examination showed pleocytosis and elevated protein concentration. During the first day of hospitalization the patient had a fever (39°C), complained of haemicranial headache and was temporarily confused. Despite using anticonvulsional drugs and Mannitol, numerous convulsions of the left side of the face appeared. The left facial nerve was paralyzed and features of the left hemiparesis were observed. In the brain CT, no heamorrhage was observed, although there was an area of hypodensity in the right temporal lobe, most probably ischemic, the right hemisphere of the brain was characterized by flattened sulci, and the narrower right brain ventricle.

Control examination performed 3 weeks after admission of CSF showed inflammatory features. Analysis of the CSF showed lymphocytic pleocytosis. The presence of anti Herpes antibodies (IgM, IgG) was detected in the serum. There was no elevation of the concentration of CRP (C-Reactive Protein) and ESR (Erythrocyte Sedimentation Rate), as well as no leucocytosis.

During hospitalization the patient complained of dizziness appearing at the change of the body position. *Romberg's* test was negative. Symmetric sensory hypoacusia was found.

In week 5 of hospitalization, the patient was emotionally unstable with tendency to moria and garrulity. Brain MRI image revealed coro-subcortical atrophy with widening of intracranial fluid spaces. In the right temporal region, the area of a high signal was shown in the T 2-dependent picture and FLAIR. After the contrast medium application, fairly poor garland-like contrast amplification of the temporal gyrus was observed at the basis of the temporal lobe. It was described that the MRI image might correspond to the lesions in viral encephalitis of *Herpes simplex* etiology.

Acyclovir, anti-oedematous, antipyretic and anti-inflammatory medications were administered, resulting in fever resolving and improvement of a clinical status. The control CSF examination revealed regression of inflammatory changes (Table 1).

CASE REPORT II

A 28-year-old woman, treated in the out-patient department due to influenza-like symptoms was admitted to the hospital because of severe headaches and fever.

At admission meningeal symptoms of mild intensity (neck stiffness on 2 cm) were found. The cerebro-

Table 1. Results of examination of cerebrospinal fluid of 4 patients

	Examination of cerebrospinal fluid							
	Color	Cytosis cell/ul	Protein mg/dl	Nonne-Apelt	Pandy	Glucose mg/dl	Cl mmol/l	Pleocytosis consist of(%)
Patient I	xantochromic, turbid, after centrifugation – aqueous-light, clear	245	222,8	(+)	(+++)	39	116	Lymphocytes 98%, Monocytes 2%
	xantochromic, clear	44	126	(++)	(+++)	40	115	Lymphocytes 96%, Monocytes 4%
	xantochromic, turbid; after centrifugation xantochromic clear	21	97,1	(+/-)	(++)	45	121	Lymphocytes 92%, Monocytes 8%, Erythrocytes very numerous
Patient II	aqueous-light, clear	770	96,7	+	++	46	117	Lymphocytes 93%, Monocytes 1%, Neutrophils 6%
	aqueous-light, clear	78	32,2	+/–	+	55	124	Lymphocytes 92%, Monocytes 2%, Neutrophils 6%
Patient III	aqueous-light, clear	88	33,5			74	120	Lymphocytes 77%, Neutrophils 23%
	aqueous-light, clear	4	38,5	–	+/–	56	130	–
Patient IV	aqueous-light, clear	5	31,5	+	+	68	113	–

spinal fluid had inflammatory characteristics (Table 1). CSF evaluation showed lymphocytic pleocytosis. In immunoserological examinations antibodies against *B.burgdorferi* in IgM class and *Herpes simplex* in IgM and IgG class in serum were revealed. No antibodies against B.burgdorferi in the CSF were found. No increase in CRP, ESR or leucocytosis was observed in biochemical tests.

MRI examination, FSE and SE sequences, T1- and T2- dependent images and FLAIR in three planes proved a slightly elevated signal seen in T2-dependent pictures within the medial part of the left temporal lobe – inflammatory changes. Apart from this, cerebral structures and intracerebral fluid spaces were found normal.

Based on the case history, physical examination and the results of neuroimaging the herpetic encephalitis was diagnosed. Treatment with Acyclovir was instituted. Symptoms and ailments subsidized and parameters of the CSF normalized on the 5 th day of hospitalization.The patient was discharged in the satisfactory condition with recommendation of a sparing life style, treatment continuation and follow-up in the outpatient department. The control lumbar puncture was performed after 4 weeks. Inflammatory changes regressed. (Table 1).

CASE REPORT III

A 35-year-old woman was admitted to the ward with symptoms of encephalitis. At admission the patient complained of nausea, lack of appetite, dizziness and a temperature of 39°C. Blood evaluation: ESR:72/80, CRP:107mg/l, leucocytosis:10200/ml. CSF examination excluded hemorrhage and pleocytosis confirmed inflammation process. (Table 1) During hospitalization gradually increasing disturbances of consciousness appeared. The patient was anxious and agitated. Despite antibiotic therapy (Ceftriaxon), anti-oedematous treatment (Dexamethasone, Mannitol), the patient's status deteriorated. On the 5 th day the body temperature decreased and consciousness cleared up gradually. CT revealed the hypodensive focus in the right parietotemporal region. The MRI announced wide hyperintensive regions in both temporal and basilar parts of frontal lobes regions (more intensified lesions in the right side covering partially the occipital lobe) as well as the effect of mass in the form of tightening of both temporal horns were described.

The MRI image corresponded to the lesions in the course of herpetic encephalitis.

During further hospitalization, in spite of a better general status, verbal contact was still illogical and there was an episode of sudden loss of consciousness with disturbed breathing. The patient was transferred to the Intensive Care Unit.

After 5 days the patient's status stabilized, she returned to the department for further anti-edematous, antiviral (Acyclovir) treatment, antibiotic therapy (Cefotaxime) and rehabilitation. Control CSF showed normality of inflammatory parameters. In the immunoassay, antibodies against *Herpes simplex* in IgG class were detected both in the serum and CSF. The results of laboratory tests were within normal range. In a control MRI, a decrease in the extent of lesions in both temporal lobes, widening of pericerebral spacer and temporal horns, especially the right and regression of odeomatous lesions were observed.

During hospitalization significant qualitative consciousness disturbances were still reported. *Korsakow's* syndrome was recognized and Lorazepham and Risperidone were introduced into the treatment. After improvement of the clinical state the patient was transferred to the Psychiatric Department for follow-up treatment.

CASE REPORT IV

A 38-year-old man was referred to the Department, with suspicion of encephalomeningitis. This patient complained of severe headaches with a temperature of 39 °C. He was treated unsuccessfully with antibiotics in the outpatient department. The brain CT showed no lesion. At admission the patient was in a severe general condition, conscious, but confused with a difficult verbal contact, periodically agitated and aggressive. During physical examination, no meningeal symptoms were observed. Lumbar puncture was performed and the CSF parameters were within the normal ranges. (Table 1) Laboratory tests showed leucocytosis: 22700/ml, ESR: 34/70, CRP: 67mg/l. Anti-oedematous, anti-viral and antibiotic therapy caused regression of fever and improvement of a general state after 3 days. A consulting psychiatrist found outcoming qualitative disturbances in patient's consciousness. Headaches, balance and consciousness disturbances in the form of a difficult verbal contact and orientation disturbance returned. Serological examinations confirmed presence of antyherpetical antibodies in IgM class in the serum and in IgG class in the cerebrospinal fluid. MRI showed hyperintensive foci in the white matter above the lateral ventricle, in the region of the frontal horn of the left side ventricle and the left internal capsule in the T2-dependent picture. Dexamethasone and Acyclovir were administered again, causing fast regression of symptoms, improvement of a general status and normalization of the laboratory parameters. The patient was discharged from the hospital in a

good general state and with recommendation to continue treatment in the outpatient department and follow-up with the Neurological Outpatient Department.

DISCUSSION

The beginning of herpetic encephalitis may not be characteristic and the disease itself may take various courses. In presented cases 3 of 4 patients were younger than 40 years. In the patients history there were no risk factors and none of the patients was immunoincompetent. Mechanisms leading to reactivation are not known up to date. Probably it may be overloading by duties, stress and lack of sleep.

The patients complaints varied from a mild headache (case II, IV), nausea, lack of appetite, dizziness and fever (case III) to loss of consciousness (case I). The clinical state of patient may worsen during the course of the disease and disturbances of consciousness may appear a few days after first symptoms (case III, IV).

The meningeal signs may not be present or may be slightly expressed (case II, IV).

There may be no abnormalities in biochemical tests, like no increase in CRP, ESR or leucocytosis (case I, II). Serological tests of our patients were not equivocal. In some cases IgM titer was present neither in serum, nor in CSF, which can be explained by quick seroconversion to IgG (case III). CSF pleocytosis and protein concentration may vary from almost normal, especially when a patient is at the early state of the disease (case IV) to very high values (case II). We have to underline that no correlation between a clinical state and pleocytosis was observed (case II, IV). MRI proven to be a valuable diagnostic tool. In all analyzed cases we have observed specific abnormalities located in the temporal lobes. We conclude that MRI examination, because of high sensitivity, should be conducted in each case suspected of herpetic encephalitis. It may confirm a diagnosis even if serological tests are negative.

In our patients standard antiherpetic treatment was used. Patients were treated with Acyclovir (case I, II, III, IV). Mannitol was used to reduce oedema (case I, II, III, IV). Dexamethasone may be administered in specific cases with high intracranial pressure (case III, IV).

CONCLUSIONS

1. Herpetic encephalitis may have non characteristic beginning of disease and various clinical course.
2. In the course of herpetic encephalitis peripheral markers of inflammation may not be present.
3. Non specific beginning of illness may contribute to diagnosis delay, which might cause treatment lag.
4. In each case suspected of herpetic encephalitis treatment with the antiviral drug – Acyclovir should be administrated.
5. Negative serological tests may not exclude herpetic etiology of encephalitis.
6. MRI examination, because of high sensitivity should be performed in each case suspected of herpetic encephalitis.

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