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Herpes Simplex Type 1 Encephalitis

Feyzi Birol Sarica

*Başkent University, Faculty of Medicine, Department of Neurosurgery
Turkey*

1. Introduction

Encephalitides, an acute infection of the brain parenchyma, are characterized by fever, headache and altered consciousness. Neurological deficits and focal or generalized epileptic seizures may also be seen. There are important differences in clinical presentations between encephalitides caused by viruses. While some viral encephalitides, such as Herpes simplex virus type-1 (HSV type-1) encephalitis, cause sporadic infection; others, such as Japanese B encephalitis virus and Eastern equine encephalitis virus, cause epidemic infections with specific geographic distribution. Some viruses like HSV cause fulminant encephalitis leading to death within a couple of days whereas viruses such as Measles virus can cause progressive subacute sclerosing panencephalitis lasting several months and years. HSV type-1, HSV type-2, LaCrosse encephalitis virus, St. Louis encephalitis virus usually causes encephalitis in healthy individuals, whereas HSV type-1, Cytomegalovirus, Varicella-zoster virus, Epstein-Barr virus, Human herpes virus type-6 and Enteroviruses are associated with encephalitides in immunodeficient or immunocompromised patients (Mathewson Commission, 1929; Meyer et al., 1960; Roos, 1999).

Herpes simplex virus (HSV) is the most common cause of sporadic fatal encephalitis (Mathewson Commission, 1929; Meyer et al., 1960; Smith et al., 1941). Smith et al. detected inclusion bodies consistent with HSV infection from a newborn's brain with encephalitis and virus was isolated from brain tissue then (Smith et al., 1941). The first adult case of HSE was reported by Zarafonitis et al. (Zarafonitis et al., 1944). The pathological findings in this patient's brain were prominent perivascular cuffing of lymphocytes and a large number small hemorrhages in left temporal lobe. Later in several studies, this temporal lobe localization was reported to be characteristic for HSE in patients older than 3 months. In the mid 1960s, Nahmias and Dowdle found two distinct antigenic type of HSV, as HSV type-1 and HSV type-2 (Nahmias & Dowdle, 1968).

The HSE, observed in adults, is caused by HSV type-1 predominantly (Dennett et al., 1997; Whitley & Lakeman, 1995). HSV type-2 is rarely seen in healthy adults and usually causes benign CNS infection, whereas severe meningoencephalitis is seen in immunosuppressed individuals (Mommeja-Marin et al., 2003). Herpes neonatorum, transmitted from perinatal area, causes severe encephalitis in neonates (Corey et al., 1983). HSV type-1 and HSV type-2 are from Herpesviridae family. The common feature of Herpesviridae family is that they stay in life-long latent (persistent) form in the organism and they can reactivate later leading recurrent infections. Also other viruses from Herpesviridae group may lead CNS diseases (Garcia-Blanco et al., 1991).

Herpes simplex encephalitis (HSE) continues to be one of the most devastating infections of the central nervous system despite available antiviral therapy. In patients taking no treatment or receiving an ineffective anti-viral treatment such as Idoxuridine and Cytosine Arabinoside, the mortality rate is higher than 70 % (Chien et al., 1975; Longson, 1979; Whitley et al, 1977; Whitley et al, 1981). Approximately one-third of all patients diagnosed with HSE are composed of children and adolescents. In clinical diagnosis, an encephalopathic disease process with focal neurological symptoms is seen. However, these clinical findings are not pathognomonic, and many other disorders involving the central nervous system have these symptoms and these diseases can mimic HSE.

In neurodiagnostic evaluation, demonstration of temporal lobe edema and /or bleeding with magnetic resonance imaging (MRI) is supportive for diagnosis. In electroencephalogram, spike and slow wave activity is observed. HSV isolation from brain tissue with brain biopsy was a diagnostic method used in the past. Today, detection of herpes simplex virus (HSV) DNA by cerebrospinal fluid polymerase chain reaction (PCR) is the gold standard for diagnosis. PCR is an excellent test and preferred over brain biopsy. 95% of cases can be diagnosed by PCR (Chien et al., 1975; Longson, 1979; Whitley et al, 1977; Whitley et al, 1981). However in the early period after the onset of the disease, false-negative results by PCR may be seen.

Acyclovir is the preferred method of treatment and administered 10 mg / kg every 8 hours for 21 days. Even if the treatment is started early after the onset of the disease, significant neurological deficits are observed in nearly two-thirds of the surviving patients. Today in current studies, quantitative prognostic value of viral DNA by PCR both at the beginning as well as at the end of treatment and contribution of long-term anti-viral therapy for improvement in neurological outcomes are investigated (Tyler, 2004).

2.1 Etiology

HSV type-1, member of the herpes virus family, is an enveloped-virus with a large (150-250 nm in size) linear double-stranded DNA (Mathewson Commission, 1929). The viral particle is wrapped from outermost by an envelope, which is made of lipid. Viral DNA is encased within a capsid that is 85-110 nm diameter in size. The structure between the envelope and capsid is called tegument (Davison & Clements, 2005; Jerome & Ashley, 2003; Whitley, 1996). In these 3 layers, there are 25-30 structural proteins which form the structure of the virion. There are 11 glycoprotein protrusions on the surface of the envelope with antigenic properties (gB, gC,....., gM). While gB and gD glycoproteins play an important role in the attachment to and entrance of the virus into target cells, gC, gE, gG, gI, gJ and gM glycoproteins play an important role in the penetration of the virus to the cell. gG is the major protein providing antigenic specificity of the virus (Erturk, 1999; Whitley,1996; Whitley & Roizman, 2001). gC glycoprotein binds to C3b component of complement system on the surface of infected cells. gE and gI glycoproteins bind to Fc part of IgG. The antibodies against to these envelope glycoproteins neutralize the infectivity of the virus with competitive binding to receptors. The protein named as transinducing factor (Vmw65) is localized in the region of tegument and related with latent or lytic infection (Mathewson Commission, 1929). Capsid, surrounding the viral genome, and consists of 162 kapsomers and is icosahedral in shape. Icosahedral structure of capsid is supported by structural proteins VP21 and VP22a particularly (Davison & Clements, 2005; Jerome & Ashley, 2003; Whitley, 1996). Non-structural proteins, so-called Infected cell proteins (ICP), play role in

DNA replication and transcription regulation. In addition, there are some other non-structural proteins that act especially as enzymes. The most important of these enzymes are; DNA polymerase, deoxyribonuclease, ribonucleotide reductase, protein kinase and thymidine kinase. These enzymes, in similar, have also important roles in important functions such as viral DNA replication (Erturk, 1999; Whitley & Roizman, 2001).

HSV is unstable in the external environment. HSV is heat-labile. Half-life of the virus is 1.5-3 hours at 37 ° C. The virus is inactivated at temperatures above 56 ° C. It can live for months at -70 ° C and protect its infectivity. It can remain alive for 48 hours at 4 ° C in humid conditions, while it is inactivated under dry conditions. It is sensitive to most proteolytic enzymes, such as trypsin, protease and aminopeptidase. Like other enveloped viruses, it is easily inactivated by ether, phenol, chloroform and formalin (Mathewson Commission, 1929; Whitley, 1996).

2.2 Epidemiology

The most common cause of acute viral encephalitis is Varicella zoster virus and it causes a mild encephalitis course (Koskiniemi et al., 2001). Herpes simplex viruses are the agents in approximately 10% of all acute encephalitides. The most common cause of acute sporadic viral encephalitis (95% cases) is Herpes Simplex Type-1 and it causes fatal encephalitis. The incidence of HSE is reported as 2-4/1 million/year (Johnson, 1998; Koskiniemi et al., 2001; Levitz, 1998; Rantalaaho et al., 2001). All over the world, irrespective of the seasons, encephalitis occurs sporadically in all ages and does not show gender difference throughout the year (Whitley et al., 1982). Virus usually spreads via infected aerosols and through saliva (Griffin, 2000; Loon et al., 2004; Serter, 2002). Throat carriers are responsible for person to person spread of infection. The infection occurs with direct inoculation of the agent to oral, ocular, genital, anal mucosa, respiratory tract and bloodstream of susceptible people. No infection is seen through intact skin. Viral antibodies are positive in 70-90% of adults (Griffin, 2000; Roos, 1999).

HSV-induced central nervous system (CNS) infections are much more severe than all other viral infections observed in the human brain. Today, the incidence of HSE is estimated to be approximately 1/250.000-500.000. Studies in United States, Britain and European countries show similar incidence rates and annual incidence has been reported as 1/300.000 (Longson, 1984; Skoldenberg et al., 1984). It was reported that medical costs for the young and adult patients hospitalized with the diagnosis of HSE in the United States in 1983 was more than \$ 1 billion (Khetsuriani et al., 2002; Straus et al., 1985). HSE does not show seasonal variation throughout the year and can be seen in individuals of all ages. Approximately one-third of the cases are younger than 20 years and half of the patients are over the age of 50 (Whitley et al., 1982a, Whitley et al., 1982b).

2.3 Pathology and pathogenesis

HSV replication is a regular and a multi-step process. All herpes viruses induce long-term latent infections in the host. However, this process is not fully elucidated (Griffin, 2000). Pathological changes are characterized by ballooning degeneration of cells infected with replicated HSV and accumulation of chromatin within the cell nucleus following cellular core degeneration. Cells lost intact plasma membranes. During this process; multinucleated giant cells are formed by amitotic dividing of the nucleus. Also inside them, Cowdry type A intranuclear inclusion bodies formed by newly synthesized DNA masses are observed

(Serter, 2002). Usually, a clear area surrounded by chromatin is seen around the zone characterized by an obvious eosinophilic homogeneous appearance. These intranuclear inclusion bodies are supportive for diagnosis and usually observed in the first week of the infection, whereas they are only seen in 50% of patients. Then, migration of mononuclear cells in infected tissues, showing host immune response, can be detected. In this acute stage of HSE, congestion and / or bleeding may also be seen in the inflammatory field formed by mononuclear cells particularly in temporal lobes. This is usually asymmetrical in adults whereas a more diffuse involvement is seen in newborns (Boos & Esiri, 1986). Similar involvement can be seen in the adjacent limbic areas. After about 2 weeks, neurophagia with necrosis is observed in neurons and glial nodules occur. In addition, host immune response is also responsible for the severity of tissue damage (Serter, 2002).

Microscopic examination is usually abnormal due to enlargement of the involved areas. In the first stages, histological changes may not be dramatic and they are non-specific. Congestion of capillaries was observed in the cortex and all other changes, including petechiae, were significantly observed in subcortical white matter. Vascular changes are usually seen in the infection areas of hemorrhagic necrosis and perivascular cuffing. Perivascular cuffing becomes apparent in the second and third week of the infection. Glial nodules have been observed more frequently after the second week of the infection (Boos & Kim, 1984; Kapur et al., 1994). Microscopic appearance is characterized by inflammation dominated by necrosis, extensive perivascular mononuclear cell infiltration, gliosis and satellitosis neuronophagia (Boos & Esiri, 1986; Garcia et al., 1984). The most striking finding is observation of large areas of hemorrhagic necrosis reflecting the area of infection. In the later stages of the disease, oligodendrocytic participation and gliosis (astrocytosis as well) has been observed more often.

2.4 Pathogenesis of human disease

HSE development occurs by reaching of CNS disease causing virus to the brain. Course of illness and disease pathogenesis in humans is well known, but the arrival of virus to brain and issues related to reactivation of the virus present in the temporal lobe is still not clear. Partial understanding of the pathogenesis of HSE is a common feature for all age groups. Primary and recurrent HSV infections lead CNS disease eventually.

Primary infection in humans occurs via secretion of HSV and its spread to a seronegative sensitive person. For the occurrence of infection, contact of virus with mucosal surfaces or damaged skin is required (Cook & Stevens, 1973). As a rule, primary infection of HSV type-1 is often associated with oral mucosal disease in children or young adults. Tissue lesion, as a result of local virus replication, is usually in the form of asymptomatic gingivostomatitis (Schmutzhard, 2001). Then, viruses penetrate to mucosal receptors. As a result of viral replication in primary infection area, HSV Type-1, due to its affinity to sensitive and autonomic nerves, settles into the trigeminal nerve and olfactory tract ganglion neurons which are usually found in dorsal root ganglions.

Studies on the reactivation of the virus within the CNS have shown that certain viruses have enhanced neurotropism potential. Classical studies on animals proved that HSV reaches CNS through by both olfactory and trigeminal nerves (Johnson et al., 1968). However, especially in primary infection of humans, usage of trigeminal nerve by virus as a means of access to the CNS in a more preferred way is still a controversial issue. In HSE, settlement of the virus in temporal lobe through this route and spreading into the limbic system with

replication is called as anatomical spread hypothesis. In studies conducted on patients diagnosed with HSE, herpes virus particles along the olfactory tract were shown by electron microscopic examination of tissue samples in some patients (Dinn, 1980; Ojeda et al., 1983; Twomey et al., 1979; Whitley et al., 1986).

Animal studies showed that virus transmission to CNS has occurred through a neurological pathway via olfactory tract and an infection is seen in animal brain regions similar to the medial temporal lobes in humans (Schlitt et al., 1986; Stroop & Schaefer, 1986). However, for humans, there is no evidence for such an access route. HSV reactivation is another confusing issue in the process of HSE formation. There are documentations regarding virus latency in infected brain tissue (Rock & Frasher, 1983), but there is not enough information about the virus reactivation also taking place in this area. The disease has been suggested to occur via neuronal transmission of reactivated growing viruses to CNS right after virus reactivation in peripheral regions such as olfactory bulb or trigeminal ganglia (Davis & McLaren, 1983; Griffith et al., 1967; Johnson et al., 1968; Stroop & Schaefer, 1986). As a result, HSV type-1 settles in its preferred remote residential areas of CNS such as the basal parts of the frontal lobes and limbic system parts of the temporal lobe via retrograde axoplasmic transport (Barnett et al., 1994; Cook & Stevens, 1973; Schmutzhard, 2000). Then type HSV-1 remains latent until another viral replication occurs. Also in animal studies, it was shown that virus can remain latent in the neuronal sub-populations of brain stem and cerebellum (Baringer & Pisani, 1994; Boggian et al., 2000; Lewandowski et al., 2002; Rock & Frasher, 1983).

In the later stages, reactivation occurs in nuclei of these latent virus infiltrated neurons and virus proliferation is seen. Viral DNA synthesis is built together with the virus capsule and an acute infection occurs clinically (Hill, 1985). This asymptomatic acute infection, caused by reactivation of HSV type-1, is characterized with infections such as herpetic keratoconjunctivitis in residual regions (oropharyngeal, orofacial and corneal) of distribution area of trigeminal ganglia. This infection is also accompanied by typical mucocutaneous vesicular eruptions (such as herpes labialis) and mucosal ulcers. In addition, proliferating viruses of viral reactivation in this acute infection period are secreted to the external environment and constitute a source of infection for HSV type-1 (Schmutzhard, 2001).

In this infection situation, formation of infectious virus particles is accompanied by deterioration in host cells. These events are shown in various animal studies (Hill, 1985). This infection situation in latent areas can be diagnosed at this stage by demonstration of viral DNA content (20-100 copies per cell) in neural cell nuclei. Detection of viral antigenic structure is rarely possible in the latent phase. In general, synthesis of the single viral gene, called Latency Associated Transcripts (LATs), occurs in infiltrated cells. In many studies, LATs are shown to be responsible from prevention of apoptosis in infiltrated cells and that they reflect late viral reactivation (Millhouse & Wigdahl, 2000; Perng & Ciacci-Zanella, 2000).

Eosinophilic inclusion bodies containing viral antigen and herpes virus particles are found in related neurons and glial cells. Chemotherapy and UV-rays trigger immune system changes, latent virus activation leading to formation of the HSE and development of herpes labialis. HSE has been noticed to be not more frequent in immunosuppressed people. In several studies, it was observed that the disease had a more severe course in immune-competent patients. Because, the CNS disorders are estimated to occur as a result of serious contributions of immune-mediated mechanisms (Hudson et al., 1991; Levitz, 1998; Whitley & Lakeman, 1995).

Recurrent reactivation (such as herpes labialis infections) and viral replication rarely causes acute hemorrhagic necrotizing encephalitis (involving temporal cortex and the limbic system) (Barnes & Whitley, 1986; Roos, 1999). Despite extensive researches in animal models, pathogenesis of HSE is not fully explained. 3 different hypotheses have been proposed in formation of the HSE via HSV type-1 (Levitz, 1998; Schmutzhard, 2001; Whitley & Lakeman, 1995). According to examinations conducted by National Institute of Allergy and Infectious Diseases (NIAID) and Common Antiviral Study Group (CASG), the primary infection has been reported to occur in about one-third of patients with HSE. After primary HSV infections, direct CNS invasion from nasal mucosa of the mouth and throat occurs through trigeminal nerve and olfactory tract. Often patients with primary infection are younger than 18 (Barnett et al., 1994; Davis & Johnson, 1979). Whereas in two-thirds of the cases, the disease occurs in the presence of existing antibodies (Nahmias et al., 1982). In 1/3 of HSE cases in this group, reactivation is seen as a result of recurrent herpes diseases in latent viruses in trigeminal ganglion and viruses multiply to cause a retrograde infection (Johnson, 1998; Schmutzhard, 2000). Endonuclease analysis of peripheral (labial) and CNS DNA isolates were compared and often the isolates were identified as similar. Only 10% of the patients had a medical history of recurrent herpes labialis (Nahmias et al., 1982). Also in 1/3 of the HSE cases, reactivation of existing latent viruses in CNS, such as brain stem and cerebellum, plays role (Levitz, 1998; Rock & Frasher, 1983; Whitley & Lakeman, 1995). Finally, acute hemorrhagic necrotizing viral encephalitis in gray matter, particularly basal portions of the frontal lobe and limbic system of temporal lobe is seen (Barnett et al., 1994). Bilateral asymmetrical inflammation of temporal lobes is the main finding and intracerebral amygdaloid nucleus, hippocampus and insular region involvement is usually observed (Mutluer, 2002).

2.5 Clinical variability

Primary HSV infection and first viral replication usually occurs in the oropharyngeal mucosa. During this asymptomatic period, influenza infection findings, such as fatigue and general feeling of illness, are observed. Then a period of symptomatic disease which is characterized by high fever, headaches and difficulty in chewing caused by cheek and gum mucosa lesions begins and this period lasts 2-3 weeks.

High fever (89%) and headache (78%) are the most common non-specific symptoms seen in the early period of HSE. Also within this period, the basic neurological disorders are added to the course. Listed among the characteristic findings; changes in level of consciousness (confusion, hallucinations and personality changes, etc.), from sleep tendency leading to coma, were observed in 96%. Personality change was observed in 61%, whereas dysphasia was observed in 51%. Sensory aphasia (Wernicke's aphasia) due to dominant hemisphere involvement in the early period describes mild organic psycho-syndrome seen in HSE. Epileptic seizures (focal and generalized) are observed in 38% of patients and to a lesser extent, 36%, hemiparesis accompanies. Papilledema was observed in 14%, whereas ataxia is rarely observed (Bewermeyer et al., 1987; Johnson, 1998; Maihofner et al., 2002; Schmutzhard, 2000; Whitley et al., 1982). It was reported that meningeal irritation findings were not significant. Symptoms usually reach maximal level in 2-3 weeks (Loon et al., 2004; Roos, 1999). Nothing is observed in herpetic skin flora (Shoji et al., 2002). In late HSE period, findings ranging from neurological residual syndrome, mild grade cognitive deficits, behavioral changes or personality changes are seen. Mostly post-infectious therapy-refractory epilepsy remains permanent (Bewermeyer et al., 1987; Schmutzhard, 2001).

However, completely atypical or chronic illness courses have also been reported (Bewermeyer et al., 1987; Panagariya et al., 2001; Whitley et al., 1989). Besides very mild courses, recurrent brain stem encephalitides were also defined (Klapper et al., 1984; Tyler et al., 1995). Because of this diversity of clinical symptoms, the diagnosis of the disease remains difficult and this causes the virostatic therapy to be applied very late.

Active mucocutaneous HSV infection accompanying immunocompromised patients is rarely observed with immunocompetent patients. Immune-suppression increases the risk of reactivation of latent HSV in cranial nerves and immune-suppressive agents in animal model studies have been shown to induce HSE. HSV type-1 was described as the main factor in brain stem and limbic system encephalitis in AIDS patients. Immune reaction that causes classical necrotizing encephalitis in advanced AIDS cases may not be seen (Roos, 1999). As a result of some studies, the risk of reactivation of HSE during intracranial surgery was found and therefore pre-, peri- and post-operative application of Acyclovir treatment was proposed (Bourgeois et al., 1999). In an experimental study, induction of hypothalamic-pituitary adrenocortical axis and production of IL-1 and PG-E2 in the brain, independent of viral replication, by HSV type-1 was shown and also HSV type-1 was suggested to be a factor in the emergence of the symptoms, such as high- fever, motor hyperactivity and aggressive behavior.

2.6 Diagnosis

Clinical findings in HSE are non-specific so they cannot be used for empirical diagnosis. The presence of clinical symptoms and a localized lesion in the temporal lobe usually reflects HSE, but other diseases can also mimic this condition (Whitley et al., 1989). CSF examination is indicated for patients with mental changes even if intracranial pressure is increased. In addition, presence of a lesion in brain computed tomography (CT) or magnetic resonance imaging (MRI) was found to be related with poor neurological outcomes (Domingues et al., 1997; Domingues et al., 1998a; Domingues et al., 1998b).

In HSE cases in which viral replication cannot be blocked with early treatment, surviving patients are known to suffer heavy and large number of neurological sequelae. Therefore, early diagnosis is of great importance. Diagnosis is made with clinical symptoms, MRI, EEG and CSF examination. The sensitivity is increased with the combination of these neurodiagnostic tests, but the specificity is still insufficient (Griffin, 2000; Dupuis, 1999). In the past, the only method used to prove HSE was brain biopsy, whereas today HSV-DNA presence in CSF with PCR method is valid for the diagnosis (Lakeman & Whitley, 1995).

Specificity and sensitivity of brain CT for diagnostic aspect is less. Hemorrhagic brain lesions in temporal lobe on CT show areas of low density causing localized mass effect (Enzmann et al., 1978; Zimmerman et al., 1980). Especially bilateral involvement of temporal areas at the later stages of the disease shows that the disease is resistant to therapy. Typical changes in HSE, correlated with brain CT, show large brain damage but these changes are not compatible with the prognosis (Morawetz et al., 1983).

When HSE is suspected; cranial MRI should be applied as an emergency to prove neuropathologic changes very early. MRI suggests the findings of HSE earlier than CT (Schlesinger et al., 1995). Because MRI is a more sensitive and specific diagnostic tool, it is used instead of CT scans in majority of patients (Schlesinger et al., 1995; Sener, 2001, 2002). The characteristic MRI finding of HSE is hyperintense areas in inferior lobes including the medial part and insula and this characteristic involvement may also be observed in the

frontal and parietal lobes, furthermore bilateral temporal lobe involvement has been reported to be pathognomonic as well (Aribas, 1996; Gordon, 1999; Roos,1999). This frontobasal and temporobasal hyperintense signal changes and diffusion limitation especially observed in T2-FLAIR sequences are typical (Djukic et al., 2003; Maihofner et al.,

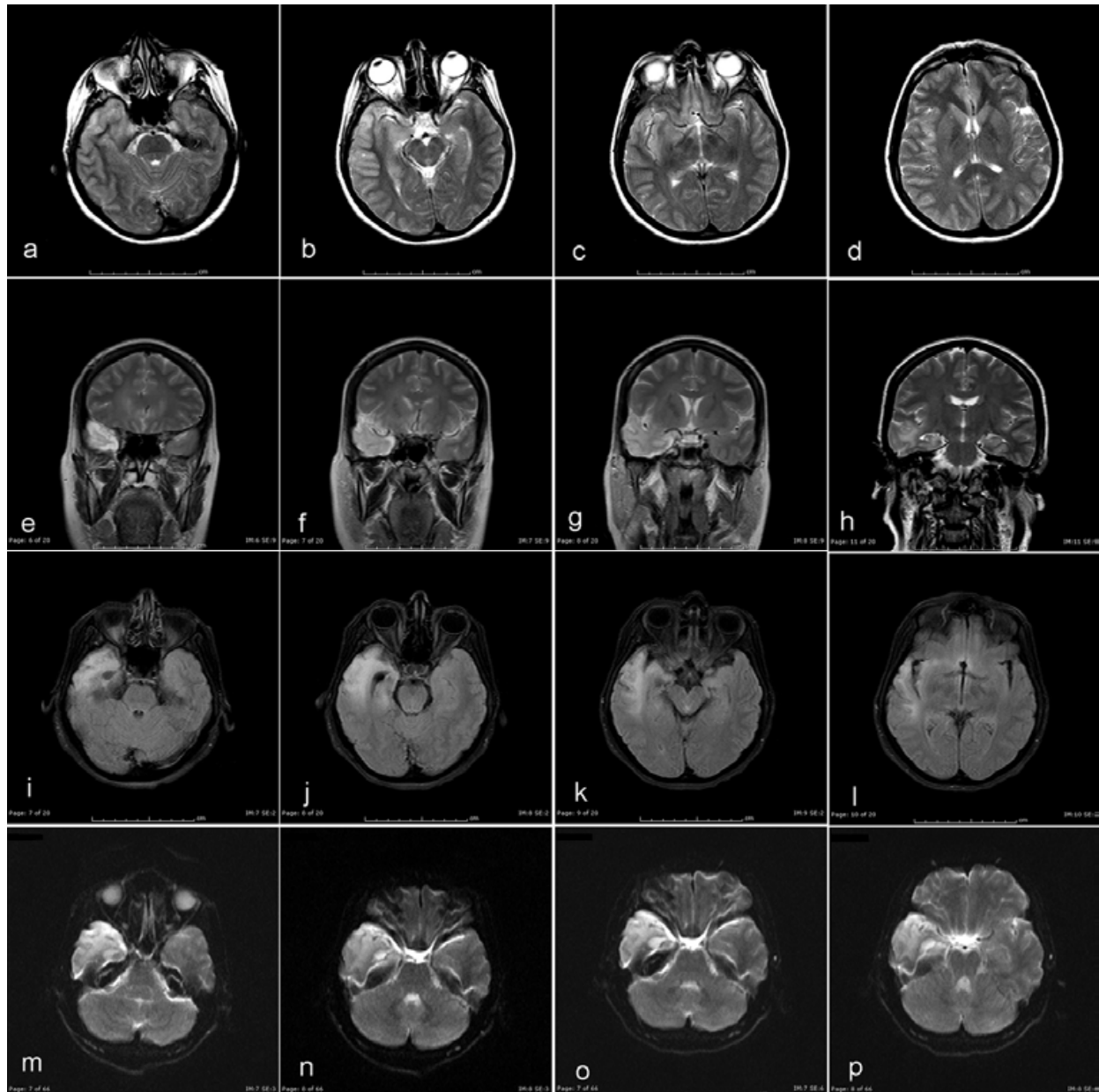


Fig. 1. T1-SE images in axial and sagittal planes, T2-TSE images in axial and coronal planes, FLAIR images in axial plane, T1-weighted SE images in axial, coronal and sagittal planes after intravenous contrast agent administration were obtained. Diffusion-weighted images of brain were obtained ($b=0$ $b=500$, $b=1000$ sn/mm² and ADC mapping). Lesion consistent with herpes encephalitis was observed in examination of right supratentorial region. The lesion was in the temporal lobe, involving parahippocampal gyrus and the hippocampus, and was extending to frontobasal region. The lesion was hyperintense on T2 and FLAIR-weighted sequences, showing diffusion limitation and no contrast enhancement after intravenous injection of Gadolinium.

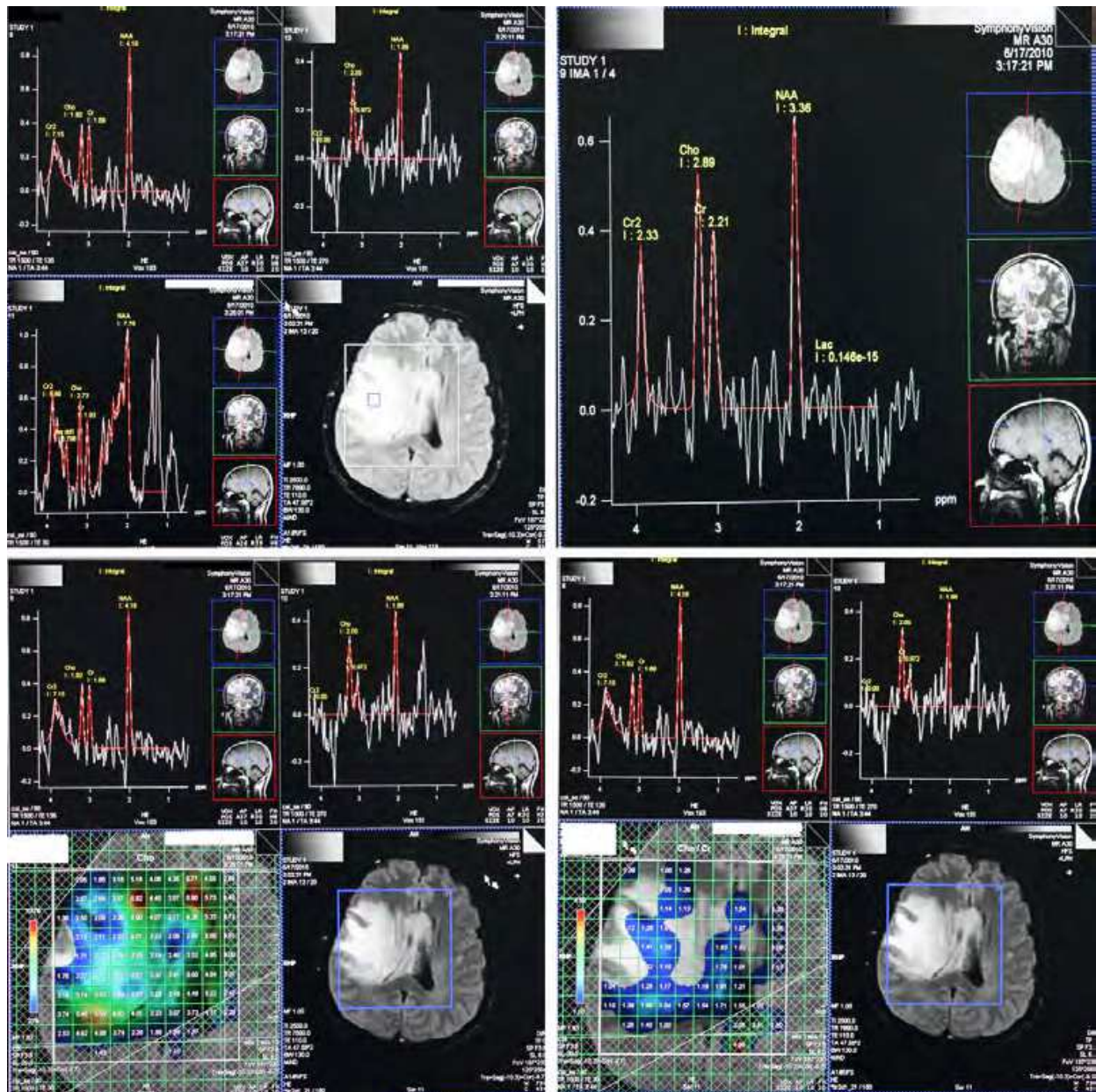


Fig. 2. Brain MR Spectroscopy evaluation of another patient was performed with CSI technique and TE of 30ms, 135ms and 270ms. Millimetric nodular lesions consistent with encephalitis were seen in right frontotemporal region, brain stem diffusely involving pons and left centrum semiovale. In spectroscopic examination, no significant choline peak was detected and a decrease was observed in NAA/Creatinine ratio.

2002; Schroth et al., 1987). In other sequences, parenchymal injury observed in the initial stage has been documented as areas of abnormal diffusion and these areas was observed to be reversible with virostatic treatment (McCabe et al., 2003). In addition, as a result of further studies, the severity of involvement observed in cranial MRI was reported to be compatible with the severity of clinical symptoms (Lamade et al., 1999).

CSF examination is another helpful method in the diagnosis of HSE and guiding in differentiation of diseases that mimic HSE. CSF examination is particularly indicated for patients with mental changes. CSF is transparent and cerebrospinal fluid pressure is usually

increased in HSE (Whitley et al., 1989). Polymorphonuclear leukocyte domination is seen in CSF in the early periods of HSE (Griffin, 2000). With disease progression, increase in WBC (lymphocytic pleocytosis) and protein level is determined. The average protein and WBC counts in CSF are approximately 100 mg / dL and 100 cells / L, respectively. The frequency of lymphocytic pleocytosis in CSF, especially when compared to patients with diseases that mimic HSE, is determined to be higher (Whitley et al., 1989). HSE leads to early hemorrhagic encephalitis so erythrocytes are often seen in CSF and this is a helpful finding for diagnosis (Mutluer, 2002). CSF glucose level is almost always within the normal range but reduction of glucose level due to consumption is typical in bacterial meningitis (Griffin, 2000; Roos,1999). In 5-10% of cases observed especially in children, the first evaluation of CSF examination can be found normal. However, CSF examination should be repeated within 24 hours, so in most cases, abnormalities can be observed (Whitley et al., 1989).

The success of CSF virus culture does not exceed 5% in encephalitis, so detection of nucleic acid by PCR in CSF at the first two weeks of infection and intrathecal antibodies at late period (after the 10th day) is recommended (Linde et al., 1997). Intrathecal specific IgG positivity begins at 10-12th day reaches its peak level at 20th day and may continue for years. Timing of CSF sampling is important for PCR. CSF sampling in early stage (first 48-72 hours) or after treatment can lead to negative results in PCR. In cases that the test is negative but there is clinical suspicion, repeated sampling of CSF for PCR and investigation of intrathecal antibodies at late stage may be diagnostic (Cinque et al., 1996; Puchhammer-Stöckl et al., 2001; Sauerbrei & Wutzler, 2002).

2.6.1 PCR detection of viral DNA

The most commonly used method for the isolation of virus is cell culture cultivation. However, CSF viral cultures of HSV type-1 are often negative (Griffin, 2000; Serter, 2002). Therefore, viral nucleic acid exploration by PCR in the CSF has become very important in patients with encephalitis. With this method, there is a possibility of detecting even small amounts of DNA and the test results within 24 hours often. Over time, CSF HSV DNA detection by PCR has become the gold standard for diagnosis (Boos & Esiri, 1986; Davis & McLaren, 1983; Dinn, 1980; Hill, 1985; Radermecker, 1956). Different genome regions (thymidine kinase, DNA polymerase, GPB, GPC, GPG, GPD, etc.) can be used for PCR (Cinque et al., 1996; Tang et al., 1999). Studies conducted by NIAID and CASG reported that this method had a very high sensitivity (98%) and specificity (94%). In 80% of tested samples, HSV-DNA positivity still remained within 1 week or more despite anti-viral treatment in HSE patients. As a result of the studies, HSV-DNA positivity in CSF by PCR was 100% within 10 days after the onset of symptoms, 30% in 11-20th and 19% in 21-40th days (Griffin, 2000; Roos,1999; Serter, 2002). The recently developed real-time PCR method has also examined CSF samples from patients with suspected HSE. As a result of the studies, a statistical correlation between the amount of virus (viral DNA copies / mL) and decrease in level of consciousness was showed, and a direct correlation was reported between CSF viral load (HSV-DNA amount), clinical outcome and prognosis (Domingues et al., 1998a; Domingues et al., 1998b; Domingues et al., 1997). PCR negativity shows either the absence of virus in the sample or presence of inhibitory activity. False-negative results may be observed in the PCR at the beginning of HSE symptoms (the first 24-48 hours) or 10 days to 2 weeks after onset of symptoms. False-negative results may also be observed in hemorrhagic CSF samples due to inhibition of the PCR reaction by erythrocytes (Serter, 2002).

The presence of HSV-DNA in CSF shows CNS infection due to HSV. However, in immunocompromised individuals, especially low amounts of HSV-DNA may not always be the evidence of the disease. Viral DNA quantitation may be guiding in diagnosis (Aberle & Puchhammer-Stöckl, 2002). Although the clinical significance of quantification of the controversial yet, as real-time PCR quantitation can be made with precision and speed, it can provide the knowledge needed in this regard. HSV-DNA in CSF can remain positive up to 1 week after beginning of acyclovir treatment (Cinque et al., 1996). HSV-DNA positivity in spite of treatment was associated with poor prognosis (Najioullah et al., 2000).

Though difficult to perform, brain biopsy protects its value in confirmatory of diagnosis (Djukic et al., 2003; Maihofner et al., 2002; Schroth et al., 1987). Isolation of HSV from the tissue samples taken by brain biopsy is sensitive (96%) and specific (100%) method for diagnosis. However, HSV-DNA detection in CSF by PCR has replaced brain biopsy due to being a less invasive method, easy to implement and achieving faster results. Brain biopsy is preferred in cases where CSF findings are atypical, HSV-DNA detection in CSF by PCR cannot be done, antibody tests are negative and MRI and EEG findings are non-specific (Roos, 1999). In patients with suspected HSE, HSE rate confirmed by brain biopsy has been reported to be 45% (Whitley, 2004). Brain biopsy procedure-related acute and chronic complications are observed in approximately 3% of patients. Brain sample collection from a diseased area with incision has the potential for acute disease and can cause epileptic seizures at chronic stage. As a result, even though in some cases it is confusing, brain biopsy is a helpful method in diagnosis.

2.6.2 Serologic evolution

Demonstration of HSV antigens via immunoperoxidase method is specific in diagnosis. Viral particles can be shown by electron microscopy in 50% of all cases (Serter, 2002). Detection of anti-HSV antibodies in CSF is another method used for the diagnosis of HSV encephalitis (Cesario et al., 1969). Detection of specific antibodies in CSF may be diagnostic when other methods are inadequate and at periods of removal of virus from CSF (usually the first 1-2 weeks after infection) (Lanciotti et al., 2000). Detection of specific IgM in CSF is diagnostic (Holzmann, 2003; Petersen & Marfin, 2002). Detection of specific IgG in CSF is also significant. However, transition of IgG from serum to CSF may be seen as a result of blood-brain barrier disruption, so demonstration of intrathecal synthesis is required. For this purpose, specific antibodies are examined quantitatively in serum and CSF samples which are taken at the same time and index obtained by proportion to each other is evaluated. If IgG in CSF is from serum origin, CSF / serum antibody ratio is 1/200-1/300 (Link & Muller, 1971). During infection of the CNS, this ratio is increases in parallel with the increase in intrathecal antibody production. This method can be used as a reliable method except conditions causing polyspecific immune activation like Multiple Sclerosis or causing severe immunosuppression. Monteyne et al. compared a variety of index calculation formulas in detection of intrathecal HSV antibody response and determined that the results are compatible except with MS patients (Blennow et al., 1994; Linde et al., 1997; Reiber & Lange, 1991).

HSV type-specific IgM and IgG antibodies can be measured via immunological methods (neutralization, complement incorporation reaction, haemagglutination, indirect immunofluorescence, "radioimmunoassay" and ELISA) (Serter, 2002; Griffin, 2000). As a rule, detection of anti-HSV antibodies in CSF at the initial phase of the disease is not possible, but after 10-14 days, intrathecal production of virus-specific antibodies becomes

provable and thus makes a retrospective diagnosis possible. Especially between 2-4th weeks of infection, an increase in antibody titers is observed. A slight increase can be seen in subsequent recurrent infections, but specific antibody levels will persist for life (Pfister & Eichenlaub, 2001). However, the sensitivity and specificity of this method is low. Because increase in antibody titers up to four times at acute and convalescent stages of primary infection has been found neither sensitive nor sufficiently useful for the diagnosis of disease in patients diagnosed with HSE via other diagnostic procedures such as biopsy. In addition, increase in antibody levels may be detected in cases of herpetic infection causing fever, such as herpes labialis (Pfister & Eichenlaub, 2001).

Increase in CSF anti-HSV antibody titers up to four-fold or greater is diagnostic. A significant increase (from 29% to 85%) is detected in 1 month till the onset. Four-fold

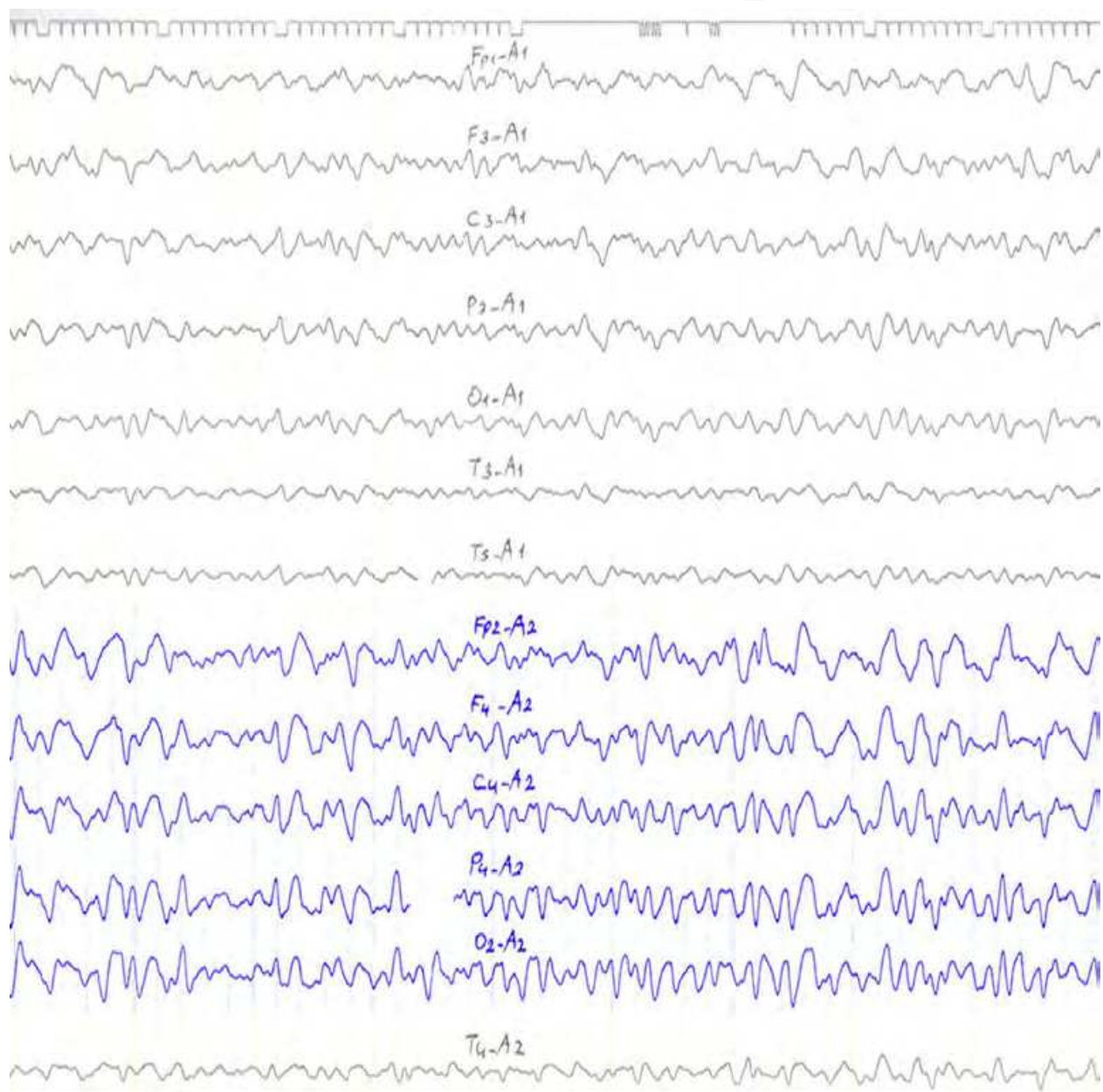


Fig. 3. PLED formation was observed in left hemisphere of the brain in EEG of the patient.

increase in CSF anti-HSV antibody titers 10 days after the start of clinical symptoms are observed in only 50% of patients diagnosed as HSE with brain biopsy. Therefore, this test is valuable only in retrospective diagnosis. In addition, a CSF / serum antibody ratio value of 20 or less has shown that there is no sensitivity during the first 10 days of the disease (Pfister & Eichenlaub, 2001).

Increased pathological levels of markers (neuron-specific enolase, NSE and S-100, etc.) showing destruction of neuronal and glial tissue in the CSF may occur in HSE. In some studies, a correlation between brain injury and these values was able to be used to estimate prognosis. However, these parameters increase in cerebral ischemia and dementia so they are not HSE specific (Studahl et al., 2000). Similarly, observation of various signal peptides, proteins, cytokines and soluble cytokine receptors (Neopterin, beta-2 microglobulin, Interleukin, interferon gamma, etc.) should be understood as an expression of strong intrathecal immune response (Griffin, 2000; Serter, 2002). In addition, a few values also increased actively in the course of HSE correlated with increases (Aurelius et al., 1993; Aurelius et al., 1994; Griffin, 2000). Serial changes observed in intrathecal cytokine and chemokine levels in patients with HSE were investigated in 4 separate clinical trials in detail. As a result of these studies; HSE identified in the acute stages of IFN- γ and IL-6 levels increased and these values, confirming the diagnosis has been reported to be helpful (Asaoka et al., 2004; Aurelius et al., 1994; Ichiyama et al., 2008; Rösler et al., 1998).

Another preferred method of early diagnosis of HSE is EEG. Frontotemporobasal dysrhythmia and a slowdown in frequency are observed in the EEG (Bewermeyer et al., 1987; Whitley et al., 1982). Periodic lateralized epileptiform discharges (PLEDs) are relative characteristic findings resulting from the temporal lobe, observed as slow and sharp wave complexes repeatedly (Chien et al., 1977; Longson, 1984; Miller & Coey, 1959; Panagariya et al., 2001; Smith et al., 1975; Upton & Grumpert, 1970). They are often observed between 2-15th days of the disease (Roos, 1999). Early in the disease, abnormal electrical activity usually involves one temporal lobe, but as the disease progresses (over a period of 7-10 days), similar electrical activity may be observed in the contralateral temporal lobe. For the diagnosis of HSE, EEG sensitivity is 84% whereas specificity is only 32.5% (Enzmann et al., 1978; Zimmerman et al., 1980).

2.7 Differential diagnosis

In a study by NIAID and CASG; brain biopsy has been performed in 432 patients with encephalopathic foci and HSE was diagnosed in 45% of these patients. Diseases mimicking HSE were found in the remaining 55% of the cases (Whitley et al., 1989; Whitley & Gnann, 2002). In this group, brain abscess, tuberculosis, cryptococcal infection and brain tumor were detected in 38 patients and other viral encephalitides caused by enterovirus and Epstein-Barr virus were detected in 38 patients. As a result, CNS HSV infection must be distinguished from these diseases mimicking HSV encephalitis (Roos, 1999). Emergency medical treatment of patients with these statements is required even if PCR investigation of HSV-DNA is negative.

2.8 Treatment and prognosis

Idoxuridine is the first antiviral drug used for the treatment of HSE. However, as a result of a controlled clinical trial, this anti-viral agent was found to be ineffective and toxic (Chien et al., 1975). Later Vidarabine was defined as an effective therapeutic agent in the treatment of

HSE, but over time was replaced by Acyclovir, a more effective anti-viral agent (Whitley et al, 1977; Whitley et al, 1981).

An improvement has been achieved in the prognosis of HSE with anti-viral therapy with acyclovir. In 1984 and 1986, two studies compared the efficacy and clinical use of Acyclovir and Vidarabine (Skoldenberg et al., 1984; Whitley et al., 1986). Acyclovir (9 - [2-Hydroxymethyl] guanine) is a nucleoside analogue of deoxyguanosine. For the effectiveness of acyclovir in infected cells, phosphorylation with viral thymidine kinase is required. Acyclovir is converted to acyclovir monophosphate by viral thymidine kinase phosphorylation. The monophosphate is further converted into diphosphate and triphosphate by cellular kinases. Acyclovir-triphosphate inhibits viral DNA-polymerase selectively and competitively. In conclusion, the viral DNA chain is broken, and thus complete viral DNA synthesis is stopped. Due to lesser affinity to host cell DNA polymerases, causing a very little toxic effect in host cell is another important feature of Acyclovir-triphosphate (Dorsky & Crumpacker, 1987; Van Landingham et al., 1988).

Acyclovir prevents virus proliferation but has no protective effect on primary and secondary immune-mediated damage that developed in previously virus infected cells. Therefore, early treatment is mandatory in patients with HSE and prophylactic Acyclovir treatment should be given even if HSE is suspected (Djukic et al., 2003; Dorsky & Crumpacker, 1987; Whitley et al., 1986). When administered intravenously, Acyclovir may crystallize and cause temporary renal failure. Therefore, intravenous drug should be administered both slowly and with adequate fluid support. Similarly, especially in patients with renal failure, renal function tests should be followed closely. Acyclovir should be applied intravenously every 8 hours at 10 mg / kg dose slowly (over 1 hour). The duration of treatment should be at least 14 days, but 21 days will be better (Djukic et al., 2003; Levitz, 1998). Because worsening of the disease was defined in short-term treatment with reactivation of the virus (Baringer & Pisani, 1994; Van Landingham et al., 1988). CSF acyclovir levels are approximately 30-50% of corresponding plasma levels (Serter, 2002). HSV-DNA viral load in CSF may be used as a marker for treatment efficacy, but is independent from clinical course and cannot be correlated with it (Wildemann et al., 1997).

Factors influencing the success and long-term clinical results in a positive way are patient age <30, Glasgow coma score (GCS) >10, <4 days of disease before the treatment with Acyclovir and early start time of the therapy (Griffin, 2000). Therefore, for the effectiveness of Acyclovir, the treatment should be initiated before a significant deterioration (GCS > 10) at the level of consciousness, the symptoms of initial phase (first 4 days) and particularly before start of the dominant temporal lobe hemorrhagic necrosis. Glasgow coma scale is the preferred scale indicating the level of consciousness in literature. Regardless of the age, a patient with a GC score 6 or less was shown to have worse treatment outcomes. Children and adolescents constitute 90% of HSE diagnosed patients under the age of 30. This group of patients likely to return to normal functions with mortality rates reported to be higher than in elderly patients (Whitley et al., 1986).

The treatment of HSE is difficult and the mortality and morbidity rates still remain high despite treatment. The mortality rate decreases from 70% to 20-30% with the use of acyclovir (Gnann & Salvaggio, 2004; Loon et al., 2004). In a study conducted by CASG and NIAID, 6 and 18 months of treatment with Acyclovir decreased mortality rates to 19% and 28% respectively. Regardless of their age, 38% of patients return to normal lives with normal or minor neurological sequelae. However, even with treatment, most patients have a significant permanent neurological deficit. 9% of patients with neurological deficits had

moderate neurological sequelae, while 53% developed severe neurological sequelae that become permanent or fatal. Permanent neurological deficit or death occurs not by reactivation of HSV infection but as a result of the disease. The mortality rate is lower than that of children and adolescents, but studies did not show statistically significantly lower rates of mortality in elderly individuals.

In a study recurrence of HSE was reported as 26%, while other studies have reported rate as 4% and 8% (Ito et al., 2000). In a study by NIAID, no recurrences were observed after completion of treatment. As a result, even after Acyclovir treatment only a few patients had recurrence of HSE (Van Landingham et al., 1988; Wang et al., 1994). Treatment failure was attributed to post-infectious encephalomyelitis, reactivation of latent virus, inadequacy of 14-day standard treatment regimen and possible drug resistance (Griffin, 2000). In addition, despite anti-viral treatment and clinical improvement, MRI follow-ups should be done frequently for progressive changes secondary to tissue damage (Lamade et al., 1999).

As a result of a mutation in viral genes encoding thymidine kinase, resistance to acyclovir may occur in HSV. Resistant isolates of HSV had been identified in encephalitides of patients with organ transplant and HIV infection. Especially in HIV-infected patients, the prognosis is very poor if Acyclovir-resistant HSV infections were not treated (Roos, 1999).

Vidarabine may be used at a dose of 15 mg / kg / day in case of acyclovir resistance. However, although in vitro effect has been shown, Vidarabine was determined to be inadequate for treatment due to failure to reach target tissues and cells adequately and its side effects. In NIAID CASG studies, new morbidity development was demonstrated in about 15-20% of patients undergoing Vidarabine treatment during long-term follow-ups. In the same study, only 13% of patients treated with Vidarabine had none or mild neurological sequelae. 22% of the patients had moderate or severe neurological sequelae and death occurred in 55% of patients during the follow-up.

Therefore, in case of intolerance to acyclovir, Foscarnet, a more effective anti-viral drug with lesser side-effects than Vidarabine, is suggested to be used (Schmutzhard, 2001). The effect of Foscarnet in the treatment of resistant HSV infections has been proven. 40 mg / kg Foscarnet administration every 8 hours for a period of 10-42 days is recommended in resistant cases. However, the recurrence rate is high after treatment with this anti-viral agent (Roos, 1999; Serter, 2002).

Famcyclovir, another alternative anti-viral drug used to treat HSE, is a pro-drug. In the organism, its structure changes into Pencyclovir, having a similar effect as acyclovir. However, its affinity for the viral-DNA polymerase is less than acyclovir. Therefore, the effectiveness for the treatment of HSE is less than acyclovir (Perry & Wagstaff, 1995). Valacyclovir, developed upon mild grade modification of acyclovir, reaches a high effect level when taken orally. However, a successful HSE therapy with Valacyclovir has been defined as casuistic in the literature. Similarly, as an alternative to acyclovir in the treatment of HSE; nucleoside analogues were used (Alrabiah & Sacks, 1996; Chan et al., 2000).

Because the majority of cellular damage is immune-mediated, simultaneous use of corticosteroids in HSE treatment is controversial. However, in recent studies, combined therapies of Acyclovir and corticosteroids are mentioned (Meyding-Lamade et al., 2003; Thompson et al., 2000).

Acute treatment of HSE should be done in intensive care unit. Intracranial pressure monitoring is required in order to intervene complications more quickly and in case of increased intracerebral pressure; mild hyperventilation and administration of osmotic diuretics (Mannitol, Glycerosteril) are recommended. If sufficient effect cannot be obtained

despite these treatments, craniectomy should be considered as an option to relieve intracranial pressure. Especially in cases complicated by tentorial herniation or massive brain edema, anterior temporal lobe resection and / or decompressive craniectomy is suggested to be useful (Griffin, 2000).

Epileptic seizures in the acute phase should be treated with benzodiazepines, Valproic acid or diphenylhydantoin. In the treatment of permanent symptomatic epilepsy; similarly Carbamazepine, Oxcarbazepine and Valproic acid treatment is recommended. In addition, combinations of other anti-epileptic drugs like Lamotrigine, Topiramate or Levetiracetam are often necessary (Bewermeyer et al., 1987; Djukic et al., 2003; Pfister & Eichenlaub, 2001; Schmutzhard, 2001).

3. Conclusion

Marked improvement in prognosis has been achieved with modern diagnosis and Acyclovir treatment in the last 10-15 years. However, HSE is a severe, dangerous and progressive disease. As a result of an actual multi-center study, severe permanent neurological deficits or mortalities were reported in 35% of HSE patients despite treatment with Acyclovir (Raschilas et al., 2002). As documented in past studies, late admission to hospital and administration of anti-viral therapy are the reasons for the poor prognosis (Marton et al., 1996; Raschilas et al., 2002; Schmutzhard, 2000). The prognosis is worse in older patients and those with impaired general and mental status before the onset of the therapy. Therefore, early diagnosis and anti-viral treatment should be done as quickly as possible with Acyclovir.

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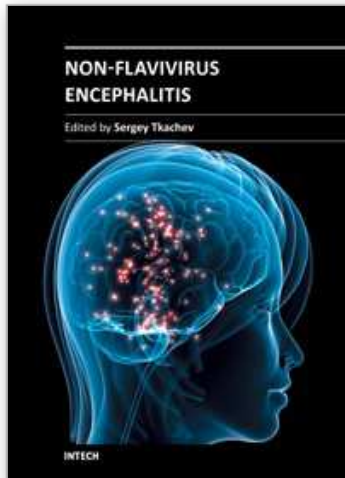
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Non-Flavivirus Encephalitis

Edited by Dr. Sergey Tkachev

ISBN 978-953-307-720-8

Hard cover, 360 pages

Publisher InTech

Published online 16, November, 2011

Published in print edition November, 2011

This book covers the different aspects of non-flavivirus encephalitis of different etiology. The first section of the book considers general problems of epidemiology such as study of zoonotic and animal vectors of encephalitis causative agents and methods and approaches for encephalitis zoonoses investigations. The members of different virus species are known to be the causative agents of encephalitis, so the second section of the book is devoted to these viral pathogens, their epidemiology, pathology, diagnostics and molecular mechanisms of encephalitis development by such viruses as HIV/SIV, herpes simplex virus type 1 and equine herpesvirus 9, measles virus, coronaviruses, alphaviruses and rabies virus. The next section of the book concerns the study of protozoan pathogens such as toxoplasma and amoebae. The last section of the book is devoted to multicellular pathogen as human *Filaria Loa Loa* - a filarial worm restricted to the West Africa.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Feyzi Birol Sarica (2011). Herpes Simplex Type 1 Encephalitis, Non-Flavivirus Encephalitis, Dr. Sergey Tkachev (Ed.), ISBN: 978-953-307-720-8, InTech, Available from: <http://www.intechopen.com/books/non-flavivirus-encephalitis/herpes-simplex-type-1-encephalitis>

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Phone: +86-21-62489820
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