Herpes simplex encephalitis – diagnostic imaging

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ABSTRACT

The phenomena of neuroinvasiveness, latency and reactivation are characteristics of Herpes simplex virus (HSV). Herpes simplex encephalitis (HSE) prevalence rate is 1 up to 3 in a million cases, which is about 10-20% of all viral encephalitis cases. The course of the disease shows the prodromal period and the symptomatic one; the clinical course is usually rapid and may lead to sudden death. As for the symptomatic period there are usually neurological focal symptoms and seizures as well as fluctuating consciousness leading to coma. Mortality rate in the course of HSE in non-treated individuals reaches up to 70%, it is lowered to 15% with early treatment with Acyclovir. However, most patients present persistent neurological and cognitive disorders.

There are usually no changes in the CT scan as far as the early stage of the disease is concerned. Thus, the imaging technique of choice is MR scan, which shows the changes already on the second day after clinical symptoms. On the basis of MR scans, on T2-weighted images, more or less symmetrical hyperintense cortical and subcortical white matter lesions occur with gyral and/or leptomeningeal contrast enhancement. MR spectroscopy can be helpful in lesions diagnosis and monitoring while diffusion-weighted imaging (DWI) may be used to evaluate the activity of inflammatory process. Differentiation of HSE in imaging should consider limbic encephalitis, gliomatosis cerebri, cerebral ischemia, cerebral oedema after seizure episodes and MELAS syndrome (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes), among others. HSV identification in cerebrospinal fluid by PCR (polymerase chain reaction) method is the confirmation of the diagnosis.

Key words: Herpes simplex encephalitis, limbic encephalitis, computed tomography, magnetic resonance imaging; MR spectroscopy

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INTRODUCTION

Herpes Simplex encephalitis (HSE) is one of the most serious viral diseases of the central nervous system (CNS). Despite its low prevalence HSE still remains a very important clinical problem due to its severe course. High mortality rate, even in patients with treatment initiated early, justifies the necessity of fast and effective diagnostics, in which neuroimaging is a significant element. Recent data indicate that autoimmunological mechanisms play a significant role in the pathogenesis of HSE. They are probably responsible for neurological sequel consequences recognized in large number of patients after HSE.

REVIEW

Epidemiology

Herpes simplex encephalitis is the most frequently occurring type of viral severe encephalitis [1]. There are two types of HSV, HSV-1 and HSV-2 of *Herpetiviridae* family, which are characterized by latency and reactivation abilities. Approximately 60% of adults have serological evidence of previous HSV-1 infection although HSE occurrence rate is 1-3 individuals in 1 million cases [2].

According to Whitley et al., HSE comprises 10-20% of the overall number of viral encephalitis [3]. Both HSV-1 and HSV-2 can cause CNS infection, wherein HSV-1 virus is responsible for about 90% of all HSE cases [4]. The occurrence of HSE is not connected with sex or season but it depends on age. It develops in a group of patients under 20 years-old in 30% of all cases, but also in groups over 50 years of age [5].

The course of the disease can be a primary infection or a reactivation of the past disease (more often in adults) occurring spontaneously or caused by an injury, stress, immune disorder, although specific mechanisms of reactivation are still not known [4].

CNS is affected due to the hematogenous spread or spreading lesions along nerve fibers from extra cerebral focal lesions. During latency, the infection is symptomless while the reactivation phase, in which new particles of virus move along axons, induces clinical symptoms of the disease. Herpes simplex virus has the ability to spread to the limbic system responsible for emotions, memory and behavior. Spreading the infection to medial parts of temporal and frontal lobes occur as a result of spreading the infection along meningeal branches of the trigeminal nerve, or along other peripheral nerves [6]. The same mechanism is probably responsible for spreading the lesions along pathways linking hippocampus with cingulate gyrus [7].

The clinical course and diagnostics

The clinical course is usually sudden and can lead to death, but there are some exceptions with mild symptoms [8]. In the course of the disease, two periods are distinguished: prodromal phase and neurological symptoms period. In the beginning, the clinical picture is non-characteristic, it can resemble a flu-like infection and last 2-5 days. It is characterized by malaise, weakness, lack of appetite, fever, shivers, nausea, vomiting, pain in muscles and joints [9]. The localization in temporal lobes causes memory and bearings impairment, excitation resembling alcohol intoxication or other intoxicants, which often delays diagnosis. Symptoms of meningism in the form of headache and neck stiffness appear. Symptoms of encephalitis gradually develop and are characterized by consciousness disturbances leading to coma. Moreover, there are other symptoms, such as focal neurological symptoms, muscle weakness, hyperreflexia and aphasia. Seizures, dysphagia and anarthria also appear very often. Psychiatric disorders: changes in temperament, lethargy, mood swings, confusion and hallucinations may also appear. Sometimes, symptoms of the autonomic nervous system can develop: cardiac arrhythmia, fluctuations in blood pressure or even asystole [10]. The character of symptoms depends on anatomical localization of inflammatory lesions [11]. Considerable difficulties in early diagnosis can be caused in cases with discreet olfactory disorders and changes in behavior [12].

People with lowered immunity resulting from concurrent diseases (e.g. patients after transplantation or AIDS patients) as well as pregnant women are more exposed to HSE, especially with severe course of the disease [13]. In this group of patients, the course of HSE is often atypical with rare prodromal signs and neurological focal symptoms [14]. Herpetic infections of CNS, caused by HSV-2 (virus), have usually the course of aseptic meningitis, myelitis or radiculitis. Such cases were named „Mollaret's meningitis". Nowadays, this term should be reserved only for idiopathic recurrent aseptic meningitis [15].

In infants, HSV-2 infections occur as acute necro-hemorrhagic encephalitis with spread on frontal lobe and paraventricular area. In such cases, virus transmission is vertical during childbirth [16,17].

Biochemical and serologic tests

Lymphocytic pleocytosis, the increase in protein, the normal level of glucose and the presence of erythrocytes in cases of bleeding are found in cerebrospinal fluid (CSF) test [18]. Polymerase chain reaction is the method which identifies HSV in CSF and helps to confirm the

diagnosis. Its sensitivity response and specificity is about 95-100% [19].

Imaging examinations

The typical localization of changes in HSE course comprises different parts of the limbic system. These are anterior and medial parts of the temporal lobes and inferior parts of frontal lobes. Cingulate gyrus/gyri and insular cortex , except basal ganglia, are very often affected [20] (Fig. 1 a-d).

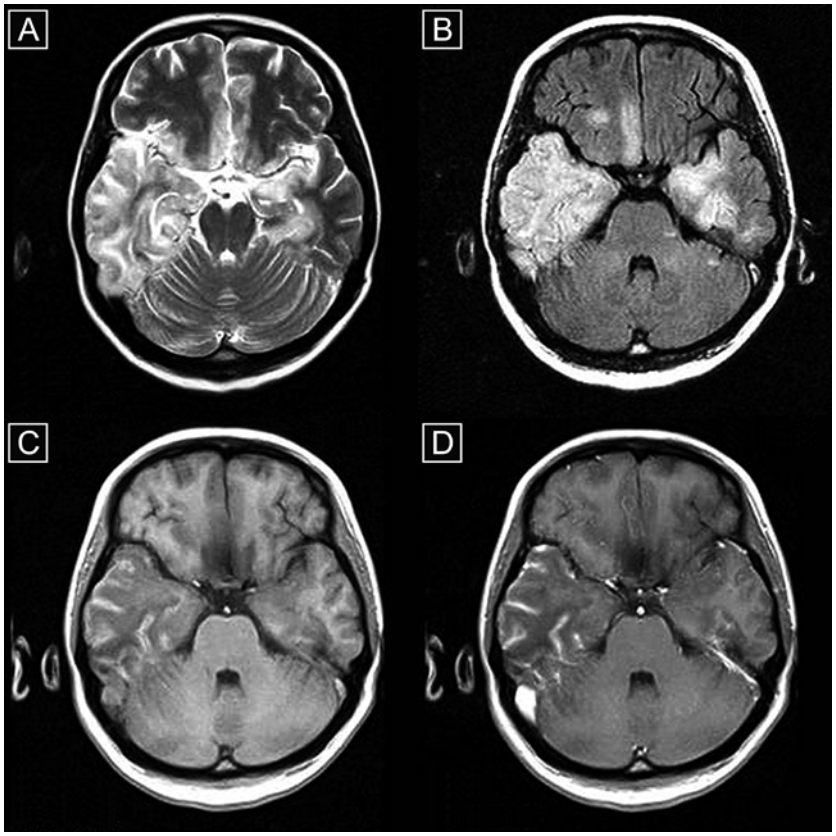

Figure 1 a-d. Bilateral, asymmetrical lesions in acute phase of HSE. On T2-weighted images (1.5T, TR/TE=5200/105) involvement medial parts of temporal lobes, more severe on the right side (a). The straight gyrus of the right frontal lobe involvement visible on FLAIR sequence (TR/TE=8000/120) (b). Cortical laminar necrosis of the right temporal lobe as linear hyperintense areas on T1-weighted images (TR/TE=585/15) (c), with band enhancement after contrast administration (d).

The involvement of other parts of the brain, except temporal lobes, is found in about 55% of patients and about 15% of cases appears as only extratemporal localization [21]. Basal ganglia changes are rare, lesions in thalami were described only in single cases [22,23]. Lesions are usually bilateral but asymmetrical. Sometimes they can affect occipital cortex [20] or, occasionally, they affect midbrain and pons. Pons is affected probably in consequence of backward dissemination along the trigeminal nerve [7]. Selective involvement of midbrain and hindbrain happens rarely [24]. In patients with immune deficiencies, the CNS changes are usually more extensive and may cover brainstem and cerebellum, very often without typical lesions in temporal lobes [14]. It should be pointed out that these are HSE cases without lesions visible both in CT and MRI scans [25].

At an early stage of the disease, CT scan usually does not show any changes [21]. In subsequent phases, blurred separated/isolated areas with lowered density can be found. They are characterized by inconsiderable mass effect and weak heterogeneous or band contrast enhancement along cortex gyri. Haemorrhagic areas can occur within lesions, but the frequency of haemorrhage occurrence is very low [26].

The imaging technique of choice is MR imaging with contrast, including FLAIR and GRE T2* sequences [23,27]. MRI scans show lesions on the second day after clinical symptoms occurrence. More or less symmetrical hyperintense lesions in cerebral cortex and subcortical white matter are visible on T2-weighted images and on FLAIR sequence (Fig. 2 a-d).

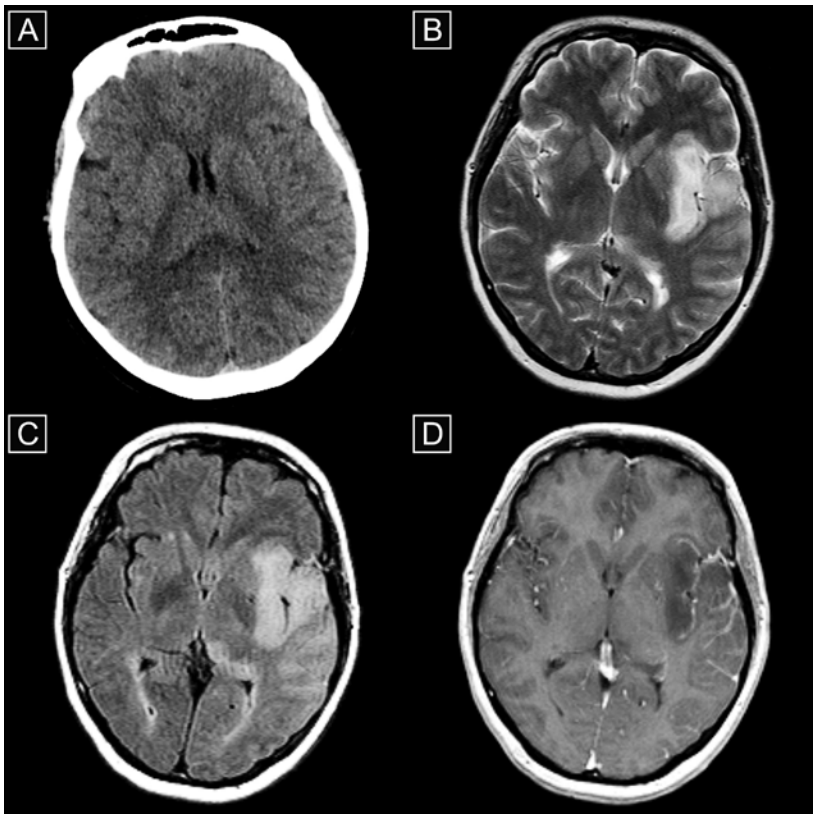

Figure 2 a-d. Lesions in acute phase of HSE. CT scan shows only a delicate asymmetry of lateral sulci (a). A wide hyperintense area on T2-weighted images (1.5T, TR/TE=5200/105) with the mass effect including the left temporal lobe insula except basal ganglia (b). On FLAIR sequence (TR/TE=8000/120) the extent of lesions and hyperintense lesion in the left thalamus well seen (c). Dilatation of insular cortex with gyral contrast enhancement on T1-weighted images (TR/TE=585/15) (c, d).

The affected cortex is extended, cortical-subcortical diversity is erased [28]. Hemorrhagic areas are seen on T1-weighted images or on gradient sequences (GRE) T2* [27]. The gyral enhancement of the cortex appears usually one week after the first symptoms [29].

In early stage, DWI imaging states restriction of diffusion with features of cytotoxic oedema. Diffusion disorders regress approximately in the second week of the disease and change into vasogenic oedema [30]. It is believed, that DWI method can be used to estimate the activity of the inflammatory process and has a predictive value [31,32].

MR spectroscopy (MRS) is helpful in lesions diagnosis and monitoring. In acute phase the decrease in N-acetylaspartate (NAA), a slight increase in the choline/creatine (Cho/Cr) ratio (lower than in most tumors) and the presence of lactate and lipids bands can be observed. Control MRS examination showed partial normalization of metabolic changes (with NAA restoration) and the increase in mioinositol (mI) that resemble gliosis processes (Fig. 3 a-b) [33,34].

In SPECT examinations, using 99mTc-hexamethylpropyleneamineoxime (99mTc-HMPAO), hyperperfusion areas, with features of "luxury flow", are stated in early HSE phase. They are connected with acidosis and have adverse prognostic factor according to some authors [35]. These changes are confirmed by PET and the latest reports using CT perfusion [36,37]. Perfusion disorders regress relatively fast, regardless of lesions in MRI scans [36].

Atrophic changes with more or less extended gliosis areas occur after inflammatory changes. The temporal cortex is usually thinned, cortical laminar necrosis can appear as linear hyperintense area on T1-weighted imaging (Fig. 4 a-c). Autoimmune mechanisms with formation of antibodies against NMDA receptors, similar to reactions observed in limbic encephalitis are probably responsible for long-lasting persistence or even progression of involutions after HSE [38].

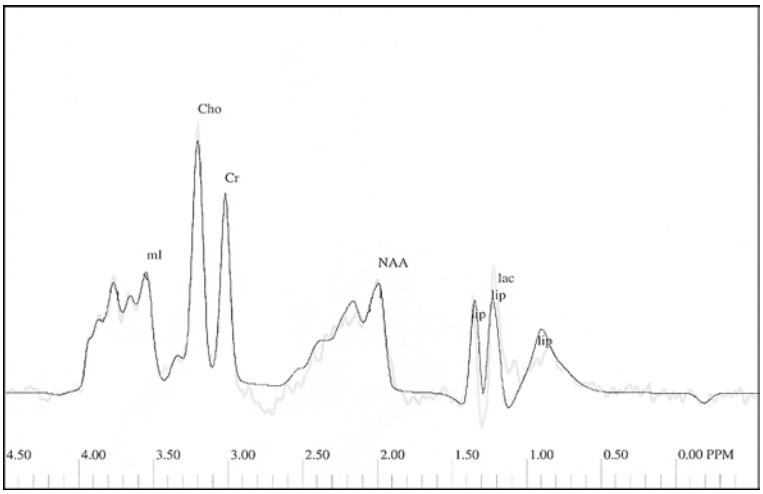

Fig. 3a

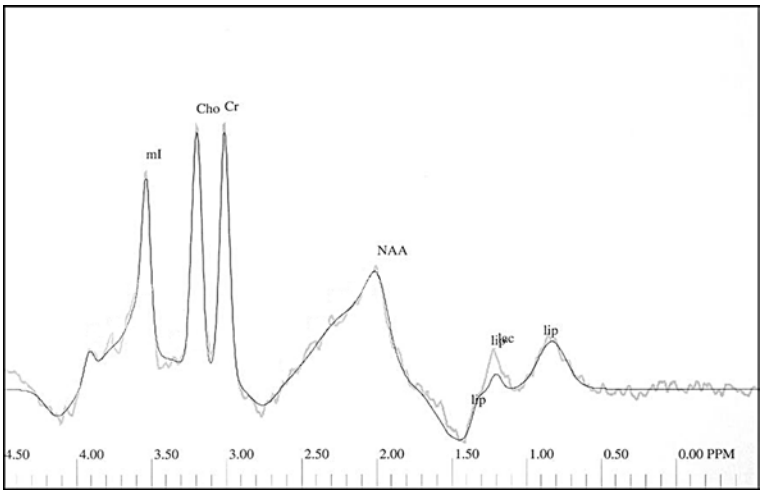

Fig. 3a

Fig. 3 a-b. MR spectroscopy in acute phase of HSE (1.5T, PRESS, TR/TE=1500/35, nex=192); the decrease in N-acetylaspartate (NAA), the increase in the choline (Cho) and the presence of lactate (Lac) and lipids (Lip) bands (a). In the follow-up MRS, partial normalization of NAA and the increase in mioinositol (mI) responsible for intensive gliosis process (b).

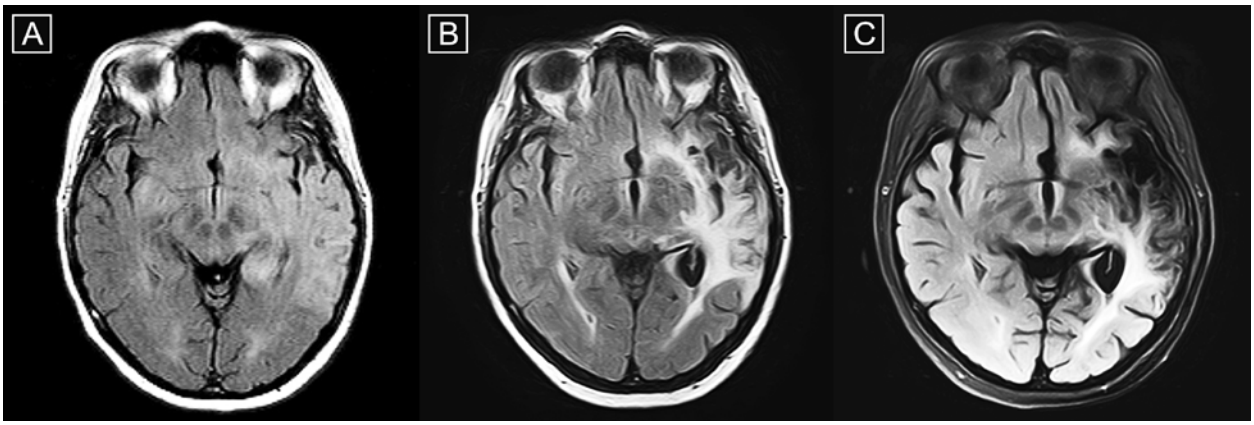

Fig. 4 a-c. Progressive left temporal lobe atrophy after HSE. Extensive, hyperintense gliosis area, hyperintensive on FLAIR images, with gradual enlargement of the CSF spaces in follow-up studies (a-c; a-b: 1.5T, TR/TE=8000/120; c:3T: FLAIR Fatsat TR/TE 8000/96).

Histopathological examinations

Morphologically, HSE has its course as necrotic-hemorrhagic inflammation affecting cortex and subcortical white matter. As the disease develops lesions in capillaries and in small cortex vessels and subcortical white matter become visible as small extravasations. In the second and third week of the disease, hemorrhagic necrosis and perivascular oedema develop in inflammatory areas. According to the latest studies, it seems that changes in HSE course are the result of the virus itself as well as immune response, in which microglia elements and cytotoxic lymphocytes (inducing cytokine and interleukin production) are involved [4,39].

Differential diagnosis

HSE differentiation in imaging should take into account first of all limbic encephalitis, gliomatosis or infiltrative gliomas, ischemic lesions of the middle cerebral artery territory**,** cortical oedema due to sustained seizure activity and MELAS syndrome (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes)**.**

Limbic encephalitis (LE) was first associated with disseminated malignancy, most often as microcellular lung carcinoma or testicular cancer due to onconeuronal antibodies against intracellular antigens [40]. Recent studies show that LE can also develop as a result of occurring antibodies against superficial antigens of cellular membranes, e.g. voltage-gated potassium channels, glutamic acid decarboxylase or NMDA receptors, which are not accompanied by neoplastic tumor [41]. MRI scans usually show diffuse, unilateral or bilateral involvement of frontal or temporal lobes with cingulate gyrus, insular cortices or amygdales and hypothalamus. Early stage gives changes with cortical oedema and slight body mass effect; moderate, non-typical contrast enhancement occurs in 25% of all cases [41]. Basal nuclei, brainstem and spinal cord are occupied rarely [42]. Lesions can disappear in the course of the disease or can evolve in the direction of degenerative and atrophic changes concerning both temporal lobes - mesial temporal sclerosis [41,43]. In differential diagnosis in imaging examination, lack of typical cortical contrast enhancement and body mass effect as well as lack of haemorrhagic areas that point to HSE etiology [44].

Cerebral gliomatosis is a rare extensive form of the neoplastic process of the CNS. According to WHO, it is an entity of unknown origin, separated from neuroepithelial tumors [45]. Two types of gliomatosis can be distinguished: type I is a classical diffuse infiltration without solid tumor, in type II, apart from diffuse process, discrete mass is noticed [46]. According to WHO classification, at least 3 lobes should be involved to diagnose gliomatosis. Hyperintense changes mainly affect white matter, sometimes with corpus callosum. They are best seen with T2-weighted imaging and FLAIR. On T1-weighted imaging they are iso- or hypointense, usually without enhancement after contrast administration because of lack of blood-brain barrier damage and low mass effect [47]. MR spectroscopy shows the increase in choline and the decrease in NAA level and the presence of lactate bands, which correlate with degree of malignancy [48].

The temporal lobes can be affected in more or less extensive manner due to acute or subacute ischemic changes. Most of these changes have arterial origin, resulting from atheromatic thrombosis of large vessels, changes in small peripheral vessels, or embolic incidents. Localization consistent with the territory of arterial supply is characteristic for ischemic lesions. This is particularly important in case of temporal lobes with middle and posterior cerebral arteries and anterior choroidal artery supply. Typical symptoms comprise cortical oedema and blurring of cortical-subcortical differentiation with early involvement of basal ganglia. Mass effect increases together with infarction and intensity of vasogenic oedema. Haemorrhagic extravasation, larger bleeding focuses or laminar cortical necrosis can occur in the ischemic area [49]. MRI is a better method than CT scan in early ischemic strokes diagnostics, especially while using DWI and PWI techniques, which enables differentiation of infarction and penumbra areas. However, in recent years, the increase in CT perfusion is stressed [50,51].

Periictal and postictal cortical oedema in a course of epilepsy or generalized tonicoclonic seizure can be visible in MRI scans even for several days [52,53]. The increase in signal intensity on T2-weighted images concerns mainly cortex and, to a lower extent, white matter, usually frontal lobe or hippocampus. Lesions are accompanied by mass effect and discrete contrast enhancement, which can be visible in peri- as well as in postictal period. MR perfusion imaging or SPECT demonstrate hyperperfusion, while DWI shows diffusion restriction, however, these changes are usually reversible [54]. These lesions are caused by cytotoxic and vasogenic oedema induced by seizures activity and usually regress leaving residual area of increased T2 signal intensity [53]. Focal areas of crossed cerebellar diaschisis or ipsilateral thalamic lesions can be seen [55]. Sometimes involutions develop with cortical laminar necrosis, cortical atrophy and gliosis leading to mesial temporal sclerosis [52].

MELAS syndrome is a multiorgan disorder caused by mutations in the mitochondrial genome. MRI scans shows numerous confluent cortical and subcortical stroke-like lesions with predilection to involvement posterior, temporal, frontal or parietal

regions. Lesions are usually asymmetrical, crossing the cerebral vascular territories. Changes can occur in different phases of evolution. Focuses in acute phase can show enhancement after contrast administration. In DWI unlike typical ischemic lesions, shows increase in signal intensities (due to T2 shine through effect), with small increase or without any changes in ADC (Apparent Diffusion Coefficient) as a result of dominance of the vasogenic oedema over the cytotoxic one [56]. Decrease in NAA and significant increase in lactates contents are characteristic in MR spectroscopy [57].

Treatment and prognosis

Mortality in the course of HSE is very high in untreated patients and rates up to 50-70% [58,59]. While treating with Acyclovir, mortality decreases to 15-25% [3,59], however, half of patients suffer from neurological disorders – seizures, dysphasia, memory impairment and personality changes [3]. Only about 2-5% of patients recover from the disease [60]. Mortality among patients with immune deficiency is six times higher [14]. Acyclovir is a first line treatment. Its efficacy was proved by randomized study conducted in the 1980's [61]. When the HSE is suspected, treatment should be initiated as quickly as possible, up to 6 hours after admission, even if the diagnosis is not proved by CSF test or by imaging methods [18]. Decreased immunity, low pleocytosis in the cerebrospinal fluid and the late inclusion of acyclovir therapy are adverse prognostic factors [14]. Advanced age, coma, impaired immunity, low pleocytosis in CSF and late initiation of acyclovir treatment, are adverse prognostic factors [14,62].

CONCLUSIONS

Imaging examinations are significant in the diagnostic process in patients with HSE. The imaging technique of choice is MR imaging with contrast administration including FLAIR and GRE T2* sequences. MRI is the best method to specify the extent of damages and secondary changes. Differentiation in imaging examinations is difficult and requires careful clinical – radiological analysis because of the wide range of changes which have similar presentations and imaging features. DWI, MRS and perfusion imaging are additional techniques, which strengthen the value of imaging methods in diagnosis and monitoring of the disease as well as estimate the activity of inflammation.

Conflict of interest

The authors declare that they have no conflict of interest.

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