Herpes simplex encephalitis – diagnostic imaging

Tyrakowska-Dadełło Z.[1A-E], Kułakowska A.[2B,C,D], Zajkowska J.[3B,C,E], Pancewicz Sł.[3C,E,F], Tarasów E.[1,4 A,E,F]

1. Department of Radiology, Medical University of Bialystok, Bialystok, Poland
2. Department of Neurology, Medical University of Bialystok, Bialystok, Poland
3. Department of Infectious Diseases and Neuroinfections, Medical University of Bialystok, Bialystok, Poland
4. TMS Diagnostyka, Bialystok, Poland

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ABSTRACT

The phenomena of neuroinvasiveness, latency and reactivation are characteristics of the Herpes simplex virus (HSV). The 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. The 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, more or less symmetrical hyperintense cortical and subcortical white matter lesions occur on T2-weighted images with gyral and/or leptomeningeal contrast enhancement. MR spectroscopy can be helpful in lesion diagnosis and monitoring, while diffusion-weighted imaging (DWI) can be used to evaluate inflammatory process activity. Differentiation of HSE in imaging should consider limbic encephalitis, gliomatosis cerebri, cerebral ischemia, cerebral edema 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 a confirmation of the diagnosis.

Keywords: Herpes simplex encephalitis, limbic encephalitis, computed tomography, magnetic resonance imaging, MR spectroscopy

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***Corresponding author:**
Zuzanna Tyrakowska - Dadełło
Department of Radiology, Medical University of Bialystok
Sklodowskiej 24a St, 15-276 Bialystok, Poland
Tel.: +48-85-8318901; Fax: +48-85-8318926; e-mail: zuza1405@op.pl

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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. The 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 the neurological sequel consequences recognized in a 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 the *Herpetiviridae* family, which are characterized by latency and reactivation abilities. Approximately 60% of adults have serological evidence of previous HSV-1 infection, although the 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 a CNS infection, wherein the 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 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, an immune disorder; although specific mechanisms of reactivation are still not known [4].

CNS is affected due to the hematogenous spread or spreading of lesions along nerve fibers from extra cerebral focal lesions. During latency, the infection is symptomless, while in the reactivation phase, in which new particles of the 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 the temporal and frontal lobes occurs as a result of spreading the infection along the 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 the hippocampus with the cingulate gyrus [7].

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: the prodromal phase and the 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 the muscles and joints [9]. Localization in the 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 nature of the symptoms depends on the anatomical localization of the 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 the 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 the CNS, caused by HSV-2 (virus), have usually have the course of aseptic meningitis, myelitis, or radiculitis. Such cases used to be 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 to the frontal lobe and paraventricular area. In such cases, virus transmission is vertical during childbirth [16,17].

Biochemical and serologic tests

Lymphocytic pleocytosis, an increase in protein, normal glucose levels, and the presence of erythrocytes in cases of bleeding are found in the cerebrospinal fluid (CSF) test [18]. The polymerase chain reaction method identifies HSV in CSF and helps to confirm the diagnosis. Its sensitivity

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

Imaging examinations

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

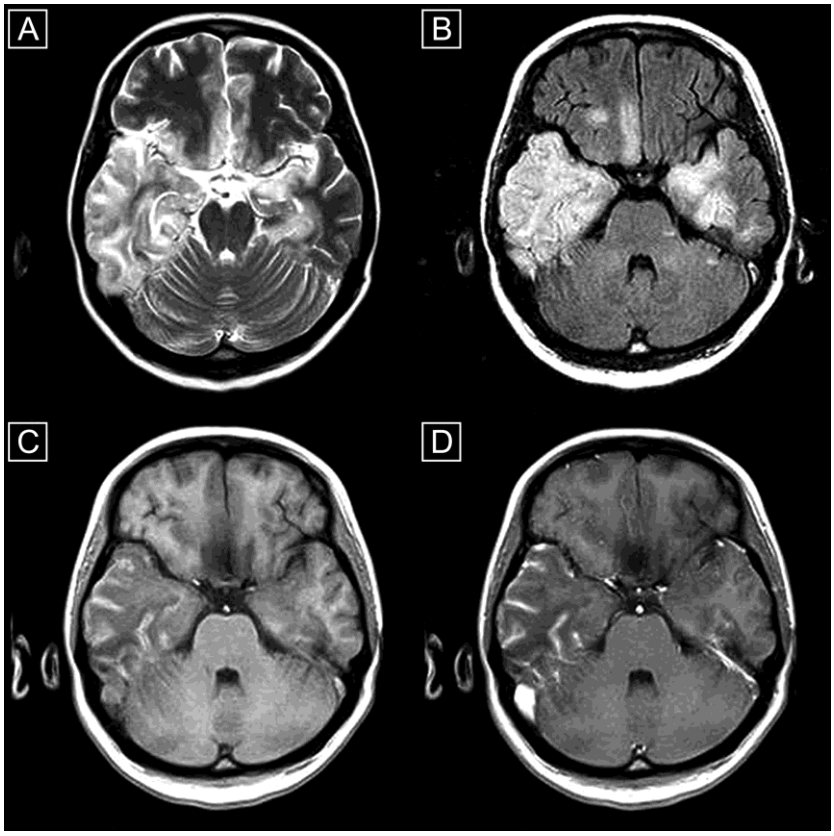

Figure 1 a-d. Bilateral, asymmetrical lesions in acute phase of HSE. On T2-weighted images (1.5T, TR/TE=5200/105) involvement of medial parts of the temporal lobes, more severe on the right side (a). Straight gyrus of the right frontal lobe involvement visible on FLAIR sequence (TR/TE=8000/120) (b). 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 the temporal lobes, is found in about 55% of patients and about 15% of cases appear as only extratemporal localization [21]. Basal ganglia changes are rare, lesions in the thalami were described only in single cases [22,23]. Lesions are usually bilateral but asymmetrical. Sometimes they can affect the occipital cortex [20] or occasionally they affect the midbrain and pons. The pons is probably affected as a consequence of backward dissemination along the trigeminal nerve [7]. Selective involvement of the midbrain and hindbrain happens rarely [24]. In patients with immune deficiencies, the CNS changes are usually more extensive and may cover the brainstem and cerebellum, very often without typical lesions in the 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, the 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 an inconsiderable mass effect and weak heterogeneous or band contrast enhancement along the cortex gyri. Hemorrhagic areas can occur within the lesions, but the frequency of hemorrhage 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 symptom occurrence. More or less symmetrical hyperintense lesions in the cerebral cortex and subcortical white matter are visible on T2-weighted images and on FLAIR sequence (Fig. 2 a-d).

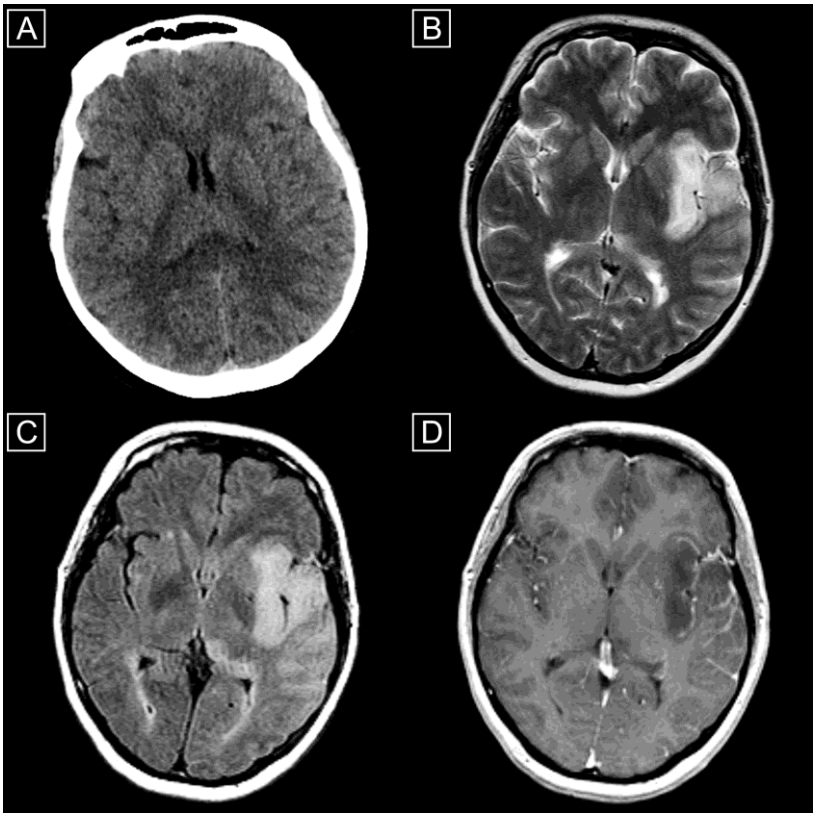

Figure 2 a-d. Lesions in acute phase of HSE. CT scan shows only a delicate asymmetry of lateral sulci (a). A wide hyperintense area on T2-weighted images (1.5T, TR/TE=5200/105) with the mass effect including the left temporal lobe insula except the basal ganglia (b). On FLAIR sequence (TR/TE=8000/120), 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 the early stage, DWI imaging states restriction of diffusion with features of cytotoxic edema. Diffusion disorders regress approximately in the second week of the disease and change into vasogenic edema [30]. It is believed, that the DWI method can be used to estimate inflammatory process activity and has a predictive value [31,32].

MR spectroscopy (MRS) is helpful in lesions diagnosis and monitoring. In the 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 lipid bands can be observed. Control MRS examination showed partial normalization of metabolic changes (with NAA restoration) and an increase in mioinositol (mI) that resemble gliosis processes (Fig. 3 a-b) [33,34].

In SPECT examinations, using 99mTc-HMPAO (99mTc-hexamethylpropyleneamineoxime), hyperperfusion areas, with features of "luxury flow," are stated in the early HSE phase. They are connected with acidosis and have an 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 a 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].

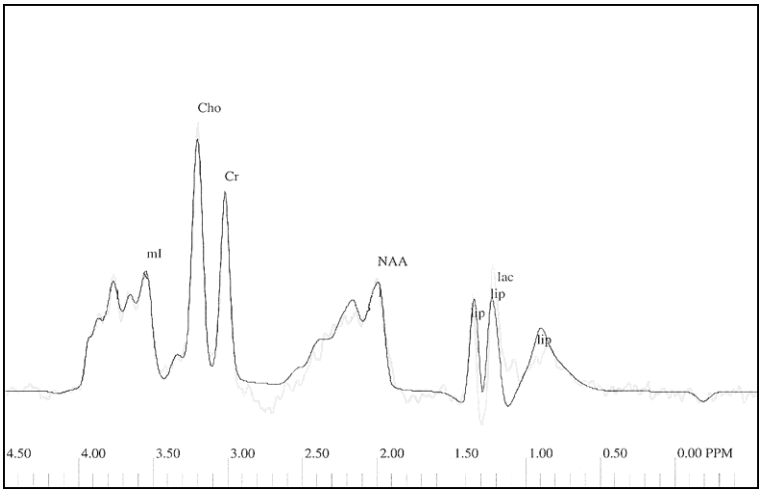

Fig. 3a

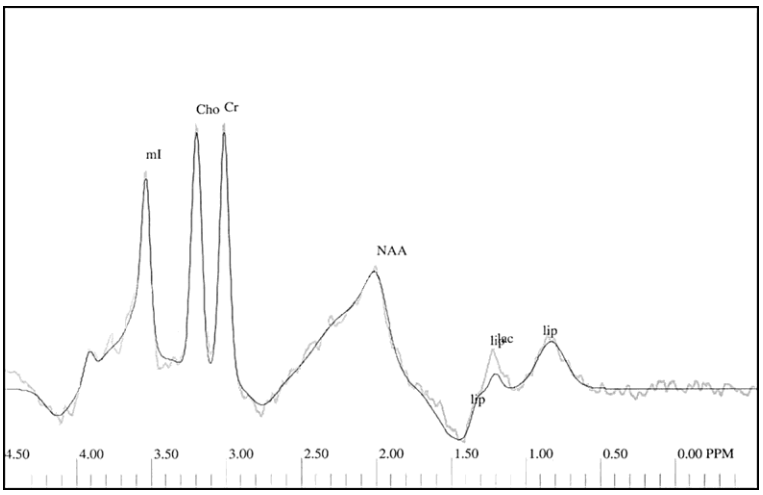

Fig. 3a

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

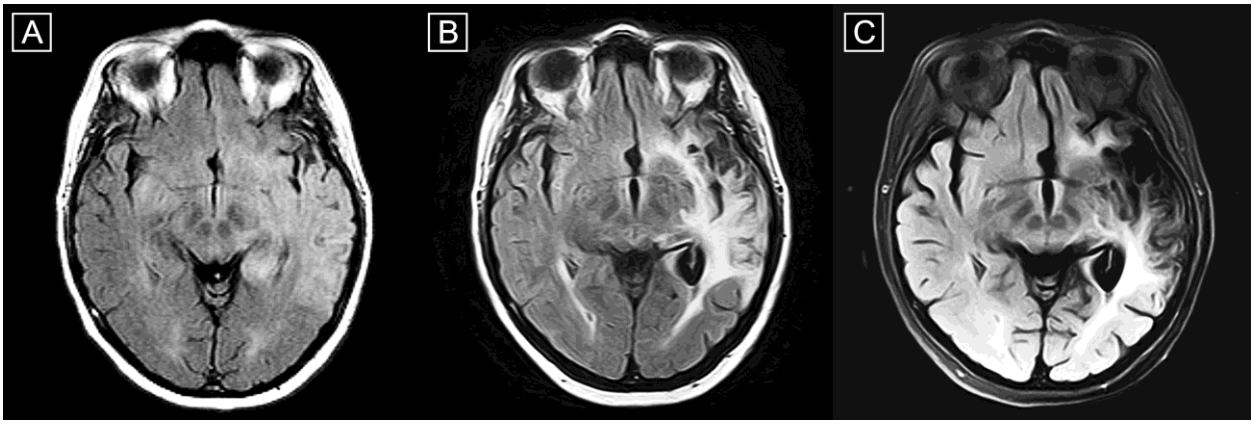

Figure 4 a-c. Progressive left temporal lobe atrophy after HSE. Extensive, hyperintense gliosis area, hyperintensive on FLAIR images, with gradual enlargement of CSF spaces in follow-up studies (a-c; a-b: 1.5T, TR/TE=8000/120; c:3T: FLAIR Fatsat TR/TE 8000/96).

Histopathological examinations

Morphologically, HSE has its course as necrotic-hemorrhagic inflammation affecting the cortex and subcortical white matter. As the disease develops lesions in the capillaries, small cortex vessels, and subcortical white matter become visible as small extravasations. In the second and third weeks of the disease, hemorrhagic necrosis and perivascular edema develop in inflammatory areas. According to the latest studies, it seems that changes in the course of HSE 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 edema due to sustained seizure activity, and MELAS syndrome (Mitochondrial Encephalo-myopathy, 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 a neoplastic tumor [41]. MRI scans usually show diffuse, unilateral or bilateral involvement of the frontal or temporal lobes with the cingulate gyrus, insular cortices or amygdales and hypothalamus. The early stage exhibits changes with cortical edema and a slight body mass effect; moderate, non-typical contrast enhancement occurs in 25% of all cases [41]. The basal nuclei, brainstem and spinal cord are rarely occupied [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 hemorrhagic areas that point to HSE etiology [44].

Cerebral gliomatosis is a rare extensive form of the neoplastic process of the CNS. According to the WHO, it is an entity of unknown origin, separate from neuroepithelial tumors [45]. Two types of gliomatosis can be distinguished: type I is a classical diffuse infiltration without a solid tumor, in type II, apart from the diffuse process, a discrete mass is noticed [46]. According to the WHO classification, at least 3 lobes should be involved to diagnose gliomatosis. Hyperintense changes mainly affect white matter, sometimes with the 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 a lack of blood-brain barrier damage and low mass effect [47]. MR spectroscopy shows an increase in choline and decrease in NAA level and the presence of lactate bands, which correlate with the degree of malignancy [48].

The temporal lobes can be affected in a more or less extensive manner due to acute or subacute ischemic changes. Most of these changes have an arterial origin, resulting from atheromatic thrombosis of large vessels, changes in small peripheral vessels, or embolic incidents. A 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 edema and blurring of cortical-subcortical differentiation with early involvement of the basal ganglia. The mass effect increases together with infarction and intensity of vasogenic edema. Hemorrhagic 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 stroke diagnostics, especially while using DWI and PWI techniques, which enables differentiation of infarction and penumbra areas. However, in recent years, an increase in CT perfusion is stressed [50,51].

Peri-ictal and postictal cortical edema in the 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 the cortex and, to a smaller extent, white matter, usually the frontal lobe or hippocampus. Lesions are accompanied by mass effect and discrete contrast enhancement, which can be visible in the 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 edema induced by seizure activity and usually regress, leaving a 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 show numerous confluent cortical and subcortical stroke-like lesions with predilection to the involvement of the posterior, temporal, frontal

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

Treatment and prognosis

Mortality in the course of HSE is very high in untreated patients, with rates up to 50-70% [58,59]. While treating with Acyclovir, mortality decreases to 15-25% [3,59]; however, half of the 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 of treatment. Its efficacy was proved by a randomized study conducted in the 1980s [61]. When 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 imaging methods [18]. Decreased immunity, low pleocytosis in the cerebrospinal fluid, and 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 damage and secondary changes. Differentiation in imaging examinations is difficult and requires a careful clinical and radiological analysis because of the wide range of changes which have similar presentations and imaging features. DWI, MRS, and perfusion imaging are additional techniques that strengthen the value of the imaging methods in the diagnosis and monitoring of the disease as well as estimate inflammation activity.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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