Follow-Up MR and MRS Studies in Herpes Simplex Encephalitis

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Abstract

The paper presents imaging studies in eight patients with polymerase chain reaction proven Herpes Simplex encephalitis (HSE). MRI studies in the acute phase of infection have presented both typical and unusual changes. 3-year follow-up results of imaging examinations have also been described. DWI (Diffusion-weighted Imaging) and MR spectroscopy (MRS) values in the course of HSE infection have been shown in addition to conventional MR studies. In the article, particular emphasis is put on the importance of ischemic changes during HSE infection, which have not been widely discussed so far.

Keywords: Diffusion weighted imaging; Herpes simplex encephalitis; Limbic encephalitis, Magnetic resonance imaging; MR spectroscopy

Introduction

Herpes Simplex encephalitis (HSE) is one of the most serious viral diseases of the central nervous system (CNS). The imaging abnormalities most commonly observed in HSE have been well-described, yet there are also unusual forms that are diagnostically difficult [1-3]. High mortality rate justifies the necessity of fast and effective diagnostics [4,5]. Additionally, advanced atrophic changes occur after an acute phase of inflammation even in patients who received appropriate treatment early enough. Neuroimaging is a significant component in the diagnosis of HSE in the acute and chronic phases. MRI has a very high sensitivity and specificity in the diagnosis, especially in the early period of inflammation [6,7]. The work aims to present and summarize neuroimaging changes in the acute phase and long-term follow up of HSE with particular attention on the importance of ischemic changes during HSE infection, which until now have not been widely discussed.

Materials and Methods

A total of 8 patients with polymerase chain reaction proven HSE were included in our study, 6 women and 2 men, ranged from 45 to 66 years (median 51.5). MR imaging was performed in the acute phase of the disease (3-5 days since the onset of symptoms) and after a month (± 1 week) of acyclovir treatment. The sequential MR examinations were performed after 9 months, 1 and 3 years (n=7) after the onset of symptoms (± 1 month).

MR imaging and MR spectroscopy examinations were performed on 1.5T and 3.0T scanners (Picker Eclipse, Picker International Inc., Highlands Hts, OH, USA and Toshiba Vantage and Toshiba Titan, Toshiba Medical System Corporation, Japan). In all patient's routine MR sequences were performed including examination after contrast administration. Chronological changes were visually assessed basing on T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images.

In 5 patients DWI (Diffusion-weighted Imaging) was also performed. Diffusion images with b=1000s/mm2 and the ADC maps (Apparent Diffusion Coefficient) were studied. 1H MR spectroscopy examinations were carried out in 4 patients by means of single voxel PRESS (Point-resolved spectroscopy) sequence. Voxels of 2 × 2 × 2 cm3 were positioned in the regions of both temporal lobes.

Results

In the initial MR study, hyperintensive changes were observed in T2-weighted images in the anterior and medial parts of the temporal lobes in all patients. Bilateral, asymmetric changes occurred in 6/8 patients, unilateral in 2/8 (Figures 1 and 2). In 6/8 patients’ lesions were observed in the temporal lobe island and in basal parts of the frontal lobes and only in 1 in the lateral ventricles. Only 1 patient had a hyper intensive focus in the left thalamus (Figure 2). In 3 subjects corticomedial hyperintensity in temporal lobes was found in T1-weighted images (Figure 1c). In all cases prominent swelling was found with moderate mass-effect; contrast leptomeningeal enhancement was present in 4/8 patients and gyral enhancement in 2/8, while in 2/8 no contrast enhancement was noted (Figures 1-3).

In the follow-up studies after 1 month, the changes regressed, the severity of swelling decreased, with the lack of contrast enhancement in almost every patient, with the exception of one, who developed strong cortical band enhancement (Figures 3a and 3b).

In the acute phase, 3 patients had diffusion restriction in DWI i.e., high signal on DWI and low signal on ADC. In 2 patients a mixed hypo-/hyperintense signal in the ADC sequence was found. In all patients in the follow-up study after 1 month, the signal in DWI remained slightly elevated, while ADC signal began to rise above the normal patency level and became hyperintense in subsequent control examinations with low DWI signal (Figures 4a–4f).

In subsequent follow-up studies after 9 months, 1 and 3 years, there was a gradually progressing cystic encephalomalacia with volume loss (dominant in 5 individuals), combined with shrinking gliosis zone (prevaling in 2 patient) in the affected area (Figures 5a–5f).

In MR spectroscopy in the acute phase (n=4), the decrease in N-acetylaspartate (NAA), a slight increase in the choline/creatinine (Cho/ Cr) ratio and the presence of lactate and lipids bands were observed. Follow-up MRS examination (n=3) showed partial NAA restoration and the increase in miosinotol/creatin (mi/Cre) ratio (Figures 6a and 6b).

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Discussion

Typical changes described in the course of HSE were found in all our patients. The changes usually comprised different parts of the limbic system - most often anterior and medial parts of the temporal lobes. Insular cortex and inferolateral frontal lobes were also often affected. Lesions were usually bilateral but asymmetrical, similarly as in another authors’ report [1]. According to the literature, the involvement of other parts of the brain, except temporal lobes, is found in about 55% of patients, and about 15% of cases occur as extratemporal form exceptionally [3]. We found changes in the thalamus in 1 patient, though basal ganglia are also infrequently occupied, and lesions in thalamuses were described only in single cases [8].

MRI with contrast administration is the imaging technique of choice and shows lesions from the second day after clinical symptoms occurrence [2,6]. Hyperintense lesions in cerebral cortex and subcortical white matter are visible in T2-weighted images and in FLAIR sequence [9]. Hemorrhagic areas may be seen in T1-weighted images, in gradient echo sequences (GRE) or SWI (Susceptibility-weighted Imaging) [6], but the frequency of haemorrhage occurrence is very low [10]. In the study group, there was no bleeding in any case. Contrast enhancement along with the affected cortex appears usually one week after the first symptoms [11]. In the examined group we found leptomeningeal or gyral enhancement in 6/8 of patients in the acute phase, with no enhancement in the remaining 2. Contrast enhancement was no longer visible in almost every patient in the 1-month follow-up MRI.

One patient had leptomeningeal enhancement in the first study, while after 1 month, cortical/gyral enhancement appeared. Considering the recent studies indicating that 30% of patients develop autoantibodies against N-Methyl-D-aspartate receptor (NMDAR) in the course of HSE, we suspected limbic autoimmune inflammation in this case [12]. Nevertheless, anti-NMDA receptor antibodies in serum and CSF in the case described above were negative, which indicates that the patient showed the persistence of the inflammatory process in the course of HSV infection (relapsing post-HSE).

Anti-NMDA antibodies were determined in 4/8 patients and, there was only one patient in our group who had NMDAR-antibodies. This patient had bilateral hyperintensive in T2-weighted images changes in temporal and frontal lobes and leptomeningeal enhancement in only
first MRI. In this patient we did not find any specific changes in neuroimaging studies, which most likely resulted from the fact that no additional examination was performed during the period of symptoms severity. According to the literature in most patients with anti-NM-DAR antibodies MRI showed new areas of contrast enhancement that are only detected in some patients with HSE [12,30].

In the early stage of HSE, DWI imaging states restriction of diffusion with features of cytotoxic edema [14,15]. In our group, cytotoxic or mixed (cytotoxic/vasogenic) edema was present in all patients. Signal changes in DWI appear probably due to the fact that diffusion disorders regress approximately in the second week of the disease and change into vasogenic edema [14]. These observations indicate that DWI can be used to estimate the activity of the inflammatory process [15].

In our 2 subjects, cortical hyperintensity was found in T1-weighted images in the acute stage, so far not described in the course of HSE. Similar changes in patients with ischaemic stroke are determined as cortical laminar necrosis [16]. Other studies confirm that HSE leads to perfusion disorders and ischemic changes. In SPECT examinations hyperperfusion areas, with features of “luxury flow”, are stated in the early HSE phase. They are connected with acidosis, and according to Launes et al. [17] are considered as adverse prognostic factor. These changes are also confirmed by PET and CT perfusion [18,19]. Perfusion disorders regress relatively fast, regardless of lesions in routine MRI scans [18].

In the acute phase of HSE, the decrease in N-acetylaspartate, a slight increase in the choline/creatinine (Cho/Cr) ratio (lower than in most tumors) and the presence of lactate and mobile lipids bands were found in all patients. Control MRS examination showed partial normalization of metabolic changes, with small degree of NAA restoration and the increase of mioinositol. These changes reflect neuronal or axonal injury (NAA), demyelination processes (Cho, Lip) and anaerobic metabolism (Lac). Such changes are confirmed in histopathological studies in which necrosis with loss of neurons, macrophage infiltration and prominent gliosis with reactive astrocytosis were found [20-22]. We concluded that MRS is able to show specific histological findings, and MRS is a helpful tool in lesion diagnosis and HSE monitoring.

In the whole group, we demonstrated atrophic changes, which showed progression even within 3-year follow-up. We distinguished two types of the atrophy - cystic encephalomalacia combined with less severe gliosis zone and with volume loss was found in most cases. In 2/8 of patients prevailing shrinking gliosis zone with less severity of cystic changes was depicted. Atrophic changes after HSE are well known. However, the two types of post-HSE changes have not been described so far. Multicystic encephalomalacia (MCE) is a variant of encephalomalacia seen in neonates as a result of an extensive brain insult [23,24], but may also be secondary to meningoencephalitis or abusive head trauma [25,26]. The rise of MCE results from the presence of necrosis areas that develop into numerous loculated pseudocysts within the white matter and cortex. There are no studies showing these changes in adults, but we suppose that in HSE it may stem from extremely cytopathic effect of the virus, which causes vasculitis and both ischemic and hemorrhagic lesions in the nervous tissue of the brain. It may cause disorder in the vascular autoregulation or reperfusion, and lead to the oxidative stress [27-29]. The long-lasting changes may indicate that HSE is a very serious damaging factor, and the elimination of the effects of inflammatory changes and the formation of glial scars is prolonged. Autoimmune mechanisms may also be considered, although antibodies are only detected in some patients with HSE [12,30].

Conclusions

The long-lasting changes in MRI studies may indicate that HSE is a very serious damaging factor and the elimination of the effects of inflammatory changes and the formation of glial scars is prolonged in time. It seems that ischemic mechanisms play an important role in the course of HSE.

Both MRS and DWI are useful techniques in the diagnosis and monitoring of HSE and can be used to estimate the activity of the inflammatory process.
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