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Progressive multifocal leukoencephalopathy in HIV-infected patients – MR findings and metabolic changes in 1H MR spectroscopy

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Summary

Background:

We present magnetic resonance (MR) and 1H magnetic resonance spectroscopy (MRS) imaging alterations in four HIV-infected patients with progressive multifocal leukoencephalopathy (PML).

Material/Methods:

In three of those subjects, changes typical of PML imaging were disclosed. MRS examinations showed a decrease in N-acetylaspartate content as well as an increase in choline and myoinositol content with presence of lactate and lipids signals. In one case of atypical MR image, MR spectroscopy confirmed PML diagnosis.

Results/Conclusions:

The influence of antiretroviral treatment on central nervous system imaging as well as prognostic aspects of MR and MRS in subjects with progressive multifocal leukoencephalopathy are discussed.

Key words:

HIV • progressive multifocal leukoencephalopathy • magnetic resonance spectroscopy

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Background

Introduction of highly active antiretroviral therapy (HAART) has markedly reduced the incidence of opportunistic infections of the central nervous system in HIV-infected patients. However, the spectrum of these diseases remains unchanged in AIDS; toxoplasmosis, cryptococcosis, and progressive multifocal leukoencephalopathy (PML) still belong to the most common CNS infections in the HIV infection course.

The diagnosis is based on neuroimaging studies in most cases of CNS abnormalities in HIV-infected patients. The range of available diagnostic modalities has increased, including currently not only structural imaging techniques, such as computed tomography (CT) or magnetic resonance

(MR) but also MR-based functional techniques. Diffusion and functional imaging, as well as magnetic resonance spectroscopy (MRS) support the diagnostic role of MR imaging and allow more precise diagnostics of cerebral anomalies in HIV-infected patients.

Materials and methods

The studied group consisted of 4 patients diagnosed with PML, 2 women and 2 men (mean age 37.6±5.3 years) treated in the Observation and Infectious Diseases Department of the Medical University of Białystok. The diagnosis was based on clinical examinations and neuroimaging.

All the patients received HAART composed of two nucleoside transcriptase inhibitors and one non-nucleoside

transcriptase inhibitor or protease inhibitor. The mean duration of treatment was 21 months (12-36).

MR imaging was performed using a Picker Eclipse system (Picker International Inc., Highland Heights, OH) with magnetic field intensity of 1.5 T with a tube designed for head scanning protocols. The protocol included T1-weighted FAST (Fourier-Acquired Steady State) sequence imaging, T2-weighted FSE (Fast Spin Echo) sequence and FLAIR (Fluid Attenuation Inversion Recovery) sequence in the axial plane. The scans were performed before and after i.v. contrast administration (Magnevist, Schering, Germany) at 0.1 ml/kg b.w. dose.

MRS was performed using the PRESS (Point Resolved Spatially Localised Spectroscopy) sequence with the following parameters: TE 35 ms, TR 15000 ms, number of repetitions 192, Voxels of 8 cm³ (2 cm x 2 cm x 2 cm) size were localized in the regions of most severe anomalies identified on the basis of MR. Recording of the spectra was preceded by unification of the field homogeneity in the scanned area. Then the surface area of unsuppressed water signal was measured in 8 repetitions. Water signal suppression was effected using the MOIST (Multiply Optimized Insensitive Suppression Train) sequence. The obtained spectra were processed automatically using the manufacturer's automatic procedure (Picker, Via 2,0), including the correction of phase, baseline and automatic curve adjustment using an iterative, non-linear Levenberg-Marquardt least square method.

Spectrum analysis included the signals of N-acetylaspartate (NAA), creatine (Cr), choline (Cho) myoinositol (mI), lactates (Lac) and lipids (Lip). Proportions of these compounds in relation to creatine level were analyzed: NAA/Cr, Cho/Cr, mI/Cr, Lip/Cr, Lac/Cr. In order to exclude the differences of internal standard levels, the level of creatine was assessed in relation to unsuppressed water signal according to the following formula: creatine surface area x 1000/ unsuppressed water signal surface area.

The obtained results were compared with the levels of chemical compounds obtained in the control group consisting of 12 health volunteers with similar age (mean age 37.4±5.8 years) and gender distribution (6 men, 6 women).

Results

In all the patients, the changes were characterized by hyperintense signal in T2-weighted images and FLAIR sequence (Fig. 1a). In 3 out of 4 patients, the lesions were hypointensive in T1-weighted images (Fig. 1 b), while in 1 patient only a slight signal decrease was observed (Fig. 2 c). In 3 out of 4 patients, the lesions were asymmetric, in 2 in the occipital region and in 1 in the occipital and parietal regions. Bilateral, symmetric involvement of the occipital and parietal regions was observed in 1 patient (Fig. 2 a, b). In 3 out of 4 patients, subcortical arcuate fibers were involved (Fig. 1 b). In none of the analyzed cases contrast-enhancement or mass effect was observed. However, all the patients demonstrated various extent of cortical and subcortical atrophy with distension of the ventricular system and paracerebral fluid spaces.

The results of MR spectroscopy in the studied group of patients are presented in Table I. Taking into account the low number of patients, the results have been presented as ranges, without statistical analysis. Figure 3 presents MR spectra with typical (Fig. 3 a) and atypical (Fig. 3b) pattern of changes in MR.

Analysis of results and discussion

Progressive multifocal encephalopathy is a subacute demyelination process caused by *Papovavirus* (JC virus), belonging to the group of polyomaviruses replicating in CNS glial cells. PML develops as a result of reactivation of latent JC virus infection in immunodeficiency conditions [1]. The incidence of PML in HIV-infected population is estimated at ca. 0.7-7% [2]. The clinical course is usually progressive and most patients die within one year [3, 4].

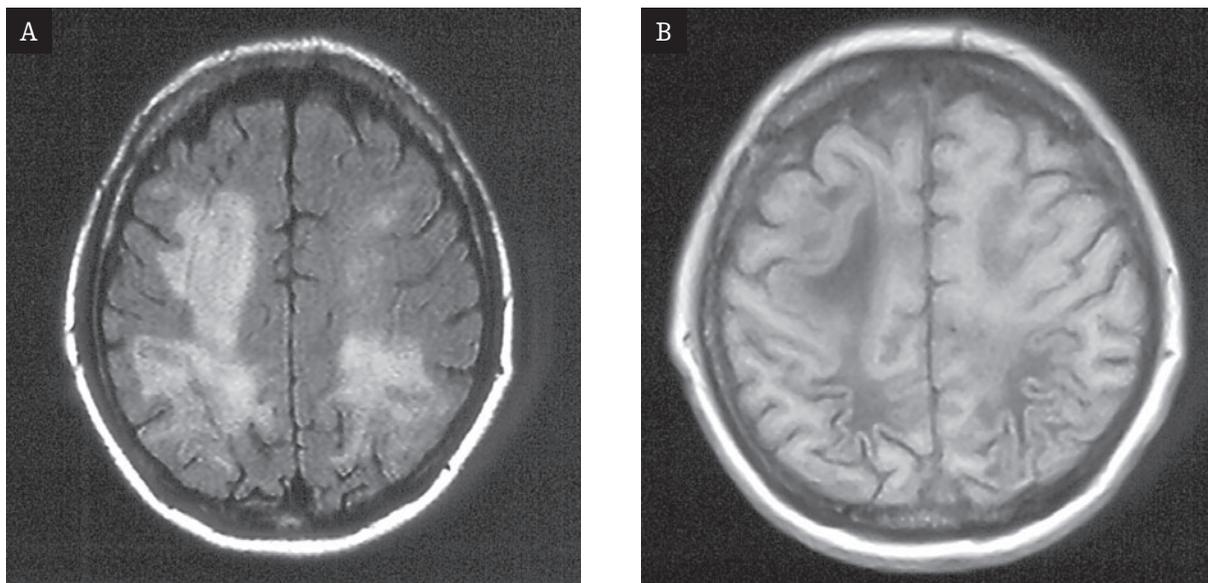


Figure 1 A, B. Typical changes in MR images in a patient with PML. Widespread, asymmetric, hyperintense in FLAIR (A) and hypointense in T1-weighted (B) images of demyelinating lesions with involvement of arcuate fibers.

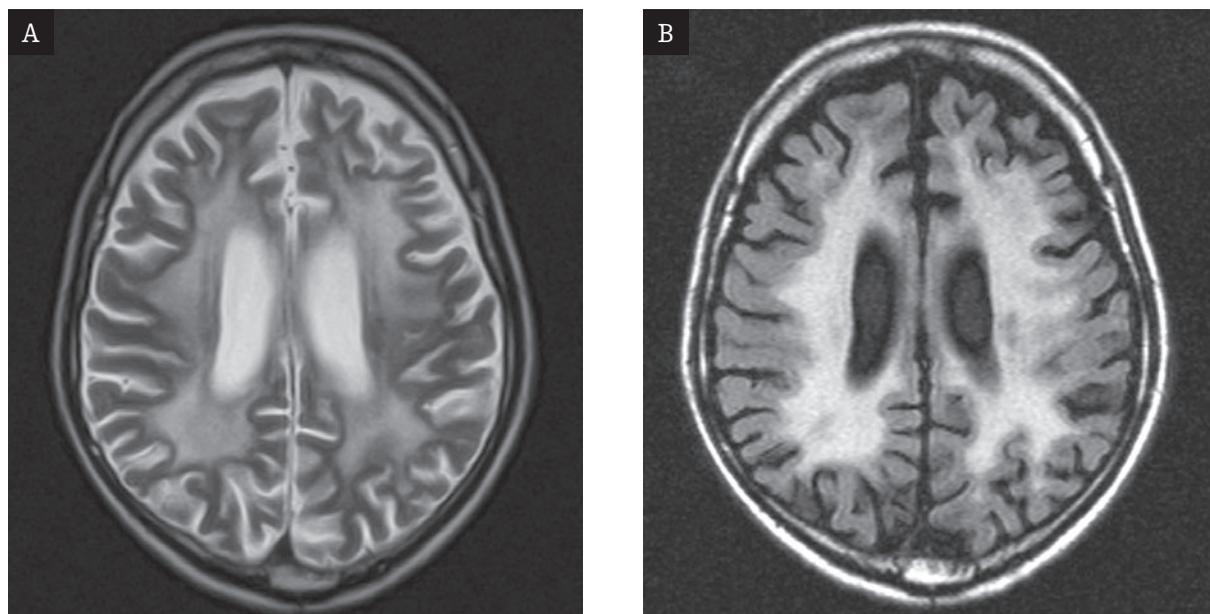


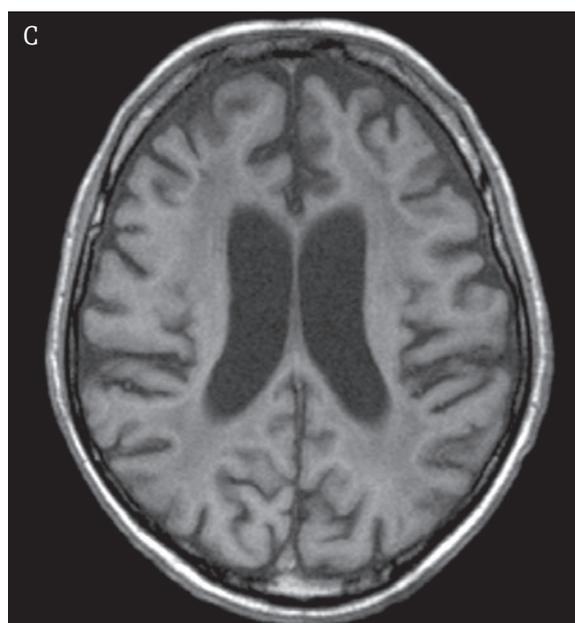
Figure 2 A, B, C. Bilateral, symmetric involvement of parietal white matter in a patient with atypical MR pattern. High signal intensity areas in T2-weighted (A) and FLAIR (B) sequence with slightly decreased signal intensity in T1-weighted images (C).

Demyelination changes developing in the course of this encephalopathy are multifocal, asymmetric, involving the periventricular and subcortical white matter, most frequently localized in the occipital, parietal and frontal lobes. Usually they progress rapidly, with merging of the pathologic foci [5].

The demyelinated areas are usually invisible in CT images. Enting et al. [3] found hypodense areas in CT only in 1 out of 14 patients with PML. On the other hand, MR reveals zones of high signal intensity in T2-weighted images and hypointense in T1-weighted ones. The lesions usually show no enhancement after contrast administration and do not cause a mass effect. However, contrast enhancement or mass effect findings during HAART may indicate favorable response to treatment. Such observations were reported, among others, by Berger et al. [6] and Kotecha et al. [7]. The appearance of contrast enhancement is explained by partial restoration of perivascular inflammatory reaction potential as a result of improved immune status after antiretroviral treatment.

A characteristic symptom of PML is involvement of the subcortical arcuate fibers (U fibers), which causes sharp demarcation of the white matter and the cerebral cortex, the so-called „scalloping” sign [5].

In 90% of PML patients, the changes detectable on neuroimaging are typical; atypical forms present with focal



hemorrhages, involvement of the basal nuclei or predominant cortical and subcortical atrophy [5]. A case of JC infection limited to the granular layer of the cerebellar cortex with no white matter lesions typical of PML visible on MR, but only cerebellar atrophy, confirmed by stereotaxic biopsy, has also been described [8] Cerebellar lesions in the course of PML were also described by Chang et al. [9].

The differential diagnosis of PML should take into account primarily HIV-encephalitis-related changes, formed as a result of subacute inflammatory process caused directly by

Table 1. MR spectroscopy results in PML patients.

	NAA/Cr	Cho/Cr	ml/Cr	Lac/Cr	Lip/Cr	Cr/H ₂ O
PML (n=4)	0.94-0.99	1.15-1.32	0.86-0.98	1.94-3.63	0.43-1.68	0.20-0.22
Control group	1.55-2.12	0.66-0.89	0.43-0.72	(-)	(-)	0.24-0.29

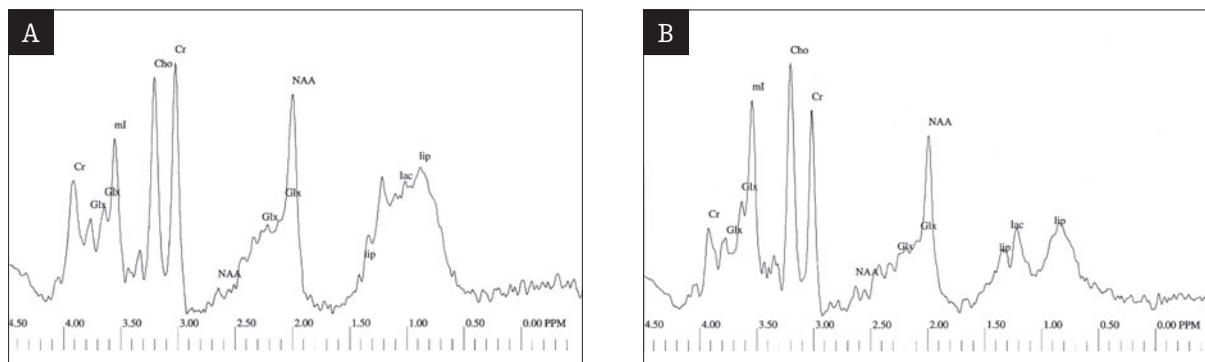


Figure 3 A, B. MR spectra in patients with typical (A) and atypical (B) PML appearance on MR images. Reduced NAA, significantly increased choline, myoinositol and lipids levels with marked lactate presence in both cases.

HIV. The changes take a form of foci localized in the periventricular white matter, usually in the frontal region. They are isointense in T1-weighted and hyperintense in T2-weighted images, without mass effect and contrast enhancement. At more advanced stages, the focal lesions merge presenting as extensive, bilateral, symmetric areas of white matter involvement, including the centrum semiovale. Also the basal nuclei and the cerebral cortex may be involved.

Demyelinated areas are in the course of PML, in contrast to HIV-encephalitis, hypointense in T1-weighted images. The differentiating sign is also, in case of PML, involvement of subcortical arcuate fibers with typical "scaloping" pattern [5]. The FLAIR sequence is very useful in diagnostics of both types of anomalies, particularly for detection of small foci. Also magnetization transfer technique, recommended as a method allowing to differentiate between PML and HIV-encephalitis, is used [10].

In our material, 3 PML patients demonstrated typical manifestations and localization of the lesions (Fig. 1 a, b). In 3 patients, the involvement of brain structures was asymmetric, in 2 it was located in the occipital, in 1 more extensive, localized in the occipital and parietal lobes. Neither contrast enhancement nor mass effect was observed in any case, but all the patients demonstrated cortical and subcortical atrophy. In all the cases, typical characteristics of the lesion signal in T2-weighted images was observed. Involvement of subcortical arcuate fibers was found in 3 out of 4 patients.

In one patient with extensive, symmetric involvement of the white matter, only a discrete decrease of the lesion signal in T1-weighted images. Bilateral, symmetric, extensive changes were found in the occipital and parietal regions without involvement of the arcuate fibers (Fig. 2 a-c).

Spectroscopic changes in PML patients have been described in single reports only. The MR spectra demonstrated reduced N-acetylaspartate content, inncreased content of choline, lipids and the presence of lactate bands [11]. Chang et al. (9) additionally observed increased myoinositol and lipid levels, with low creatine content.

Also in HIV-encephalitis patients, MR spectra revealed a number of metabolic abnormalities. Decreased NAA/Cr ratio and increased choline and myoinositol (Cho/Cr and ml/Cr) levels were observed [12].

Simone et al. [13], who compared the groups of patients with PML and HIV-encephalitis, observed that a decrease of the NAA/Cr ratio is much more pronounced in PML. Both in PML and in HIV-encephalitis the authors observed high Cho/Cr levels, whereas the presence of lactate and lipid bands, observed in 75% of cases, was characteristic of PML.

In MRS studies, all the patients demonstrated similar changes in the levels of the evaluated compounds – decreased NAA and increased choline and myoinositol with a slight decrease of creatine level (Fig. 3). In all the examined patients lactate and lipid bands were also present (Table 1). Similar metabolic changes were also observed in the patient with atypical MR results (Fig. 3 b), which allowed to confirm the diagnosis of PML.

MRS studies confirm the neuropathological observations indicating that the course of PML involves destruction of the cell membranes and demyelination of glial cells [2]. In PML patients, JC viruses were found mainly in the nuclei of oligodendrocytes and astrocytes with their subsequent apoptosis and viral proliferation along the myelin sheaths [14].

Because of unavailability of an effective and specific therapy, HAART remains the only therapeutic option in patients with PML. Although some patients show no response to antiretroviral treatment [15], induction of the immune system gives a chance of improvement of the prognosis in PML patients and can be used safely in patients with high and stable lymphocytes T CD4 response [16]. The observations of Thurnher et al. [17], who reported survival times of 22-43 months in 2/4 patients with PML, provide evidence supporting the efficacy of HAART. Stabilization of the changes or improvement after antiretroviral treatment was also observed by Miralles et al. [18]. Also Giudici et al. (19) observed stabilization of the images in serial MR scans after 12 months of HAART.

Reconstitution of the immune status as a result of antiretroviral treatment is considered to inhibit the lytic changes in oligodendrocytes caused by JC viruses, and consequent demyelination, which is very important for prolonging survival [6]. Moreover, inhibition of HIV replication by HAART and reducing the level of transcription proteins encoded by HIV leads to a reduction of JC virus gene [20]. This is confirmed by the observations of Thurnher et al. [17], which

found in PML patients who responded well to HAART a reduction in the number of HIV copies and an increase of CD4 lymphocyte count.

According to the current point of view, both imaging studies and the results of MRS can be useful in monitoring of the response to antiretroviral treatment. Post et al. [21] suggest that decreasing signal intensity in T1-weighted images in consecutive MR examinations indicates an aggressive form of the disease and is an unfavorable prognostic factor. It was not confirmed by the observations of Thurnher et al. [17], who observed signal decreases in T1-weighted images both in long- and short-term survivors. The authors suggest that signal intensity decreases in T1-weighted images result from degradation due to the demyelination process prior to its inhibition by HAART. Instead, they report progressive signal decrease T1-weighted images accompanied by an increase in FLAIR sequence as an unfavorable prognostic factor.

These observations indicate a considerable dynamics of changes detected in neuroimaging in the course of PML in patients on HAART, which may cause diagnostic problems.

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Therefore, it seems that MR spectroscopy can be especially useful in such cases, allowing to establish a more precise diagnosis. As the metabolic changes correlate with the clinical condition, MRS is considered to be potentially useful for monitoring efficacy of antiretroviral therapy. Katz-Brull et al. [22] suggest that high myoinositol levels are a favorable prognostic factor in PML patients. It was also confirmed by Chang et al. (9), who observed in a longitudinal study high levels of this compound in PML patients with long survival time.

Conclusions

- MRS spectra obtained in PML patients reveal decreased levels of NAA and elevated concentrations of myoinositol and choline; an increase in lipid content and the presence of a lactate band is also characteristic.
- MR spectroscopy can be useful in differential diagnosis of PML.
- MRS studies confirm the neuropathological observations indicating that the course of PML involves destruction of the cell membranes and demyelination of glial cells.