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Reversible Posterior Leukoencephalopathy Syndrome

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1. Introduction

Hinchey et al used the term „reversible posterior leukoencephalopathy syndrome“ in 1996 to describe a syndrome characterized by headache, confusion, seizures and vision disturbances, including cortical blindness, connected with reversible changes on brain magnetic resonance imaging (MRI) which pointed to the white matter edema, predominantly in the posterior brain regions (1). Initially, this syndrome was believed to be secondary to arterial hypertension, with or without hypertensive encephalopathy, renal disease, or immunosuppressive therapy, such as *cyclosporin A*, tacrolimus and interferon- α . However, it has recently been identified in a wide variety of conditions, including eclampsia, hemolytic-uremic syndrome, connective tissue diseases, vasculitis, malignancies, chemotherapy, transfusions, intravenous immunoglobulin (IVIG) therapy, therapy with erythropoietin, thrombotic thrombocytopenic purpura, porphyria, etc. (2-14).

The normal response of the cerebral arterioles to acute rising blood pressure is sympathetic nerve-mediated vascular constriction to prevent increasing blood flow (autoregulation). But in the case of reversible posterior leukoencephalopathy syndrome, the response does not work well when there is excess high pressure or recent onset of a modest increase in blood pressure, and excess dilatation of the arterioles following disruption of cerebral small vessel endothelial cells (i.e., the blood-brain barrier) can occur, resulting in vasogenic brain edema. Therefore, disruption of cerebral vascular endothelial cells plays a critical role in the pathogenesis of reversible posterior leukoencephalopathy syndrome

In this article we describe a case of a patient with clinical signs and neuroradiological presentation typical for reversible posterior leukoencephalopathy syndrome.

2. Case report

A 72-year-old woman with a history of arterial hypertension in June 2009 suddenly developed headache, confusion, left homonymous hemianopsia, and left hemiparesis, associated with high blood pressure (220/110 mm Hg). From her case history we have

revealed that she was treated for pulmonary tuberculosis in the youth. Brain MRI performed in another institution revealed extensive white matter lesion in the right parietal and occipital lobe, splenium corpus callosum and left occipital lobe, suggestive of expansive process (Figure 1a and 1b). There were also bilateral chronic vascular lesions in the

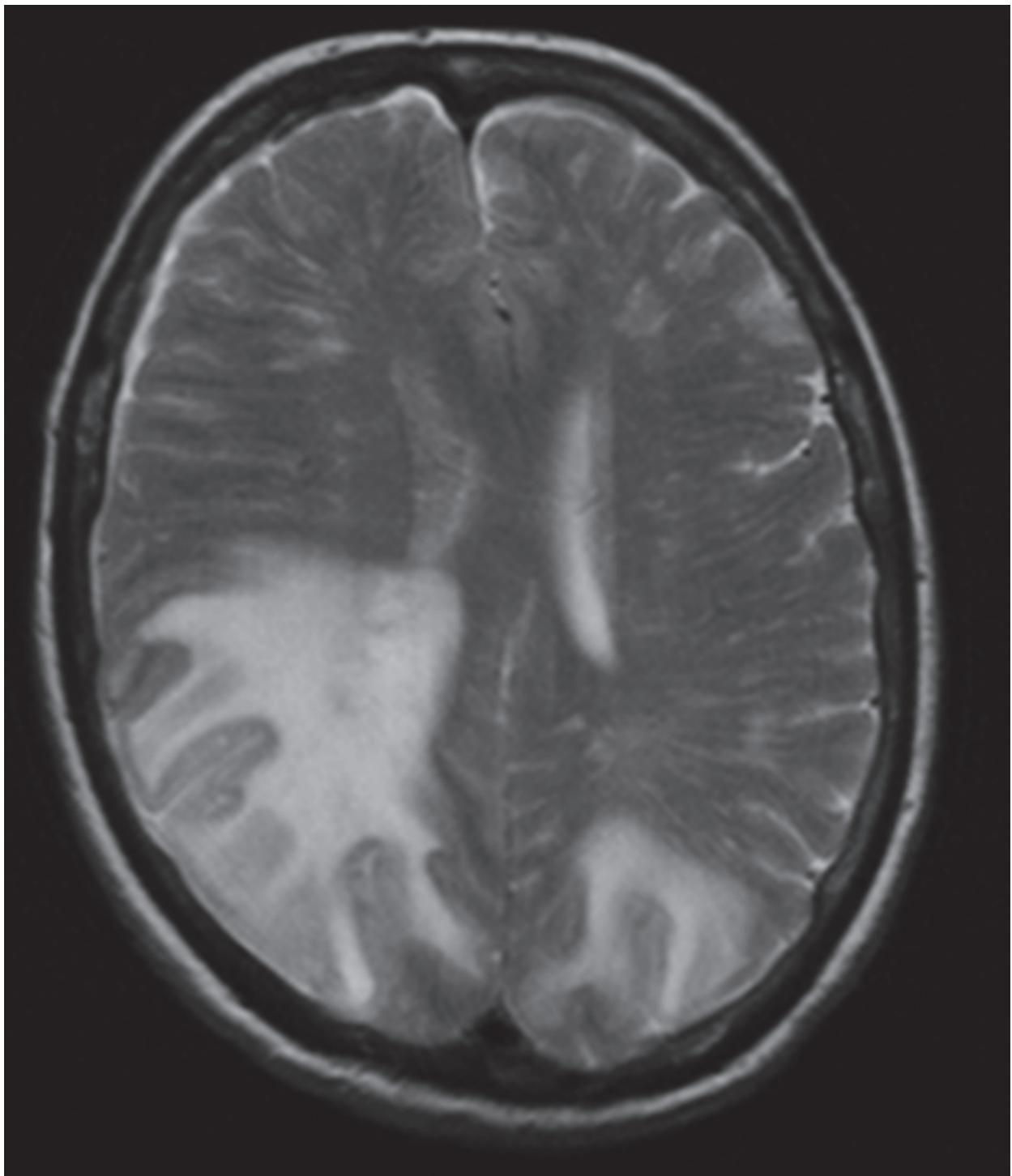


Fig. 1. Brain MRI in 72-year-old woman performed in June 2009 reveals extensive white matter lesion in the right parietal and occipital lobe, splenium corpus callosum and left occipital lobe. Figure 1a – transversal MRI section, hyperintense lesion on T2 – weighted image.

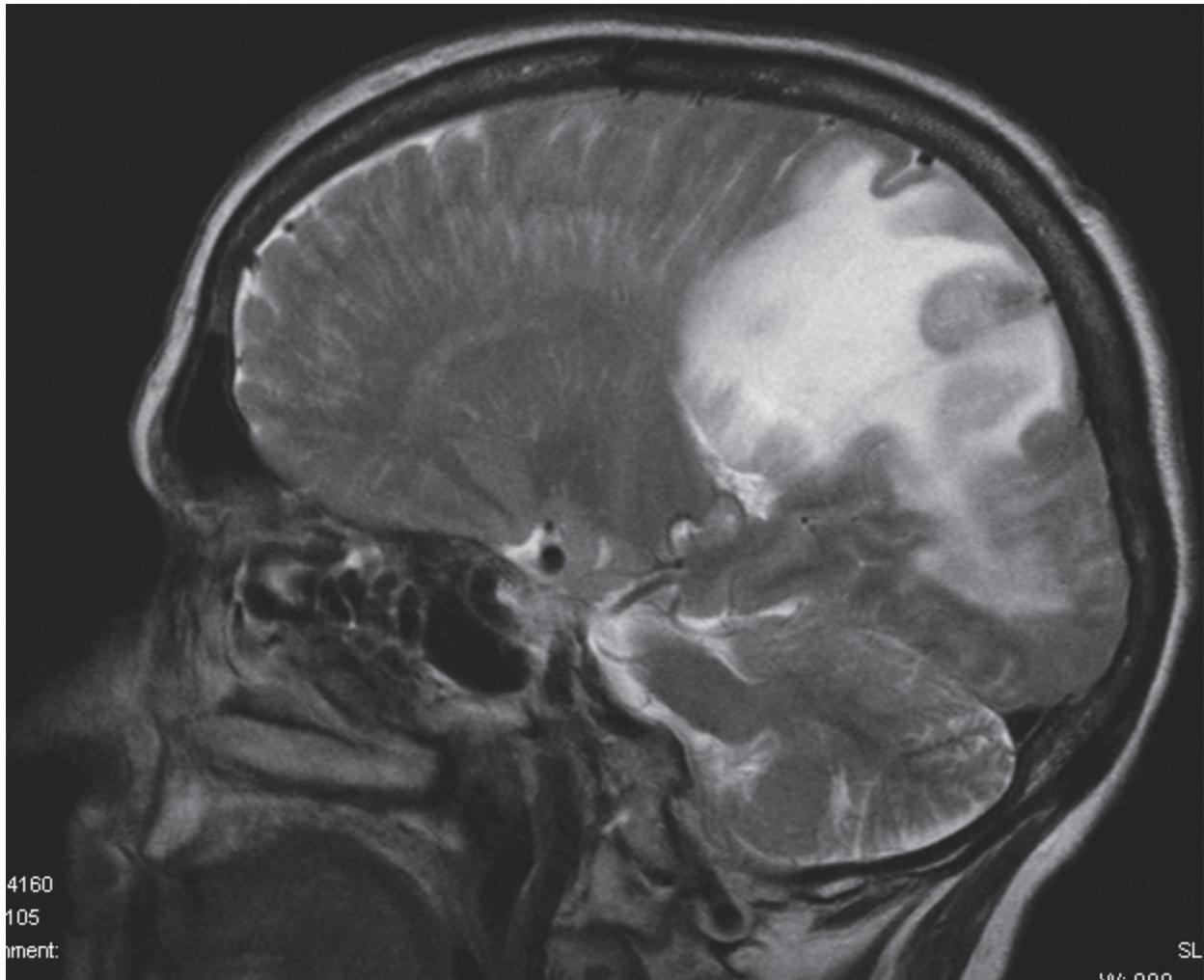


Fig. 1b. Sagittal MRI section, hyperintense lesion on T2 - weighted image.

subcortical white matter. Electroencephalogram (EEG) was diffuse paroxysmal dysrhythmic with focus of slow waves (frequency 2-3 Hz) above the parieto-occipital regions. Laboratory tests revealed hypercholesterolaemia and sideropenic anemia, as well as increased erythrocyte *sedimentation rate* (ESR) and fibrinogen levels, while complete blood cells count, electrolytes, tests of liver and renal function, as well as other biochemical tests were within normal levels. After one month patient was transferred to our institution in order to perform stereotactic biopsy and pathohistological verification. In the meantime antihypertensive and antiedematous therapy was introduced with gradual normalization of blood pressure levels (130/80 mm Hg) and significant improvement of neurological status, with only discrete residual left hemiparesis. Control brain MRI revealed unexpected regression of the formerly described white matter lesion. MR spectroscopy verified increased levels of choline in the described area, with the inversion of the choline/creatine ratio, but with preserved values of *N-acetylaspartate* (NAA), and preserved NAA/choline ratio. In cerebrospinal fluid there were 5 lymphocytes/mm³, 0.29 g/L of total proteins, oligoclonal bands were negative. Immunological blood tests were normal, as well as analysis of serum and cerebrospinal fluid on *Borrelia burgdorferi*, neurotropic viruses including HIV, syphilis, tuberculosis, mycosis, and serum on hepatitis.

Carcinoembryonic antigen (CEA), Ca 19.9, Ca 15.3, Ca 125, neuron specific enolase (NSE), CYFRA 21-1 were also negative, as well as findings of paraneoplastic antibodies (anti-Hu, anti-Yo and anti-Ri). Finding of visual evoked potentials pointed to neuronal lesion of the both optic pathways. Control EEG was diffuse paroxysmal dysrhythmic. Considering all mentioned findings, especially finding of the brain MRI and MR spectroscopy, which points to the leukoencephalopathy of vascular genesis (arterial hypertension), and improvement in neurological status, initially diagnosis of brain tumour was rejected and we did not proceed with the planned stereotactic brain biopsy.

Control brain MRI performed after three months pointed to further regression of the described white matter lesion. At the moment patient is clinically stable and has normal neurological status. Brain MRI performed in October 2010 pointed to complete regression of the white matter lesion.

3. Discussion

Diagnostic criteria of the reversible posterior leukoencephalopathy syndrome include clinical and neuroradiological findings. Very often clinical manifestations are altered consciousness, headache, seizures and vision disturbances (1). According to the literature data, all patients do not develop all mentioned clinical symptoms. Our patient developed all mentioned clinical symptoms except seizures, however, she also had motorical weakness – left hemiparesis.

Neuroradiological findings include reversible abnormalities of the white matter of the brain which present as hypodense areas on the brain CT, or hypointense areas on the T1-weighted images, hyperintense areas on the T2-weighted and FLAIR (“fluid-attenuated inversion recovery”) brain MR images, and isointense areas on the DWI (“diffusion-weighted imaging”) sequences, which all points to vasogenic edema (15, 16). Neuroradiological findings of the patient described in this paper correspond with the findings in the literature – edema was localized predominantly in the parieto-occipital brain regions. Although in most of the cases distribution of edema is symmetrical, there are cases with asymmetrical lesion localisation, as it was in the case of our patient.

Involvement of grey matter and other brain regions including brainstem, cerebellum, basal ganglia and frontal lobes has also been described in the literature (17).

The pathophysiology of RPLS appears to be multifactorial. The mechanism of the syndrome is a brain-capillary leak syndrome related to hypertension, fluid retention, and possibly the cytotoxic effects of immunosuppressive agents on the vascular endothelium. Severe hypertension per se is perhaps the most common cause. The sudden elevation in blood pressure exceeds the auto-regulatory capacity of the brain vasculature. A region of vasodilatation and vasoconstriction develops, especially in the arterial boundary zone, and there is breakdown of the blood-brain barrier with transudation of fluid and petechial hemorrhage. In experimental rats that were made suddenly hypertensive, these signs appeared and disappeared suddenly, within hours after relieving hypertension, suggesting the functional vascular changes and vasogenic edema. There is rapid resolution of clinical signs and symptoms and imaging abnormalities of reversible posterior leukoencephalopathy when blood pressure is lowered in such patients. While the reversibility of such vasogenic edema is most characteristic, it should be noted that it might

result in permanent neurological deficit and cerebral infarct. Uremic encephalopathies represent additional etiologies of RPLS that have a greater tendency for central distribution for unknown reason.

The predilection for the more posterior involvement in leukoencephalopathy may be due to relatively fewer sympathetic innervations in the posterior cerebral vasculature, which helps auto-regulate the cerebral vessels during an acute rise in blood pressure. The calcarine and paramedian occipital lobe structures are usually spared. This distinguishes RPLS from bilateral infarction of the posterior cerebral artery territory. Simultaneous bilateral infarction of the posterior cerebral artery territory occurs in patients with embolism to the rostral basilar artery, but with "top of the basilar embolism" the calcarine regions are invariably involved and often there are accompanying thalamic and midbrain infarcts. It has been observed that an incorrect diagnosis of gliomatosis cerebri, progressive multifocal leukoencephalopathy, demyelinating disease, or infarction may be advanced on the basis of MRI, if all aspects of the clinical presentation are not mentioned to the radiologist. This may result in unnecessary invasive therapy and biopsies. In most cases the leukoencephalopathy is reversible within 1–2 weeks. However, prolonged seizure, hypertension, or both may result in permanent neurological deficit and cerebral infarction. The multiple cerebral infarctions may result in early dementia. A few patients may not recover completely or may have neurodevelopmental sequelae (18, 19).

The role of the immunosuppressive therapy in the etiology of this syndrome is not so clear. According to the literature data, immunosuppressive or cytotoxic agents can cause this syndrome by toxic effect on the vascular endothelial cells or directly causing axonal damage (6,7,19,20).

After extensive diagnostic evaluation that excluded brain tumour that was initially suspected, as well as other factors that could cause leukoencephalopathy such as systemic tissue diseases, renal diseases, inflammatory diseases and malignant diseases, we believe that the main cause of development of reversible posterior leukoencephalopathy syndrome in our patient was arterial hypertension, respectively abrupt and severe increase of arterial blood pressure. That supports improvement of clinical symptoms after correction of blood pressure, as well as finding of MR spectroscopy.

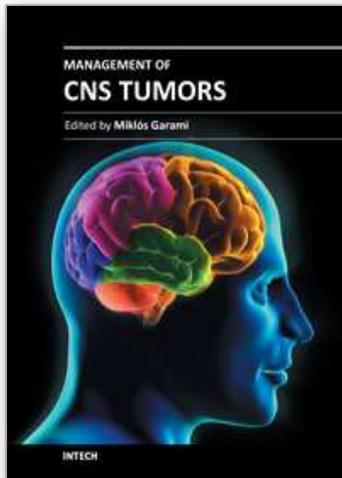
4. Conclusion

Early recognizing of the reversible posterior leukoencephalopathy syndrome is of great importance, because prompt regulation of elevated blood pressure, or in certain cases decreasing of dose or discontinuing immunosuppressive therapy, that is treatment of specific causes, can improve clinical condition of the patient and cause complete regression of the lesion of the brain white matter. Great importance has the fact that the proper diagnosis, and distinction from expansive process, can stop invasive diagnostic procedures. If in some cases we suspect that patient could have reversible posterior leukoencephalopathy, it is better to wait few weeks and then repeat brain MRI before the patient undergoes to the invasive diagnostic procedure such as stereotactic brain biopsy.

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