Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

Cerebralna autozomno dominantna arteriopatija sa supkortikalnim infarktima i leukoencefalopatijom

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Abstract

Introduction. Fast and precise diagnostics of the disease from the large group of adult leukoencephalopathy is difficult but responsible job, because the outcome of the disease is very often determined by its name. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is caused by the mutation of Notch 3 gene on chromosome locus 19p13. Beside the brain arterioles being the main disease targets, extracerebral small blood vessels are affected by the pathological process. Clinically present signs are recurrent ischemic strokes and vascular dementia. CADASIL in its progressive form shows a distinctive pattern of pathological changes on MRI of endocranium. The diagnosis is confirmed by the presence of granular osmiophilic material (GOM) in histopathological skin biopsies.

Case reports. Two young adult patients manifested ischemic strokes of unknown etiology, cognitive deterioration, migraine and psychopathological phenomenology. MRI of endocranium pointed on CADASIL. Ultrastructural examination of skin biopsy proved the presence of GOM in the basal lamina and near smooth muscle cells of arteriole dermis leading to CADASIL diagnosis. The patients were not searched for mutation in Notch 3 gene on chromosome 19, because some other leukoencephalopathy was disregarded.

Conclusion. Suggestive clinical picture, distinctive finding of endocranium MRI, the presence of GOM by ultrastructural examination of histopathological skin biopsies are sufficient to confirm CADASIL diagnosis.

Key words: cadasil; magnetic resonance imaging; immunohistochemistry; muscle, smooth, vascular; diagnosis; drug therapy.

Apstrakt


Ključne reči: cadasil; magnetska rezonanca, snimanje; immunohistohemija; mišići glatki, krvnih sudova; dijagoza; lečenje lekovima.
Introduction

Complex and heterogeneous etiology of adult leukoencephalopathy introduces differentially and diagnostically a large number of diseases which are difficult to classify due to overlapping of clinical, histopathological, the gene or molecular criteria. In etiology of adult leukoencephalopathy we can roughly distinguish hereditary diseases such as: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (Cadasil); leukodystrophies; mitochondrial miopathy, encephalopathy, lactic acidosis and stroke (MELAS); infective diseases – lyme disease, acquired immune deficiency syndrome (AIDS); intoxications – heroin abuse; tumors – gliomas, lymphomas; traumas; degenerative disease – Alzheimer’s disease; vascular diseases –Binswanger disease; metabolism disorders – subacute combined degeneration; immunological diseases – multiple sclerosis, vasculitis.

A precise etiologic diagnosis is crucial because the outcome of leukoencephalopathy is conditioned by its true name. This paper showed how the diagnosis of Cadasil was set using indicative clinical picture, characteristic changes of endocranium magnetic resonance imaging (MRI) and determination of granular osmiophilic material (GOM) presence in histopathological preparation of a skin biopsy. Cadasil is a cerebral autosomal dominant hereditary arteriopathy caused by gene mutation of notch 3 gene on chromosome locus 19p13 coding transmembrane receptor notch 3. This receptor is responsible for maturation of blood vessels in perinatal period and their homeostasis in adult period. Clinical picture is dominated by repeated ischemic events, cognitive disorders leading to dementia, headache, psychological manifestations and a wide range of various pathologic events caused by vasculopathy which damages the central and peripheral nervous system, skeletal muscles, skin, heart and other organs. Considering the availability of biopsy skin, it enables quite elegant solution of differential diagnostic dilemmas.

Case report 1

A patient, 36-year-old married woman with three children was admitted for hospital examination due to headache and vertigo. Headaches met the criteria for migraine; the patient has suffered since childhood. Vertiginous symptoms were suggestive for panic attacks. The patient negated the existence of vascular risk factors. Objectively, the patient was anxious, with sad mood and low intellectual capacities. Neurological status then registered slight weakness of the right arm, hypesthesia for superficial sensitivity of the right half of the body, vibration sensibility shortened from the foot level towards distal, bilateral; tandem walking was performed with difficulties. MRI showed multifocal, confluent lesions of white matter on both cerebral hemispheres, lesion in pons paracentrally. Serum lab analyses (sedimentation, blood chemistry, B12, T3, T4, TSH, anti Tg ab, anti TPO ab, ANA, ANCA, anti DS DNA, anticardioliopin ab, immune complexes, cryoglobulin, ACE, Elisa on Borrelia Burgdorferi) were well. Liquor examination showed a slightly disturbed blood brain barrier with a little increased albumin coefficient (6.76, reference values are up to 5.7), normal IgG index finding and the absence of oligoclonal bands. Somatosensory and visual evoked potentials were in the physiological range. Brain-stem auditory evoked potentials (BAEP) showed discretely lower amplitude V wave left which was the only deviating from physiological values. MRI of cervical spine showed dorsomedial protrusion of C3 disc with a mild stenosis of the spinal channel and without myelopathy. Ultrasound of neck blood vessels registered slightly higher resistance index in the vertebral arteries whereas the finding of transcranial ultrasound blood vessels was normal. The patient was observed further and treated with symptomatic therapy. A slight cognitive disorder (Mini-Mental State Examination – MMSE 26/30), serious anxiety (Hamilton Anxieity Scale – HAM-A 25/30), severe depression (Hamilton Depression Rating Scale – HDRS 20) were noticed, whereas neurological status showed no significant dynamics. EEG examination showed epileptic focus temporal and frontal on the left side. The last control of EEG showed amplitude and frequently unbalanced basic activity of dominantly alfa type and the overall finding indicated an increased irritability of temporocentral regions of bilaterally milder expression. Due to the absence of clinical manifestation of epileptic attacks, antiepileptic therapy was cancelled. Repeated MRI due to the persistent signs of leukoencephalopathy, lacunar infarcts, intact blood brain barrier after paramagnetic application directed the radiologist to suggest it as Cadasil (Figure 1). A skin biopsy sample was taken for histopathological analysis and ultrastructural examination proved the presence of GOM in the basal lamina and near smooth muscle cells of arterioles in the dermis (Figure 2), thus confirming the diagnosis.

Fig. 1 – Magnetic Resonance Imaging (MRI) of the endocranium of the patient 1 – multifocal and confluent lesions of the white matter of both hemispheres especially the left one

Case report 2

A patient, 31-year-old married male, father of two children, had strong vertigo, double vision, instability during walking few years ago. MRI of endocranium was done and some damages of brain mass in the area of centrum semiovale and corona radiata were detected bilaterally. BAEP easy dysfunction on the level of pons-mesencephalon right. Somatosensory evoked potentials (SSEP) from the level of n. tibialis showed disturbances in conducting from the level of Th12 to the sensitive cortex. Visual evoked potentials (VEP) revealed prechiasmatic subclinical lesion in the left optical tract. It was then assumed as multiple sclerosis and the patient was treated with pulse corticosteroid therapy in local regional medical center. Symptoms reduced afterwards but the feeling of weakness, fatigue during slight physical activities and lower mood persisted.

It was found out that the patient had tick bite in the area of head skin which has not been medically removed. His mother experienced frequent headaches. Clinical status was dominated by serious anxiety (HAM-A 25/30), moderate severe depression (HDRS 20), and mild instability during the Romberg test with eyes closed and insecurity during tandem walking were registered. Repeated MRI of endocranium showed signs of progressive changes indicative for microischemic lesions (Figure 3). Numerous examinations were performed (sedimentation, blood chemistry, basic biochemical analyses, APTT, INR, antithrombin III, D dimer, coagulation factors, immune complexes, cryoglobulin, immunoglobulin, protein electrophoresis, rheumatism factor, ACA, ANCA, ANA, anti ds DNA, Western blot on Borellia Burgdoferi, liquors examination – cytological, immunochemical analysis with albumin coefficient and immunoglobulin index, cardiac examination including heart ultrasound); vasculitis, neuroborreliosis, coagulation disorder, cardioembolic mechanism of brain ischemia were excluded. In search for the cause of ischemic lesions, the patient underwent skin biopsy and histopathological examination. CADASIL was confirmed as an etiological diagnosis (Figure 4).
Discussion

We presented the two patients examined in the Military Medical Academy, Belgrade to etiologically clarify the signs of leukoencephalopathy. Clinical doubt in CADASIL was resolved by analysis of histopathological preparations of skin biopsy in the Institute of Histology and Embryology, School of Medicine, Belgrade.

The patient 1 demonstrated a wide spectrum of pathological manifestations typical for CADASIL: ischemic stroke (present in 85% of patients), cognitive deficit (present in 60% of patients), history of migraine (30% of patients), existence of epileptic focus during EEG examination (epileptic attacks in 10% of patients) 7.

MRI of the head imposed CADASIL as a differential diagnostic possibility. CADASIL in its developed form manifests a specific pattern of MRI abnormality with maximum distribution of lacunar infarcts and massive lesions of a white brain matter in frontal and temporal lobes, insula as well as external capsule and middle pons 7-9. It helps in differential diagnosis but certain specific characteristics such as the involvement of frontotemporal polarity can be absent 8. A total volume of T1 lesions on MRI is an important parameter useful for prediction of the course of the disease 7. A relatively high difference in findings of the endocranium MRI of the patients is the consequence of a variable course of the disease. It can pass 3 to 43 years from the first manifestation of symptoms to lethal outcome 10.

The patient 2 was misdiagnosed with multiple sclerosis and was treated with corticosteroids. Persistent observation and consideration of differential diagnostic possibilities, histopathological examination of skin arteriole proved CADASIL. In spite of specific clinical and neuroimaging characteristics it often happens that a patient with CADASIL is misdiagnosed with multiple sclerosis 11. Unilateral retrobulbar optic neuritis diagnosed with multiple sclerosis gives similar clinical picture as acute loss of visual acuity due to ischemia of optic nerve within CADASIL 12. A total of 11% of patients showing radiological signs of leukoaraiosis and lacunar infarcts had CADASIL with clinical manifestation before 50 years of age, that is 2% of patients before 65 years of age 13. Leukoencephalopathy in younger patients often leads to suspicious is multiple sclerosis. We find it important to point out that CADASIL is not as rare disease as it was considered earlier.

CADASIL leads to degeneration of smooth muscle cells of brain arterioles. Extracerebral blood vessels are also included in the pathological process. Expressed destruction of vascular smooth muscle cells leads to hypotony of cerebral arterioles and hemodynamic changes responsible for MRI changes and clinical symptoms 6. Pathological signs of the disease are deposits of GOM in basal lamina of smooth muscle cells 10. The nature of GOM is not completely clear. The latest results have shown that the largest part of GOM consists of accumulated extracellular domain of Notch3 receptor. There are opinions that GOM originates from degenerated smooth muscle cells of arteriole 6,10. Ultrastructural examination of skin biopsy preparation proved the presence of GOM in basal lamina of smooth muscle cells of arteriole dermis in the presented patients and therefore undoubtedly showed the diagnosis of CADASIL. In regard to molecular genetic results, skin biopsy is 100% specific and 57% sensitive for CADASIL. Relatively low sensitivity of this method can be explained by difficulties in observation of sufficient number of arterioles and focal changes of vascular tissue.

In examination of a smaller number of patients with CADASIL, mean blood pressure was monitored in a course of 24 hours. It was noticed that the drop of values during the night is less than 10%. In the control group matched by age and gender the drop of mean blood pressure during the night measuring was more than 10% 14. Monitoring of mean blood pressure might be an useful diagnostic method which could strengthen suspicion of CADASIL before skin biopsy 11.

The patients were not searched for mutations in Notch3 gene on 19th chromosome. Notch3 mutations can happen on any part of this big gene which has 33 exons 17. Examination of 48 families in Great Britain showed approximately 90% of mutations on exons 3, 4, 5, 6 13. A research on 28 families in Italy with CADASIL showed only 18% of patients had mutations on exon 4, whereas the commonest mutation was on exon 11 with the frequency of 21%. All this supports the fact that distribution of mutation depends on the region of the country the family comes from 15. Until today a great number of Notch3 mutations has been described. Searching for them is time-consuming and relatively expensive 13. All patients with positive skin biopsy showed to have mutations on Notch3 gene 7. It leads to a conclusion that the presence of GOM in histopathological skin preparations confirms the CADASIL diagnosis and therefore there is no need to do genetic examination due to diagnostic reasons. We must point out the importance of genetic counseling due to non-existence of specific treatment of CADASIL positive patients what was done in the presented patients 11.

A great clinical variability in patients with the confirmed diagnosis of CADASIL even within the same family members is considered to be caused by other genetic environmental factors 11.

Adult leukoencephalopathies belong to a large group of diseases. A completely different therapeutic approach demands fast diagnostics and correct therapeutic intervention in order to achieve favorable therapeutic outcome. The presented patients were given antiaggregation therapy. Considering a possibility that increased level of homocistein in blood or abnormality in metabolism of homocistein is significant in pathogenesis of the disease, we found it suitable to introduce folic acid in the therapy 16. Bearing in mind a suggestion that a damage of cholinergic neurons in patients with CADASIL, the presented patients with the signs of cognitive disorders, i.e. vascular dementia were given cholinomimetic therapy 17. Setting etiologic diagnosis in the shown patients is a crucial step for the most

adequate treatment. Indicative anamnesis, clinical picture, MRI results suggest the obligatory skin biopsy if there are doubts in CADASIL. The authors have been so far selecting patients successfully with no negative results in ultrastructural skin examination. Thus, there was no need to prove CADASIL with genetic analyses.

**Conclusion**

Suggestive clinical picture, distinctive finding of endocranium MRI, the presence of GOM by ultra-structural examination of histopathological skin biopsies are sufficient to confirm CADASIL diagnosis.

**REFERENCES**


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