**CASE REPORTS**

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Case report
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**CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY: DIFFERENT CLINICAL FEATURES IN A FAMILY – A CASE REPORT**

**CEREBRALNA AUTOZOMNO DOMINANTNA ARTERIOPATIJA SA SUPKORTIKALNIM INFARKTIMA I LEUKOENCEFALOPATIJOM: RAZLIČITA KLINIČKA EKSPRESIJA UNUTAR JEDNE PORODICE – PRIKAZ SLUČAJA**

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**Summary**

Introduction. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is the most common monogenic disease of small blood vessels. It commonly presents with repeated episodes of brain ischemia leading to progressive subcortical vascular dementia, migraines and mood disorders. Case Report. A 46-year-old male patient was admitted with clinical presentation of stroke. The neurological examination revealed mild divergent strabismus and a left homonymous hemianopia. Brain magnetic resonance imaging showed subacute infarction in the region of the posterior cerebral artery to the right, as well as similar lesions in the splenium of the corpus callosum, numerous mostly confluent and some discrete T2-weighted/fluid attenuated inversion recovery hyperintense lesions of the centrum semiovale, corona radiata, frontoparietal subcortex, capsula externa, periventricularly at the level of occipital and temporal horns of lateral chambers bilaterally, and small punctiform lesions in the region of the corpus callosum. The magnetic resonance angiography findings were normal. The patient’s brother underwent neurological examination at the age of 42 due to severe headaches, double vision, confusion, and numbness in the right arm. The neurological examination revealed mild divergent strabismus, homonimic hemianopia and similar lesions in the splenium of the corpus callosum. Genetic testing showed a heterozygote mutation in exon 3 of the neurogenic locus notch homolog protein 3 gene was confirmed (c.505C > t, p.R169C).

**Sažetak**

Uvod. Cerebralna autozomno dominantna arteriopatija sa supkortikalnim infarktima i leukoencefalopatijom najčešća je monogenska bolest malih krvnih sudova koja se često prezentuje ponovljenim ishemijama, migrainima i promenama raspoloženja. Prikaz slučaja. Muškarac star 46 godina primljen je pod kliničkom slikom moždanog udara. U neurološkom nalazu blag divergentni strabizam, homonimna hemianopsija levo. Magnetorezonantski imidžing mozga pokazao je subakutni infarkt u regiji zadnje mozdana arterije desno, kao i promene sličnih karakteristika u splenijumu korpusa kaulazuma, brojne slivene, delimično i pojedinačne T2-weighted/fluid attenuated inversion recovery hiperintenzne lezije centruma semiovale, corona radiata, frontoparijetalnog supkorteksa, kapsule eksterna, periventrikularno u nivou okcipitalnih i temporalnih rogov lateralnih komora obostano, manje puntiformne lezije u regiji tela korpusa kaulazuma. Genetni test podnio je heterozigotnu mutaciju u egzonu 3 gena neurogenic locus notch homolog protein 3 (c.505C > t, p.R169C).

**Sažetek.**

Vod. Cerebralna autozomno dominantna arteriopatija je najbolj prekateni monogenezni bolezn na malih krvnih komunikacijah. Obično se prezentira ponavljajućim epizodama mozdana ishemi, migrenama i promenama raspoloženja. Prikaz slučaja. Muškarac star 46 godina, postavljen pod kliničkom slikom moždanog udara. Neuroradiološki nalazi ukazali su na blag divergentni strabizam, homonimnu hemianopsiju. Genetska analiza pokazala je heterozigotnu mutaciju u egzonu 3 gena neurogenic locus notch homolog protein 3 (c.505C > t, p.R169C).
Abbreviations
CADASIL – Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
PCA – posterior cerebral artery
FLAIR – fluid attenuated inversion recovery
NOTCH3 – neurogenic locus notch homolog protein 3
CVD – cerebrovascular disease
MRI – magnetic resonance imaging

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common hereditary cause of cerebral angiopathy and vascular dementia in adults. Clinically, CADASIL is associated with repeated episodes of brain ischemia leading to progressive subcortical vascular dementia, migraine attacks and mood disorders. Brain magnetic resonance imaging (MRI) shows diffuse, often confluent and symmetric white matter lesions, multiple lacunar infarctions, and cerebral micro hemorrhages. The CADASIL diagnosis is confirmed by identification of the neurogenic locus notch homolog protein 3 (NOTCH3) gene mutation located on the 19p13 chromosome [1–3]. The criteria for diagnosis include: 1. Onset of illness before the age of 50 years; 2. At least two of the following clinical symptoms attack with persistent neurological signs, migraines, mood disorders, subcortical dementia; 3. Absence of vascular risk factors; 4. Autosomal dominant inheritance, and 5. White mass lesions without cortical infarction [1–3]. There is no causal treatment. We present a case with different clinical expressions of the same gene mutation within one family.

Case Report

A 46-year-old male patient was admitted due to sudden visual disturbances, confusion, disorientation in time and space, and occipital headaches. The complaints started a few days before the admission. The patient was a smoker, moderate alcohol consumer, and had no other previously registered risk factors for cerebrovascular disease (CVD). On admission, he presented with bradypsychia and disorientation in time and space. His eyes were slightly divergent, and he reported diplopia in all directions of gaze. Right-sided homonymous hemianopia (National Institutes of Health Stroke Scale - NIHSS 4, modified Rankin Scale - mRS III) was evident. Brain computed tomography (CT) showed a subacute ischemic lesion in the right posterior cerebral artery (PCA) circulation, chronic ischemia in the pons, hypodensity in the supratentorial white matter, mostly subcortically. Ultrasonographic findings of the head and neck blood vessels were all normal. Contrast transcranial Doppler (TCD) was normal, and electrocardiography (ECG) did not show heart rhythm disturbances. Brain MRI examination confirmed an extensive subacute PCA lesion on the right, similar changes in the splenium of the corpus callosum, numerous mostly confluent and some discrete T2W/fluid attenuated inversion recovery (FLAIR) hyperintense lesions of the centrum semiovale, corona radiata, frontoparietal subcortex, capsule externa, periventricularly at the level of occipital and temporal horns of lateral chambers bilaterally, and smaller punctiform lesions in the corpus callosum region. Similar bilateral changes were found in the temporal subcortical region, slightly more pronounced on the left, all corresponding to CADASIL or vasculitis. The magnetic resonance angiography was normal (Figure 1). Immunological tests were within standard ranges, and routine hemostasis parameters and thrombophilia markers were normal. The patient was methylenetetrahydrofolate reductase (MTHFR) A1298C heterozygous. The results of psychological testing indicated global mild to moderate cognitive impairment, resulting from dysfunction of prefrontal-subcortical circuits. Most pronounced were deficits in executive functions, and there were also disturbances in performing movements. Medical history data were obtained. The patient had a twin brother who had no complaints at the time, and a year elder brother who was neurologically examined at the age of 42 due to severe headache, double vision, confusion, and numbness in the right arm. Brain MRI recorded multifocal confluent ischemic lesions predominantly in the frontal and temporal lobes as well as focal microangiopathic bilateral changes in gangliocapsular regions in the stem and cerebellum (Figure 2).

Figure 1. Subacute extensive lesion located occipitally on the right and in the corpus callosum splenium; confluent, partly discrete hyperintense lesions on T2 FLAIR in frontoparietal subcortex and periventricularly; chronic lacunar ischemia of the pons

Slika 1. Subakutna ekstenzivna lezija okcipitalno desno i u splenijumu korpusa kalozuma. Slivene, delomi i pojedinačne hiperintenzne lezije T2/fluid attenuated inversion recovery sekvence frontoparijetalnog supkorteksia i pre-riventrifikularno. Hronična lakunarna ishemijsa ponsa

The recommended genetic testing for CADASIL was not performed. Thereafter, the patient was taking aspirin and had no new complaints. Neurological examination registered only divergent strabismus of the left eye. He was depressed because his daughter had migraine headaches and epileptic seizures. Neuroimaging was not done. Their mother had similar problems. Our patient and his brother agreed to undergo genetic testing and it confirmed a mutation in the exon 3 of the NOTCH3 gene (c.505C > t, p.R169C). Genetic counseling and testing of other family members was recommended, but it has not been accepted by the time of writing this report.
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is the most common and most recognized monogenic disease of small blood vessels. Several smaller and national registers estimate that its prevalence reaches 2 – 5 cases per 100,000 people [4]. Morphologically, CADASIL represents non-atherosclerotic, non-amyloid arteriopathy which most commonly affects the penetrating and leptomeningeal arteries. The pathohistological basis involves the accumulation of granular osmophilic material around the smooth muscle cells and their subsequent degeneration. The changes are systemic and may also be detected in blood vessels of various organs and the skin. The disease develops due to mutations in the NOTCH 3 gene on the chromosome 19p13 [2]. This gene encodes a large transmembrane protein receptor on smooth muscle cells of the arteries and plays an important role in organogenesis and vasculogenesis. The penetrance of the disease is probably 100%. However, the expression varies in the age of onset, severity of the clinical picture and disease progression within one family [4]. The diagnosis of CADASIL is established based on the typical clinical picture, characteristic brain MRI findings, biopsy of the nerves, muscles and skin, and genetic analysis. The disease manifests clinically between 30 and 50 years of age. The most frequent clinical manifestation is recurrence of lacunar ischemic strokes in the absence of conventional risk factors for CVD, usually between the ages of 35 and 45, although there are huge discrepancies in the literature (from 20 to 70 years) [5]. Recent studies have shown that smoking in these patients doubles the risk of stroke and increases the risk of dementia by three times [6]. Development of territorial infarcts in the vascularization areas of large arteries is rare and probably accidental. In patients of East Asian origin, a higher prevalence of intracranial stenosis was reported, which suggested in several studies that in the absence of vascular risk factors the involvement of large blood vessels was associated with CADASIL [7, 8]. Approximately 20 – 40% of patients have migraine with aura and up to 60% of patients have migraine headache without aura. Migraine may precede stroke even by several years [5]. Impairment of the executive functions and working memory may be present even before the occurrence of transient ischemic attack (TIA) and stroke. Episodic memory may be preserved until the advanced stage of the disease. However, repeated lacunar strokes lead to pseudobulbar palsy and pronounced subcortical vascular dementia before the age of 65. Psychiatric disorders may vary from mild personality disorders to severe depression and mania. Migraine and development of psychiatric disorders are seen in the earlier stage of the disease and in some families represent the dominant clinical finding. Approximately 10% of patients with CADASIL have epileptic seizures [3]. Neuroradiological findings obtained by MRI are specific. Prior to the first clinical manifestations, white matter hyperintensity on the T2W and FLAIR sequences may be registered, which tend to be symmetrical, bilateral, distributed periventricularly, in the deep white matter, with predilection sites in the parietal and frontal lobes, temporopolar white matter and in the capsula externa [1]. Changes in the frontal temporal lobe have high sensitivity and specificity (90%) and are useful in establishing the diagnosis. Changes in the capsula externa have high sensitivity (90%) but lower specificity (50%) [1]. Abnormalities in the corpus callosum are rarely present in small vessel disease; they have been described in CADASIL and are common in multiple sclerosis, which is one of the reasons why CADASIL may be misdiagnosed as multiple sclerosis. Lacunar infarcts are most frequently localized in the centrum semiovale, thalamus, basal ganglia and pons. This is the most important MRI parameter that correlates with the degree of cognitive impairment. Cerebral microbleedings are registered on T2 sequences and T2* in 30 – 70% of patients, most commonly in the thalamus but also in the cortex, subcortically, in the white matter and brainstem, usually outside ischemic lesions [9]. CADASIL is primarily a subcortical disease, and recent studies using 7T MRI recorded changes in the cortex in the form of microinfarctions and initial diffuse cortical changes [4]. The diagnosis can also be established by skin biopsy; it is a standard procedure, however, the results of almost one half of the studies were false negative. The gold standard for establishing the diagnosis is the genetic confirmation of point mutations of the NOTCH gene, most frequently in exon 4 in the European population, followed by exons 8 and 3. In Serbia, three families (now four) with the diagnosis of CADASIL and point mutations in the exon 3 of this gene have been described so far [10, 11]. To date, over 150 mutations in exons 2 – 24 in over 500 families have been reported worldwide. Although these mutations have been registered in patients with a family history of CADASIL, recently de novo mutations have also been confirmed [12, 13]. That is why genetic testing should be carried out if there is clinical and morphological suspicion of CADASIL, regardless of the absence of family history of the disease, and it is recom-

Figure 2. Multiple confluent changes of increased intensity on T2 and FLAIR, localized temporopolarly, periventricularly and in the deep subcortical white matter, with several lacunar lesions of the same MRI characteristics.
mended in cases with positive family history even in the absence of clinical manifestations or with atypical clinical picture. Differential diagnosis includes multiple sclerosis, acute disseminated encephalomyelitis, hypertensive arteriosclerotic encephalopathy, cerebral angitis, amyloid angiopathy, fabric disease, and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy.

Conclusion

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is the most common monogenetic disease of the small blood vessels that should be suspected in a younger population with registered signs of small blood vessels disease, especially if they are without detected conventional risk factors for cerebrovascular diseases and there is a positive family history for cerebrovascular disease. The penetrance of the disease is high, but the clinical expression varies widely in terms of age of onset and presentation, as well as the severity of the clinical symptoms. Although causal therapy does not exist, it is very important to diagnose cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy in order to implement prevention measures for both the patients and their family members.

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