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A Rare Case of CADASIL and Lyme disease in a Bulgarian Patient

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ABSTRACT

We present a patient with CADASIL - the first genetically proven case in Bulgaria. This is a 53-year-old man with complaints of headache, several cerebrovascular accidents, mild cognitive and affective changes and MRI findings of extensive vascular damage in the brain with typical localization and presence of micro haemorrhages. This case highlights the need to conduct MRI and purposefully search for CADASIL in younger patients with severe cerebrovascular disease without the presence of emphasized vascular risk factors. As far as we know, this is also the first described case of a patient with CADASIL and neuroborreliosis.

Keywords: Case, CADASIL, Neuropsychology, Neuroborreliosis, MRI

Abbreviations: CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; MRI: Magnetic Resonance Imaging; CT: Computer Tomography; SWI: Susceptibility Weighted Imaging; MMSE: Mini-Mental State Examination; CSF: Cerebrospinal Fluid

CASE PRESENTATION

We present the clinical case of a 53-year-old man with onset of clinical symptoms at 51 years of age. The initial complaints were frequent headaches, because of which MRI of the brain was performed in February 2016 (**Figure 1**) which revealed a lacunar stroke in the pons, as well as a number of high-signal lesions on T2-predominantly periventricular but also subcortical, with tendency for more diffuse damage in the periventricular regions Magnetic resonance angiography was normal.

In August 2016, due to a sudden feeling of numbness and weakness in the left extremities, the patient was hospitalized in a neurological ward in the city of Pleven. The neurological exam revealed moderate left-sided central hemiparesis and positive pathological reflexes on the left. Computer tomography (CT) revealed a right middle cerebral artery ischemic stroke, as well as left middle cerebral artery and vertebrobasilar strokes in a chronic phase. Doppler sonography of cervical arteries revealed only increased vascular resistance, haemodynamically significant stenoses were absent.

In September 2016, the patient underwent a neurological consultation at City Clinic in Sofia, where the presence of CADASIL was suspected and the patient was directed for the conduction of a genetic study. The presence of a germinal mutation in exon 4 of the NOTCH3 gene was detected: c.581 G> A, p.Cys194Tyr - a pathological variant. As part of the differential diagnosis plan, blood testing was performed for the presence of antibodies to Borrelia burgdorferi for Lyme disease - the patient had positive IgG antibodies (1.874 with reference range <0.8) with negative IgM antibodies.

The patient was hospitalized in the Neurology department at University Hospital "Alexandrovska" in January 2018. Headaches with the above-described characteristics had been persisting. Family history revealed an undiagnosed condition in the patient's mother that had progressed within 7-8 years and resulted in her death - progressively worsening motor function that had necessitated the use of a wheelchair, dysphagia, memory and language disorders. The patient's grandmother on the mother's side had suffered a stroke, but no detailed information was available.

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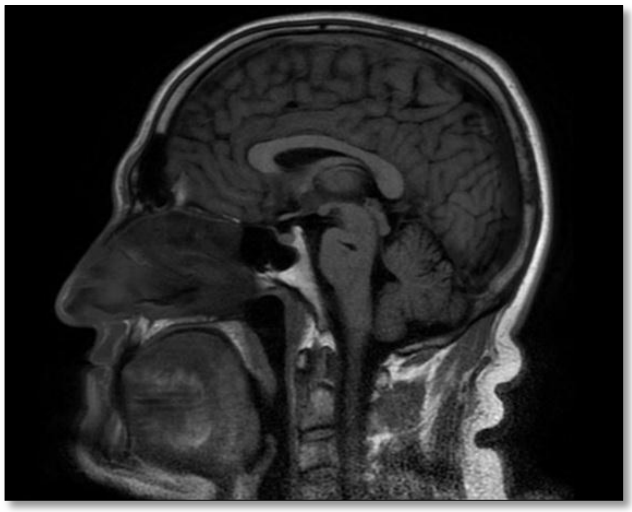

Figure 1. MRI of the brain (sagittal section through brainstem on T1).

The current neurological examination revealed persisting pyramidal signs on the left - hyperactive reflexes in the left extremities, positive pathological reflexes on the left. MRI of the brain was performed revealing multiple clustered and of irregular shapes focal lesions engaging the subcortical white matter of the two hemispheres, including the short interceptive fibers, bilaterally symmetrical damage with predominance in the temporopolar (**Figure 2**) and fronto-orbital regions; typical changes in the external capsules (**Figure 3**) and the heads of the caudate nuclei were observed; single lesions with rounded shapes were located in the left thalamus, band-like focal changes were observed in the posterior limbs of the internal capsules; two confluent lesions with band-like, irregular shapes were observed in the pons; SWI (Susceptibility Weighted Imaging) sequence presented haemosiderine deposits in the head of the left caudate nucleus and in the periventricular white matter around it (**Figure 4**).

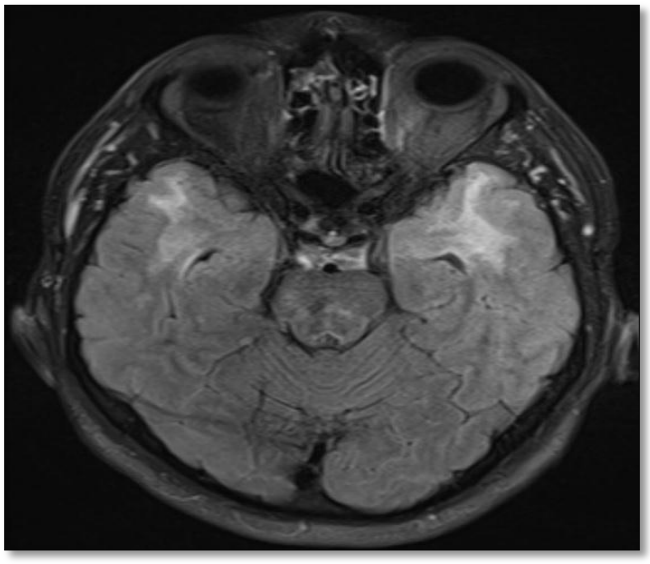

Figure 2. MRI of the brain (axial section through temporal poles FLAIR).

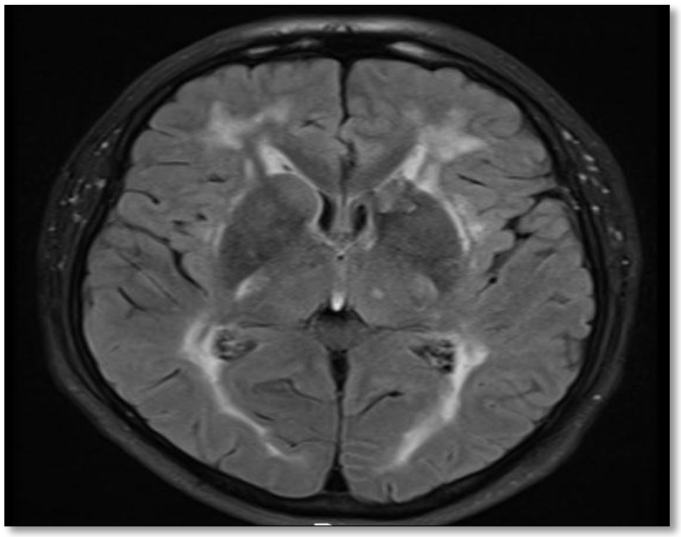

Figure 3. MRI of the brain (axial section through thalami/external capsules).

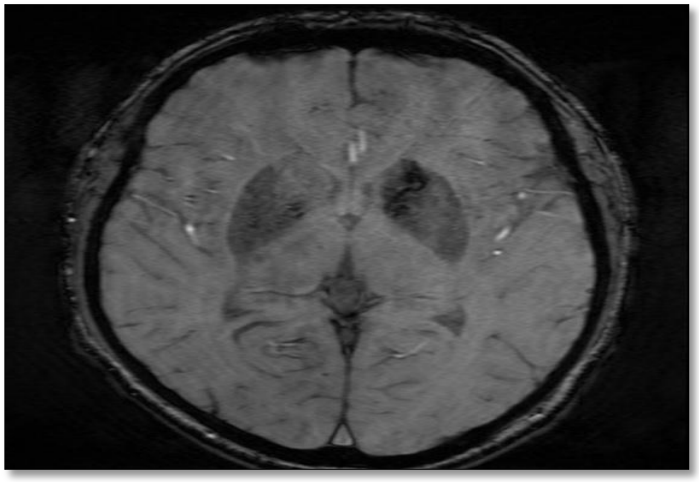

Figure 4. MRI of the brain (SWI).

The patient underwent a detailed neuropsychological study. In general cognitive functioning assessed with the Mini-Mental State Examination (MMSE), the patient received a score of 28-29/30 points. On the test for verbal episodic memory, the patient received a consecutive score of 3, 6 and 8/10 words in the three immediate recall attempts and 7/10 in delayed recall with the occurrence of several intrusions, both in immediate and delayed recall. Recognition was preserved - 19/20. The digit span was 6 in the right order and 5 in the reverse. Isaac's verbal fluency test resulted in a score of 36/40, the semantic fluency resulted in 21 words in 1 min, but the phonemic fluency was suboptimal - 11 words in 1 min. The clock-drawing test revealed no pathology. The

above mentioned results were interpreted as a mild cognitive impairment with mostly subtle dysexecutive symptoms and suboptimal results in verbal episodic memory testing. Depressive tendencies were looked for with the Beck Depression Inventory questionnaire with a score of 17 points, indicating the presence of mild to moderate depression. Given the positive result for IgG antibodies against Borrelia burgdorferi in the serum from 2016 a lumbar puncture was performed. The cerebrospinal fluid (CSF) had a normal cell count (2.106/l erythrocytes and 3.106/l leukocytes), normal protein values (0.36g/l) and sugar values (3.8mmol/l), slightly elevated IgG (54.44mg/l) and IgM (0.85mg/l), and the CSF electrophoresis revealed two areas with limited heterogeneity in the γ-region. The Lyme disease test in the CSF revealed the presence of IgG antibodies against B. burgdorferi in the absence of IgM.

These results necessitated another hospitalization at the end of January 2018 to start antibiotic treatment. In a more detailed conversation, it was revealed that the patient had been exposed to multiple tick bites in connection with his occupational activity, as well as that his wife had also had Lyme disease and had been later treated. A genetic study was conducted on the two daughters of the patient with inheritance of the mutation in one of them.

DISCUSSION

The mutation in the NOTCH3 gene in CADASIL affects the number of cysteine molecules in the extracellular portion of the Notch3 transmembrane receptor found in smooth muscle cells of blood vessels. This affects the tertiary structure of the protein, leads to its aggregation, and initiates a pathological pathway leading to the formation of granular osmophilic inclusions in the walls of affected vessels. Numerous mutations in NOTCH3 lead to a clinical picture typical of CADASIL, most of which include the mechanism of injury described above. However, certain NOTCH3 mutations exist that do not lead to a change in the number of cysteine molecules in the transmembrane protein but nevertheless lead to the clinical manifestation of CADASIL, albeit without the typical inclusion of the temporal pole in the pathological process. This fact, together with the discovery that there is clinical and morphological variability in patients with the same mutation, including in one family [1], emphasizes CADASIL's complex nature and the presence of additional factors beyond the genetic ones affecting the phenotype of the disease.

Migraine headaches are detected in up to ¾ of the patients with CADASIL and compared to the general population, migraine with aura is more common (up to 90% of cases). Like in the general population, on the other hand, it is more common in women. Despite the typical association between CADASIL and migraine headaches, a variation in the clinical characteristics of headaches is reported among patients from different parts of the world, with the Asian population experiencing tension type headaches in 87-88% of the patients [2].

Neuroimaging presents the disease-specific extensive vascular damage in the brain. It includes confluent high-signal on T2 lesions in the white matter, lacunar infarctions and microhaemorrhages. The white matter lesions are bilateral, symmetrical, located in the periventricular and deep white matter. Disease-specific regions of injury are, first of all, the temporal poles, and secondly, the external capsules. Lacunar infarctions are restricted areas of loss of brain parenchyma with a density equivalent of that of CSF. They are most often found in the center semiovale, the basal ganglia and the pons. Microhaemorrhages are represented by restricted areas of signal loss on the T2, T2* and SWI sequences [3]. The presence of microhaemorrhages is a prognostic factor for a more severe ischemic injury [4]. Although conventional MRI reveals extensive white matter damage, current advanced MRI techniques, such as magnetic resonance spectroscopy, detect microstructural pathology in the so-called "normal-appearing white matter" in CADASIL, similarly to other white matter diseases. This turns these imaging studies into an ideal tool for detecting pathology in the earlier stages of progression in patients with CADASIL [5].

The profile of neuropsychological dysfunction in CADASIL is typical of white matter diseases and correlates with the lesion load in the white matter. Attention deficit, memory disturbance (mostly retrieval of information), visual-spatial and executive dysfunction can largely be interpreted as a result of disconnection, mostly in the frontal lobe, given its density of neural connections, its specific functions, and the tendency for frontal lobe damage in CADASIL [6]. However, as in other white matter diseases, cognitive functions are also dependent on some imaging markers for neurodegeneration - the response time in CADASIL, for example, increases with volume loss in the corpus callosum [7].

The predilection for frontal and particularly temporal injury in CADASIL also explains the early neuropsychiatric dysfunction that can be observed in the disease. The tendency for the presence of cognitive impairment, which is preceded by psychiatric dysfunction, has been observed in CADASIL, similarly to other white matter diseases. Affective disorder is considered to be the dominating feature of neuropsychiatric dysfunction in CADASIL with mood swings, depressive symptoms, and it is also not uncommon that the disease debuts with the diagnosis of bipolar affective disorder [8]. These manifestations, as well as their degree of expression, assessed by subjective scales, similarly to cognition, correlate with the severity of T2 high-signal lesions in the disease, while such correlation has not been established with lacunar foci and microhaemorrhages. This makes CADASIL a suitable medical model that supports the hypothesis of "vascular depression" [9].

CONFLICT OF INTERESTS

The authors report no conflict of interest.

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