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Case Report

Ophthalmic Manifestations of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infracts and Leucoencephalopathy (CADASIL)

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Abstract: Aim of the study: Presentation of ophthalmic symptoms of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infracts and Leucoencephalopathy (CADASIL). **Material and methods:** Clinical presentation of female patient with diagnosed CADASIL, manifested by transient loss of vision, migraine, convergence insufficiency, diplopia, increased deep tendon reflexes of upper left limb, subcortical infarcts, mood disturbances and dementia. **Results:** Confirmed NOTCH3 gene mutation (p.Cys212Gly), and presence of granular osmiophilic material (GOM) in cutaneous small vessel wall in immunohistochemistry laboratory test (IHC). Magnetic resonance imaging (MRI) revealed bilateral focal vasogenic lesions in white matter of cerebral hemisphere with single micro-focal infarct in the left external capsule. Furthermore, a left eye exophoria, a bilateral peripheral visual field loss of 20 degrees and a loss of nasolabial fold was confirmed during ophthalmic tests. An eye fundus examination as well as a fluorescein angiography (FA) revealed vessel constriction of retinal arteries and a peripheral retinal pigment epithelium (RPE) atrophy with focal drusen in the left eye. The doppler ultrasonography (USG) confirmed a decreased blood flow and an increased vascular resistance of the extraocular vessels. The pattern electroretinogram (PERG) revealed a reduced P50 wave amplitude in the patient's left eye. **Conclusions:** intermittent blindness, migraine, convergence failure, diplopia with specific MRI signs, NOTCH3 mutation, and the presence of GOM in the skin of small blood vessels in a young or middle-aged patient suggests CADASIL. New observations include: atrophic changes in the RPE, hemodynamic disturbances in blood flow in the short posterior ciliary arteries and in the central retinal artery, single drusen in the retina, and a reduced amplitude of the P50 wave in PERG.

Keywords: CADASIL; small vessel disease; retinal and choroidal blood flow disturbance; reduced amplitude of the P50 wave in PERG; retinal drusen

Introduction

CADASIL belongs to the group of small vessel diseases (SVD) and is a fairly rare (1.98/100 000), genetic disorder, caused by the mutation in NOTCH3 gene on chromosome 19 (locus 19p13.1-p13.2), that determines the amino acid sequence of NOTCH3 protein. It plays a crucial role not only in receptor binding, but also in intercellular communication [4,5].

The accumulation of extracellular domain of a receptor protein in smooth muscle cells of small and medium-sized vessels leads to formation of 10-15 nm GOM deposits (Figure 1 A-B), and is responsible for a pathophysiology of CADASIL. Furthermore, NOTCH3 mutation causes explicit changes in a basal membrane and in the pericytes of

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the capillaries. A progressive vessel wall thickening and a constriction of the vessels leads to disseminated microangiopathy, followed by a formation of pathological changes mainly in white matter of the brain (Figure 2 A). This process is further intensified by the accumulation of elastic and collagen fibrils in the vessel wall. The alternative hypothesis assumes, that GOM deposits is probably caused by the degeneration of smooth muscle cells.

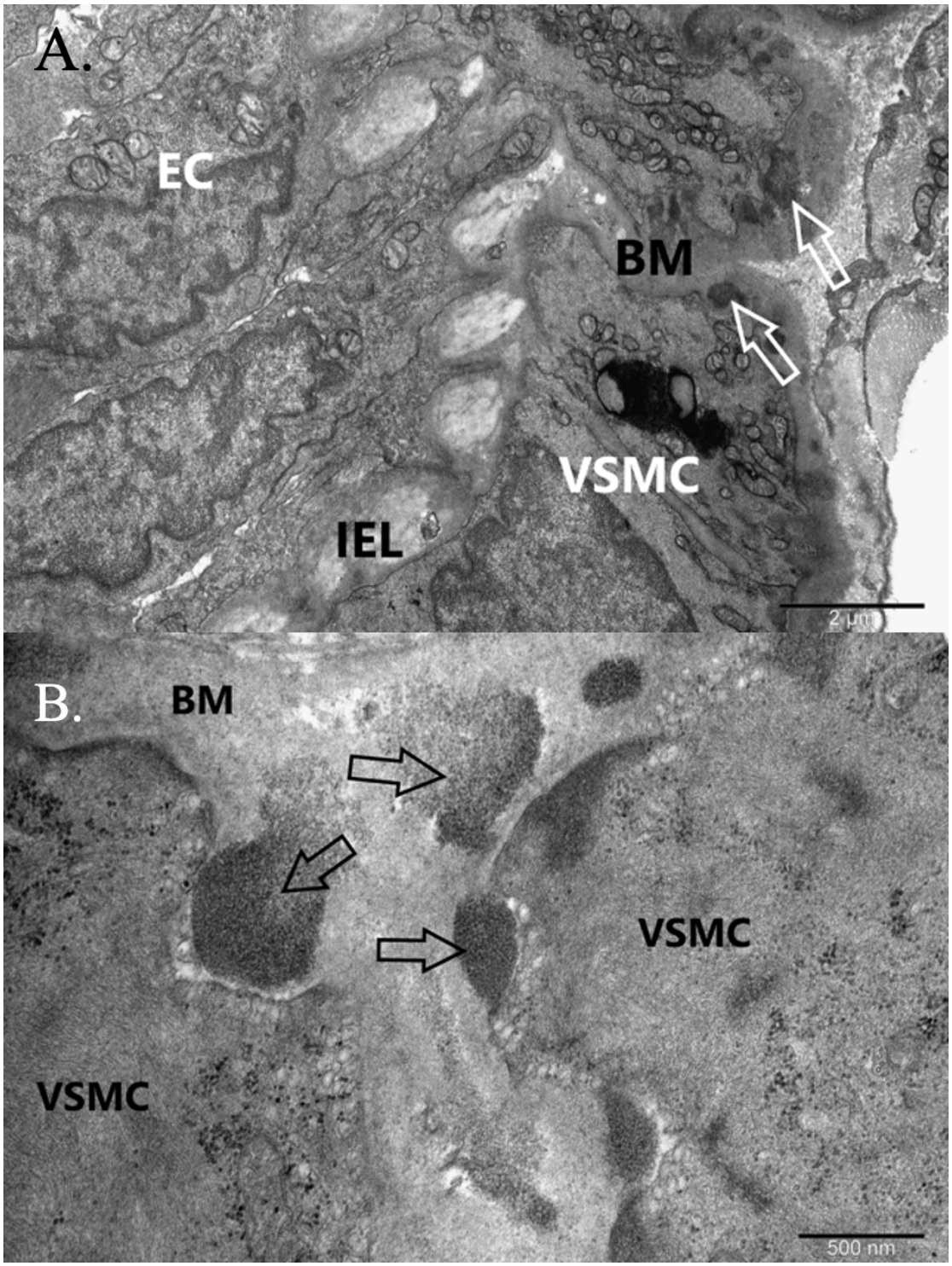

Figure 1 A. Cross-section of an arteriole with GOMs. VSMC – vascular smooth muscle cell, EC – endothelial cell, BM – basement membrane, IEL – internal elastic lamina, arrow – GOM. Orig. Magn. x15000.Figure **B.** GOMs magnified. VSMC – vascular smooth muscle cell, BM – basement membrane, arrow – GOM. Orig. Magn. x50000.

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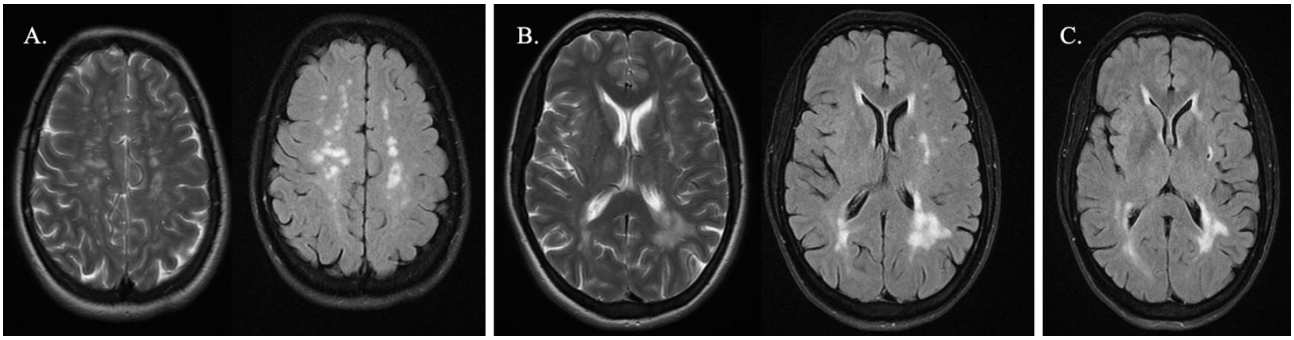

Figure 2 A. The formation of pathological changes mainly in white matter of the brain demonstrated in MRI. **B.** Subcortical and periventricular areas of the white matter of the brain demonstrated in MRI along with multiple focal vasogenic lesions in white matter of both hemispheres, partly merged in the occipital horn region. **C.** Single focal subcortical microinfarct in the left external capsule demonstrated in MRI.

The similarity of the structure between retinal and cerebral cortical vessels results in a formation of histopathological changes simultaneously in both types of abovementioned vessels. That is why in such cases MRI reveals characteristic disseminated focal infarcts. These lesions are most often found in subcortical and periventricular areas of the brain white matter (Figure 2 B), mainly in a temporal lobe, an external capsule, a frontal and a parietal lobe, subcortical nuclei and in a centrum semiovale. Characteristic lesions are located in the grey matter of a brain as well and are resulted by a neuronal apoptosis, particularly in the third and the fifth ventricle.

A gradual onset of CADASIL symptoms ranges from the age of 30 and 50, and is most often manifested as subcortical infarcts (Figure 2C), ***transient ischemic attack (TIA), episodes of migraine (often with aura), apathy, dementia and other psychiatric disorders followed by acute encephalopathy with mood disturbances [1, 2, 3].***

According to the literature, most common manifestations of CADASIL syndrome include neurological symptoms, including ophthalmic symptoms such as transient vision loss (TIA). Of the 1,517 available publications, only 17 publications with ophthalmic features of this disease were reported. Some of them concern the interpretation of the results of electrophysiological (pERG) and angiographic examinations. A new insight is the peripheral RPE atrophic lesions along with focal drusen, not described so far. Therefore, it seems important to present new ophthalmological observations in this disease.

Clinical history

A 43-year-old female was referred to the II Department of Ophthalmology PUM because of medical history positive for several microinfarcts, severe migraines, transient aphasia, loss of memory, skin sensation disorder and numbness of the right upper limb. The patient's mother had been diagnosed with CADASIL. Cardiovascular findings included tachycardia and premature supraventricular contractions (PVCs). Neuropsychological examination did not reveal any cognitive functions disorders. Despite microinfarcts, the patient has been suffering from ophthalmic symptoms, including transient loss of vision convergence insufficiency and double vision as revealed by the alternating eye covering test.

The acuity of vision of both eyes was not disturbed, once the episode of transient loss of vision had subsided (Snellen chart 1.0; no retractive disorders: the right eye +0,25/-0,5/93; the left eye +2,0/-0,5/45). Concomitant symptoms included loss of nasolabial fold as well as increased deep tendon reflexes of upper left limb. The orthoptic examination revealed convergence insufficiency and a left eye exophoria (Figure 3), whereas neither the assessment of binocular vision nor the examination of the mobility of the extraocular muscles on the Hess screen revealed any dysfunction. The abnormalities confirmed: distal

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narrowing of the visual field up to 20° in both eyes with a defect in the lower part of the left eye's visual field.

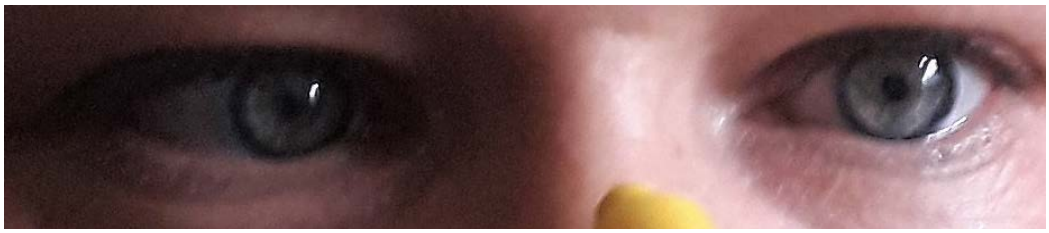
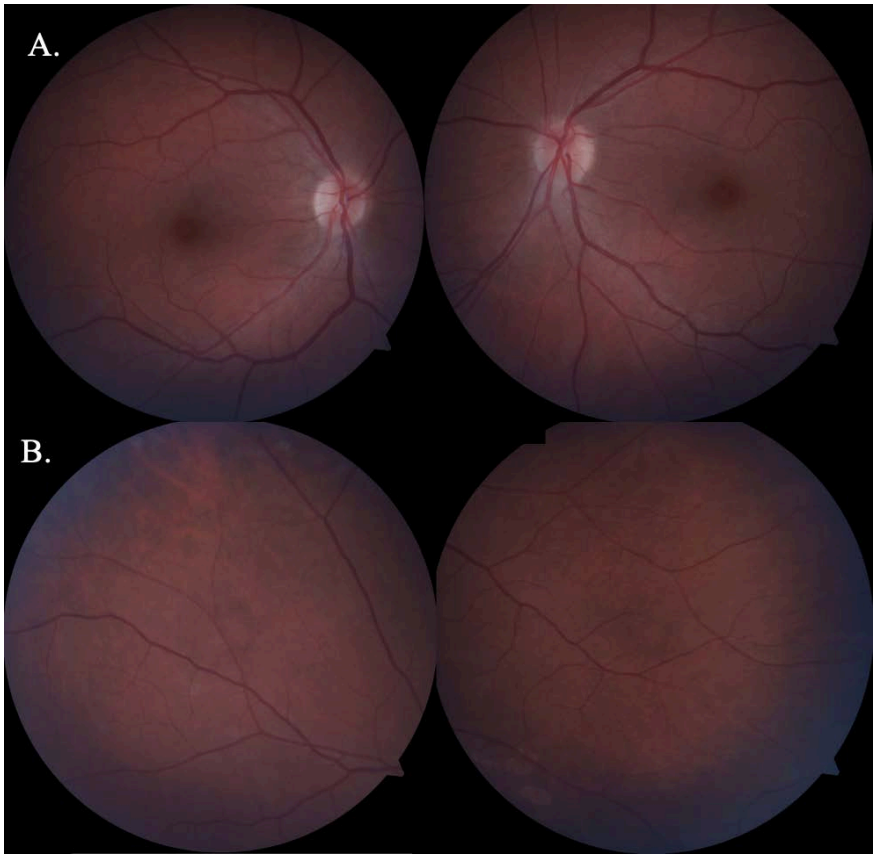


Figure 3. Convergence insufficiency of the left eye. The patient has agreed to the publication of the photo – a proper consent has been obtained.

The intraocular pressure (ICARE-tonometr) was within the normal range (20.6 mmHg). There were no abnormalities in optical coherent tomography (OCT) of optic nerve, macula, ganglion cell complex (GCC) (GCL+IPL) nor in static perimetry. Macular angio-OCT and visual evoked potentials (VEP) tests without any anomalies. Indirect ophthalmoscopy revealed the constriction of retinal arteries, arterial wall thickening and arteriovenous nicking. There were no other lesions of the retina (Figure 4 A). Nevertheless, there were other interesting findings, namely the peripheral RPE atrophy and focal hyperfluorescence in the temporal macula at the inferior vascular temporal arch (Figure 4 B-C), which was thereafter confirmed in the fluorescein angiography (FA) in the left eye (Figure 5). The retinal drusen were observed in the retina of the left eye (Figure 6). The late phase of indocyanine green angiography (ICGA) also confirmed aforementioned lesions, by the demonstration of the small, linear, focal hyperfluorescence of the lower part of central fovea exclusively in the left eye (Figure 7). There is no certainty, whether these changes are the focal RPE atrophic lesions. Macular OCT revealed the thickening of the central part of the macula, mainly in the left eye (Figure 8).



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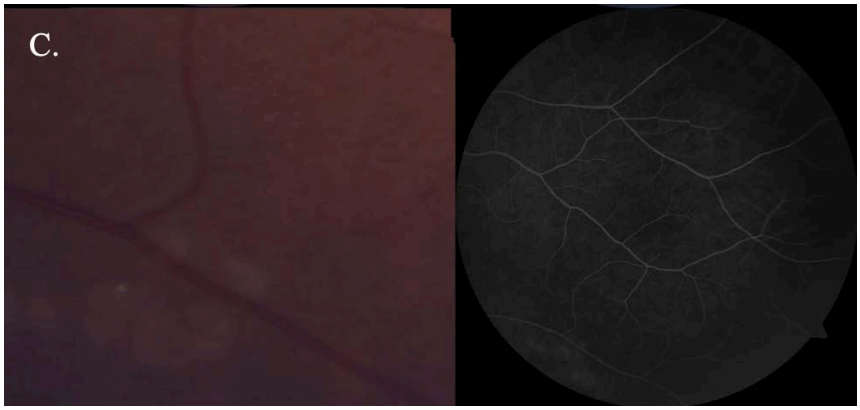

Figure 4. Eye fundus fluorescein angiography of the patient with CADASIL. **A.** Constricted retinal arteries in both eyes. **B.** Retinal pigment epithelium (RPE) atrophy in both eyes, but mainly in the left eye. **C.** Retinal pigment epithelium (RPE) atrophy with focal drusen in the left eye.

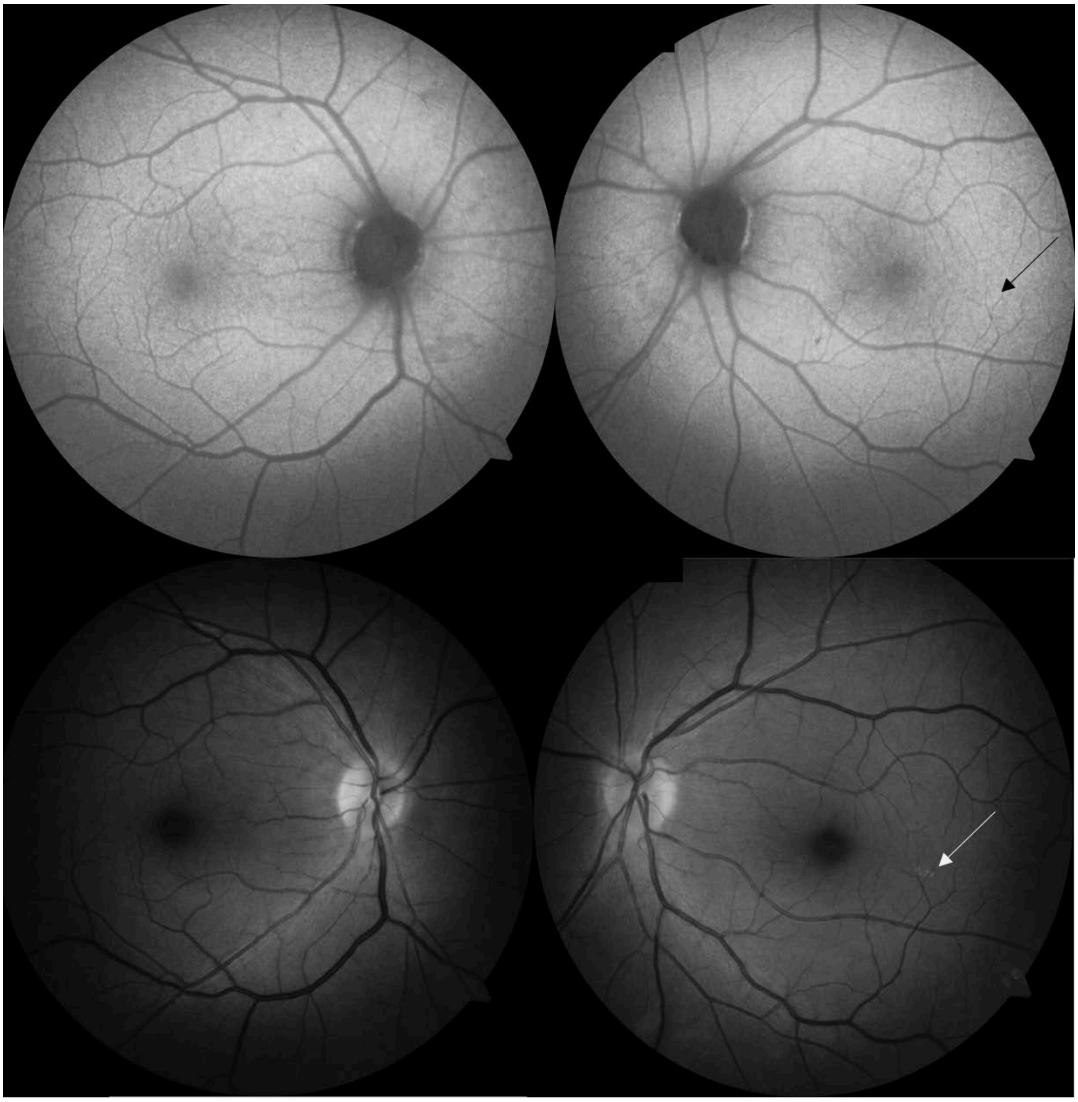

Figure 5. Fluorescein angiography of the right and the left eye. Discrete retinal lesions in the left eye (the arrow demonstrates focal drusen).

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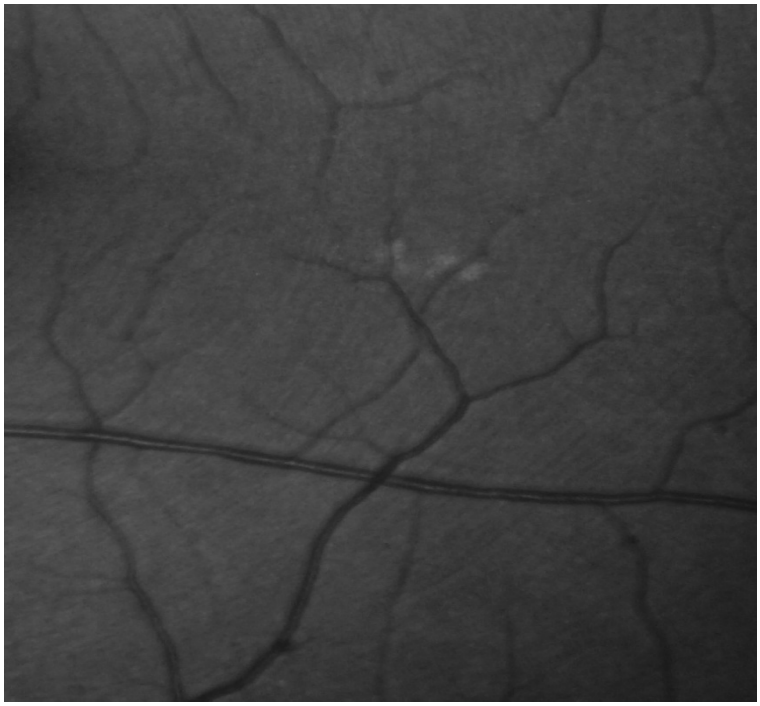

Figure 6. Focal drusen around the subretinal region of the left eye demonstrated in the fluorescein angiography.

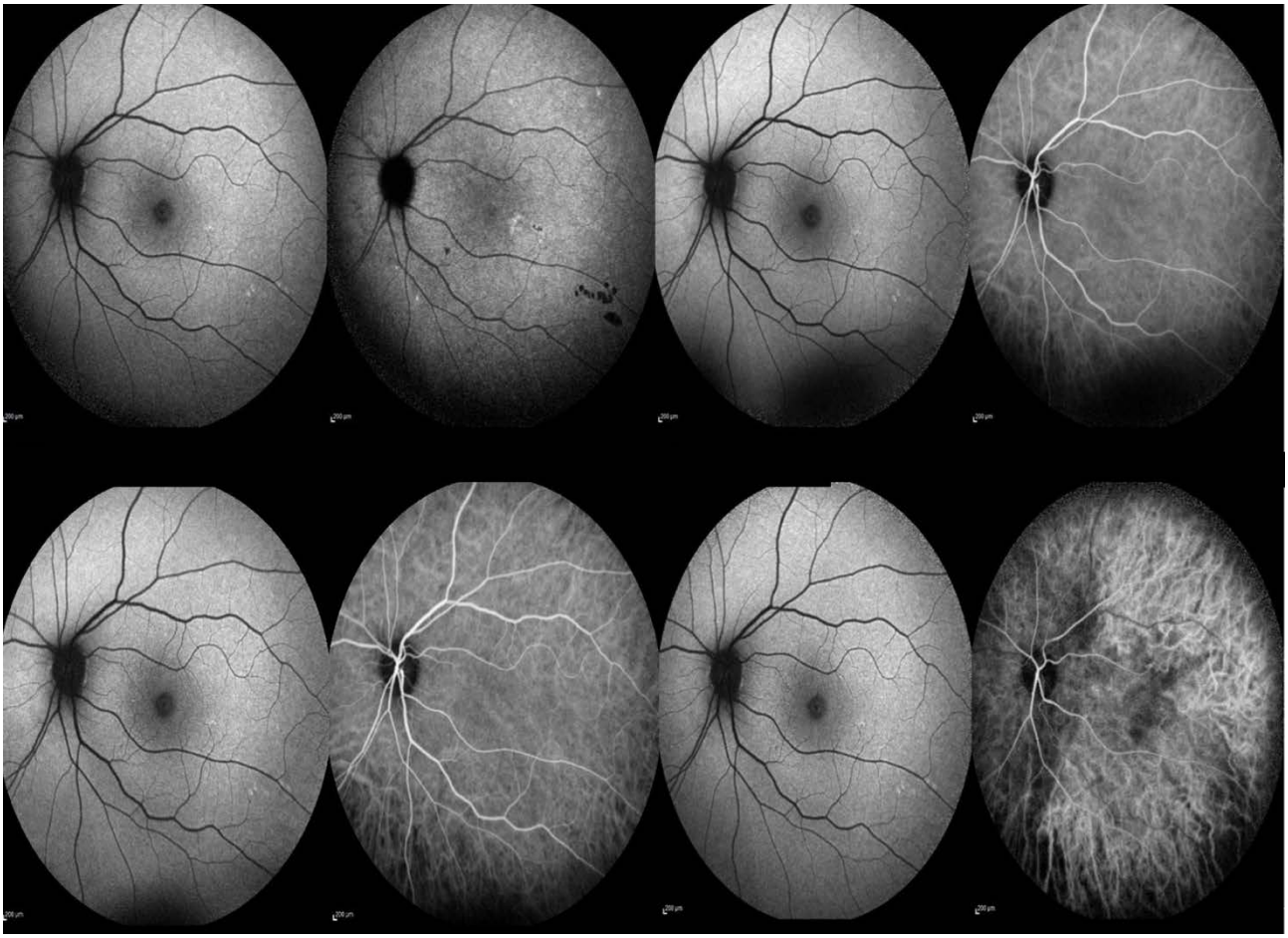

Figure 7. Small, linear, focal hyperfluorescence of the lower part of central fovea exclusively in the left eye, demonstrated in the indocyanine green angiography.

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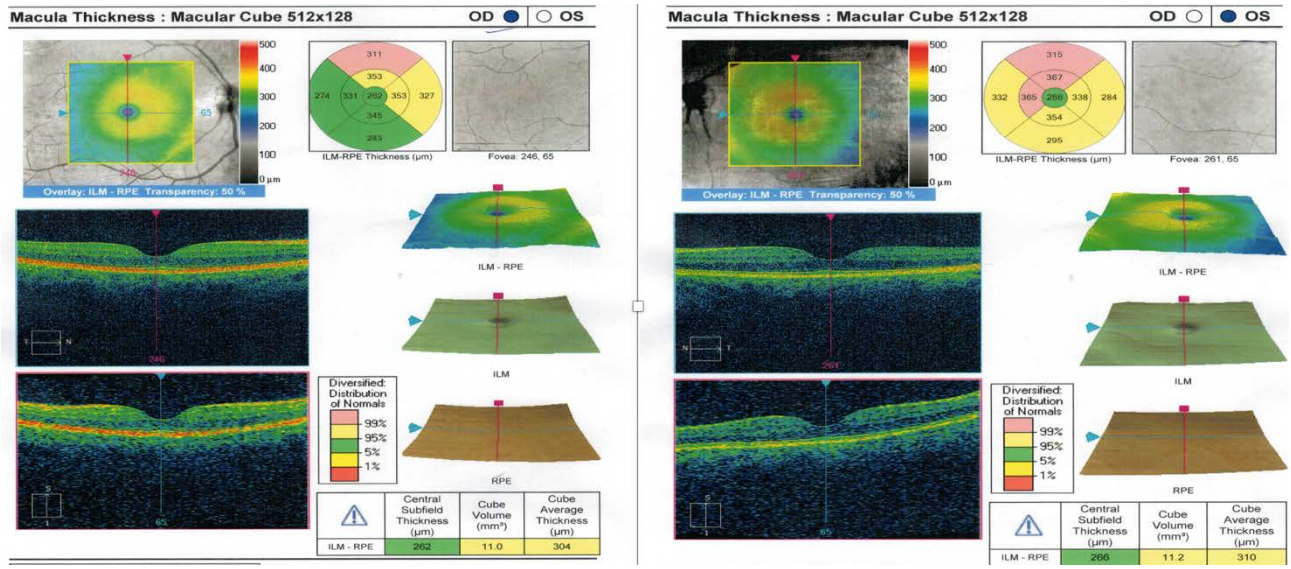


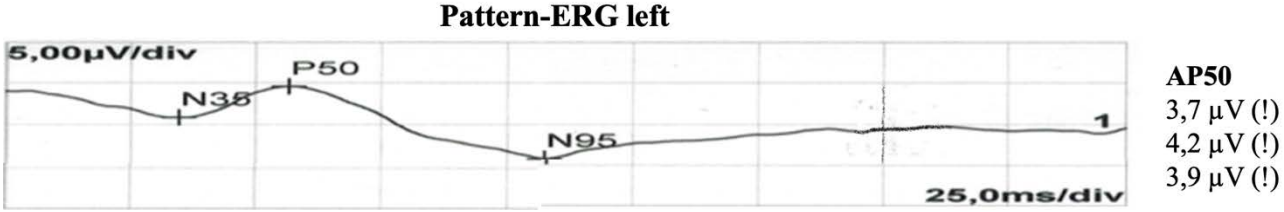
Figure 8. Thickening of the central part of the macula demonstrated in macular OCT, mainly in the left eye.

Color doppler USG confirmed a decreased blood flow in both retinal and choroid arteries (central retinal artery and posterior ciliary arteries), mainly in the left eye, as well as an increased vascular resistance of these arteries (Table 1). PERG demonstrated reduced P50 wave amplitude in the patient's left eye, while visual evoked potential (VEP) did not reveal any abnormalities (Figure 9).

Table 1. The blood flow parameters of the extraocular vessels demonstrated in doppler ultrasonography.

	Vs RE cm/s	Vs LE cm/s	Vd RE cm/s	Vd LE cm/s	RI RE	RI LE	PI RE	PI LE
Ophtalmic artery	58,59	56,60	23,24	21,45	0,61	0,62	0,94	0,99
Central retinal artery	11,72	8,06	2,99	1,17	0,71	0,90	1,21	1,60
Medial posterior ciliary artery - PCA medial	17,04	10,74	5.99	3,12	0,65	0,71	0,98	1,21
Lateral posterior ciliary artery - PCA l	20,73	12,21	3,45	3,22	0,71	0,83	0,89	1,35

OA - ophtalmic artery; CRA - central retinal artery; PCA - posterior ciliary artery; PCA m - medial posterior ciliary artery; PCA l – lateral posterior ciliary artery; RI - resistivity index; PI - pulsatility index; RE - right eye; LE - left eye; Vs - systolic velocity; Vd - diastolic velocity.



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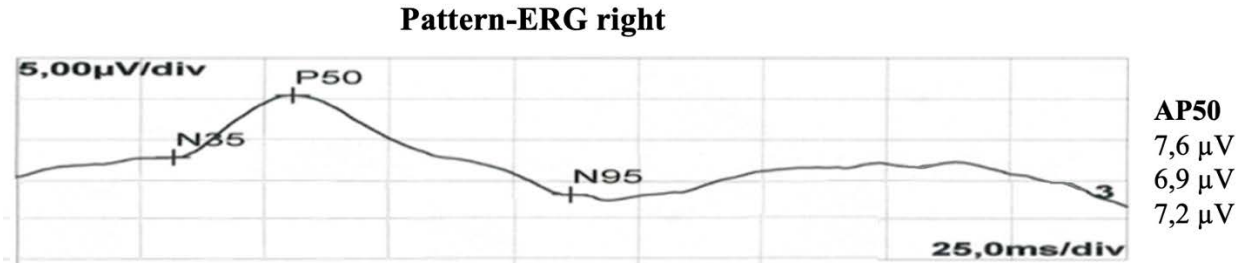

Figure 9. Pattern electroretinogram demonstrating the reduced P50 wave amplitude in the patient's left eye. No abnormalities in the right eye.

MRI of central nervous system demonstrated multiple focal vasogenic lesions in white matter of both hemispheres, which were partly merged in the occipital horn region (Figure 2B). Single microinfarct lesion was found in left external capsule (Figure 2C). There were also two 10x4 mm cysts in the pineal gland.

Ultrastructural examination of endothelial changes in both muscle and skin biopsies revealed the presence of GOM in small vessels of the skin and the muscle. The examination also demonstrated discrete degenerative lesions of the pericytes and myocytes of the vessels, along with vacuolation and constriction. Finally, the genetic testing has confirmed NOTCH3 gene mutation (p. Cys212Gly allele). As it turned out, the same diagnosis has been confirmed in the patient's mother, who also has manifested CADASIL symptoms, including dementia, muscle and neurological dysfunction with.

Discussion

First reports concerning CADASIL were described as familial Binswanger disease by Van Bogaert in 1955 [36]. First symptoms of this affliction were labeled in 1977, but it was not until 1993 when the entire description of the disease was published by French authors (Turnier-Lasserve E, Joutel A, Melki J *et al.* [1]), as a co-ocurrence of ischemic infarcts, progressive dementia and migraines. Because of the fact, that histopathological lesions were only found in the arteries, the disease was described as autosomal dominant arteriopathy with subcortical infracts and neurodegeneration of the white matter of the brain. In 1996, it was confirmed that NOTCH3 gene, located on chromosome 19 (p13.1-13.2) is responsible for the onset of the symptoms of the disease.

CADASIL steadily impairs everyday functioning of the affected patients because of the numerous neurological implications, which are the implications of vasogenic defects. The source of this condition is thought to be found in GOM deposits, which were found not only in retina and brain, but also in skeletal muscles, kidneys, pericardium and skin [19].

The retinal changes in CADASIL include the retinal arteriolar stenosis, decreased A/V ratio, arteriovenous nicking), artery straightening, enhanced vascular reflex [20], all of which were manifested by the patient in this clinical presentation.

The authors emphasize the importance of peripheral RPE atrophic lesions along with focal drusen, that have not been widely described before. The drusen were observed in the region of retinal vessels, and they might be related to GOM deposits. In the available literature it is reported, that other manifestations of CADASIL include the reduction of optic nerve fiber layer thickness [31, 32] as well as reduced vessel density in the deep retinal plexus [33]. Such abnormalities are correlated with a decreased blood flow and an increased vascular resistance of central retinal artery and posterior ciliary arteries, confirmed in USG doppler mainly in the left eye (Table 1).

Early changes of functional retinal ganglion cells and retinal photoreceptors were confirmed in the pattern electroretinogram (PERG), which revealed a reduced P50 wave amplitude in the patient's left eye (Figure 9). Similar phenomenon has been described as cholinergic deficiency in the pathogenesis of the Alzheimer's disease (AD). Other retinal

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lesions described in the literature include cotton wool spots, which are a result of the obliteration of the arterioles, caused by the deposits of axoplasm in retinal nerves. The correlation between retinal effusion and lacunar infarcts in patients with SVD has also been proven [35, 39].

Manifestations typical for CADASIL also include multiple, recurrent TIAs, along with ischemic infarcts, mainly in the fourth or fifth decade of life (60-85% of patients suffering from CADASIL). Visual disturbance might be the first symptom in younger patients without typical risk factors of vascular diseases. Another symptom characteristic for CADASIL, is transient loss of vision, which might be a result of ischemia caused by the embolism in ruptured atheroma of the internal carotid artery, heart, aorta or focal thrombosis of retinal vessels or posterior ciliary arteries [23, 24]. Similar symptoms can be observed during vasospasm in association of hypercoagulability, migraines or giant-cell arthritis (GCA).

Abovementioned afflictions are some of the consequences of disruption in blood flow that impairs the perfusion of the optic nerve or the retina. This conclusion was confirmed by the authors of the research in USG doppler, which revealed hemodynamic disturbance in the extraocular vessels (including central retinal artery and posterior ciliary arteries), mainly in the left eye [25].

The co-occurrence of diplopia and transient vision loss requires excluding the vertebral artery insufficiency with the disturbance of blood flow in the optic nerve head [26]. It is a fairly rare symptom described in patients with CADASIL. According to Davous, diplopia might be triggered by vasogenic lesions in the brain stem, which are caused by the vertebrobasilar insufficiency [37]. Tumor or stroke of the occipital region rarely leads to diplopia [27]. Double vision might be the only manifestation of CADASIL, anticipating the neurological disorders by many years [30].

In this clinical report, a convergence insufficiency might have been a result of impaired extraocular muscle innervation (III-cranial nerve) or exophoria (latent divergent strabismus), other literature items mention: ophthalmoplegia, Perinaud syndrome, myasthenia, oculomotor nerve palsy or thyroid related orbitopathy [28].

In the course of CADASIL, the strokes are characterized as focal regions of necrosis (sinus or lacunar infarcts), and are mainly located in the white matter of the brain, particularly around frontal lobe, temporal lobe as well as in cortical nuclei. Rarely are they located in the region of spinal cord or brain stem, although such localization was affected in the history of our patient. An infarct in the temporal lobe most often than not leads to disturbance of visual spatial orientation, narrowing interests, apathy, behavioral changes, memory and concentration disturbance, all of which were manifested by our patient.

Further examples of manifested symptoms include frequent migraines with visual or sensory aura, which are mostly manifested between the third and fourth life decade, and usually proceed the disclosure of morphological vascular lesions. The correlation between the patent foramen ovale and unilateral sensory deficits, speech disorder or hemiparesis. Migraine episodes are less frequent after the onset of the first stroke.

Pseudobulbar affect, dementia (31-60% of patients with CADASIL), cognitive and psychiatric disorders (symptoms similar to the AD, aboulia, agitation, aggression, mania, paranoid personality disorder), subcortical structures impairment, bladder control problems as well as gait disturbance, among other clinical manifestations, are worth mentioning. The clinical presentation of CADASIL might differ even among the family members, who are carriers of the same gene mutation.

Ultrastructural examination of both muscle and skin biopsies, revealing the presence of GOM in small vessels of the skin and the muscle, are strong indicator of CADASIL, which are further confirmed by the presence of degenerative lesions of the pericytes and myocytes of the vessels, along with vacuolation and constriction. The genetic testing for NOTCH3 gene mutation (p. Cys212Gly allele) is the final confirmation of the disease. Such diagnosis was made in case of our patient.

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Wide variety of disease should be taken under consideration as far as differential diagnosis is concerned, including acute encephalitis and myelitis, Behcet disease, neuroborreliosis, multiple sclerosis, neurosarcoidosis and syphilis. Many pathologies might manifest with similar neurological symptoms, that is why radiographic imaging, along with its possibility to evaluate the onset of the symptoms, plays a crucial role in differential diagnosis, despite laboratory results alone. MRI can often detect first symptoms of the disease even up to 10-15 years prior to the onset of clinical symptoms. Such early MRI findings include enhancement in white matter, lacunes, microinfarcts or broadened vascular spaces [38].

Psychiatric disturbances in CADASIL, especially dementia, draw particular interest. The cholinergic deficit might be a culprit, as it is responsible for the pathogenesis in AD [17]. The PERG revealed a retinal bioelectric dysfunction in a form of reduced P50 wave amplitude in the patient's left eye, which was also confirmed in our patient. These changes may indicate the possible impairment of ganglion cells and their axons, as a result of the macular photoreceptors dysfunction, and simultaneously normal VER results, which is said to be an early marker of AD [21].

In differential diagnosis other maculopathies, such as Stargardt macular dystrophy or macular edema, should also be taken into consideration [21]. Among the patients suffering from AD, the correlation between PERG abnormalities and the reduction of optic nerve fiber layer thickness has been confirmed in OCT [22], which on the other hand was not demonstrated in case of our patient.

The positive history for cerebral infarct or TIA carries the higher risk of another thromboembolic event, which is why the post stroke rehabilitation and modification of potential causative factors (including arterial hypertension, diabetes and hyperlipidemia) is highly recommended. The crucial part of prevention is anticoagulant therapy in patients with concomitant atrial fibrillation (AF), coronary artery disease (CAD), patent foramen ovale (PFO) or carotid vessel stenosis [18]. Administration of vasoconstrictor agents, such as ergotamine, is contraindicated as they intensify tissue ischemia and broaden the focal stroke lesions.

The causal treatment includes gene therapy and inhibition of culprit protein translocation. The new *in vitro* and *in vivo* trials have been carried out lately, and they aim to find the new therapeutic possibilities for patients suffering from genetic diseases. The researchers hope to succeed in immunotherapy [9, 10], growth factors implementation [11, 12, 13] and exons skipping [14]. The initial results are promising and have already been implemented as groundbreaking therapeutic options for patients suffering from other neurological diseases. For instance, antisense oligonucleotide-induced exon-skipping enables synthesis of party functional dystrophin in patients with Duchenne muscular dystrophy [15]. Another successful example is alternative splicing of SMN2 protein pre-MRA, that consecutively leads to higher expression of functional SMN protein in patients with spinal muscular atrophy (SMA) [16].

The abovementioned new treatment options have already been implemented in patients suffering from other neurological diseases [15, 16], although the side effects of such therapies still limit their use on a large scale. That is why it is crucial to find such NOTCH3 gene expression variants, that would provide successful therapeutic effect with minimal side effects.

Conclusions

Clinical symptoms in the form of transient vision loss, diplopia, convergence disorders, migraine episodes (with aura) together with ischemic stroke and premature dementia in young and middle-aged patients, without the presence of risk factors for vascular disease, can be considered in the diagnosis of CADASIL. Additional new symptoms are RPE retinal atrophy, retinal vasoconstriction, focal drusen, decreased blood flow in the macular retinal-choroidal region, and pERG reduction in P50, possibly as a result of a cholinergic deficit or possible dysfunction of macular or ganglion cells. Hyperintensive

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changes in the white matter of the brain in MRI, GOM deposits in small vessels of the skin and muscles revealed in ultrastructural examination of muscle and skin biopsies, as well as confirmed mutation of the NOTCH3 gene are particularly important in the CADASIL diagnostic process.

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Author Contributions

Concept/design: M.M. and P.W.; data analyses/interpretation: M.M., P.W. and A.K.; drafting of the article: M.M. and P.W.; critical revision of the article: M.M.; approval of the article: M.M., P.W. and A.K. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

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Data Availability Statement

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Conflicts of Interest

The authors declare no conflict of interest.

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