Acute Unilateral Visual Loss as the First Symptom of Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

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Background: Although cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is considered a cerebrovascular disorder with almost exclusively neurological symptoms, the arteriopathy is generalized and involves choroidal and retinal vasculature as demonstrated by fluorescein angiographic and ocular electrophysiological abnormalities. The occurrence of acute visual loss due to nonarteritic anterior ischemic optic neuropathy (NAION) has not previously been reported in CADASIL.

Objective: To describe acute visual loss due to NAION as a possible manifestation of CADASIL.

Patients and Methods: The patient was a 60-year-old man with subcortical diffuse leukoencephalopathy, multi-infarct dementia, tetraparesis, visual loss, and a family history of stroke. We performed clinical and neuro-ophthalmological evaluation, electrophysiological assessment, brain magnetic resonance imaging, and genetic screening for mutations or small deletions of the \( \text{Notch3} \) gene, (causing CADASIL).

Results: The patient’s first symptom was acute visual loss in the right eye due to NAION at age 27 years, in absence of the common cardiovascular risk factors and before any neurological impairment. The patient was re-evaluated at age 60 years, and neuro-ophthalmological examination showed optic disc atrophy in the right eye with arteriolar narrowing and a reduction in visual acuity in the left eye. Fluorescein angiography of the right eye showed evidence of persistent peripapillary hypofluorescence with a retinal pigment epithelial windows defect in the inferior temporal area. Pattern reversal visual evoked potentials were abolished in the right eye. The P100 latency of the left eye was delayed and reduced in amplitude. The diagnosis of CADASIL was confirmed by molecular analysis (heterozygotes for the C406T mutation on exon 3 of the \( \text{Notch3} \) gene). There was a family history of cerebrovascular disorders and ocular impairment.

Conclusions: Visual loss due to transient or stable ischemic events involving the optic nerve head should be considered in the CADASIL phenotype. The possibility of CADASIL should also be evaluated in patients with NAION who do not have cardiovascular risk factors but do have a family history of stroke.

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small artery disease due to mutations of the \( \text{Notch3} \) gene at chromosome locus 19p13. The \( \text{Notch3} \) gene encodes for a large transmembrane receptor protein, which in adults is expressed only in vascular smooth muscle cells. Gradual accumulation of the extracellular domain of the receptor protein leads to progressive loss of function of these cells with subsequent wall thickening and lumen narrowing in small and medium-sized penetrating arteries. Although the symptoms of CADASIL are almost exclusively neurological, vascular abnormalities are not limited to the cerebral arterioles but are observed in the small arteries of almost all organs. Symptoms appear at ages 30 to 50 years, beginning with transitory ischemic attacks or strokes, migraine, mood disturbances, and seizures and progressing to severe motor disability, dementia, and premature death. Although the clinical picture can vary greatly and differences in the onset and progression of symptoms have been reported in affected members of the same family, acute visual loss is not usually included in the classical phenotype.
In this article, we report the case of a patient with nonarteritic anterior ischemic optic neuropathy (NAION) leading to visual loss as the first symptom of CADASIL.

REPORT OF A CASE

Our patient was a 60-year-old man with a long history of migraine and recurrent stroke. Symptoms began at age 27 years with acute visual loss in the right eye. The patient was diagnosed as having NAION on the basis of acute painless visual loss, afferent pupillary defect of the right eye, impaired color vision, inferior altitudinal visual field defect, ophthalmoscopic evidence of optic disc swelling, and absence of clinical and laboratory evidence of arteritis. At that time, well-established cardiovascular risk factors such as hypertension, diabetes, cardiopathy, carotid artery disease, and coagulopathy were excluded. During the subsequent 33 years, the patient had recurrent transient ischemic attacks and strokes as well as progressive mental decline. At age 60 years, neurological examination showed spastic tetraparesis, dysarthria, a severe cognitive deficit, and urinary incontinence.

Laboratory tests excluded cardiovascular risk factors, systemic vasculitis, coagulopathy, sarcoidosis, and metabolic anomalies. Results of carodiographic examination, electrocardiography, and transesophageal echocardiography were normal. Doppler ultrasonography of the extracranial arteries revealed no significant abnormalities. Neuro-ophthalmological examination showed best-corrected visual acuities of 20/200 OD and 20/50 OS. Color vision (Ishihara plates) was 1/15 OD and 10/15 OS, and dilated funduscropy showed generalized optic disc pallor and peripapillary atrophy with arteriolar attenuation in the right eye. Funduscopic of the left eye showed arteriolar narrowing and a hyperemic optic disc (cup-disc ratio, 0.2). Goldmann perimetry showed peripheral constriction in the right eye associated with a central scotoma. A relative central scotoma (10° nasally and 40° temporally) was evident in the left eye. Early-phase fluorescein angiography of the right eye showed perfusion delay of the optic disc and irregular filling of the retinal arteriole. A late-phase angiogram showed persistent hypofluorescence of the peripapillary region associated with retinal pigment epithelial windows defects (in inferior temporal). Pattern reversal visual evoked potentials (VEPs) were abolished in the right eye, and there was a P100 implicit time delay with reduced amplitude in the left eye. A flash electroretinogram (ERG) showed a- and b-wave implicit time prolongation associated with low amplitude, more severe in the right eye. Pattern ERG trace was abolished in the right eye, and a- and b-waves were not recognizable in the left eye. Conventional magnetic resonance imaging of the brain showed diffuse atrophy and extensive white matter signal hyperintensity with long echo time sequences (Figure 2A and B).

There was a family history of ischemic cerebrovascular episodes. The patient’s father had died at age 56 years with a long history of sensorimotor and cognitive impairment due to recurrent brain ischemic attacks. The clinical history contained no neuro-ophthalmological symptoms. The patient’s elder son, aged 31 years, had a stroke at age 25 years with right hemiparesis and aphasia. He had complained of migraine since adolescence and had experienced transient visual loss in the right eye at age 15 years, which recovered completely without therapy in 48 hours. At age 25 years, funduscropy showed bilateral arteriolar narrowing, and pattern VEPs indicated bilateral P100 implicit time prolongation with reduced amplitude. Results of a flash ERG were normal, but a pattern ERG showed delayed P50 latency and bilateral reduction of N35-P50 amplitude. A computed tomographic scan of the brain showed hypodensity of the left frontoparietal white matter and thalamus.

The patient’s younger son, aged 26 years, was asymptomatic. However, there was magnetic resonance imaging evidence of cerebral white matter abnormalities and ophthalmoscopic evidence of arteriolar narrowing. In both father and sons, the diagnosis of CADASIL was confirmed by molecular genetic analysis of the Notch3 gene, which showed a C406T mutation on exon 3.

COMMENT

Nonarteritic anterior ischemic optic neuropathy is a well-recognized phenomenon in which infarction of the optic nerve head occurs as a result of local vascular impairment. This is due to anatomical predisposing factors (“disc at risk”) associated with vascular impairment of the prelaminar portion of the optic nerve head, which is supplied by an anastomotic circle of arterioles that is highly sensitive to variations in blood flow. Although more frequently associated with hypertension and diabetes, NAION may occur in any systemic condition associated with vessel wall changes. As shown in our study, this could include CADASIL. In our patient, the arteriolar wall changes typical of CADASIL presumably reduced blood flow in the anastomotic circle of the optic nerve head, causing NAION. The pathogenesis of transient monolateral visual loss experienced by his...
elder son at age 15 years is less clear. The most common cause of transient monolateral visual loss is embolism of the retinal arterioles of cardiac or ipsilateral carotid origin. Less commonly, this condition may be due to hyperperfusion (compression, hypotension, hyperviscosity, or hypercoagulability) or vasospasm. These causes were not found in the patient’s son at the time of his visual problem. When we reexamined the son, arteriolar narrowing was evident in the retinas of both eyes. The VEPs and pattern ERG responses were also abnormal.

Involvement of the ocular vessels is supported by published evidence of early retinal and choroidal vasculature impairment leading to abnormal ocular electrophysiological responses. In this respect, patients with CADASIL showed dysfunction of the outer, middle, and innermost retinal layers, as demonstrated by alterations in ERG, pattern ERG, oscillatory potentials, and VEP responses. Our patient and his elder son showed abnormal ocular electrophysiological responses, indicating outer retinal and ganglion cell impairment. In addition, VEPs and pattern ERG responses of the right eye were absent in our patient because of severe optic nerve damage. Evidence of ocular vascular impairment has been reported in CADASIL using fluorescein angiography.

In conclusion, we suggest that acute visual loss due to optic nerve ischemia may occur in CADASIL. The diagnosis of CADASIL should be considered in patients with NAION who do not have common cardiovascular risk factors but do have a family history of cerebrovascular disease.

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REFERENCES


