Hemodynamic Evaluation of the Optic Nerve Head in 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, arteriopathy is generalized and also involves the choroid and retina.

Objective: To study optic nerve head microvascular function in CADASIL by assessing blood flow, volume, and velocity with a retina flowmeter.

Patients and Methods: Scanning laser Doppler flowmetry permits the noninvasive assessment of relative blood velocity, volume, and flow in a sample volume of either retina or anterior optic nerve head. Measurements were performed in a first group of 9 eyes of 5 patients with CADASIL and a second group of 8 eyes of 4 healthy subjects. Hemodynamic parameters were computed in 4 quadrants of the optic disc (superior nasal, superior temporal, inferior nasal, and inferior temporal). The Wilcoxon rank sum test was used to assess differences in relative flow, volume, and velocity in each quadrant and between the 2 groups and differences in overall optic nerve head blood flow, volume, and velocity.

Results: Patients with CADASIL had a significant decrease in overall blood flow and volume compared with healthy subjects (P < .05). The reduction in blood flow and volume was particularly significant in the superior and inferior temporal quadrants. No significant differences were found nasally between the patients and the control groups.

Conclusion: Our results suggest that hemodynamic parameters are abnormal in the superficial nerve fiber layer of the optic nerve head of patients with CADASIL, especially in the temporal quadrants of the neuroretinal rim.

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited late-onset brain arteriopathy. Symptoms usually appear at 30 to 50 years of age and are characterized by recurrent transient ischemic attacks, stroke, migraine, psychiatric disorders, and seizures, progressing to severe motor disability, subcortical dementia, and premature death. The disease is caused by mutations or small deletions in the Notch 3 gene. In adults, Notch 3 is only expressed in vascular medial smooth muscle cells. Progressive accumulation of the extracellular domain of Notch 3 at the surface of medial smooth muscle cells of arterioles, capillaries, and venules leads to degeneration of smooth muscle cells and progressive adventitial fibrosis of brain vessels.

Vascular abnormalities in CADASIL are not limited to the cerebral arterioles but are also observed in systemic arterioles, including those in the retina and optic nerve head. Optic nerve and retinal vascular hemodynamic changes have not yet been investigated. The Heidelberg Retina Flowmeter (HRF) (Heidelberg Engineering, Dossenheim, Germany) is a noninvasive and standardized method for retinal or optic nerve head blood flow measurement. Reproducibility and reliability of the HRF measurements have been documented extensively. The aim of this study was to assess optic nerve head blood flow, volume, and velocity using an HRF in 9 eyes of 5 patients with genetically confirmed CADASIL and in 8 eyes of 4 healthy, age-matched controls.

Methods

Patients and Controls

A first group of 9 eyes of 5 patients with genetically confirmed CADASIL (5 men; 3 symptomatic, 2 asymptomatic; mean age, 38.8 years; range, 27-50 years) and a second group of 8 eyes of 4 healthy age- and sex-matched, nonsmoker control subjects (3 men, 1 woman; mean age, 40 years; range, 29-55 years) were enrolled in the study. None of the subjects had any other systemic, vascular, or ocular pathologic features or had under-
Table 1. Main Neurological, Genetic, and Magnetic Resonance Imaging Abnormal Findings in Patients With Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

<table>
<thead>
<tr>
<th>Patient/ Age, y</th>
<th>First Symptom</th>
<th>Neurological Findings</th>
<th>White Matter Lesions, mL</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1/27</td>
<td>Asymptomatic</td>
<td>Normal</td>
<td>1.8</td>
<td>Exon 3</td>
</tr>
<tr>
<td>C2/45</td>
<td>Confusion, episodes</td>
<td>Mood disturbances</td>
<td>36.6</td>
<td>Exon 4</td>
</tr>
<tr>
<td>C3/41</td>
<td>Asymptomatic</td>
<td>Normal</td>
<td>4.5</td>
<td>Exon 20</td>
</tr>
<tr>
<td>C4/50</td>
<td>Stroke</td>
<td>Behavioral changes, hemiparesis</td>
<td>20.2</td>
<td>Exon 20</td>
</tr>
<tr>
<td>C5/31</td>
<td>Transient monocular visual loss</td>
<td>Not performed</td>
<td></td>
<td>Exon 3</td>
</tr>
</tbody>
</table>

Table 2. Main Ocular Findings

<table>
<thead>
<tr>
<th>Subjects</th>
<th>IOP</th>
<th>GVF</th>
<th>PERG</th>
<th>RV</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>C2</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Segmental narrowing</td>
</tr>
<tr>
<td>C3</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>C4</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Segmental narrowing</td>
</tr>
<tr>
<td>C5</td>
<td>Normal</td>
<td>RCS (right eye)</td>
<td>Abnormal</td>
<td>Diffuse arteriolar narrowing</td>
</tr>
<tr>
<td>N1</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>N2</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>N3</td>
<td>Normal</td>
<td>Normal</td>
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<td>Normal</td>
</tr>
<tr>
<td>N4</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Abbreviations: GVF, Goldmann visual field; IOP, intraocular pressure; PERG, pattern electroretinography results; RCS, reduction of central sensitivity; RV, retinal vessels.

*Best-corrected visual acuity ranged from 20/30 to 20/15. Subjects C1 through C5 are patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; subjects N1 through N4 are control subjects.

TECHNICAL PROCEDURES

The HRF is an ocular device using the optical Doppler effect to measure the number and rate of moving erythrocytes within retinal or optic nerve head microcirculation. Technical details of the instrument have been published elsewhere. Briefly, the HRF contains a 780-nm diode laser probe, confocal optics, and a focal diode to measure the intensity of backscattered light from the stationary targets (vessel wall) and moving targets (blood corpuscles) of the retina and optic nerve head micro-vessels. After multiple lines scanning (64 lines, each 128 times) with a penetration depth of 300 mm in a rectangular slice of tissue (10° × 2.5°) of the posterior pole, the instrument computes a 2-dimensional map of variations in backscattered-light intensity at different points of the retina or optic nerve head. Spectral analysis by fast Fourier transformation of the intensities is performed for each point (pixel), and a power spectrum is calculated for each pixel. Computed in arbitrary units, the variables from this spectrum are the volume, flow, and velocity.

DATA ACQUISITION

To ensure a good reproducibility of the perfusion data, 2 sessions (with a 1-week interval) were performed. The measurements, acquired by the same technician, were obtained after selecting a window of 10 × 10 pixels (area, 100 mm × 100 mm) on the HRF monitor across 4 quadrants of the neuroretinal rim (superior temporal, superior nasal, inferior temporal, and inferior nasal). To provide a better reproducibility of the results, mean blood flow volume and velocity of the entire image of the optic nerve head were also obtained for each eye. Three readings of the same anatomical area were acquired at each session to overcome physiological hemodynamic variations occurring because of the cardiac cycle. The 10 × 10-pixel box site was chosen away from visible large vessels to measure capillary parameters only. Traces of retinal rim vasculature for each fundus and blood vessel landmark were obtained before the examination to ensure the same image location. During the examination, patients were instructed to focus on a red dot 1.5 m from the instrument. Only well-focused images were taken. Results were analyzed by 2 different blinded observers. The obtained values reflect hemodynamic parameters of the superficial nerve fiber layer, which is supplied by branches of the central retinal artery.

STATISTICAL ANALYSIS

Values were expressed as mean ± SD. The Wilcoxon rank sum test was used to test for differences in overall optic nerve head blood flow, volume, and velocity and for differences in blood flow, volume, and velocity in each quadrant (superior temporal, superior nasal, inferior temporal, and inferior nasal) of the neuroretinal rim in patients with CADASIL and in control subjects; P < .05 was considered significant.

All patients were confirmed to have CADASIL by molecular analysis. Demographic, neurological, and genetic information of the patients with CADASIL are reported in Table 1. In the same table, the quantitative assessment of white matter lesions, measured as previously described, is also reported. At the time of our examination, 2 patients were clinically asymptomatic. Three had a history of migraine, recurrent ischemic attacks, and strokes. Rankin scores ranged from 0 to 3 (mean, 0.8); and Mini-Mental State Examination scores ranged from 22 to 29 (mean, 26). Patients with CADASIL did not show abnormal laboratory values. In addition, results from systemic blood pressure, intraocular pressure, carotid arteries Doppler evaluation, electrocardiographic, and echocardiographic examinations were normal. Abnormal neuro-ophthalmological findings are reported in Table 2.

Control subjects had no past history of cardiovascular, metabolic, neurological, or ocular diseases; no family history of cardiovascular disorders; and no clinical, neurologi-
Patients with CADASIL showed a significant reduction of overall mean ± SD optic nerve head blood flow (232.66±87.4 arbitrary units [AU] vs 306.62±55.1 AU; P < .05) and volume (121.07±2.2 AU vs 141.21±3.1 AU; P < .05), as compared with healthy subjects (Figure 1A and B). In addition, we found significantly lower mean ± SD temporal superior blood flow (221.80±57.7 AU vs 330.14±60 AU; P < .05), mean ± SD temporal superior blood volume (12.3±2.6 AU vs 15.9±3.8 AU; P < .05), and mean ± SD temporal inferior blood volume (11.9±2.0 AU vs 14.9±2.5 AU; P < .05) in patients with CADASIL than in controls (Figure 2A and B).

New emphasis has recently been given to funduscopic examination in patients with cerebral small vessel diseases, including CADASIL, because retinal and optic nerve head arterioles share common anatomical and physiological properties with small cerebral arteries. A major similarity between small cerebral vessels and retinal and optic nerve arterioles is that the latter are also endarteries that do not anastomose, and the size of visible retinal arterioles is in the range of 50 mm to 250 mm. There is also evidence that blood flow is autoregulated in retinal and optic nerve tissue as in the brain; in this respect, healthy eyes maintain stable perfusion despite wide variations in systemic blood and intraocular pressure. As in the brain, the vascular reactivity of the retina and optic nerve head depends on the integrity of medial smooth muscle cells.

Pathological changes in CADASIL consist of diffuse cerebral small vessel medial smooth muscle cell degeneration with progressive adventitial fibrosis, which is particularly severe in arterioles less than 100 mm in diameter. These arterioles progressively lose their capacity for autoregulation. An abnormal vascular reactivity may be an important factor causing the cerebral hemodynamic changes reported in CADASIL. The typical ultrastructural changes of CADASIL have been reported in retinal vessels. In addition, studies have recently revealed an impaired visual function in these patients by showing abnormal ocular electrophysiological responses in symptomatic and asymptomatic subjects.

The present HRF study provides evidence that hemodynamic changes also occur in the superficial nerve fiber layer of the optic nerve head in patients with CADASIL. Patients with CADASIL showed lower optic nerve head blood flow and volume than healthy subjects. The hemo-
dynamic abnormalities were significant not only in patients with disabilities but also in asymptomatic patients, suggesting early microvascular changes in CADASIL.

Anatomically and physiologically, the optic nerve head can be divided into 4 regions: the superficial nerve fiber layer, the prelaminar region, the lamina cribrosa, and the retro-laminar region. The superficial nerve fiber layer is supplied by the retinal arterioles, the other regions by posterior ciliary arteries, partially via the peripapillary choroidal and short posterior ciliary arteries. Because the sampling depth of the HRF is 300 mm, we measured the blood flow within the superficial nerve fiber layer, which mostly originates from the retinal arterioles. However, changes in blood flow deeper within the nerve head influencing the HRF results may not be excluded. Our data indicate that hemodynamic abnormalities were more severe in temporal sectors of the neuroretinal rim in patients with CADASIL. Interindividual variability in optic nerve head supply must be considered because the number of posterior ciliary arteries and superficial capillaries and the localization of the respective perfusion areas vary depending on physiological conditions. In normal subjects, the neuroretinal rim is less perfused temporally than nasally. This may be due to physiologically lower capillary density or locally insufficient vessel autoregulation. Heidelberg Retina Flowmeter evidence of altered blood flow has been reported in microvascular conditions, such as those associated with advancing age, age-related macular degeneration, nonarteritic ischemic optic neuropathies, and internal carotid artery stenosis.

Our patients with CADASIL did not complain of visual symptoms at the time of examination, and the integrity of extracocular visual pathways was documented by normal visual evoked potentials responses and Goldmann visual field examination, except for a monocular reduction in central sensitivity in patient C5. Conversely, we found abnormal pattern electroretinography responses in all patients and ophthamoscopic evidence of arteriolar narrowing in 3. These data suggest functional alteration of the retina congruent with microvascular changes. Our results demonstrate that the perfusion of the neuroretinal rim, mostly due to retinal microvascular changes, is reduced in patients with CADASIL. The hemodynamic changes were more evident in the temporal portion of the rim, which physiologically shows an insufficient autoregulation as compared with the nasal sector. The hemodynamic abnormalities were also evident in asymptomatic patients with CADASIL.

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Author Contributions: Study concept and design: Rufa. Acquisition of data: Frezzotti and De Stefano. Analysis and interpretation of data: Dotti, Caporossi, and Federico. Drafting of the manuscript: Rufa. Critical revision of the manuscript for important intellectual content: Dotti, Frezzotti, De Stefano, Caporossi, and Federico. Obtained funding: Caporossi and Federico. Administrative, technical, and material support: Dotti, Frezzotti, and De Stefano. Study supervision: Rufa.

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REFERENCES


