Study of Enhanced Depth Imaging Optical Coherence Tomography in Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

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Abstract

Background: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary small artery disease caused by NOTCH3 gene mutation. We performed enhanced depth imaging optical coherence tomography (EDI-OCT) to evaluate the retinal vessel changes in CADASIL patients and assessed their consonance with brain magnetic resonance imaging (MRI) findings.

Methods: Of 27 genetically confirmed patients and an equal number of controls were recruited at the Peking University First Hospital from January 2015 to August 2016. All patients underwent 7T-MRI of the brain. Fazekas score, number of small infarcts and microbleeds were evaluated. All patients and controls underwent EDI-OCT to measure subfoveal choroidal thickness (SFCT), inner and outer diameters as well as arterial and venous wall thickness, and arterial venous ratio of the inner (AVRᵢ) and outer diameters (AVRₒ). The relation between retinal vessel changes and Fazekas scores, numbers of small infarcts, or microbleeds was analyzed. Paired t-test was used to compare the SFCT and retinal vessel measurement data between patients and controls. Spearman’s correlation was used to investigate the correlation between retinal vessel changes and MRI lesions.

Results: In CADASIL patients, mean SFCT (268.37 ± 46.50 µm) and mean arterial inner diameter (93.46 ± 9.70 µm) were significantly lower than that in controls (P < 0.001, P = 0.048, respectively). Mean arterial outer diameter (131.74 ± 10.87 µm), venous inner (128.99 ± 13.62 µm) and outer diameter (164.82 ± 14.77 µm), and mean arterial (19.13 ± 1.85 µm) and venous wall thickness (17.91 ± 2.76 µm) were significantly higher than that in controls (P = 0.023, P = 0.004, P < 0.001, P < 0.001, respectively). Arterial inner diameter (r = −0.39, P = 0.044), AVRᵢ (r = −0.65, P < 0.001), and AVRₒ (r = −0.56, P = 0.002) showed a negative correlation with the number of small infarcts. Venous inner diameter (r = 0.46, P = 0.016) showed a positive correlation with the number of small infarcts. Venous inner diameter (r = 0.59, P = 0.002), outer diameter (r = 0.47, P = 0.017), showed a positive correlation with the number of cerebral microbleeds (CMBs). AVRᵢ (r = −0.52, P = 0.007) and AVRₒ (r = −0.40, P = 0.048) showed a negative correlation with the number of CMBs.

Conclusions: Measurement of retinal vessels using EDI-OCT correlates moderately well with MRI parameters. EDI-OCT might be a useful evaluation tool for CADASIL patients.

Key words: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; Magnetic Resonance Imaging; Optical Coherence Tomography; Retinal Vessels

INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited cerebral small and medium vessel disease caused by mutations in NOTCH3, which encodes Notch3 receptor expressed in vascular smooth muscle cells (VSMC).[1,2] Pathological changes include deposition of...
granular osmiophilic material on the surface of smooth muscle cells with subsequent fibrosis in the wall of arterioles. Clinical manifestations of CADASIL include migraine with aura, subcortical ischemic events, mood disturbances, apathy, and cognitive impairment. Brain magnetic resonance imaging (MRI) is used for diagnosis and follow-up in these patients. Hallmark findings include white matter hyperintensities (WMHs), small infarcts and cerebral microbleeds (CMBs). Recently, High-resolution Magnetic Resonance was used to study the cerebral vessel in arteriosclerosis, moyamoya disease and CADASIL, microbleed and microinfarct detection in amyloid angiopathy, the changes of perivascular spaces and perforating arteries. De Guio et al. have revealed loss of venous integrity in CADASIL patients using 7T-MRI.

CADASIL is a systemic arteriopathy, which is typically well-characterized in the retinal vessels. The retinal arteriolar narrowing, arteriovenous nicking, and bilateral peripapillary arteriolar sheathing are common changes seen on fundus photography examination. Recent technological advances in optical coherence tomography (OCT) allow measurement of retinal vessel diameters and vessel wall thickness in vivo. Allen et al. documented a significant increase in arterial and venous outer diameters as well as arterial and venous wall thicknesses in German CADASIL patients. It needs to be confirmed if changes in retinal vessels correlate with cerebral MRI findings so that in future enhanced depth imaging (EDI)-OCT can be used as an alternative modality for a follow-up examination in these patients. In this study, we performed both EDI-OCT and high-field MRI in CADASIL patients to measure retinal vessel diameters and subfoveal choroidal thickness (SFCT). Further, the correlation between cerebral MRI findings and retinal vessel changes was investigated.

**Methods**

**Ethical approval**

The study was conducted in accordance with the Declaration of Helsinki. The institutional review board and ethics committee at the Peking University First Hospital approved this study. Written informed consent was obtained from all participants.

**Patients**

Twenty-seven CADASIL patients (15 male and 12 female; mean age, 44.9 ± 9.0 years, range 29–64 years), belonging to 19 families, were recruited from January 2015 to August 2016. All patients had Notch3 mutations confirmed on genetic analysis. Patients with any of the following were excluded in the study: high myopia (>−3 diopeters), high astigmatism (>±3 diopeters), or any concomitant ocular disease. Twenty-seven age- and sex-matched healthy controls (15 male and 12 female; mean age, 42.9 ± 8.4 years, range 31–64 years) who had no known medical conditions (e.g., diabetes, stroke, hypertension, and ischemic heart disease) or ocular diseases (glaucoma, diabetic retinopathy, age-related macular degeneration) were recruited as controls. There was no significant difference between the age of CADASIL patients and controls (t = 0.822, P = 0.117).

Complete medical history was obtained from all participants, none of the patients have hypertension or diabetes mellitus except one 61-year-old male patient has hypertension for 30 years. Disease duration was determined based on the first occurrence of neurological symptoms. The medium disease duration of the twenty-two symptomatic patients was 5.5 years (range, 0.5–12 years). Five subjects were asymptomatic, so they were excluded from the disease duration analysis. They were evaluated because of familiarity. Symptomatic stroke was the most frequent manifestation (n = 19), followed by chronic headache (n = 14), cognitive impairment (n = 7), and mood disorders (n = 6).

**Brain magnetic resonance imaging examination**

All patients underwent 7T-brain MRI examination (Siemens Healthcare, Germany). 7T-MRI examinations were performed as part of our ongoing “CADASIL patients’ 7T-MRI study”. Parameters of brain imaging protocol included the following: 3D T1-magnetization prepared gradient echo images (TR = 2200 ms, TE = 3.29 ms, voxel = 0.70 mm × 0.70 mm × 0.70 mm), fluid-attenuated inversion recovery images (TR = 14000 ms, TE = 94 ms, voxel = 0.43 mm × 0.57 mm × 3.00 mm), and susceptibility-weighted imaging (SWI)-gradient echo image (TR = 18 ms, TE = 12 ms, voxel = 0.30 mm × 0.30 mm × 1.20 mm). White matter lesions were scored using Fazekas scale (total score range: 0–6). The location and the numbers of small infaracts were recorded. The total number of CMBs was counted according to the Microbleed Anatomical Rating Scale. All MRI of good quality were included for rating of brain lesions. SWI images of two patients were excluded due to artifacts introduced by head movement. The imaging analysis (presence of small infarcts and CMBs, rating of the white matter lesion) was performed by two experienced neurologists by consensus and without any knowledge of clinical information.

**Enhanced depth imaging optical coherence tomography examination**

All participants were examined with EDI-OCT (Heidelberg Engineering, Heidelberg, Germany). SFCT was defined as the vertical distance from the hyperreflective line of the Bruch’s membrane to the hyperreflective line of the inner surface of the sclera [Figure 1a and 1b]. The measurements were performed using the Heidelberg Eye Explorer software (Heidelberg Engineering Co, Heidelberg, Germany). Both eyes of each participant were assessed. The images were taken by one technician and assessed by two ophthalmologists.

**Retinal vessel diameter and vessel wall thickness**

A circular scan (diameter = 3.5 mm) centered on the optic disc provides cross-sectional images of all major retinal arteries and veins [Figure 1c and 1d]. As reported previously, OCT light projected vertically to the vessel walls and lumen. Normal vessels had heterogeneous reflectivity, appeared oval in shape, and often had four hyperreflectivities in a linear configuration. Inner and outer vessel diameters of the
The four largest retinal arteries and veins, vessel wall thickness ([outer vessel diameter plus minor inner vessel diameter]/2), arterial inner diameter/venous inner diameter ($\text{AVR}_{\text{in}}$), and arterial outer diameter/venous outer diameter ($\text{AVR}_{\text{out}}$) were measured by two raters who were blinded to the clinical information [Figure 1c and 1d]. Three veins were excluded in CADASIL group due to questionable border discrimination of vessel walls.

**Statistical analysis**

Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). SFCT and vessel diameter values are presented as mean ± standard deviation (SD). Paired sample $t$-test was used to compare the SFCT and retinal vessel measurement data between patients and controls. Both eye values were used for statistical comparisons between the groups. The eye with the most obvious changes was chosen for each CADASIL patient to draw a correlation with the corresponding MRI lesions. The bivariate relationships between MRI lesions and retinal vessel measurements were analyzed using Spearman’s correlation coefficient. Statistical significance was defined as $P < 0.05$.

**RESULTS**

**Subfoveal choroidal thickness, retinal vessel diameter, and vessel wall thickness measurements on enhanced depth imaging optical coherence tomography**

Mean SFCT in CADASIL patients was significantly lower than that in controls. Mean arterial outer diameter and mean venous outer diameter in CADASIL patients was significantly larger than that in controls. The mean arterial inner diameter in CADASIL patients was significantly smaller than that in controls, while the mean venous inner diameter in CADASIL patients was significantly larger than that in controls. The mean vessel wall thickness of arteries and veins in CADASIL patients were significantly greater than those in controls [Table 1 and Figure 2]. The $\text{AVR}_{\text{out}}$ and $\text{AVR}_{\text{in}}$ in CADASIL patients were significantly smaller than those in controls [Table 1].

**Magnetic resonance imaging findings**

In addition of one asymptomatic case in early stage of the disease (age 27 years), the white matter lesions were observed in 26/27 (96.0%) patients [Figure 3a] including involvement of the temporal lobe in 25/27 (92.0%) patients and involvement of the external capsule in 20/27 (74.0%) patients. The Fazekas score was 4.14 ± 1.36. Infarcts with diameter ranging from 1.4 mm to 15.0 mm were observed in 23/27 (85.0%) patients; these were distributed in the subcortical white matter (42.3%), basal ganglia (30.2%), thalamus (16.4%), brain stem (10.0%), cerebellum (1.0%), and the cortex [Figure 3b and 3c]. The median number of small infarcts was 15. Two SWI scans were excluded because of insufficient quality, leaving 25 participants for evaluation. CMBs were observed in 13/25 patients (52.0%), with a median number of 3. CMBs were most commonly located in thalamus (41.8%), cortex (24.7%) (6.5% in frontal, 5.9% in temporal, 8.8% in parietal, 1.2% in occipital, and 1.2% in insular lobe), and basal ganglia (17.6%) [Figure 3d].

**Phenotype-genotype correlation**

The $\text{NOTCH3}$ gene mutation of these 27 patients showed 18 mutations, with hotspots in exon 4 ($n = 19, 70.4$%), followed by exon 11 ($n = 4, 14.8$%), exon 3 ($n = 2, 7.4$%), and exon 20 ($n = 2, 7.4$%). The considerable variability in retinal vessel measurements and MRI lesions in patients carrying a mutation in the same exon suggested no obvious phenotype-genotype correlation [Figure 4].
Table 1: Comparison of retinal vessel parameters and SFCT between CADASIL patients and healthy controls

| Vessel parameters | CADASIL (n = 27) | Control (n = 27) | t     | P       |
|-------------------|------------------|-----------------|-------|---------|
| SFCT (µm)         | 268.37 ± 46.50*  | 300.53 ± 39.31  | −3.401| <0.001  |
| Arteries (µm)     |                  |                 |       |         |
| Inner diameter    | 93.46 ± 9.70*    | 96.94 ± 8.28    | −2.068| 0.048   |
| Outer diameter    | 131.74 ± 10.87*  | 127.36 ± 8.67   | 2.224 | 0.023   |
| Vessel wall       | 19.13 ± 1.85*    | 15.21 ± 1.47    | 12.367| <0.001  |
| Veins (µm)        |                  |                 |       |         |
| Inner diameter    | 128.99 ± 13.62†  | 121.97 ± 11.29  | 2.737 | 0.004   |
| Outer diameter    | 164.82 ± 14.77‡  | 149.60 ± 11.96  | 5.414 | <0.001  |
| Vessel wall       | 17.91 ± 2.76†    | 13.81 ± 1.47    | 9.656 | <0.001  |
| AVR               |                  |                 |       |         |
| AVR<sub>out</sub>| 0.72 ± 0.08†     | 0.79 ± 0.07     | −5.718| <0.001  |
| AVR<sub>in</sub>  | 0.80 ± 0.06†     | 0.85 ± 0.06     | −4.904| <0.001  |

Data are presented as mean ± SD. *Means the SFCT and arterial parameters in CADASIL patients (n = 54) versus control (n = 54); †Means the venous parameters and AVR data in CADASIL patients (n = 51) versus control (n = 51); ‡Three veins were excluded in CADASIL group due to questionable border discrimination of vessel walls; Paired t-test was used to analyze the date of normal distribution. SFCT: Subfoveal choroidal thickness; CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; AVR<sub>out</sub>: Arterial venous ratio of outer diameter; AVR<sub>in</sub>: Arterial venous ratio of inner diameter; SD: Standard deviation.

**Discussion**

We used SFCT to evaluate the choroid because it is highly reproducible and is widely used in other small-vessel diseases. [25-27] The present study revealed reduced SFCT in CADASIL patients. Young adults with systemic arterial hypertension were shown to have significantly lower SFCT as compared to that in healthy controls. [25] Thinner SFCT is also seen in diabetic patients without diabetic retinopathy. [26,27] In addition, a decrease in mean SFCT was also described in ocular ischemic syndrome. [29] Although no other information was available on SFCT measurement in CADASIL patients, these results are consistent with those reported by Robinson et al., [30] they found irregular choroidal filling on fundus fluorescein angiography. We hypothesize that reduced SFCT might be a common change in cerebral microvascular disease, the underlying pathophysiological mechanism of which is not clear and might be attributable to reduced vascular diameter or hypoperfusion of the vessels.

We further confirmed that the outer diameters of arteries and veins were significantly larger than those in healthy controls. Since the vessel wall was significantly thicker in veins and arteries, the inner diameters of arteries in CADASIL patients was significantly lower and which narrowed the arterial lumen. This finding is also consistent with that of a pathological study that CADASIL is characterized by thickening of the arterial wall leading to luminal stenosis. [31] Similar findings for outer diameters and vessel wall in arteries and veins were reported in CADASIL patients by Alten et al. [18] However, Alten et al. [18] found no significant difference of arterial inner diameter between CADASIL patients and controls. Muraoka et al. [24] reported an increase

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**Correlation between brain magnetic resonance imaging lesions and retinal vessel measurements**

The arterial inner diameters, AVR<sub>in</sub> and AVR<sub>out</sub> showed a significant negative correlation with the number of small infarcts. The venous inner diameter showed a significant positive correlation with the number of small infarcts. The venous inner and outer diameters showed a significant positive correlation with CMB numbers. AVR<sub>in</sub> and AVR<sub>out</sub> showed a significant negative correlation with CMB numbers. Neither the diameter of the retinal vessels nor the AVR correlated with white matter Fazekas score. There was no correlation between SFCT and the number of small infarcts, CMB numbers and Fazekas score in CADASIL patients [Table 2].

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**Figure 3:** MRI of CADASIL patients. FLAIR image of a CADASIL patient (a), arrows indicate external capsule white matter lesions and periventricular white matter lesions. Lacunar infarcts in the pons (b), arrow indicates hypointense in the pons. Cortical microinfarct on FLAIR image (c), arrow indicates hyperintense microinfarcts on the cortex. Cerebral microbleeds in basal ganglia and cerebral cortex (d), arrow showing small, round, hypointense microbleeds on SWI-gradient echo image. MRI: Magnetic resonance imaging; CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; FLAIR: Fluid-attenuated inversion recovery; SWI: Susceptibility-weighted imaging.
in both mean arterial and venous wall thickness in retinal vessels of patients with hypertension. However, the arterial inner diameters, venous inner and outer diameters did not show a significant difference from that in healthy controls. Compared to patients with hypertension, CADASIL patients also showed enlarged inner and outer diameters of veins. We suggest that small veins in patients with CADASIL might also be altered. The mechanism and significance of venous involvement need further study. Narrowing of retinal arterial lumina and larger venous lumina were associated with the severity of infarcts. This is in accordance with former studies performed using fundus photography, which showed an association of arterial narrowing with a greater risk of infarcts and leukoaraiosis.\[12,23\] We also observed a relationship between venular dilation (both inner and outer diameter) and the severity of small infarcts and CMBs. A possible explanation might be that retinal venular dilation reflects cerebral venular function abnormalities. CMBs can be caused by high venous pressure, which is usually associated with venular dilation and disruption of the blood-brain barrier. In the Rotterdam Scan Study, larger retinal venular diameters were associated with progression of white matter lesions, but not with the severity of leukoaraiosis.\[24\] Leukoaraiosis is no specific change which

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**Table 2: Correlation between retinal vessel measurements and MRI findings in CADASIL patients (n = 27)**

| Vessel parameters         | Infarcts  | Fazkas score | CMBs  |
|---------------------------|-----------|--------------|-------|
|                           | $r_s$     | $P$          | $r_s$ | $P$          | $r_s$ | $P$          |
| SFCT                      | −0.05     | 0.812        | 0.26  | 0.195        | 0.26  | 0.203        |
| Arterial inner diameter   | −0.39*    | 0.044        | −0.22 | 0.267        | 0.02  | 0.926        |
| Arterial outer diameter   | 0.21      | 0.303        | 0.09  | 0.661        | 0.13  | 0.548        |
| Arterial vessel wall      | 0.23      | 0.257        | 0.25  | 0.201        | 0.07  | 0.751        |
| Venous inner diameter     | 0.46*     | 0.016        | 0.02  | 0.897        | 0.59* | 0.002        |
| Venous outer diameter     | 0.32      | 0.104        | −0.12 | 0.561        | 0.47* | 0.017        |
| Venous vessel wall        | 0.09      | 0.665        | −0.17 | 0.386        | 0.11  | 0.595        |
| $\text{AVR}_{\text{in}}$  | −0.65*    | <0.001       | −0.30 | 0.125        | −0.52* | 0.007       |
| $\text{AVR}_{\text{out}}$ | −0.56*    | 0.002        | 0.08  | 0.691        | −0.40* | 0.048       |

The bivariate relationships between MRI lesions and retinal vessel measurements were analyzed using Spearman’s correlation. *Means the data of retinal vessel parameters correlate with brain lesions, $P<$0.05. MRI: Magnetic resonance imaging; CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CMBs: Cerebral microbleeds; SFCT: Subfoveal choroidal thickness; $\text{AVR}_{\text{in}}$: Arterial venous ratio of inner diameter; $\text{AVR}_{\text{out}}$: Arterial venous ratio of outer diameter.
can be found in many diseases, such as mitochondrial disease.\(^{[51]}\) The temporal pole involvement appeared also in myotonia dystrophy type 1.\(^{[56]}\) The severity of leukoaraiosis was found to be related to the loss of cerebral venous integrity in CADASIL patients using 7T-MRI.\(^{[14]}\) Therefore, we should pay more attention to the venous functional and morphological changes in CADASIL.

In this study, we used the conventional MRI evaluation index to evaluate brain lesions in CADASIL, due to which we cannot show the superiority of high field strength MRI.\(^{[17]}\) Small sample size was another limitation of the study. However, the results might reflect the changes in CADASIL patients.

In conclusion, we used EDI-OCT examination to confirm the decrease in SFCT and retinal artery lumina in Chinese CADASIL patients. Retinal artery outer diameter, venous inner and outer diameter and vessel wall thickness of both arteries and veins was increased in CADASIL patients. Narrowing of the retinal arterial lumen is related to infarcts and dilation of vein related to CMBs. The measurement of retinal vessels using EDI-OCT is a useful evaluation tool for follow-up of CADASIL patients.

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Conflicts of interest

There are no conflicts of interest.

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