Ocular signs of carotid stenosis in ipsi- and contralateral eyes before and after carotid endarterectomy: a prospective study

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ABSTRACT.

Purpose: We describe hypoperfusion-related and embolic ocular signs of carotid stenosis (CS) before and six months after carotid endarterectomy (CEA) in a CS population.

Methods: We enrolled prospectively 70 CEA patients (81% male, mean age 69) and 41 non-medicated control subjects (76%, 68), from March 2015 to December 2018, assessing intraocular pressure (IOP), best-corrected visual acuity (BCVA) in logMAR units and performing a bio-microscopy examination.

Results: Main index symptoms included amaurosis fugax (Afx) (29, 41%) and hemispheric TIA (17, 24%), and 17 (24%) were asymptomatic. Of the 70, 17 patients (24%, 95% CI 16-36) showed ocular signs of CS. Of four embolic (Hollenhorst plaques) findings, one small macular plaque disappeared postoperatively. Four had hypoperfusion, that is ocular ischaemic syndrome (OIS), requiring panretinal photocoagulation: one for multiple mid-peripheral haemorrhages, two for iris neovascularization and one for neovascular glaucoma (NVG); only the NVG proved irreversible. Nine (de novo in three) showed mild OIS, that is only few mid-peripheral haemorrhages, ranging pre-/postoperatively in ipsilateral eyes from one to eleven (median two) / one to two (median one), and in contralateral eyes from three to nine (median five) / one to six (median three). Pre- and postoperative median BCVA was 0 or better, and mean IOP was normal, except in the NVG patient. Temporary visual impairment from 0 to 0.3 occurred in one eye soon after CEA due to ocular hyperperfusion causing macular oedema.

Conclusions: Ocular signs of CS are common in CEA patients, ranging from few mid-peripheral haemorrhages to irreversible NVG. Clinicians should be aware of these signs in detecting CS.

Key words: amaurosis fugax – carotid endarterectomy – carotid stenosis – ocular ischaemic syndrome – ocular signs of carotid stenosis

Introduction

Carotid stenosis (CS) is a common consequence of atherosclerosis and poses a significant risk for cerebral stroke and ocular circulatory disturbances. Narrowing of the arterial lumen may lead to hypoperfusion of the eye (Hayreh 2015), and a co-existing vulnerable plaque may result in emboli into the distal arteries (Rubin 2006), resulting in transient or permanent tissue damage to the ocular or cerebral tissues. Ocular hypoperfusion can cause signs such as conjunctival and episcleral injection, corneal oedema, anterior chamber reaction with flare and cells, iris transillumination and neovascularization, asymmetric cataract, narrowed retinal arterioles, dilated retinal veins, microaneurysms, microinfarcts and retinal haemorrhages especially in the mid-periphery, vitreous haemorrhage, new vessels on the optic disc or retina, anterior optic neuropathy or spontaneous retinal artery pulsations, or the most devastating event, neovascular glaucoma (NVG) (Brown & Brown 2007; Mendrinos et al. 2010). When such findings occur in relation to CS, the entity is called ocular ischaemic syndrome (OIS), a syndrome underdiagnosed and relatively rare (Dugan & Green 1991; Lawrence & Oderich 2002; Mendrinos et al. 2010). At present, we lack defined diagnostic criteria and...
Vulnerable carotid plaques may lead to a variety of thromboembolic episodes, depending on embolus size, location and other factors (Rubin 2006). The atheromatous embolus known as Hollenhorst plaque may occur in asymptomatic patients or may cause occlusion of the central retinal artery (CRAO) or its branch (BRAO), sometimes leading to permanent vision loss. An umbrella term for various patterns of transient monocular visual loss, with a broad range of differential diagnoses, is amaurosis fugax (Afxs) (Petzold et al. 2013a). The most frequent mechanism of Afxs is arterial embolism, but haemodynamic disturbance due to CS, which causes hypoperfusion of the globe, may also lead to Afxs (Hayreh & Zimmerman 2013a). The most frequent mechanism of Afxs is arterial embolism, but haemodynamic disturbance due to CS, which causes hypoperfusion of the globe, may also lead to Afxs (Hayreh & Zimmerman 2013a).

For symptomatic CS patients, the risk for subsequent stroke can be significantly reduced by carotid endarterectomy (CEA), which according to the present guidelines should occur within two weeks after the index event (Barnett et al. 1991). What remains still incompletely known is how CEA affects the eye (Mizener et al. 1997). We aimed to study CS patients to enhance our understanding on ocular signs of CS, and the effect of CEA by examining patients before and 6 months after CEA, and age- and sex-matched healthy control subjects at the same 6-month interval. In addition, we assessed ocular findings in general to find possible associations with CS and also recorded symptoms leading to suspicion of CS.

Methods

This prospective non-randomized ophthalmological study is part of the Helsinki Carotid Endarterectomy Study-Brain and Eye Sub-Study (HeCES-BEST) (Nuotio et al. 2018) designed as a multidisciplinary joint effort including ophthalmologists, neurologists, neuroradiologists, vascular surgeons and neurosurgeons to evaluate structural and functional changes in the brain and eye before and six months after CEA. From March 2015 to December 2018, the recruitment of 71 patients and 42 healthy control subjects took place in Helsinki University Hospital, Finland. The same all-Caucasian study population took part in our study concerning subfoveal choroidal thickness (SFCT) (Ala-Kauhaluoma et al. 2020).

The main inclusion criterion was a haemodynamically significant CS defined as 70% or more in the first CTA evaluation leading to surgery. The exclusion criterion for the patients was a recent (<6 months) cerebral infarction. The healthy, unmedicated control patients matched for age, sex and social class were recruited from senior- and exercise clubs, and from hospital staff, relatives and friends. Control subjects underwent carotid ultrasonography to rule out CS.

After excluding one patient with recent stroke and one control subject with cancer, we examined both eyes of 70 patients and 41 control subjects. One control subject excluded from the previous work, for lacking SFCT measurements, was included in this work (Ala-Kauhaluoma et al. 2020). CEA was right-sided in 29 patients (41%) and left-sided in 41 (59%). In control subjects, the right eye served as the control for the ipsilateral eye in 17 (41%) and the left eye in 24 (59%). We chose the eyes randomly in this proportion. All patients underwent surgery within 2 weeks after baseline examination, except one, whose operation was delayed until 11 weeks due to anaemia. Altogether, 12 patients (17%) had undergone contralateral CEA a median of 0.6 (range, 0.2–17.2) years before ipsilateral CEA. Furthermore, eight patients (12%) underwent contralateral CEA a median of 0.6 (range, 0.1–2.8) months after the ipsilateral CEA. The postoperative visit took place at a median of 5.9 (range, 5.3–9.1) months. Seven (10%) patients were lost to follow-up: one had a postoperative cerebral infarction, two did not respond to the invitation, three withdrew, and one was not invited, because instead of scheduled CEA the procedure was carotid ligation. All control subjects made both visits at a median 5.9 (range, 4.8–6.9) months of interval.

We collected patient data from clinical records, from an interview by a research assistant, and from a questionnaire completed by the patients concerning ophthalmological diseases and symptoms (especially the duration, pattern, number, and associated and triggering factors of Afxs). From the blood samples collected at baseline, we made the diagnosis of dyslipidaemia, when low-density lipoprotein (LDL) level was >3 mmol/L. We measured blood pressure with automatic sphygmonanometer (Omron, Omron Healthcare, Kyoto, Japan) once in a sitting position from the brachial artery. Mean arterial pressure (MAP) we calculated with the formula: MAP = [Diastolic blood pressure (DBP)] + 0.412 × [Systolic blood pressure (SBP) – DBP] (Papaioannou et al. 2016). We calculated body mass index (BMI) by dividing weight (in kg) by the square of the height (in metres).

The 70 patients did not differ from the 41 control subjects in terms of age, gender, presence of glaucoma and SBP (Table 1A). Control subjects showed higher DBP (p < 0.001, two-sample t-test), higher MAP (p = 0.006) and lower BMI (p = 0.002) compared to patients. Only the patients used medications such as antiplatelet, hypertensive, antihyperglycaemic, and statin therapy, which were unchanged during follow-up. Of patients with dyslipidaemia, 94% used statins.

We utilized computed tomography angiography (CTA) to analyse grade of CS according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method (Barnett et al. 1991). A decrease of 1.0 mm in distal luminal diameter beyond a tight stenosis served as the cut-off for subtle near-occlusion (NO-s). Full collapse of near-occlusion (NO-fs) required the luminal reduction to exceed 2.5 mm (Koskinen et al. 2017; Meershoek et al. 2018). Table 1B shows our patients’ grade of stenosis in the ipsi- and contralateral side. Six patients had ipsilateral CS under 70%.

Ophthalmological examination

ETDRS charts allowed us to measure best-corrected visual acuity (BCVA) in logMAR units. We measured intraocular pressure (IOP), using the mean of three reliable measuring cycles, with a rebound tonometer (Icare TA01i Tonometer, Icare Finland OY, Vantaa, Finland) and did anterior biomicroscopy. Arcus senilis was recorded as classic when peripheral corneal opacification was total. Lens opacification (cataract) was recorded as significant, when it was suspected to reduce BCVA by two lines. Papillary dilatation we achieved with tropicamide (Oftan Tropikamid 5 mg/ml, Santen, Tampere, Finland). We obtained ultra-widefield
Table 1A. Baseline characteristics in patients with carotid stenosis versus control subjects, in patients with or without amaurosis fugax (Afx), and in patients with or without ocular signs of carotid stenosis (CS)

| Carotid stenosis (grade) | Ipsilateral | Contralateral | p-value |
|-------------------------|-------------|---------------|---------|
| <50% (0)                | 3 (4%)      | 52 (74%)      | <0.0011 |
| 50-69% (1)              | 3 (4%)      | 5 (7%)        |         |
| 70-99% (2)              | 29 (42%)    | 7 (10%)       |         |
| Subtle near-occlusion (3) | 28 (40%)   | 2 (3%)        |         |
| Near-occlusion with full collapse (4) | 6 (9%)      | 1 (1%)        |         |
| Total occlusion (5)     | 1 (1%)      | 3 (4%)        |         |

Data presented in number (%).  
1 McNemar–Bowker test

images with Optos 200 Tx (Optos, Dunfermline, United Kingdom) and took 50° colour anterior segment, and colour and red-free fundus photographs (FF450plus, Carl Zeiss, Jena, Germany). We assessed the posterior segment by bi-o-microscopy using 60 and 90 D Volk lenses. We defined posterior pole as the retina within and just slightly beyond the arcades, and mid-periphery as the region outside the former up to the posterior edge of the vortex vein ampulla.

We recorded all known embolic and hypoperfusion-related signs of CS. Eyes needing treatment for hypoperfusion-related signs we classified as OIS. In patients with diabetes, microaneurysm, haemorrhage and/or microinfarction typically in the posterior pole were regarded as diabetic retinopathy (DR) and graded accordingly (Davis et al. 1998). Similar changes occurring in a general ageing population with or without hypertension were called age- or hypertensive-related retinopathy (HRP) (Klein et al. 1993; Yu et al. 1998). Classification of conjunctival and episcleral vessels from anterior segment photographs, and venular and arterial diameters from fundus photographs, will be under evaluation in a separate report. Clinical classification of age-related macular degeneration (AMD) (Ferris et al. 2013) served to distinguish between early, intermediate and late AMD. The vertical and horizontal cup-to-disc-ratio (CDR) estimate was subjective (MA-K).

Statistical analysis

We present statistics for continuous normally distributed variables as means (standard deviations) and for non-normally distributed variables as medians (ranges), and for categorical variables as frequencies (percentages). We used two-sample t-test for continuous variables and chi-square or Fisher’s exact for categorical variables to compare the variables between different patient groups, and between patients and control subjects. We analysed change in number of mid-peripheral haemorrhages pre- and postoperatively with Wilcoxon signed rank test. The differences in CS and ocular signs of CS between ipsi- and contralateral eyes were examined with Fisher’s exact test. We examined the differences in CS between ipsi- and contralateral sides with McNemar–Bowker test. The change in BCVA was tested with Wilcoxon signed rank test and the change in IOP with paired samples t-test. Statistical analyses were done using SPSS for Windows (version 26, IBM, Armonk, NY). Statistical significance was set at 0.05.

Results

Symptoms

The index symptoms which led to diagnosis of CS among our patients were Afx (29, 24%), hemispheric transient ischaemic attack (TIA) (17, 24%), stroke (2, 3%), indefinite neurological complaints (2, 3%) and reduced visual acuity (3,
4%), whereas 17 (24%) were asymptomatic. The latter were most often diagnosed with CS after detection of carotid bruit. Table 2 shows detailed features and findings on Afx. The transient loss of vision was complete in 15 (52%) and incomplete in 13 (45%) patients. In one (3%) patient, the pattern of vision loss was variously either complete, or incomplete in the upper or lower visual field. The pattern of Afx varied: black in 10 (34%), blurred in 7 (24%), grey in 6 (21%), with phosphenes in 2 (7%), patchy in 2 (7%), white in one (3%) and one (3%) experienced multiple patterns (black or phosphenes). Median duration of Afx was 3 min, ranging from 5 second to 2 hr. Median number of attacks prior to CEA was four (range, 1-120), which occurred during a median time period of one month, ranging from one day to ten years. Of 29 patients with a history of Afx, 5 (17%) had ocular signs of CS: 3 with mid-peripheral haemorrhages, one with Hollenhorst plaque and one with BRAO. Patients with Afx compared to those without were younger (67 versus 71 years, \( p = 0.039 \), two-sample t-test, Table 1A). Afx was associated with neither degree of ipsi- \( (p = 0.318, \text{Fisher’s exact test}) \) nor contralateral \( (p = 0.254) \) CS.

**Ocular findings**

Median BCVA in patients’ ipsi- and contralateral eyes was logMAR 0 or better before and after CEA, and in control subjects at two examinations (Table 3). Only one patient with unilateral NVG had subnormal BCVA, before and after CEA, at logMAR 0.8 and at 0.9. Temporary visual impairment, BCVA from 0 to 0.3, occurred in one eye one week after CEA due to macular oedema and multiple mid-peripheral haemorrhages (ocular hyperperfusion), which responded to intravitreal corticosteroid. Mean IOP was comparable at two examinations in both the patients and control subjects (Table 3). At the time of the NVG diagnosis, the IOP was 46 mmHg; after panretinal photocoagulation (PRP) (6500 burns in two sessions), peripheral retinal cryotherapy, cyclophotocoagulation and topical medication (travoprost, timolol, brinzolamide and brimonidine), the IOP had dropped to 17 mmHg at the preoperative visit. Despite the same topical medication and one anti-VEGF antibody injection, iris neovascularization remained active, and the IOP was 38 mmHg postoperatively. BCVA and IOP remained normal in two other eyes with iris neovascularization; one was detectable at the preoperative examination, and, accordingly, that eye received prompt treatment with PRP prior to surgery (carotid ligation instead of CEA). The other was detectable 3.5 months before CEA, when multiple mid-peripheral haemorrhages had raised suspicion of OIS at a regular glaucoma check-up.

**Table 2. Features and findings in 29 patients with amaurosis fugax**

| Pat | Pattern | Average duration (min) | Number of attacks prior CEA | Time period | Associated features | Triggering factors |
|-----|---------|-----------------------|-----------------------------|-------------|---------------------|-------------------|
| 1   | black   | 10                    | 2                           | 1 day       | headache            | bright light      |
| 2   |         | 3-10                  | 9                           | 10 mo       |                     |                   |
| 3   |         | 3-5                   | 3                           | 1 week       |                     |                   |
| 4   |         | 5                     | 1                           | 1 day       |                     |                   |
| 5   |         | 2                     | 1                           | 1 day       |                     |                   |
| 6   |         | 0.2-3                 | 5                           | 10 days       |                     |                   |
| 7   | grey    | 3-5                   | 15                          | 1 mo         |                     |                   |
| 8   |         | 2                     | 2                           | 2 mo         |                     |                   |
| 9   |         | 0.2-0.3               | 4                           | 1 year       |                     |                   |
| 10  | blurred | 3-5                   | 4                           | 1 week       |                     |                   |
| 11  |         | 2                     | 50                          | 10 mo       |                     |                   |
| 12  |         | 1-3                   | 10                          | 2 days       |                     |                   |
| 13  |         | 0.3-1                 | 3                           | 6 months     |                     |                   |
| 14  | patchy  | 120                   | 1                           | 1 day       | ocular pain         |                   |
| 15  | white   | 2-3                   | 1                           | 1 day       |                     |                   |
| 16  | black   | 3-10                  | 3-4                          | 3.5 years     |                     |                   |
| 17  |         | 5                     | 1                           | 1 day       | headache            |                   |
| 18  |         | 1-5                   | 3                           | 1.5 mo       | chewing             |                   |
| 19  |         | 2                     | 4                           | 5 mo         |                     |                   |
| 20  | grey    | 5                     | 20                          | 9 mo         |                     |                   |
| 21  |         | 1-5                   | 5                           | 1 mo         |                     |                   |
| 22  |         | <0.2                  | 10                          | 6 mo         |                     |                   |
| 23  | blurred | 2-3                   | 1                           | 1 day       | nausea              |                   |
| 24  |         | 1                     | 4                           | 2.5 mo       |                     |                   |
| 25  |         | 0.5-1                 | 14-28                       | 14 years     |                     |                   |
| 26  | patchy  | 1                     | 30                          | 3 mo         |                     |                   |
| 27  | phosphenes | 3-30                | 120                         | 10 years     | bright light        |                   |
| 28  |         | 5-10                  | 20                          | 3 mo         |                     |                   |
| 29  | black or phosphenes | 10-15               | 7                           | 1 mo         | bright light/ upright position | |

CEA: carotid endarterectomy
after PRP and one anti-VEGF antibody injection the iris neovascularization had subsided by the time of our preoperative visit. In the eye with ocular hyperperfusion, intravitreal corticosteroid led to IOP rise, which responded to topical dorzolamide–timolol medication, and at the six-month postoperative examination, IOP was rated normal.

Ophthalmic findings considered stable (not expected to change after CEA) included classic arcus senilis, iris transillumination, pseudoexfoliation, cataract (previously operated or currently significant), cup-to-disc-ratio and AMD (Table 4). Only AMD was more common in the ipsilateral eyes of the patients compared to those of control subjects (p = 0.04, Fisher’s exact test). The greatest difference appeared in the prevalence of intermediate AMD.

### Ocular signs of CS

In total, 17 patients (24%, 95% CI 16-36) had ocular signs of CS in either eye at the two examinations. They did not differ in baseline characteristics from patients without these signs (Table 1A). All had posterior segment findings, and two also showed anterior segment signs, that is iris neovascularization: one in the pupillary margin only, the other showing advanced NVG and closed angle (Table 5).

Preoperatively, 12 patients (17%, 95% CI 10-28) had ocular signs of CS in the ipsilateral eye, with bilateral signs in 3, and in 2 patients only in the contralateral eye, altogether in 14 patients (20%, 95% CI 12-31). Ten patients (14%, 95% CI 8-25) had only hyperperfusion-related signs of CS and four patients (6%, 95% CI 2-14) embolic signs. One showed bilateral findings presenting both embolic and hyperperfusion features: a Hollenhorst plaque in the contralateral papilla, and microaneurysms and microinfarctions in the posterior pole in the ipsilateral eye. The other three eyes with Hollenhorst plaque included two with related BRAO and one with a small macular plaque.

Of 4 patients with OIS, multiple (12, 30, and 44) mid-peripheral haemorrhages were present in 3 patients, only one who had had PRP 4 months earlier, showed no haemorrhages (Table 5). Three patients with OIS underwent PRP before preoperative examination and one after it. In mild OIS, the number of mid-peripheral haemorrhages in ipsilateral eyes ranged from 1 to 11 (median 2), and in contralateral eyes from 3 to 9 (median 5). In total, 24 patients had DM (34%), and 4 (16%, 95% CI 6-36) had ocular signs of CS preoperatively: one eye with NVG, 2 with mid-peripheral haemorrhages (3 and 5, respectively), and one with contralateral BRAO. Five other patients had non-proliferative DR: very mild in two and mild in three, all findings merely in the posterior pole. A single posterior pole microaneurysm, HRP, appeared in one patient (1%).

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**Table 3.** Best corrected visual acuity (BCVA) in logMAR units and intraocular pressure (IOP) in mmHg, before and six months after carotid endarterectomy in patients, and at six-month interval in control subjects

| Patients, n = 70 | Ipsilateral | Contralateral |
|------------------|-------------|---------------|
| **Median BCVA**  | 0 (−0.2; 0.8) | 0 (−0.2; 0.9) |
| **Mean IOP**     | 13 (4)      | 14 (5)        |

Control subjects, n = 41

| Ipsilateral baseline | Six months | Contralateral baseline | Six months |
|----------------------|------------|------------------------|------------|
| **Median BCVA**      | 0 (−0.3; 0.2) | −0.1 (−0.2; 0.3) | 0 (−0.2; 0.9) |
| **Mean IOP**         | 15 (4)     | 14 (4)               | 14 (3)     |

Data presented in median (range) and mean (SD).

logMAR: logarithm of the minimum angle of resolution, SD: standard deviation.

1 Wilcoxon signed-rank test
2 Paired-samples t-test

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**Table 4.** Baseline ocular findings considered constant in ipsi- and contralateral eyes in 70 patients compared to 41 control subjects. Data presented in number (%) or mean (SD)

| Ocular signs of CS | Ipsilateral eye | Contralateral eye |
|--------------------|-----------------|-------------------|
| Patient n = 70     | Control subject n = 41 | p-value |
| Patient n = 70     | Control subject n = 41 | p-value |
|--------------------|-----------------|-------------------|
| Classic arcus senilis | 12 (%) | 9 (%) | 0.53² | 12 (%) | 9 (%) | 0.57² |
| Iris TI            | 31 (44%) | 17 (41%) | 0.77² | 31 (44%) | 18 (44%) | 0.88² |
| Pseudoexfoliation  | 1 (1%) | 2 (5%) | 0.55³ | 3 (4%) | 2 (5%) | 1.00³ |
| Cataract           | 23 (33%) | 7 (17%) | 0.07³ | 23 (33%) | 7 (17%) | 0.06³ |
| Vertical CDR       | 0.4 (0.2) | 0.4 (0.2) | 0.63³ | 0.3 (0.2) | 0.4 (0.2) | 0.13³ |
| Horizontal CDR     | 0.3 (0.2) | 0.4 (0.2) | 0.43³ | 0.3 (0.2) | 0.4 (0.2) | 0.09³ |
| AMD                | 0 (0%) | 0 (%) | 0.04³ | 0 (0%) | 0 (%) | 0.13³ |
| no                 | 57 (81%) | 36 (88%) |          | 54 (77%) | 36 (88%) |          |
| early              | 5 (7%) | 5 (12%) |          | 6 (9%) | 3 (7%) |          |
| intermediate       | 8 (11%) | 0 |          | 10 (14%) | 1 (2%) |          |

AMD: age-related macular degeneration, Cataract: previously operated or currently significant cataract, Classic arcus senilis: peripheral corneal opacification total, CDR: cup-to-disc-ratio, TI: Transillumination

¹ Two-sample t-test
² Chi-square test
³ Fisher’s exact test
Postoperatively, of the embolic signs, only the macular Hollenhorst plaque in the ipsilateral eye disappeared (Table 5). Of four patients with OIS, NVG proved irreversible and multiple haemorrhages were found in the affected eye, and some also in the contralateral eye. In two OIS eyes, the number of mid-peripheral haemorrhages had diminished, and in one eye without haemorrhages preoperatively, of multiple mid-peripheral haemorrhages related to hyperperfusion one month after CEA, four were detectable. In mild OIS, the number of mid-peripheral haemorrhages in ipsilateral eyes ranged from one to two (median 1.5), and in contralateral eyes from 1 to 6 (median 3), of which one to three de novo haemorrhages appeared in one ipsi- and in two contralateral eyes. The latter two had DM. Preoperative DR and HRP remained unchanged. When all mid-peripheral haemorrhages among patients with pre- and postoperative visits were counted together, the number diminished in ipsilateral eyes from 57 to 19 (p = 0.36, Wilcoxon signed rank test), and increased in contralateral eyes from 22 to 31 (p = 0.49), none of them had undergone CEA during follow-up. Ocular signs of CS were not associated with grade of CS on the ipsi- (p = 0.83, Fisher’s exact test) or contralateral sides (p = 0.92).

Among control subjects, HRP-like findings appeared at baseline in four (10%) and at follow-up in two (5%). In this group, four of the five had BP >130/85 mmHg. One showed flame-shaped haemorrhage at both visits, and others had changes either at baseline or at follow-up.

**Discussion**

To our knowledge, this is the first study observing ocular signs of CS before and six months after CEA in a quite large group of patients with high-grade CS with ocular, minor or no symptoms. Ocular signs of CS occurred in 20%, with hyperperfusion-related signs (14%) being more common than embolic (6%). Mid-peripheral haemorrhages were the most common posterior segment findings, while anterior segment findings appeared only in addition to posterior segment ones.

AFx is the most common ocular symptom, occurring in 19% of patients with CS (Kvickström et al. 2016), although a higher, 30-40%, prevalence is known (Dugan & Green 1991), our finding of 41% is in line with the latter. Probably the AFx prevalence is higher in those CS patients needing CEA. In our patients, AFx was complete in 52%, whereas in many series complete loss of visual field exists in less than half (Petzold et al. 2013a), although one study found it in 73% (Kvickström et al. 2016). In our series, the 'negative' visual phenomena occurring black, blurred and grey, outnumbered the patients with 'positive' visual phenomena (white or phosphenes). The exact meaning of various patterns is...
unknown, but a non-embolic aetiology underlying positive phenomena has been suggested (Petzold et al. 2013b). The Petzold group analysed patterns of non-embolic Afx, perceived as grey in 35%, white in 21%, black in 16% and as phasophenes in 9%, however (Petzold et al. 2013b). The most frequent mechanism of Afx among patients with CS is an arterial embolus from the carotid plaque [7]. A high correlation has appeared between ulcerated plaque and Afx (Perez-Burkhardt et al. 1994). In our series, two Afx patients presented with Hollohenhorst plaques. Disc swelling, typical of intracranial pressure rise, associates with very short Afx duration, such as few seconds (Petzold et al. 2013a). Very long Afx duration, such as several hours, has causes other than thromboembolic (Bidot & Biotti 2018). Nevertheless, our study showed one case with short (5s) and one with long (2h) Afx duration. Our median Afx duration was 3 min, in line with others’ findings (Petzold et al. 2013a; Kvickström et al. 2016). We found associated features and triggering factors occurring in 14%, headache and bright light being most common. The latter phenomenon has been called ‘retinal claudication’ (Bruno et al. 1990), of which the underlying mechanism remains incompletely understood.

Our normal and unchanged BCVA after CEA in CS patients was in line with others (Geroulakos et al. 1996; Heßler et al. 2015). Moreover, improvement in BCVA in eyes with OIS has occurred after CEA (Nerov et al. 2012; Qu et al. 2015). We had only four eyes with OIS needing treatment, two with normal and unchanged BCVA, one with post-operative macular oedema resolving after steroid injection, and one NVG eye with constantly poor BCVA since the detection of CS. Our eight ipsi- and ten contralateral eyes showed intermediate AMD, compared to one control subject’s eye. Ocular blood flow may play a role in the pathogenesis of AMD (Ehrlich et al. 2008), which could explain why our CS patients had more advanced AMD compared to healthy individuals. We could not discover whether this association had been suspected earlier. Classic arcus senilis, iris transillumination and cataract, all of which can be associated with impairment of circulation (Brown & Brown 2007; Mendrinos et al. 2010; Terelak-Borys et al. 2012), did not differ between our patients and control subjects.

Iris neovascularization is associated with poor visual prognosis, although also regression of iris neovascularization has been detectable after CEA (Sivalingam et al. 1991). Our patient who had irreversible NVG, with active iris neovascularization and occlusion of the angle both pre- and postoperatively, responded at first to treatment, but during the study period had a rise in IOP despite further treatment. In two other OIS patients who received PRP, iris neovascularization proved reversible. The role of PRP seems critical when given in time. In our patients, mean IOP was normal and unchanged after the operation. After CEA, the ocular blood flow increases also in the ciliary body, which may result in elevated IOP. One feared adverse effect caused by ocular hyper-perfusion, the development of new and potentially blinding NVG (Ng et al. 2015; Gania et al. 2020), did not occur.

Early diagnosis of OIS is ‘essential with respect not only to visual prognosis but also to patient survival’ (Mendrinos et al. 2010). Unfortunately, compared to the well-known symptoms of Afx, other possible symptoms of OIS such as deterioration of visual acuity and ocular pain, except for dull ache (ocular ‘angina’), are less well-defined. Treatment of OIS includes ‘ocular (conservative, laser and surgical) or systemic (conservative and surgical treatment of the carotid artery)’ (Terelak-Borys et al. 2012). Earlier, it was believed that CS will exceed 90% before development of OIS (Dugan & Green 1991). However, OIS has also been detectable in CS <50% (Mizener et al. 1997), possibly due to poor collateral circulation (Mendrinos et al. 2010). In our series, out of 13 patients with hyperperfusion-related signs of CS, 5 (38%) had CS <50%, but their collateral circulation went unmeasured.

The differential diagnosis of OIS includes severe DR and central retinal vein occlusion (CRVO) with multiple haemorrhages (Brown & Brown 2007). The size and shape of haemorrhages in addition to their location helps in diagnosis, and the marked venous tortuosity seen in CRVO is lacking in OIS (Mendrinos et al. 2010). Ocular signs of CS, single or multiple mid-peripheral haemorrhage, occurred in six patients with diabetes. Especially in elderly (>65) patients with risk factors for atherosclerosis, ocular signs of CS, which may precede cerebral ones,
should be recognized in order to prevent strokes (Lawrence & Oderich 2002; Biousse et al. 2018). It should be noted that large population-based studies show the prevalence of retinopathy in healthy non-diabetic individuals as 6% to 11%, a prevalence higher among hypertensive than among normotensive individuals (Klein et al. 1993; Yu et al. 1998). In line with this, five of our control patients (12%) presented with single microaneurysm or haemorrhage.

The main limitation of our study was its limited sample size. Mainly due to our heavy and time-consuming study protocol we struggled to find enough participants. In addition, all patients were Caucasian and were predominantly male. A larger prospective cohort of patients-at-risk, for example patients with asymptomatic CS in conservative follow-up, could provide valuable information on the OIS prevalence and evolution.

Conclusions

CEA may lead to adverse effects such as ocular hyperperfusion, which is, however, uncommon. Without other obvious cause, even few mid-peripheral haemorrhages, especially in elderly (>65) individuals with atherosclerotic risk factors, should raise suspicion of CS. This includes diabetic patients with or without typical retinopathy. OIS should be recognized, and treated, before turning irreversible. At present, however, we lack guidelines for the follow-up of OIS patients with or without CEA. For CS patients with no examination by an ophthalmologist, fundus photography could be considered, and those with signs of OIS should be referred to an ophthalmologist for follow-up and treatment. Larger series would be valuable to confirm our findings.

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