

Open angle glaucoma and non-central retinal vein occlusion – the chicken or the egg?

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ABSTRACT.

Purpose: To determine whether non-central retinal vein occlusion (nCRVO) or open angle glaucoma (OAG) is the primary event in eyes suffering from both diseases.

Methods: The study has two parts. The first is a retrospective survey of a clinical glaucoma database. In eyes with OAG and nCRVO, the temporal relationship between the conditions was determined when possible. The second part is a ten-year follow-up study of eyes with isolated nCRVO.

Results: Study 1: Among 576 OAG patients, 25 (4.3%) had nCRVO. In all eyes except one, OAG occurred before nCRVO. Almost without exception a vein on the optic disk or at the disk margin was occluded. Study 2: Most eyes with isolated nCRVO had an occluded vein at a retinal artery-vein crossing. Only one of 34 patients had developed OAG after ten years.

Conclusions: This study suggests that OAG in most eyes is the primary event. nCRVO had different characteristics in eyes with OAG compared to eyes without OAG.

Key words: branch retinal vein occlusion – central retinal vein occlusion – open angle glaucoma.

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A close association has been recognised between OAG and retinal vein occlusion. CRVO or branch retinal vein occlusion are common in eyes with OAG (for a review see Sonnsjö and Krakau, 1993). These authors also consider the disk haemorrhages frequently seen in some patients with OAG to represent small vein occlusions. The coexistence of these different conditions has led to the suggestion that OAG, retinal vein occlusion and disk haemorrhage share a common pathogenesis (Sonnsjö & Krakau, 1993). This hypothesis has gained popularity because an increasing number of researchers favour some form of a “vascular” glaucoma model for the pathogenesis of OAG (for a review, see Hayreh, 1994). However, there have also been advocates, primarily in the older literature, for the hypothesis that retinal

vein occlusion is a complication of OAG (Bertelsen, 1961; Dobree, 1957; Dryden, 1965), occurring secondarily to structural disk changes (Kohner & Shilling, 1976). However, the results of many older studies are difficult to interpret because their definition of OAG is often based on intraocular pressure alone without optic disk or visual field criteria. Another problem that is apt to colour the results is the difficulty of differentiating between primary and secondary glaucoma in eyes with CRVO. While the differentiation may be simple in the full-blown case with neovascularizations of the iris, many cases are much less obvious.

This study explores the relation between OAG and nCRVO (encompassing branch retinal vein occlusion and hemispheric retinal vein occlusion) using current principles for glaucoma definition.

The reason for separating eyes with nCRVO from eyes with CRVO was that the former seldom develop secondary glaucoma (Sanborn & Margargal, 1984). This condition could be difficult or impossible to differentiate from primary OAG.

The study is presented in two parts. The first part surveys the prevalence of nCRVO in a group of patients with established OAG. The second part is a ten-year follow-up study of eyes with nCRVO without OAG.

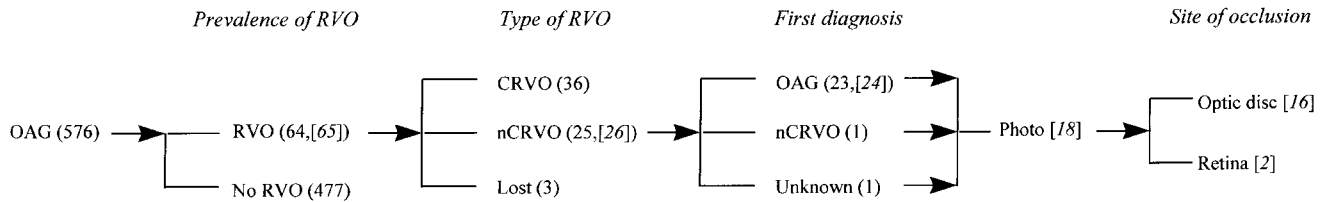
Study 1: Prevalence of nCRVO in Eyes with established OAG

Material and Methods

Beginning in 1992, all patients with glaucoma or ocular hypertension examined by the author at the University Eye Clinic in Göteborg have been registered in a computerised database. Each record contains information about the glaucoma diagnosis, other eye diseases, systemic diseases, systemic medications, and heredity. In addition, results from the most recent eye examination are recorded. Each time a patient is examined, old data is corrected if necessary, and any new relevant information is added. Only patients examined by the author are included to keep the database as homogeneous as possible, with identical inclusion criteria applied to patients in each diagnostic group. For a subject to be registered with the diagnosis of OAG, both of the following criteria have to be met:

1. Sector-shaped defects in the retinal nerve fibre layer and/or optic disk changes compatible with glaucoma.

A. Study 1. nCRVO in eyes with established OAG



B. Study 2. Incidence of OAG in eyes with nCRVO

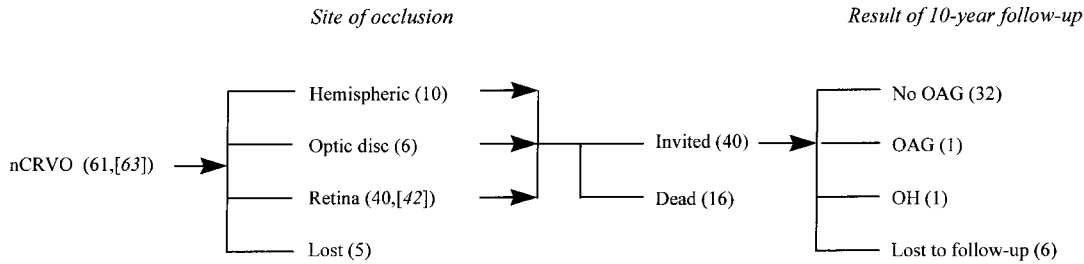


Fig. 1. Flow charts illustrating the design of the two studies. A: Study #1. nCRVO in eyes with established OAG. B: Study #2. Incidence of OAG in eyes with nCRVO. Figures in parentheses show number of patients; figures in italics between brackets show number of eyes. Abbreviations: RVO – retinal vein occlusion. CRVO – central retinal vein occlusion, nCRVO – non-central retinal vein occlusion, OAG – open angle glaucoma, OH – ocular hypertension.

2. Visual field changes consistent with glaucoma and not explained by any other condition. Computer-assisted perimetry is performed with the Ophthimus high-pass resolution technique (HighTech Vision, Mölndal, Sweden) or with Humphrey Field Analyzer (Humphrey Instruments, San Leandro, CA), program 24–2 or 30–2.

For the present study, the OAG group comprised patients with primary OAG (exfoliation and simple glaucoma) and OAG considered secondary to CRVO. A diagnosis of exfoliation glaucoma was made if pseudo-exfoliations were present in at least one eye. Both normal-tension and high-tension glaucoma were included.

All OAG patients with retinal vein occlusion were identified from the database. Fundus photographs and fluorescein angiograms were examined when available.

Results

A flow-chart summarising the study design and results is shown in Fig. 1A. Five hundred seventy-six patients with OAG were registered in the glaucoma database (295 women and 281 men). In patients still alive in 1995, mean age was 80 years (82 for women and 79 for men). Age range was 32 to 102 years (51 to 100 for women, 32 to 102 for men). Mean age at

which OAG was diagnosed was 69 years. Two hundred ninety-two subjects suffered from simple glaucoma while 284 (49.3%) had exfoliation glaucoma. Twelve patients had normal-tension glaucoma; none of them had pseudo-exfoliations.

Among all OAG subjects, 64 (10.6 per cent) had some form of retinal vein occlusion: 4.3 per cent had nCRVO and 6.3 per cent CRVO. Thirty-one were females and 33 males. One patient had nCRVO in one eye and CRVO in the other. Mean age in the nCRVO group was 79 years (range 32–92) and in the CRVO group 81 years (range 61–94). In three cases files were lost and the exact nature of the occlusion could not be established. Fifteen (24%) of the 64 subjects with OAG and retinal vein occlusion had systemic hypertension, another three (5%) had cerebrovascular disease, and seven (11%) had diabetes mellitus. Corresponding figures in OAG patients without retinal vein occlusion were 15%, 3%, and 8%, respectively. The differences were not statistically significant.

For 23 of the 25 eyes with nCRVO and OAG, OAG was obvious already at the time of the occlusion. In the majority of eyes, OAG had been diagnosed and glaucoma treatment instituted prior to the vein occlusion while in the remaining eyes the optic disk showed obvious glaucoma-

tous changes at presentation of nCRVO (Fig. 2). In only one eye was nCRVO the initial event, occurring 15 years prior to OAG. For one eye the time sequence could not be established.

Fundus photographs were available for 18 eyes with OAG and nCRVO. Fluorescein angiography had been performed in only a few eyes. A majority of the patients had lens opacities, reducing the image quality. The location of the vein occlusion was on the optic disk surface or at the disk border in 16 eyes (88.8%). In one eye the occlusion site was 0.5 disk diameters from the border (Fig. 3). This was the only eye in which occlusion of a vein peripheral to the optic disk border had occurred remote from an artery-vein crossing. The other eye with nCRVO outside the optic disk belonged to the patient in which nCRVO was diagnosed long before OAG. Of the 16 eyes with occlusion of a vein on the optic disk surface, seven were hemispheric vein occlusions, i.e., occlusion of a first-order branch of the central retinal vein. In nine eyes, the occlusion engaged a second-order branch on the optic disk. In seven eyes the occlusion site was in an area where glaucomatous changes were obvious (e.g., undermining of the disk border or an excavation notch).

Case report. A 33-year-old male ac-

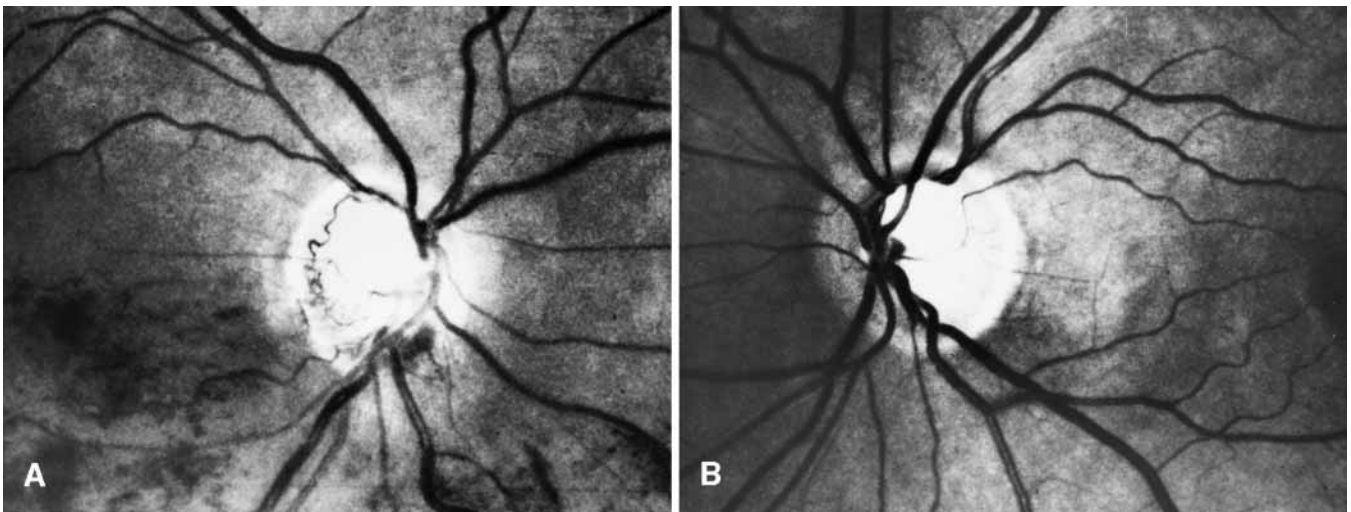


Fig. 2. A: Right eye of a 33-year-old male (see case report) showing inferior hemispheric retinal vein occlusion. Note the thin collateral vessel along the temporal disk border connecting superior and inferior retinal veins. The disk has excavation extending to the superior rim. B: In the left eye there is large excavation showing vertical asymmetry. The nerve fibre layer is more visible superiorly.

countant complained of slowly decreasing vision in the right eye for about six months. He was in perfectly good general health. Visual acuity was 20/50 in the right eye, 20/15 in the left. The right visual field showed defects, most pronounced *inferiorly*. The left eye had minor field changes. At the first examination, intraocular pressures were 19 and 32 mm, respectively. On follow-up examination, pressures were 25 and 27, respectively. Both eyes had open angles with dense pre-trabecular uveal meshworks as signs of goniodysgenesis. Media were clear. Right optic disk showed a large excavation extending to the superior rim. There was an inferior hemispheric retinal vein occlusion with haemorrhages in the right eye (Fig. 2A). The left optic disk showed a vertically asymmetric excavation and loss of retinal nerve fibre layer in the inferior arcuate bundle (Fig 2B). Because of extensive glaucoma damage and fresh haemorrhages in the right eye it was concluded that OAG was the primary event and nCRVO a secondary effect. Two years later, he was still in good health. Medical examinations including laboratory work-up remained normal.

Study 2: Incidence of OAG in Eyes with nCRVO

Material and Methods

Patients with nCRVO but without any signs of glaucoma had been enrolled in a prospective study of laser photocoagu-

lation of nCRVO during the years 1984 to 1987. Consecutive patients with nCRVO seen at the University Eye Clinic in Göteborg were registered by that time. Their files, fundus photographs, and fluorescein angiograms were examined in retrospect. All patients that could be reached in 1995 were invited to a follow-up examination. All were examined by the author. Perimetry was performed with Humphrey Field Analyzer program 24-2 and fundus photographs were obtained.

The occlusion site was identified in the fundus photographs or angiograms. The generation of the occluded retinal vessel branch was established and the distance

between the occlusion site and the optic disk border was measured. Since photographs were obtained with different fundus cameras, all distances were expressed in optic disk diameters. The vessel anatomy at the occlusion site was also studied. Special attention was paid to whether the vein was crossed by an artery at the point of occlusion.

Results

A flow-chart summarising the study design and results is shown in Fig. 1B. Sixty-one patients had been examined for nCRVO during 1984–1987. Mean age at examination was 66 years (range 37–84).



Fig. 3. Right eye from a 64-year-old male with glaucomatous disk changes. The superior temporal vein is occluded about 0.5 disk diameters above the disk border (arrow). The occlusion site is remote from the artery-vein crossing.

Twenty-four were women and 37 men. In five instances the patients' files were lost. Fundus photographs and fluorescein angiograms were examined for the remaining 56 patients (58 eyes). In 1995, about ten years after the initial examination, 16 of the patients were dead. The files from these patients were analysed. Mean follow-up time was 25 months (11–72). None of the deceased patients had developed OAG during the follow-up period.

The remaining 40 patients were invited for a follow-up examination. Three had moved from the area and another three were unable to come due to infirmity. Thus, 34 patients were examined. Mean follow-up time was 121 months (SD 13.7, range 92–152). Twenty eyes (20 patients) had been treated with argon laser photocoagulation: twelve because of macular oedema and another eight because of neovascularization in the retina or on the optic disc. One patient had developed OAG in the eye contralateral to the nCRVO. Another patient showed ocular hypertension in both eyes but no glaucomatous field changes. The remaining 32 patients showed no sign of OAG. Twelve patients had systemic hypertension.

The pattern of nCRVO was different in non-glaucoma eyes compared to eyes with OAG. Only 16 of the 58 eyes (28%) in the nCRVO group had occluded a vein on the optic disk surface. Ten were hemispheric vein occlusions and six were occlusions of a second-order branch. The remaining 42 eyes (72%) had occlusion of a retinal vein peripheral to the optic disk. Without exception, the occlusion site in eyes with nCRVO peripheral to the optic disk was at an artery-vein crossing (Fig. 4). Mean distance between the occlusion site and optic disk border in the whole group of nCRVO eyes was 0.74 disk diameters (SD 0.72). Corresponding figures in eyes with nCRVO and OAG were 0.06 disk diameters (SD 0.17) ($p < 0.0001$).

General Discussion

In this study eyes with nCRVO and OAG showed differences compared to eyes with isolated nCRVO. In eyes with OAG, the occlusion site was in most cases on the optic disk or at its border. There was a tendency for occlusions to occur in an area of the disk showing distinct glaucomatous changes. It is plausible that this finding relates to the peripapillary vasoconstriction reported in the sector with the greatest cupping in glaucoma eyes

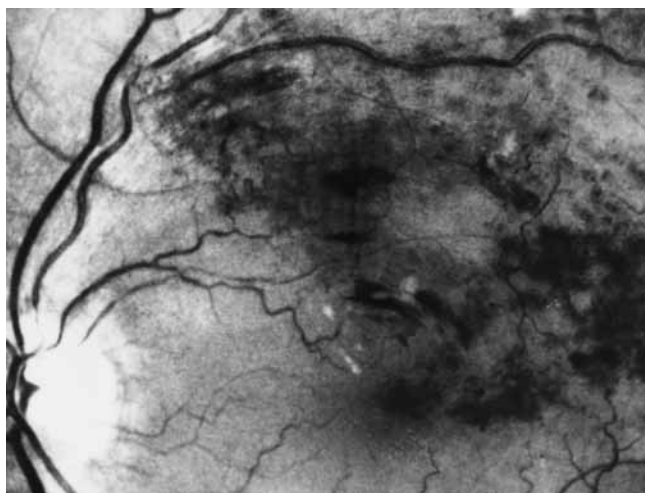


Fig. 4. Superior temporal branch retinal vein occlusion in an eye without glaucoma in a 52-year-old male. The occlusion site is at an artery-vein crossing.

(Rader et al., 1994). In contrast, most eyes with nCRVO without OAG had peripheral occlusions, always occurring at a location where an artery crossed a vein. This is in keeping with earlier studies (Zhao et al., 1993). Only one eye in the nCRVO-OAG group had an occluded vein distal to the optic disk and this was the only eye in the study in which nCRVO preceded OAG with several years. It was also the only eye in the study in which a nCRVO distal to the disk occurred at a location remote from an artery-vein crossing. In almost all eyes with nCRVO and OAG, OAG was diagnosed first and/or obvious disk and field changes consistent with glaucoma were present at the initial visit for nCRVO. These findings suggest that in eyes with both nCRVO and OAG, OAG is in most instances the primary event.

The prevalence of all retinal vein occlusions was 11 per cent in our glaucoma population. This figure may be falsely high because of selection bias. It is plausible that OAG patients with additional ocular pathology will be more readily referred to the university clinic than patients with isolated OAG. Whether the high prevalence of exfoliation glaucoma in our region is important for the incidence of nCRVO is not known. The number of eyes with normal-tension glaucoma, on the other hand, was low. One reason could be that patients often are selected on the grounds of an elevated intraocular pressure. The true prevalence of normal-tension glaucoma in the region is not known.

Only one case of OAG developed in 58 patients with nCRVO during a ten-year follow-up. A large number of patients

were lost, the majority because of death. However, none of the patients lost to follow-up was known to have OAG. Because of the eye care organisation in the Göteborg region, any nCRVO patient with a diagnosed OAG most probably would have come to our attention. The low incidence of OAG in eyes with nCRVO is in agreement with an earlier study in which only two new cases of OAG were found during a ten-year follow-up study of 143 patients with retinal vein occlusion (Rubinstein & Jones, 1976).

Recently, Sonnsjö and Krakau (1993) presented a vascular hypothesis of glaucoma. These authors found that in some cases OAG preceded the vascular occlusion while in other cases the opposite was true. However, in essential parts of their study nCRVO and CRVO were grouped together and treated synonymously. A possible disadvantage of this approach is the difficulty of differentiating between primary and secondary glaucoma in eyes with CRVO. Another explanation for the discrepancies between their findings and the those of the present study could be differences in the definition of OAG. Visual field examinations in an eye with retinal vein occlusion are difficult to interpret. Optic disc evaluation after an occlusion is also difficult because the atrophy that occurs after retinal vein occlusion can sometimes be indistinguishable from that of OAG. It is therefore impossible to eliminate a component of subjectivity in the diagnosis of OAG in these patients.

No attempt was made to differentiate hemispheric retinal vein occlusions into hemi-central retinal vein occlusion and

hemispheric retinal vein occlusion according to Hayreh and Hayreh (1980). In the former the central retinal vein has a dual trunk of which one part is occluded. As remarked by Sanborn and Magargal (1984), the distinction between the two types is not always easy to make. In the present study the most important aspect was to treat separately conditions after which development of secondary glaucoma is uncommon.

The relation between OAG and retinal vein occlusion needs to be evaluated further. In future studies it will be necessary to separate CRVO from nCRVO because the relation to OAG may differ between the two groups. For the same reason it may be sound to separate nCRVO on the optic disk from peripheral nCRVO. Recognition of these differences may help to resolve the current confusion regarding the relation between OAG and the different forms of retinal vein occlusion and may also provide new insights into the pathogenesis of glaucoma.

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