GONIOSCOPIC FINDINGS IN PATIENTS WITH ACUTE CENTRAL/HEMICENTRAL RETINAL VEIN OCCLUSIONS

D. Călugăru¹, M. Călugăru²
University of Medicine and Pharmacy "Grigore T. Popa"- Iaşi
Faculty of Medicine
1. Ph.D. student
University of Medicine and Pharmacy “Iuliu Haţieganu”- Cluj-Napoca
Faculty of Medicine
2. Discipline of Ophthalmology

GONIOSCOPIC FINDINGS IN PATIENTS WITH ACUTE CENTRAL/HEMICENTRAL RETINAL VEIN OCCLUSIONS (Abstract) Objectives: To evaluate prospectively the gonioscopic findings and their changes during a 3-year follow-up period in patients with acute central/hemicentral retinal vein occlusions (C/HRVOs). Material and methods: A comprehensive ophthalmological examination of both eyes including static and dynamic gonioscopy as well as ocular biometric measurements was performed in 57 patients with acute C/HRVOs. The angle configuration and its changes, the axial length of the globe, the anterior chamber depth and the corneal thickness were assessed. Results: 12 C/HRVO patients presented with narrow drainage angles (≤ 20º) and 45 had normal angles (>20º). Ocular globes with narrow angles had axial length and anterior chamber depth significantly smaller as well as cornea thickness significantly greater than the eyes with normal angles. Out of the 12 patients with narrow angles, 6 cases had primary angle closure suspect (PACS), 5 cases had primary angle closure (PAC) and one case primary angle closure glaucoma (PACG). 3 of the 6 PACS patients progressed to PAC in the 6th, 10th, and 18th months of the follow-up period. From the 8 PAC cases existing during the whole study interval, one case progressed to PACG during the 24th month of the follow-up interval. Conclusions: In the context of an ocular globe having its size significantly smaller than the normal eye, narrow angle may represent a local risk factor predisposing to C/HRVO. Intermittent episodes of angle closure may contribute by increasing the intraocular pressure to the occurrence of C/HRVO as well to the progression of the gonioscopic configuration from PACS to PAC and from PAC to PACG. Keywords: CENTERAL/HEMICENTRAL RETINAL VEIN OCCLUSION, PRIMARY ANGEL CLOSURE SUSPECT, PRIMARY ANGLE CLOSURE, PRIMARY ANGLE CLOSURE GLAUCOMA

Gonioscopy is considered the current reference-standard examination whose purpose is to visualize the anterior chamber angle as completely as possible. It enables identification of the iridotrabecular contact and is the only examination method that is able to differentiate appositional from synechial angle closure (1, 2).

Closure of the anterior chamber angle in central retinal vein occlusion (CRVO) may appear as a primary (in predisposed eyes) or secondary event; the latter case is caused
either by neovascularization of the angle (3) or by a marked anterior displacement of the lens-iris diaphragm due to abnormal accumulation of blood or edema fluid in the posterior segment of the eye, a non-rubeotic state having some similarities to malignant glaucoma (4, 5).

The aim of this study is to evaluate prospectively the gonioscopic findings and their changes during a 3-year follow-up period in patients with acute central/hemicentral retinal vein occlusions (C/HRVOs).

**MATERIAL AND METHODS**

**Patient population.** The study was carried out in 57 unilateral acute C/HRVO patients, was approved by the University “Grigore T. Popa” Iași Ethics Committee and conformed to the tenets of the Declaration of Helsinki.

The patients enrolled in the study had a unilateral CRVO or hemicentral retinal vein occlusion (HRVO) with duration of symptoms of venous occlusive event of < 1 month. Exclusion criteria included prior tratament (filtering surgery, corneal transplantation, pars plana vitrectomy, or photocoagulation), aphakia or pseudophakia and any vascular retinal disorders in the study eye or age-related macular degeneration (e.g. drusen, geographic atrophy and neovascular form) in any of the 2 eyes.

**Patient examination.** All patients underwent a comprehensive baseline ophthalmological examination of both eyes. Best corrected visual acuity (BCVA) score was determined using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol (Snellen equivalent plus ETDRS letters) (6). Careful testing of the visual field was performed by means of the Goldmann perimeter using I2e, I4e and V4e isopters. In case of suspicion of concomitant primary glaucoma, the Humphrey standard automatic perimetry (Humphrey Instruments, Inc, San Leandro, California; model 720i; programme SITA FAST, 30-2) was used. Biomicroscopic examination was carried out with dilated and nondilated pupil. Thorough evaluation of the ocular fundus was performed with direct and indirect ophthalmoscopy and, if needed, using a contact lens. Fluorescein angiography was focused on both disc and macula during early examination times, on middle retinal periphery of each quadrant during intermediate phases and again on disc and macula in the late examination times. Intracocular pressure (IOP) was determined by using the Perkins applanotomometer and was adjusted for the corneal thickness. A scan ultrasonic ocular biometry was undertaken with Alcon Ultrascan Imaging System (Alcon, Inc, Forth Worth, Tx). The examination included following determinations: the axial length of the eye, the anterior chamber depth and the lens thickness. Optical Coherence Tomography (Stratus OCT; Carl Zeiss Meditec, Dublin, CA, USA) was used for evaluating the macular morphology and thickness, the optic disc and the retinal nerve fiber layer (RNFL). Gonioscopy was performed with the patient sitting at a slit-lamp, at high magnification (16 x) in a dark room using a two-mirror Goldmann gonioscopic lens. Beside the usual technique of the static gonioscopy, we used also dynamic gonioscopy.

**Treatment and follow-up.** The treatment applied to acute C/HRVO patients consisted of intravitreal bevacizumab (IVB) (Avastin; Genentech Inc., San Francisco, CA) injections in a dose of 2.5 mgr per injection until a stabilization of the BCVA score, lasting at least 6 months was
achieved. Patient follow-up was carried out every two months during the first year and every 6 months thereafter within the next two years.

**Diagnostic criteria.** A) Normal (not occludable) anterior chamber angle (> 20 grade) (7): The posterior third of the trabecular meshwork (usually pigmented) is visible for more than 180 degrees, on static gonioscopy with the eye in the primary position. This configuration involves both eyes. B) Narrow drainage angle (≤ 20 grade) (2, 8, 9): Non-visibility of the posterior trabecular meshwork for ≥ 180 degrees of the angle circumference on non-indentation gonioscopy with the eye in the primary position. It has two variants, namely, moderately narrow angle (angular width 15-20º) and extremely narrow angle (≤ 10º). This configuration involves both eyes. C) Primary angle closure suspect [PACS] (1, 7), namely an eye in which appositional contacts between the peripheral iris and the posterior trabecular meshwork is considered possible/probable: -Narrow drainage angle, IOP below 22 mmHg, no peripheral anterior synechiae (PAS) in the angle, and without glaucomatous optic neuropathy (GON); -Absence of the ocular pathology, that can induce PAS formation (uveitis, neovascularization, trauma, surgery). D) Primary angle closure [PAC] (7, 9, 10, 11, 12, 13): -Narrow drainage angle; -Excluded were eyes in which narrow angles or shallow anterior chambers were thought to be secondary to the other ocular conditions, such as, lens abnormalities, chronic uveitis, trauma, ruberosis iridis or retinopathy of prematurity; -Optic disc and visual field definitely considered as nonglaucomatous; -The presence of at least one of the following features indicating that trabecular obstruction by the peripheral iris occurred: a) PAS; b) IOP > 21 mmHg; c) Excessive pigment deposition on the trabecular meshwork surface, especially superior; d) Ischemic sequelae of acutely raised IOP (distorsion of the radially orientated iris musculature, iris stromal atrophy, dilated nonresponsive pupil, focal necrosis of lens epithelium causing glaucomfleken) (1) ; e) Clear history of clinical signs or symptoms such as headaches, congestion, blurred or halo vision, corneal edema or a mid-dilated pupil, consistent with sudden IOP rise; f) Evidence of a surgical peripheral iridotomy; g) Dark room provocation test giving a rise in IOP of ≥ 8 mmHg from baseline. E) Primary angle closure glaucoma [PACG] (1, 7, 9, 13) :- Presence of PAC; - Consistent visual morbidity; - Typical GON (1,10.14) is characterized by irreversible structural and/or functional glaucomatous lesion, indistinguishable from the primary open angle glaucoma; structural glaucomatous damage includes aquired characteristic progressive optic neuropathy (eg optic disc cupping; narrowing the area of neuroretinal rim; localized “notch”; disc hemorrhages; newly appeared asymmetry in the cup/disc ratio ≥ 0.2 between both eyes; change in the cup/disc ratio > 0.2) that could be documented alongside the follow-up, and/or changes of the RNFL (diffuse or localized defects); functional glaucomatous damage comprises reproducible characteristic changes of the visual field (retinal nerve fiber bundle defects) corresponding to the optic disc lesion; - Atypical GON (1) occurs after an acute symptomatic episode of angle closure and presents with a pale but flat optic disc, suggesting an anterior ischemic optic neuropathy.

**Main outcome measures.** The primary outcome measure was emphasizing the gonioscopic configuration of the anterior
chamber angle in patients with C/HRVOs. The secondary outcome measures included: determination of the axial length of the eye, the anterior chamber depth as well as the lens and the cornea thicknesses; the cumulative prevalences of the PACS, the PAC and the PACG; the progression rates from PACS to PAC as well as from PAC to PACG.

**Statistical analysis.** The continuous variables were tested using Student’s tests (normal distributed data) and both the Man Whitney U and the Wilcoxon tests for non-parametric distributions. Categorical data were analyzed by means of the Person chi-square test and the Fisher exact test. Cumulative prevalence calculation was made by using the Kaplan-Meier estimate. The statistical analysis was performed using **SPSS** statistical software (version 16.0) and **Epi-Info 2000**.

**RESULTS**

From total, 12 C/HRVO patients presented with narrow anterior chamber angles (≤ 20º) and 45 patients had normal drainage angles (>20º) (tab. I). Venous occlusions in patients with narrow angles occurred at an age significantly greater (p=0.001) than those in patients with normal angles.

**TABLE I**

| Demographic and clinical baseline characteristics in 57 patients with central / hemicentral retinal vein occlusion |
|---|---|---|---|
| Variables | Narrow (n = 12) | Normal (n = 45) | p-value |
| Total (n = 57) |
| Age (years) | Mean ± SD | 72.08 ± 9.66 | 56.37 ± 13.12 | 0.001 | 59.68±13.97 |
| Median (range) | 72.5 (58-85) | 59 (21-75) | 0.019 | 62 (21-85) |
| Stratification n (%) | ≤ 55 | 0 (0) | 20 (44.4) | 0.005 | 20 (35.1) |
| > 55 | 12 (100) | 25 (55.6) | 0.005 | 37 (64.9) |
| Gender n (%) | Male | 9 (75) | 26 (57.8) | 0.335 | 35 (61.4) |
| Female | 3 (25) | 19 (42.2) | 0.335 | 22 (38.6) |
| Occlusion type n (%) | CRVO | 11 (91.7) | 43 (93.3) | 0.623 | 53 (93) |
| HRVO | 1 (8.3) | 3 (6.7) | 0.623 | 4 (7) |
| Occlusion form n (%) | Ischemic | 12 (100) | 9 (20) | 0.001 | 21 (36.8) |
| Nonischemic | 0 (0) | 36 (80) | 0.001 | 36 (63.2) |

CRVO = central retinal vein occlusion; HRVO = hemicentral retinal vein occlusion

Biometric measurements emphasized an axial length of the ocular globe significantly smaller (21.69±0.93 mm; p=0.004) and an anterior chamber depth significantly lower (1.8±0.09 mm; p=0.0009) in patients with C/HRVOs having a gonioscopic configuration of narrow angle compared with those with a normal angle configuration (22.69±0.94 mm and 2.58±0.55 mm, respectively). The cornea thickness was significantly great (p=0.0009) in patients with narrow angles (0.6 ± 0.02 mm) vs.
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those with normal angles (0.54 ± 0.02 mm).

Three possible clinical forms of angle closure status existed at the beginning of the study in the 12 patients with venous occlusions having narrow angles (tab. II), namely PACS in 6 cases, PAC in 5 cases and PACG in one case.

<table>
<thead>
<tr>
<th>Angle-closure status</th>
<th>PACS</th>
<th>PAC</th>
<th>PACG</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n)</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Final (n)</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>12</td>
</tr>
</tbody>
</table>

PACS = primary angle closure suspect; PAC = primary angle closure; PACG = primary angle closure glaucoma

Peripheral laser iridotomy was performed in 4 out of the five patients with PAC and trabeculectomy in the patient with PACG. One patient with PAC refused laser
3 of the 6 PACS patients (50%) progressed to PAC in the 6-th, 10-th and 18-th months of the follow-up period (16.6% per year), following some asymptomatic episodes of angle closure (unilateral progression in the occlusion eye). Peripheral laser iridotomy was performed in all three patients. So, the cumulative prevalence of PACs decreased from 11.76% (95% confidence interval (CI), 4.44-23.87) to 7.14% (95% CI 1.5-19.43) (fig. 1) while the cumulative prevalence of PAC increased from 9.6% (95% CI, 3.2-21.03) to 16.6% (95% CI, 6.97-31.36) (fig. 2).

**Fig. 2.** The Kaplan-Meier estimate of the cumulative prevalence of the primary angle closure over the entire course of the study in 57 central/hemifocal retinal vein occlusion patients. Patients at risk are those who did not present primary angle closure at the beginning of the study period. Patients who were lost before the ends of the study were censored from the last completed visit and those who died were censored at their date of death. The dotted lines represent the upper and lower bounds of the 95% confidence interval.

From the 8 cases with PAC existing during the whole study period, only one (12.5%) progressed to PACG during the 24-th month of the follow-up period (4.16% per year) follow-
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During an acute episode of angle closure (unilateral progression in the occlusion eye). This patient (a female aged 74 years) is the one who refused laser treatment during the PAC status and who declined again the surgery during PACG status. She exhibited a pale but flat optic disc with altitudinal visual field defects closely resembling anterior ischemic optic neuropathy. So, the cumulative prevalence of PACG increased from 1.78% (95% CI, 0.045-0.552) to 4.08% (95% CI, 0.05-10.85) (fig. 3).

**DISCUSSION**

An important ascertainement of this study is the great incidence (12 cases; 21%) of the narrow angles (≤ 20°) in patients with C/HRVOs, namely moderately narrow angles (15-20°) in 7 cases and extremely narrow angles (≤ 10°) in 5 cases. This frequency is evidently greater compared to that existing in the general population [between 2% (15) and 14.8% (16)].
The statistically significant difference between the mean age of the venous occlusion patients with narrow and normal angles (tab. I) caused us to suspect the possible role played by an advanced age in the occurrence of such high percentage of the narrow angles. The narrowing of the anterior chamber angle appears to be a function of normal aging (11). With advancing in age, an angle may become occludable.

In the eyes with narrow angles of our series, the ocular biometric measurements were totally different from those existing in the ocular globes with normal angles (> 20º). So, the axial length of the globe and the anterior chamber depth were significantly smaller and the cornea thickness was significantly greater in eyes with narrow angles compared to eyes with normal angles. This configuration of the ocular globe having the size of the anterior segment smaller than the average may represent a local risk factor predisposing to CRVO, especially for an ischemic form of the venous occlusions. The changes mentioned are not the result of the occlusion but an expression of the constitutional factors with inherited characteristics. Shorter axial length may also indicate crowded posterior segment. In such eyes, retinal vein and artery that share the same adventitial sheath are more crowded and impaired as they pass through the lamina cribrosa; this status may narrow the lumen of the vein with all its subsequent consequences, namely, decrease of the blood flow, increase of the blood viscosity and local turbulence that could cause thrombosis (17).

At the beginning of the study, 6 cases of CVROs with narrow angles were diagnosed as having closure of the angle, namely 5 cases with PAC and one case with PACG (tab. II). These patients were experiencing a history of symptoms of intermittent IOP rises as a consequence of the angle closure. After reversing such an episode, patients complained about the persistence of blurred vision, which determined them to have an ophthalmological examination. On this occasion the ophthalmologist ascertained the existence of the venous occlusion. In these cases, the episodes of ocular hypertension due to angle closure may have triggered the occurrence of the venous occlusions (18). Increasing the IOP induce compression, stretching, deformation, and backward displacement of the lamina cribrosa that secondarily may distort the vein (19). The collapse of the retinal vein due to compression and subsequent endothelial lesion with intimal proliferation caused the vein to occlude at the level of the lamina cribrosa.

Progression from the PACS to PAC occurred in 3 eyes with CRVOs out of the 6 cases with PACS being present at the entry (50%; 16.6% per year). This incidence per year of progression from PACS to PAC is greater than that existing in the general population (22%; 4.4% per year) (7), which plead in favor of the fact that CRVO may represent a risk factor for the progression. The progression from PAC to PACG appeared only in a single eye with CRVO out of the 8 PAC cases existing during the whole study period (12.5%; 4.16% per year); so, the incidence per year of progression from PAC to PACG is consistent with that being present in the general population (28.57%; 5.7% per year) (13).

The successive episodes of angle closure after venous occlusion occurrence may account for the progressions ascertained. Increased thickness of the lens accompanied by a change in its shape due to slackening of the zonules causing the lens to
move forward (15), represent the main growth and dynamic factors that, in the presence of the constitutional ones with inherited characteristics, determine decreasing the angular width as the age advances (7, 15, 20). All of these factors combine to hasten the closure of the angle with advancing in age.

The main limitation of the study was the lack of a control group recruited from the general population of the same location in which all the determinations should have been done, namely the evaluation of the incidence of different angle configurations as well as of the cumulative prevalence of the varied clinical forms of the angle closure and their progressions.

**CONCLUSIONS**

From our study we can conclude that the narrow angle in the context of an ocular globe having its size significantly smaller than the normal eye may represent a local risk factor predisposing to C/HRVO. Intermittent episodes of angle closure may contribute to the occurrence of the C/HRVO as well as to the progression of the gonioscopic changes.

**REFERENCES**

The objective of this review was to summarize literature describing approaches aimed at automatically identifying patients with a common phenotype. The authors performed a review of studies describing systems or reporting techniques developed for identifying cohorts of patients with specific phenotypes. Every full text article published in (1) Journal of American Medical Informatics Association, (2) Journal of Biomedical Informatics, (3) Proceedings of the Annual American Medical Informatics Association Symposium, and (4) Proceedings of Clinical Research Informatics Conference within the past 3 years was assessed for inclusion in the review. Only articles using automated techniques were included. The identification of patients who satisfy predefined criteria from a large population in an institution has numerous use cases, including clinical trial recruitment, outcome prediction, survival analysis, and other kinds of retrospective studies. However, the process of distinguishing these patients on the basis of their patient records can be extremely time-consuming and challenging depending on the complexity of the criteria. This is because the data matching these criteria are buried within multiple documents and across multiple data points in the electronic health record (EHR) of a patient. Some data, such as laboratory results, medications, and diagnoses, have a structured format. The ability to extract meaningful pieces of information from the EHR and consolidate them into a coherent structure would provide great value for automatically identifying patient cohorts that satisfy complex criteria. Studies in this review addressed different diagnoses as the phenotype of interest. A large number of papers focused on diabetes, cancer, heart failure, rheumatoid arthritis, or cataract. A few studies described generic methods that could be applied to multiple diagnoses. Several papers addressed identification of adverse drug events. Some studies also analyzed genomic data of a predetermined phenotype to gain insight into other phenotypic properties of the same cohort. Authors have developed a top of the first 10 phenotypes of interest. Although cancer has been reported as a generic phenotype, there were 12 types of cancer (with breast cancer being most prevalent) studied in seven articles. Congestive heart failure and heart failure were counted as the same phenotype. Similarly, hypertension and resistant hypertension were considered to be one phenotype. Some articles also considered other observable characteristics such as smoking status and obesity among patients. Pneumonia and a variety of other infectious diseases were studied. This review is not without limitations, especially for the vagueness of the term phenotyping, meaning that there is no exhaustive search strategy for retrieving appropriate articles across the entire available body of biomedical literature. However, because of the venues considered and the recent popularity of this topic, this review is representative of past and present efforts in this domain. (Shivade C, Raghavan P, Fosler-Lussier E, Embi PJ, Elhadad N, Johnson SB, Lai AM. A review of approaches to identifying patient phenotype cohorts using electronic health records J Am Med Inform Assoc 2014; 21: 221-230 doi:10.1136/amiajnl-2013-001935)