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Video

Predictors of anterior chamber angle status at the time of neovascular glaucoma diagnosis

Jessie Wang [a,b], Jacob Kanter [a], Mary Qiu [a,*]

[a] Department of Ophthalmology and Visual Science, University of Chicago Medical Center, Chicago, IL, USA
[b] Duke Eye Center, 2351 Erwin Rd, Durham, NC, USA 27705

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ABSTRACT

Purpose: To identify clinical features which may predict the angle status of a large cohort of NVG eyes at the time of diagnosis.

Observations: Chart review was performed for all NVG eyes from 2010 to 2022. Complete angle closure was defined as having >75 % PAS, partial angle closure as having 1–75 % PAS, and open angles as having 0 % PAS. Among 190 eyes (174 patients) with a diagnosis of NVG, 29 eyes (28 patients) had a prior NVG diagnosis and 32 eyes (31 patients) did not undergo gonioscopy; 129 eyes (115 patients, mean 65.5 years, 50 % women) had a gonioscopy documented at the time of diagnosis. There were 32 eyes (25 %) with open angles, 39 eyes (30 %) with partially closed angles, and 58 eyes (45 %) with completely closed angles. Mean BCVAs were 20/138 (logMar 0.84, CI = 0.78–0.90), 20/662 (logMar 1.52, CI = 1.41–1.62), and 20/4375 (logMar 2.34, CI = 2.17–2.51), respectively ($p < 0.05$). The mean presenting IOP was 31 mmHg, 40 mmHg, and 59 mmHg, and the proportion of eyes that were phakic were 47 %, 46 %, and 67 %, respectively. The proportion of eyes presenting to the emergency room were 6 %, 21 %, and 26 %, respectively.

Conclusions and importance: Among NVG eyes with a documented initial gonioscopy, nearly half had total synechial closure. While eyes with increasing degrees of angle closure trended towards worse vision and higher IOP, these clinical characteristics are not perfectly predictive of angle anatomy and should not replace gonioscopy. Eyes with closed angles trended towards being phakic, presenting to the emergency department (ED), having undergone prior panretinal photocoagulation (PRP), and belonging to new patients.

1. Introduction

Neovascular glaucoma (NVG) is a secondary glaucoma mediated by the release of cytokines such as vascular endothelial growth factor (VEGF) following retinal ischemia. VEGF promotes angiogenesis, leading to rubeosis iridis, or neovascularization of the iris (NVI), and angle (NVA). In the early stages of the disease process, though the angle remains open, aqueous outflow may be obstructed by a fibrovascular membrane.[1] However, as the disease progresses, myofibroblasts cause contraction and progressive peripheral anterior synechiae (PAS).[1,2] Currently, few reports distinguish between the presence and extent of PAS in NVG, though an increasing awareness for the need to standardize the disease is being recognized.[3]

A growing body of evidence has shown that outcomes in NVG may differ depending on angle status.[4–6] One retrospective study of 41 eyes from 2008 found that NVG eyes respond differently to intravitreal anti-VEGF agents based on angle status. In eyes with open angles (<75 % PAS), intravitreal anti-VEGF led to rapid regression of NVA and normalization of intraocular pressure (IOP) in 71 %, whereas 93 % of eyes with ≥75 % PAS required emergent IOP-lowering procedures.[4] Other recent reports have shown that in eyes with entirely open angles, IOP may normalize with anti-neovascular therapy alone,[5] while those with partially closed angles (<75 % PAS) may achieve IOP normalization after a combination of anti-neovascular therapy and micro-invasive gonioscopy-assisted transluminal trabeculotomy (GATT).[6]

There is no consensus treatment protocol for NVG and though several have been published, none differentiate between angle status at presentation.[7–9] Traditionally, treatment of NVG in the acute setting has been guided by assessing visual potential and IOP. However, visual potential can be unclear in the acute setting, as corneal edema, hyphema, or vitreous hemorrhage may be limiting factors. Instead, the current practice pattern by the sole glaucoma specialist at our institution

* Corresponding author.
E-mail address: maryqiu@gmail.com (M. Qiu).

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(MQ) distinguishes NVG eyes into three distinct populations: totally open, partially closed, or completely closed angles. Each undergo treatment via a different protocol. Eyes with completely open angles undergo prompt anti-neovascular treatment and medical management of the IOP; IOP-lowering surgery can often be avoided, but if needed, an attempt to salvage the physiologic outflow pathway via an angle-based procedure is pursued[5] after the NVA has regressed. Eyes with partially closed angles also undergo prompt anti-neovascular medical IOP-lowering therapies, but IOP-lowering surgery is often needed sooner, and again an angle-based procedure is oftentimes pursued.[6] However, eyes with completely closed angles are expected to require urgent IOP-lowering surgery, often prior to the full regression of angle neovascularization, so primary cyclophotocoagulation is often favored.

Since treatment may differ depending on angle status, we sought to perform a retrospective cross-sectional study to identify clinical features which may predict the baseline angle morphology at the time of NVG diagnosis. At our institution, the extent of angle closure is the determining factor that is used to guide acute NVG management, rather than presumed visual potential or IOP; this approach differs from that in most of the NVG literature.[10–14] Additionally, we sought to describe the sub-group of eyes that did not have gonioscopy documented at the time of NVG diagnosis to better elucidate why some eyes did not undergo this critical part of the eye exam.

2. Methods

A retrospective chart review was performed for all patients diagnosed with NVG, identified via a SlicerDicer search of the electronic medical record from 2010 to 2022. Open angle was defined as having 0 % PAS, partial angle closure as having 1–75 % PAS, and complete angle closure as having >75 % PAS; these cutoffs were based on those in the aforementioned study by Wakabayashi.[4]

Eyes with a new diagnosis of NVG were included, and eyes with a preexisting diagnosis of NVG were excluded. Data regarding the patient's age, gender, race, visual acuity and intraocular pressure, number of IOP-lowering medications, lens status, gonioscopic exam by a glaucoma attending, slit lamp exam, dilated fundus exam, etiology of NVG, setting of presentation, and past ocular history were collected.

Statistical analysis. Descriptive statistics were performed. An ordinal logistic regression model was used to evaluate factors associated with angle status using Stata 17.0. Differences were considered statistically significant at a p-value of <0.05.

3. Results

There were 190 eyes from 174 patients with a diagnosis of NVG. Twenty-nine eyes from 28 patients were excluded due to having a preexisting diagnosis of NVG, so there remained 161 eyes with a new diagnosis of NVG available for analysis. Among these 161 eyes, there were 32 eyes from 31 patients (20 %) with no gonioscopy documented at the time of initial NVG presentation. Among these 32 eyes, there were 8/32 (25 %) with microcystic edema (MCE), 6/32 (19 %) with hyphema, and 3/32 (9 %) with both MCE and hyphema, which may have precluded a view into the angle for gonioscopy; the remaining 21 eyes' charts did not mention any specific reason why gonioscopy was not performed. Finally, there were 129 eyes from 115 patients remaining who were stratified by angle status at the time of initial NVG presentation: 32/129 (24.8 %) with open angles, 39/129 (30.2 %) with partially closed angles, and 58/129 (45.0 %) with completely closed angles.

Among the 32 eyes without a documented gonioscopy, the mean age was 66.6 years, 13 (41 %) belonged to women, PDR accounted for 78 % of these eyes, and mean BCVA was 20/1663 (logMar 1.92) with a mean IOP of 39.7 mmHg. In this subset, 44 % of eyes belonged to new patients, 16 % of eyes presented to the ED, 47 % were phakic, and several of these eyes had undergone prior PRP (25 %) or PPVs (9.4 %). The clinical characteristics of this sub-group are shown in Table 1, and there were no statistically significant differences in any of the variables between the 32 eyes in this group and the remaining 129 eyes ($p > 0.05$ for all variables).

Among eyes with a documented gonioscopy, the mean age was 65.5 years and 64 (50 %) belonged to women. The clinical characteristics of this group, stratified by angle anatomy at time of presentation, are shown in Table 1. There was no statistically significant association between age or gender and angle status. Eyes belonging to patients self-identifying as Black trended towards having either partially closed or completely closed angles, though this did not reach statistical significance ($p = 0.35$). Underlying etiologies included proliferative diabetic retinopathy (PDR) (N = 68), retinal vein occlusion (RVO) (N = 38), chronic retinal detachment (RD) (N = 9), retinal artery occlusion (RAO) (N = 8), ocular ischemic syndrome (OIS) (N = 3), radiation retinopathy (N = 1), and idiopathic (N = 2). None were found to be significantly associated with angle status.

In the open angle, partial angle closure, and complete angle closure groups, mean BCVAs were 20/138 (mean logMar 0.84, CI = 0.78–0.90), 20/662 (mean logMar 1.52, CI = 1.41–1.62), and 20/4375 (mean logMar 2.34, CI = 2.17–2.51), respectively ($p < 0.05$ for logMar of VA) (Table 1). Presenting IOP varied widely: the average was 31 mmHg (range 8–50 mmHg) in eyes with completely open angles, 40 mmHg (range 11–73 mmHg) in eyes with partially closed angles, and 49 mmHg (range 24–77 mmHg) in eyes with completely closed angles. Eyes with any degree of angle closure presented with higher IOP than those with open angles ($p < 0.05$). The number of baseline IOP-lowering medications did not differ among groups. The proportion of eyes who presented to the emergency department (instead of the outpatient clinic) were 6 %, 21 %, and 26 % in open, partially closed, and completely closed angles, respectively ($p = 0.13$). The proportion of eyes that belonged to new rather than established patients – those who have never been seen in the eye clinic for any reason – were 41 %, 46 % and 55 % ($p = 0.34$).

Eyes with completely open angles were found to have a significantly higher rate of presenting asymptomatically (50 %) as compared to those with partially (18 %) or completely closed angles (3 %) ($p < 0.05$), while eyes with closed angles had a higher proportion of MCE ($p < 0.05$). A hyphema was not found to be statistically significantly associated with angle status ($p = 0.73$). However, eyes with closed angles had a higher proportion of vitreous hemorrhage (VH) as compared to those with completely open angles ($p < 0.05$). The proportion of phakic eyes were found to be 47 % in the open angle group, 46 % in the partially closed angle group, and 67 % completely closed angle group. Finally, despite an association between an increasing extent of angle closure and belonging to new (rather than established) patients, eyes with increasing degrees of synechial closure had undergone more prior interventions, including panretinal photocoagulation (PRP) ($p < 0.05$) and pars plana vitrectomy (PPV) ($p = 0.41$). In fact, 27/58 (47 %) eyes in the complete angle closure group had undergone prior PRP and/or PPV.

4. Discussion

As angle status may help guide treatment of neovascular glaucoma,[4–6] a gonioscopic exam on initial presentation is essential. Other clinical characteristics do not perfectly predict angle status. If microcystic edema precludes a clear view of the angle, IOP-lowering medications, topical hyperosmotics, or anterior chamber paracentesis may be used to temporarily lower the IOP and clear the cornea so that gonioscopy can be performed.[15] In our cohort, no eyes underwent anterior chamber paracentesis for the purpose of clearing microcystic corneal edema to perform gonioscopy. If the view to the angle is obscured by hyphema, then treatment can be guided by the IOP and its response to maximum medical therapy.

The presence of microcystic corneal edema and/or a hyphema may have precluded a view into the angle for some (11/32 eyes, 34 %), but not all, eyes who did not undergo a gonioscopy. For the remaining (21/

Table 1
Clinical characteristics of NVG eyes with varying anterior chamber angle status at time of initial diagnosis.

	OPEN ANGLE (N = 32, 24.8 %)	PARTIALLY CLOSED (N = 39, 30.2 %)	COMPLETELY CLOSED (N = 58, 45.0 %)	NO GONIOSCOPY AVAILABLE (N = 32)
MEAN AGE (yrs)	67.5 (SD 10.9)	67.4 (SD 15.2)	63.1 (SD 14.8)	66.6 (SD 15.0)
GENDER				
Male	15 (46.9 %)	20 (51.3 %)	30 (51.7 %)	19 (61.3 %)
Female	17 (53.1 %)	19 (48.7 %)	28 (48.3 %)	13 (38.7 %)
RACE				
Black	17 (53.1 %)	28 (71.8 %)	40 (69.0 %)	20 (62.5 %)
White	15 (46.9 %)	10 (25.6 %)	16 (27.6 %)	12 (37.5 %)
Other	0 (0 %)	1 (2.6 %)	2 (3.4 %)	0 (0 %)
ETIOLOGY				
PDR	19 (59.4 %)	20 (51.3 %)	29 (50.0 %)	26 (81.3 %)
RVO	7 (21.9 %)	13 (33.3 %)	18 (31.0 %)	6 (18.7 %)
RD	1 (3.1 %)	3 (7.7 %)	5 (8.6 %)	0 (0 %)
RAO	1 (3.1 %)	1 (2.6 %)	6 (10.3 %)	0 (0 %)
OIS	1 (3.1 %)	2 (5.1 %)	0 (0 %)	0 (0 %)
Radiation Retinopathy	1 (3.1 %)	0 (0 %)	0 (0 %)	0 (0 %)
Idiopathic	2 (6.3 %)	0 (0 %)	0 (0 %)	0 (0 %)
BCVA				
MEAN LOGMAR	0.84*	1.52*	2.34*	1.92
20/20–20/40	14 (43.8 %)	8 (20.5 %)	0 (0 %)	4 (12.5 %)
20/50–20/200s	8 (25.0 %)	7 (17.9 %)	5 (8.6 %)	4 (12.5 %)
20/250–20/1250	4 (12.5 %)	5 (12.8 %)	2 (3.4 %)	2 (6.3 %)
CF-HM	5 (15.6 %)	10 (25.6 %)	26 (44.8 %)	10 (31.3 %)
LP	1 (3.1 %)	8 (20.5 %)	15 (25.9 %)	5 (15.6 %)
NLP	0 (0 %)	1 (2.6 %)	10 (17.2 %)	7 (21.9 %)
MEAN IOP (mmHg)	31.0* (SD 11.0)	40.3* (SD 12.9)	44.8* (SD 11.9)	39.7 (SD 11.6)
MEAN # OF IOP-LOWERING MEDS	0.9 (SD 1.4)	1.3 (SD 1.7)	0.9 (SD 1.5)	0.4 (SD 1.3)
NEW PATIENT	13 (40.6 %)	18 (46.2 %)	32 (55.2 %)	14 (43.8 %)
SETTING				
Emergency Department	2 (6.3 %)	8 (20.5 %)	15 (25.9 %)	5 (15.6 %)
Clinic	30 (93.8 %)	31 (79.5 %)	43 (74.1 %)	27 (84.4 %)
SYMPTOMATIC	16* (50.0 %)	32* (82.1 %)	56* (96.6 %)	28 (87.5 %)
MICROCYSTIC EDEMA	5* (15.6 %)	13* (33.3 %)	30* (51.7 %)	8 (25.0 %)
HYPHEMA	3 (9.4 %)	7 (17.9 %)	10 (17.2 %)	6 (18.7 %)
LENS STATUS				
Phakic	15 (46.9 %)	18 (46.2 %)	39 (67.2 %)	15 (46.9 %)
Pseudophakic	16 (50.0 %)	21 (53.8 %)	18 (31.0 %)	17 (53.1 %)
Aphakic	1 (3.1 %)	0 (0 %)	1 (1.7 %)	0 (0 %)
VITREOUS HEMORRHAGE	7* (21.9 %)	4 (10.3 %)	21* (36.2 %)	4 (12.5 %)
PRIOR PRP	4* (12.5 %)	11 (28.2 %)	24* (41.4 %)	8 (25.0 %)
PRIOR PPV	4 (12.5 %)	6 (15.4 %)	12 (20.7 %)	3 (9.4 %)

PDR = proliferative diabetic retinopathy; RVO = retinal vein occlusion; RD = retinal detachment; RAO = retinal artery occlusion; OIS = ocular ischemic syndrome; BCVA = best corrected visual acuity; CF = count fingers; HM = hand motion; LP = light perception; NLP = no light perception; IOP = intraocular pressure; PRP = panretinal photocoagulation; PPV = pars plana vitrectomy.
* = $p < 0.05$.
Note: N = number of eyes; there were 129 eyes from 115 patients with a documented gonioscopy and 32 eyes from 31 patients without a gonioscopy.

32 eyes, 66 %) eyes who did not undergo a gonioscopy when a view was presumably possible, no reasons were documented in the medical record as to why gonioscopy was not performed. Differences in physician practice pattern may account for this discrepancy; all 21 eyes without documented gonioscopy without MCE or hyphema presented prior to October 1, 2019, when our current sole glaucoma specialist (MQ) started at our institution, and there were no eyes that presented after October 1, 2019 without MCE or hyphema without documented gonioscopy. This illustrates the reality of varied practice patterns in our institution over time and across other institutions nationally and internationally and supports the need for standardized nomenclature and guidelines for evaluating a new NVG patient. Additionally, discomfort and the ability to position at a slit lamp may also limit a gonioscopy exam; pain was not consistently documented in the medical record, so it was not possible to determine how much it impacted a lack of gonioscopy. However, as the mean age, patient demographics, BCVA, IOP, proportion of new patients, eyes presenting to the ED, symptomatic eyes, eyes presenting with MCE or hyphema or vitreous hemorrhage, phakic eyes, and eyes having undergone prior PRP and PPV were comparable to the proportions seen in eyes who underwent a gonioscopic exam ($p > 0.05$), this reassuringly suggests that the remaining 129 eyes should be representative of the group overall.

In this case series, 45% of eyes with a documented gonioscopy presenting with neovascular glaucoma had a completely closed angle at the time of diagnosis, 30 % of eyes presented with partially closed angles, and the remaining 25 % of eyes demonstrated entirely open angles without any PAS at the time of initial NVG presentation. It is important to note that angle morphology exists as a spectrum rather than three distinct entities; however, grading them into sub-groups can aid in formulating a treatment plan and counseling patients, much like how primary angle closure (PAC) also exists on the spectrum between primary angle closure suspect (PACS), and primary angle closure glaucoma (PACG).[16]

While there is a statistically significant trend towards higher IOPs and worse BCVAs in eyes with increasing degrees of angle closure, all groups exhibited a wide range of IOPs and BCVAs, suggesting that neither can act as an accurate surrogate for gonioscopy. Though a statistically significant correlation between age or gender and angle status was not found in this study, patients in this study self-identifying as Black (66 % of study population) had a disproportionate ratio of those having either partially closed or completely closed angles. The exact reason behind this finding is unknown, but possible contributors may

include differences in access to resources, racial disparities in health care, and/or a difference in neovascular load or inflammatory response. Though racial disparities in health care is an extensively studied and well-recognized determinant of disease outcomes in the fields of cardiology, obstetrics, and oncology,[17–21] there have not been any studies examining the role of race in the outcomes of neovascular glaucoma.

Eyes with increasing extent of angle closure also trended towards belonging to new patients and presenting symptomatically to the ED, which are perhaps indicators of a delay in seeking medical care. Additionally, we found that this group of eyes trended towards being phakic, possibly suggesting the notion that a cataract rather than an intraocular lens implant may be a sign of delayed or limited access to medical care. Further research is needed to examine these patients to reduce the barriers to accessing care or maintaining access to care.

Finally, although the group with completely closed angles had the smallest proportion of eyes belonging to established patients, this group paradoxically had the greatest percentage of eyes who had undergone prior PRP and PPV, suggesting that even among patients who had previously established care, some have aggressive disease that can progress despite prior interventions. As such, eyes with underlying retinal conditions require frequent, lifelong follow-up even after undergoing prior interventions, because development of new neovascularization of the iris or angle despite apparent prior retinal laser is still possible.[22] If these eyes are caught in the early stages when the angle is still open, less aggressive interventions such as medical therapy and angle-based procedures, rather than more drastic surgical interventions, may be sufficient.

Rather than viewing neovascular glaucoma as a single entity with oftentimes poor outcomes, the authors propose that the clinical features, management plan, and predicted response to treatment can be stratified based on the anterior chamber angle status, and identify clinical features which may predict the angle morphology in NVG eyes at the time of diagnosis. The angle anatomy cutoffs used in this study was taken from the study by Wakabayashi, where eyes with <75 % PAS had normalization of IOP with anti-VEGF, whereas 93 % of eyes with ≥ 75 % PAS required emergent IOP-lowering procedures.[4] As such, even the two separate eyes in the same NVG patient can be approached uniquely. In fact, the authors noted that in several cases during this case series, the diagnosis of early, open-angle neovascular glaucoma occurred solely because the patient presented for the symptomatic, contralateral eye with complete synechial closure.

Limitations to this study include its retrospective nature, single-site nature, and limited sample size. Though this study did not find a statistically significant association between age, gender, or underlying etiology and angle status, it is likely that our sample size was not powered to detect such differences. Additionally, as a cross-sectional analysis of angle morphology when they are first diagnosed with NVG, this study examines the clinical characteristics and angle anatomy at a single point in time and does not include longitudinal outcomes data, since many patients included in the analysis were lost to follow-up or treated by other providers who do not stratify by angle status. Future directions include examining outcomes in the three aforementioned groups depending on angle morphology at presentation, outcomes of NVG eyes according to angle morphology, and eventually developing standardized treatment protocols accordingly. Lastly, further studies are needed to improve the generalizability of these study results across various practice settings and populations.

5. Patient consent

Written consent to publish this case series has not been obtained. This report does not contain any personal identifying information.

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Precis

To identify clinical features which may predict the angle status of a large cohort of NVG eyes at the time of initial diagnosis, and to advocate that all patients with NVG require a gonioscopy.

CRediT authorship contribution statement

Jessie Wang: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Jacob Kanter:** Writing – review & editing, Methodology, Investigation, Data curation. **Mary Qiu:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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