Angle Closure in Caucasians—A Pilot, General Ophthalmology Clinic-based Study

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Purpose: To assess the rate of clinically significant angle closure in a predominantly Caucasian, clinic-based population, and consequently find out whether gonioscopy should be included in the routine ophthalmic examination.

Methods: Patients aged ≥ 40 years with hyperopia ≥ 1 D were consecutively recruited in a community general ophthalmology clinic. Detailed darkroom gonioscopy was done, and primary angle closure was diagnosed if there was iridotrabecular apposition > 180 degrees not secondary to an identifiable ocular disorder. Biometric parameters were measured and compared between the eyes with and without angle closure.

Results: Eighty-four eyes from 84 patients (aged 61.3 ± 8.9 y) were enrolled. There were 52 female (62%) and 32 male. Fourteen patients (16.7%) were diagnosed with angle closure. A statistically significant difference was observed between the eyes with and without angle closure in mean axial length (22.07 ± 0.72 vs. 22.61 ± 0.97, $P = 0.028$), anterior chamber depth (ACD) (2.45 ± 0.33 vs. 2.89 ± 0.32, $P < 0.001$), and lens thickness (4.97 ± 0.3 vs. 4.62 ± 0.4, $P = 0.002$). Degree of hyperopia was marginally significant (3.13 ± 2.3 vs. 2.45 ± 1.5, $P = 0.09$). In a logistic regression model, only ACD remained statistically significantly different ($P = 0.016$). We tested the ability of ACD to distinguish eyes with angle closure. The area under the receiver operating characteristic curve was 0.824; using a cutoff ACD value of 2.65 mm, sensitivity was 0.786 with a specificity of 0.812.

Conclusions: Clinically significant angle closure, mandating close follow-up or preventive procedures, may be more common in Caucasians than currently thought. We recommend that gonioscopy should be included in the routine ophthalmic examination of all adults with hyperopia.

Key Words: glaucoma, angle closure, Caucasians

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In recent years, there has been an increase in interest and research on the prevalence, characteristics, and treatment of angle closure glaucoma (ACG) in Asians.[1–5] In Caucasians, this disease is commonly regarded as rare,[6,7] and accordingly relatively little data has been published. The paucity of data on the prevalence of angle closure and ACG and the possibly wrong conception that it is rare in non-Asians may be key factors that contribute to underuse of gonioscopy, the current gold standard for diagnosis of angle status, during the ophthalmic examination.[8,9] In this study, we use the word "Caucasian" to indicate what is commonly referred to as "White" race, or more broadly defined by the Merriam-Webster dictionary as "a race of humankind native to Europe, North Africa, and southwest Asia and classified according to physical features—used especially in referring to persons of European descent having usually light skin pigmentation". (http://www.merriam-webster.com/dictionary/caucasian)

Indeed, some studies suggest that this form of glaucoma is more common in Caucasians than commonly thought.[10,11] However, the prevalence of the preglaucomatous stages of iridocorneal apposition remains unknown. In the absence of this data, it is difficult to provide clear guidelines with regard to the necessity and use of gonioscopy during the routine ophthalmic examination. Such guidelines and proper practice are important in view of current thought[12,13] and few studies[14–18] that suggest that ACG is preventable if angle closure is diagnosed early and treated with angle-widening procedures such as laser iridotomy. More support for the need of early diagnosis comes from studies that indicate that if angle closure is diagnosed when glaucomatous optic neuropathy has already occurred, widening the angle is no longer effective in lowering intraocular pressure (IOP), presumably because of irreversible trabecular meshwork damage that had occurred during years of chronic iris-trabecular meshwork apposition.[19–21]

The purpose of this pilot study was to assess the rate of angle closure in a predominantly Caucasian, clinic-based population, and to use this data for issuing an effective, evidence-based recommendation on whether gonioscopy should be included in the routine ophthalmic examination. Our study question could be phrased differently, that is, what is the chance of missing a clinically significant potentially treatable angle closure when not including gonioscopy in the routine examination? As is logical for any initial screening study of an infrequent condition, we focused this pilot prevalence study on what we thought was a higher-risk—hyperopic subpopulation, extrapolating from literature on non-Caucasians showing that angle closure is more prevalent in hyperopic eyes.[22–24] Our study hypothesis was that asymptomatic angle closure is clinically significantly prevalent in this population. A secondary study purpose was to identify anatomic factors that determine why only certain hyperopic eyes develop angle closure.

METHODS

This prospective cross-sectional study took place in a primary community general ophthalmology clinic serving the Ramla area in central Israel. This closely fits our study

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purpose, which is to provide the ophthalmologist with data regarding the prevalence of angle closure among his patients, rather than in the general population. However, as this ophthalmology clinic is the only one serving the population in the region of the city of Ramla, and as it provides general services (such as screening for systemic hypertension and diabetes and prescribing spectacles), we think there is only little to differentiate this study population from the general population. The study was approved by the Institutional Review Board of the Assaf Harofe Medical Center and followed the tenet of the Declaration of Helsinki. Each patient who came to the clinic who was aged 40 years or older had autorefraction performed by a technician (ARK-700A, Nidek, Japan). If the spherical equivalent in at least 1 eye was at least 1 diopter (D) of hyperopia, the patient was offered an opportunity to participate in the study.

After written informed consent, each patient had subjective refraction and slit-lamp biomicroscopic examination including nondilated stereoscopic fundus examination with a 60-D lens. IOP was measured with a Goldmann tonometer. Gonioscopy was done by a single experienced glaucoma specialist (Y.B.) in a completely darkened room using a 4-mirror lens (G-4, Volk Optical Inc.) and high magnification ($\times 16$). A 1 mm slit was used while avoiding shining light directly inside the pupil. In each quadrant, the angle width was graded according to Shaffer classification. If the pigmented trabecular meshwork was not visualized in primary position, the patient was instructed to look in the direction of the mirror being visualized, so that the angle details could be seen over the iris convexity, to avoid wrongly overdiagnosing angle closure, when indeed it was open. If the angle details still were not seen, the cornea was indented with the gonio lens attempting to force open an appositionally closed angle. If this was not successful, synechial closure was diagnosed. As sometimes pigmented Schwalbe line may be mistaken for pigmented trabecular meshwork (for photo example see http://www.drbarkana.co.il/Site/My_gonioscopy_page.html), with the result being missdiagnosis or underdiagnosis of angle closure, indentation was performed in all the eyes, even if the angle seemed open, so that this distinction could be unequivocally made. If the pigmented trabecular meshwork was not seen without indentation for at least 180 degrees, due to either iridocorneal apposition or synechiae, primary angle closure (PAC) was diagnosed and the patient was referred for laser iridotomy. Glaucomatous nerve damage was not specifically sought in this study; therefore, we referred to all such eyes as eyes with angle closure.

Keratometry (ARK-700A, Nidek, Japan) and central corneal thickness (DGH 55 Pachmate, DGH Technology Inc.) were measured. Contact ultrasound biometry (Axis II PR software version 3.05, Quantel Medical, France) was performed and anterior chamber depth (ACD), lens thickness, and axial length were recorded as the mean of 10 good quality measurements.

Exclusion criteria were earlier intraocular surgery or laser procedure, astigmatism >3 D, and any anterior segment disorder that could be the source for secondary angle closure or could interfere with viewing of the angle or biometric measurements.

One eye per patient was included in the study. If both the eyes were eligible, we enrolled the more hyperopic eye, and if refraction was symmetrical than 1 eye was chosen at random.

The clinic that was the setting for this study serves a population that can be characterized as mainly Caucasian, with predominance of immigrants from countries that constituted the Soviet Union. For the purpose of this study we categorized the origin of each patient to 1 of 4 categories—Europe, West Asia, North Africa and Middle East, and (Jews from) India.

In the absence of earlier data on the prevalence of asymptomatic angle closure in Caucasians, we planned this pilot study to obtain an initial assessment, without earlier calculating a target sample size. The Mann-Whitney test was used to compare continuous variables, and the χ^2 and Fisher exact test for noncontinuous variables. Significance was determined if the P value was under 0.05. Parameters that differed significantly were included in a logistic regression model. All analysis was carried out using SPSS for windows.

RESULTS

We enrolled 84 eyes of 84 patients. To enroll this number of >1 D adult hyperopia, we needed to screen approximately 560 patients.[25] There were 52 female (62%) and 32 male. Mean age was 61.3 ± 8.9 years (range, 40 to 82 y). For the main outcome measure, 14 patients (16.7%) were diagnosed with angle closure and referred to have laser iridotomy. Table 1 shows the demographic and ocular parameters for the whole study population and those eyes with and without angle closure. In the univariate analysis, axial length, ACD, and lens thickness were statistically significantly different between the eyes with and without angle closure ($P = 0.028$, $P < 0.001$ and $P = 0.002$, respectively). Refraction reached borderline significance. These 4 parameters were then included in a logistic regression multivariate model. In this multivariate analysis, only ACD remained statistically significantly different between the 2 groups ($P = 0.016$).

On the basis of this result, we then examined the ability of ACD to diagnose eyes with angle closure using a receiver operating characteristic (ROC) curve, in which both sensitivity and specificity are plotted on the same graph. This is shown in Figure 1. The area under the ROC curve was 0.824. Using a cutoff ACD value of 2.65 mm, sensitivity was 0.786 with a specificity of 0.812. Table 2 shows the distribution of angle width in the study population.

DISCUSSION

We conducted this pilot study to obtain an initial assessment of the prevalence of angle closure in a predominantly Caucasian clinic-based population. We did not have an estimate of the expected results, as little research has focused on the prevalence and characteristics of angle closure and ACG in Caucasians. In the past, interest might have been diverted partly due to earlier report in large series on the very low prevalence of primary ACG (PACG).[6,7] Although these results are often quoted, we question the methodology of these studies and thus challenge their conclusions. For example, in the Beaver Dam eye study, in which a 0.04% prevalence of PACG was reported, patients were examined by technicians rather than ophthalmologists, gonioscopy was not carried out, and how exactly ACD was used to diagnose angle status is not specified.[6] In the Melbourne study, in which a 0.06% prevalence of PACG was reported, no details at all are provided with regard to the method of diagnosis of angle

TABLE 1. Demographic and Ocular Parameters for the Whole Study Population, and Only Patient/Eye With and Without Angle Closure

Parameter	Whole Study Population (n = 84)	Angle Closure (n = 14)	Open Angles (n = 70)	*P*
Age (y)	61.3 ± 8.9	62.6 ± 10.4	61.0 (8.7)	0.371*
Sex				
Male (%)	32 (38.1)	4 (28.6)	28 (40)	0.421†
Female (%)	52 (61.9)	10 (71.4)	42 (60)	
Origin, no. (%)‡				
Europe	22 (26.2)	4 (28.6)	18 (25.7)	0.772§
North Africa and Middle East	24 (28.6)	3 (21.4)	21 (30)	
West Asia	27 (32.1)	6 (42.9)	21 (30)	
India	11 (13.1)	1 (7.1)	10 (14.3)	
Refraction (spherical equivalent) (D)	2.57 ± 1.7	3.13 ± 2.3	2.45 ± 1.5	0.09*
IOP (mm Hg)	16.8 ± 2.7	18.2 ± 2.7	16.5 ± 2.6	0.034*
Anterior chamber depth (mm)	2.82 ± 0.36	2.45 ± 0.33	2.89 ± 0.32	< 0.001*
Axial length (mm)	22.52 ± 0.95	22.07 ± 0.72	22.61 ± 0.97	0.028*
Lens thickness (mm)	4.67 ± 0.41	4.97 ± 0.3	4.62 ± 0.40	0.002*
Central corneal thickness	546.3 ± 28.9	540.3 ± 37.5	547.6 ± 27.0	0.601*

P value is for univariate comparison between these 2 subgroups.
*Mann-Whitney test.
†χ^2 test.
‡Europe: Russia, Poland, Ukraine, Georgia, Bulgaria, Belgium, France North Africa and Middle East: Morocco, Israel, Turkey, Yemen, Tunisia, Egypt, Iraq, Iran West Asia: Uzbekistan, Iserbaijan, Tajikistan India: India.
§Fisher exact test.
IOP indicates intraocular pressure.

status.[7] Significantly higher prevalence rates were reported in 2 population studies in which arguably better methodology was used. In the Egna-Neumarkt study, 4297 patients from northern Italy were screened for glaucoma by ophthalmologists, and suspects were subsequently examined for a definite diagnosis of glaucoma, including gonioscopy.[10] PACG was reported in 0.6% patients. In a similarly conducted study in South Brazil, among 1636 patients, 71.5% of them were Whites, prevalence of PACG was 0.7%.[11]

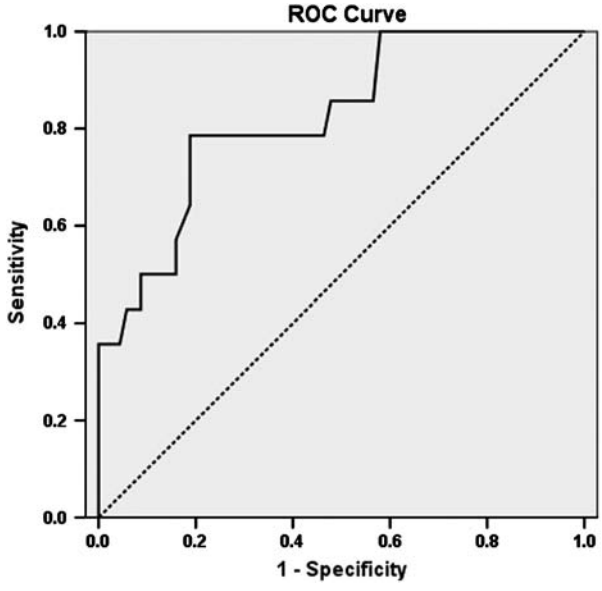

FIGURE 1. Receiver operating characteristic (ROC) curve showing sensitivity and specificity for anterior chamber depth as a diagnostic criterion for eyes with angle closure. The area under the curve was 0.824. With a cutoff value of 2.65 mm, sensitivity was 0.786 with a specificity of 0.812.

The prevalence of preglaucomatous angle closure, in absolute number and relative to ACG, has not been investigated in Caucasians. In 1 study, on a non-Caucasian population from India, among 3850 patients whose screening examination included darkroom gonioscopy with a 4-mirror lens, PAC suspect (PACS—iridotrabecular apposition in the absence of other signs) was diagnosed in 7.2%, PAC (PAC—PACS with accompanying elevated IOP or anterior synechiae) in 2.75%, and PACG (PAC in the presence of glaucomatous neuropathy) in 0.88% patients.[23] Thus, angle closure in general was 12.3 times more common than PACG. In a study—on another non-Caucasian population from China, among 1405 patients, 10.2% were diagnosed with occludable angle, and 1.5% with PACG, a ratio of 6.8.[3] From these figures on the ratio of preglaucoma angle closure to ACG in non-Caucasians, and the prevalence figures from the 2 more recent studies on PACG in Caucasians mentioned above, the extrapolated prevalence of angle closure in Caucasians would range from 4.1% (0.6 × 6.8) to 8.6% (0.7 × 12.3).

We now compare these extrapolated figures to our observations. A large study in a population very similar to ours has shown that 15.2% of adults aged 40 years or older had hyperopia of 1 D or greater.[25] Thus, we assume that the angle closure prevalence we found among patients with hyperopia (16.7%) represents 2.5% (15.2% × 16.7%) of the general population. As angle closure is rare among myopes[24,26,27] and patients with hyperopia < 1 D were not included in our study, the extrapolated prevalence for the total population is likely slightly higher. This extrapolated prevalence is somewhat lower but on the same order of magnitude as the figures calculated above based on available literature (4.1% to 8.6%).

What are the clinical consequences of our findings? If our findings are confirmed, then asymptomatic angle closure in Caucasians is not rare, but rather a significant public-health issue, and that is how it should be approached by ophthalmologists and taught to residents. For example,

TABLE 2. Number (and Percentage) of Quadrants According to Shaffer Angle Grading in all Eyes (n=84)

Grading	Superior Quadrant	Nasal Quadrant	Inferior Quadrant	Temporal Quadrant
0	13 (15.5)	11 (13.1)	12 (14.3)	12 (14.3)
Slit	4 (4.8)	1 (1.2)	3 (3.6)	0 (0)
I	21 (25)	7 (8.3)	6 (7.1)	7 (8.3)
II	22 (26.2)	34 (40.5)	20 (23.8)	34 (40.5)
III	15 (17.9)	22 (26.2)	31 (36.9)	22 (26.2)
IV	9 (10.7)	9 (10.7)	12 (14.3)	9 (10.7)

0 indicates closed; I, 10 degrees; II, 20 degrees; III, 30 degrees; IV, $\geq$ 40 degrees; Slit, $\leq$5 degrees.

in 1 editorial it was stated that all eyes with evidence for angle closure require laser iridotomy.[12] More recently, the consensus meeting of the world glaucoma association on angle closure and ACG concluded that all eyes with PAC and PACG require laser peripheral iridotomy, and that "consideration can be given to laser iridotomy in eyes with iridotrabecular apposition"[13] (also available at http://www.worldglaucoma.org). Whereas in some populations up to 20% of eyes may have asymptomatic iridotrabecular apposition,[4] confirmation of our findings may require rethinking of the recommendation to treat all such eyes. We propose that the main emphasis should be on the proper diagnosis of definite angle closure (as opposed to less decisive diagnoses such as "narrow angle" or "occludable angle"). Despite the emergence of imaging devices such as high-frequency ultrasound and anterior segment optical coherence tomography, these are expensive and not widespread and therefore diagnosis remains dependent on properly performed and interpreted gonioscopy. Our results suggest that if gonioscopy is not performed as part of a routine ophthalmic examination in a Caucasian hyperopic adult, there is a chance of 1:6 that clinically significant angle closure will be missed. Thus, our findings combined with available literature lead us to recommend that gonioscopy should be included in the examination of all these patients.

It is important to note that comparing published rates of angle closure is not a simple matter because of nonuniform terminology and methodology. Some studies report separately the prevalence of PACS, PAC, and PACG while others combine all these clinical forms into a single prevalence of "occludable" or "narrow" angles. The extent of iridotraecular apposition required to define these terms varies from 90 to 270 degrees, whereas even a single anterior synechiae may be sufficient for diagnosis.[11] As most other studies on the prevalence of angle closure, our study is based on findings during gonioscopy. Unfortunately, the technique and interpretation of this examination are subjective and not standardized. As mentioned in the methods section, several attributes pertaining to performance of gonioscopy and interpretation of its findings, in addition to observer's experience and the type of lens used, can affect its results. One example is ambient lighting conditions during examination, as it has been convincingly shown that an angle closed in the dark can appear open if examined under normal lighting conditions and thus the diagnosis of iridotrabecular apposition is missed.[28–30] In this study, all examinations were performed by a single investigator, using a technique that carefully aims to avoid erroneous underestimation and overestimation of angle closure. Finally, our study was clinic based and not a population survey. However, as the setting was a primary care clinic serving the general population for common visual and ophthalmic conditions, we do not think this is a major confounding factor. Of course the generalizability of our results to other Caucasian populations requires validation by further study in larger cohorts.

Maximizing the efficiency of any screening initiative requires optimal definition of the population at-risk. Should screening be limited to women, in which all forms of angle closure are significantly more frequent?[31–34] In 1 screening study, 12 of 1636 patients were diagnosed with PACG—all of them were women.[11] In another study, 26 of 4176 patients had PACG—22 of them were women.[10] In our small study, the 4 male patients diagnosed with angle closure accounted for 29% of those with angle closure, and 12.5% of males in the study population. Thus, we cannot conclude that screening can be optimized by exclusive examination of females. As 2 of 14 patients with angle closure had hyperopia between 1 and 1.5 D, we also cannot recommend limiting screening to eyes with greater hyperopia, but this requires validation in larger cohorts.

Our findings that hyperopic eyes with angle closure had statistically significantly shorter axial length, shallower ACD and a thicker lens compared with hyperopic eyes with open angles are in accord with earlier reports on these differences, albeit in the general (not only hyperopic) population.[24,35–37] Of these parameters, in our study ACD was the most robust as it was the only significantly different parameter in the multivariate analysis. This is consistent with the common notion that ACD is the single best predictor of angle closure and consequently it is being assessed as a screening tool in large population studies.[38–42] According to standard procedure when working with ROC curves, the cutoff of 2.65 mm was chosen subjectively to reflect the point which provides sensitivity and specificity which are most appropriate for the specific clinical question, in our case screening for angle closure. By definition, a cutoff that provides a higher sensitivity will yield a lower specificity, and vice versa. We thought that for potentially using ACD (measured with ultrasound by a technician) for mass screening of angle closure, either sensitivity or specificity much lower than 80% would not be adequate, and therefore we chose a cutoff of 2.65 to reflect this. Still, relying only on this parameter may not be optimal in view of our ROC curve results, which are similar to those in 2 large studies on Asian populations which evaluated the ability of ultrasonically measured ACD to diagnose angle closure in a general population and reported ROC curve areas of 0.86 to 0.9 and 0.81.[40,41] For the purpose of population screening, where it may not be feasible to adequately perform gonioscopy, future studies should evaluate the diagnosis of angle closure using ACD combined with other demographic, refractive, or biometric parameters.

In conclusion, we found a high rate of angle closure among hyperopic adults in a predominantly Caucasian clinic-based population. We recommend that ophthalmologists include gonioscopy as part of the general ophthalmic examination in these patients to diagnose clinically significant angle closure. The technique and interpretation of gonioscopy needs to be standardized and ubiquitously included in the ophthalmic training.

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