• Investigation •

Effects of primary glaucoma on sleep quality and daytime sleepiness of patients residing at an equatorial latitude

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Abstract

● **AIM:** To investigate the impact of primary glaucoma on sleep quality and daytime sleepiness of patients.

● **METHODS:** Prospective cross-sectional study with consecutive sampling in South-East Asian population was performed. Validated questionnaires: the Pittsburg Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) were administered prospectively. Subjects with non-glaucomatous optic neuropathy or concomitant retinal pathology were excluded. Glaucoma severity was based on HVF 24-2 perimetry. Binocular single vision was represented based on the better eye. Frequency of and predictive factors for poor sleep quality and excessive daytime sleepiness were compared.

● **RESULTS:** A total of 79 primary open angle glaucoma (POAG), 27 primary angle-closure glaucoma (PACG) patients, and 89 controls were recruited. PACG patients had higher median PSQI scores (P=0.004) and poorer sleep quality (P<0.001). Compared to controls, PACG patients were 3.34 times more likely to have poor sleep quality (P=0.008), which remained significant after adjustment for demographics (P=0.016) and predictive variables (P=0.013). PACG patients have poorer sleep quality when visual acuity (VA) was 6/15 or worse (P=0.009). Univariate and multivariate analysis of predictive variables for poor sleep quality and daytime sleepiness did not find statistical significance.

● **CONCLUSION:** PACG patients have poorer sleep quality but not daytime sleepiness. This is important in South-East Asian population with heavy disease burden. Evaluations on sleep disturbances can be considered to provide more holistic care.

● **KEYWORDS:** sleep disturbances; primary glaucoma; intrinsically photosensitive retinal ganglion cells; daytime sleepiness; sleep quality; South-East Asia

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INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide[1], with heavy disease burden especially in Asia, accounting for up to 60% of the world's glaucoma cases. In South-East Asia, the prevalence rate is about 4%, with a projected increase of people with glaucoma by more than 50% in 2040[2]. The underlying pathology in glaucomatous optic neuropathy and progressive visual loss is the degenerative loss of retinal ganglion cells[3]. This includes the loss of intrinsically photosensitive retinal ganglion cells (ipRGCs), which has been demonstrated in both animal models and humans[4-5]. ipRGCs are a class of ganglion cells that express melanopsin, and mediates non-visual functions of the eye, such as entrainment of circadian rhythm, pupillary light reflex and modulation of melatonin secretion[6-7]. Sleep disturbances are reported to occur more frequently in patients with blindness or severe visual loss compared to the general population[8-9], but the cause-and-effect relationship between varying ophthalmic conditions and loss of circadian regulation has been inconclusive. Likewise, there is limited evidence on the impact glaucoma has on sleep quality or circadian rhythm. With the death of ipRGCs in glaucoma, such an association is highly plausible[10], but few studies have explored it[10-13].

In this study, we aim to examine the effect glaucomatous damage has on sleep quality in a South-East Asian population

by comparing patients with glaucoma to normal controls using validated sleep quality questionnaires.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the domain specific review board at National Healthcare Group, Research and Development Office, Singapore. Informed consent was obtained from all individual participants included in the study.

Subjects This was a prospective cross-sectional study held in a tertiary referral centre in Singapore over 12mo. Consecutive sampling of the subject population was performed. All the subjects underwent complete ophthalmologic examinations, including Snellen best-correct visual acuity (BCVA) measurements, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement and a dilated fundoscopic examination with a 78-diopter lens, and a medical history review. Glaucoma patients underwent standard automated perimetry using the humphrey visual field (HVF), Swedish interactive threshold algorithm (SITA Standard 24-2; Carls Zeiss Meditec, Inc., Dublin, CA, USA).

The diagnoses of primary open angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) were made by glaucoma specialists in accordance with diagnostic criteria of reproducible abnormal HVF with corresponding glaucomatous optic disc appearance, retinal nerve fiber layer defect, and focal or diffuse neuroretinal rim loss[14]. Gonioscopy was performed for all patients. Patients with open angles (<180 degrees of irido-trabecular apposition on gonioscopy) along with glaucomatous optic neuropathy were diagnosed to have POAG. Normal tension glaucoma (NTG) is a subset of open angle glaucoma where a group of patients suffer from glaucomatous damage even though they have relatively low IOP[15]. However, as a formal diagnosis of NTG requires a diurnal measurement of IOP, we will classify the POAG and NTG patients as a single group in this study[16]. Patients with closed angles (>180 degrees of irido-trabecular apposition on gonioscopy) along with optic neuropathy were diagnosed to have PACG[17]. Healthy control subjects had an IOP≤21 mm Hg and a normal optic disc appearance. Glaucoma severity is based on mean deviation (MD), which is the average of the deviations across all test locations on the HVF. Patients are grouped into 3 groups based on glaucoma severity as follows: mild (MD better than -6), moderate (MD between -6 and -12), severe (MD worse than -12).

Subjects were all above 21 years old and below 99 years old. Patients were excluded if they had any concomitant retinal, corneal or orbital diseases (*e.g.* diabetic retinopathy, age-related macular degeneration) which could confound visual field outcomes or sleep quality assessment. Patients with chronic medical conditions (diabetes mellitus, cancer, stroke, rheumatoid arthritis, obstructive sleep apnoea), psychiatric related disorders (known depression, psychotic disorders), and patients involved in shift work or previous trans meridian travel within the last 3mo were also excluded as these could be potential cofounders in evaluating sleep dysfunction.

Binocular Single Vision There are various models as to how binocular single vision is determined in glaucoma patients, one of which is a model proposed by Gutierrez[18] in evaluating the relationship between visual field sensitivity and quality-of-life assessments. This particular model assumes the eye with the better overall visual field sensitivity (determined by MD) determines the binocular visual field properties of glaucoma patients. The authors found that MD of the better eye correlated better with quality-of-life measures than the MD of the worse eye. Hence, we decided to compare the better eyes between the glaucoma patients and controls for a representation of binocular single vision.

Evaluation of Sleep Quality Sleep quality was assessed in each group using the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. It has been validated and used in clinical research[19]. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields a global score. A global PSQI score greater than 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing good and poor sleepers. A cut-off score of 5 was used to determine poor sleep quality in our study. Due to the multi-ethnic nature of the cohort, English, as well as translated versions for Mandarin and Malay were used in this study. All Indian patients were able to understand the English version. The Mandarin version of the PSQI was previously validated in a Chinese study[20]. Although the Malay version has not been validated, it has been used in prior studies on sleep quality evaluation in the South-East Asian Malay population[21-22].

To screen for undiagnosed depression as a possible confounder for poor sleep quality, the Patient Health Questionnaire 2 (PHQ-2) was used. The PHQ-2 enquires about the degree to which an individual has experienced depressed mood and anhedonia over the past two weeks as a screen for depression. A cut-off score of 3 or more which gives a sensitivity of 82.9% and specificity of 90.0% for screening of major depressive disorder was used in this study[23].

Evaluation of Daytime Sleepiness The Epworth Sleepiness Scale (ESS) was used to assess excessive daytime sleepiness (EDS). The PACG is a self-rated questionnaire that measures daytime sleepiness, which is validated and used in clinical research[24-25]. There are eight questions which rate the

chances that respondents would fall asleep in conditions commonly encountered in daily life. A total score of 9 or less was considered to be normal, 10-15 would indicate mild to moderate EDS and more than 16 would indicate severe EDS. Similar to the PSQI, validated versions of the English, as well as translated versions for Mandarin and Malay ESS were used in this study. The Mandarin version of the ESS has been validated in many prior studies[26-28], while the Malay version has not been validated. The questionnaires were retrieved from ePROVIDE™[29], the official site for distribution of the ESS and leader in the dissemination of Clinical Outcome Assessments information to the scientific community.

Singapore Climate Singapore, where this study is carried out, is located near the equator. It has a typically tropical climate, with abundant rainfall, high and uniform temperatures, and high humidity all year round. The length of its day is relatively constant throughout the year, and thus so is the amount of sunshine it receives[30].

Statistical Analyses Sample size was estimated based on the only pilot study available at the time of study initiation by Wang *et al*[11], which also used PSQI to evaluate sleep quality. A sample size of 37 participants for the PACG group, 89 for the POAG group and 89 for the control group would provide 90% power to reject the null hypothesis that the proportion of subjects with poor sleep quality will be similar amongst the groups, at a two-sided type I error of 5%.

Analyses of descriptive statistics were conducted. Assumption of normality was assessed by inspecting histograms and using the Shapiro-Wilk test. The Kruskal-Wallis test was used for continuous variables. Pearson Chi-square (χ^2) or Fisher's exact test was used for categorical variables. Univariate and multivariate logistic regression was performed to examine the association between predictive factors, such as grouping (control, POAG, PACG), visually significant cataract, usage of beta-blocker, possible depression, visual acuity (VA), and glaucoma severity (based on MD) with poor sleep and EDS severity.

Statistical analysis was carried out using IBM SPSS Statistics (version 22, IBM Corp, New York, USA), and R (version 3.1.2, The R Foundation for Statistical Computing). A *P*-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

A total of 195 subjects were enrolled into the study. The population comprised of 79 POAG patients and 27 PACG patients, and 89 controls. Planned sample size for the glaucoma subjects was not obtained due to time and manpower limitations during the course of the study. Demographic data and descriptive statistics are shown in Table 1. The median PSQI score of PACG patients was significantly higher than that of controls or POAG patients (P=0.004), and the proportion of PACG patients with poor sleep quality was significantly greater than that of controls or POAG patients (P<0.001). Glaucoma severity in the better eye as qualitatively shown by MD was similar in both PACG patients and POAG patients. Amongst the glaucoma patients, comparison of MD severity did not show statistical significance in terms of daytime sleepiness or sleep quality. There was no daytime sleepiness amongst all subjects based on assessment using the ESS instrument. Presence of depression as measured by the PHQ-2 resulted in poorer sleep quality (P=0.015; Table 2). Comparison of VA in the better eye amongst the controls and glaucoma subjects showed that PACG patients had poorer sleep quality when VA is 6/15 or worse (P=0.009) with a similar trend noted in POAG patients, though not statistically significant (Table 3).

Using univariate logistic regression analysis, compared to controls, a PACG patient is 3.34 times more likely to have poor sleep quality (P=0.008). This remained significant after adjustment for age, gender and depression (P=0.016). Univariate and multivariate analysis of the predictive variables for poor sleep and daytime sleepiness did not find statistical significance for presence of visually significant cataracts, use of beta blockers or alpha-agonist, VA and glaucoma severity in the better eye. Multivariate analysis adjusted for the above predictive variables found that PACG patient were 12.8 times more likely to suffer from poor sleep quality (P=0.013; Table 4). Amongst the PACG patients, patients with more severe glaucoma were 7.18 times more likely to suffer from poor sleep quality when adjusted for glaucoma severity of the better eye (P<0.001; Table 5).

DISCUSSION

In this study, we found that the PACG subjects were more likely to have poorer sleep quality than POAG subjects or controls. POAG patients did not have poorer sleep quality when compared to healthy controls. This differs from Wang *et al*[11] who found poorer sleep quality in both PACG and POAG patients. However, Wang *et al*[11] did find that PACG patients had poorer sleep quality than the POAG patients in the age interval of 61-80, which is similar to the age demographics of our glaucoma patients. He suggests that acute IOP elevation in some PACG patients in acute-angle closure attacks may cause ischemic-reperfusion damage to the whole retina (including rods and cones) as compared to POAG where chronic IOP elevation may have only damaged the ganglion cells and their axons, which may have resulted in lower photic input to the ipRGCs in PACG patients.

We also found that PACG patients with poorer VA were more likely to have poorer sleep quality, with POAG patients having a similar trend (though not statistically significant). Glaucoma severity does not result in poorer sleep quality

Table 1 Demographic and clinical characteristics of healthy controls and subjects with glaucoma

Parameters	Control (*n*=89)		POAG (*n*=79)		PACG (*n*=27)		*P*
Median age, y (IQR)	66	(57 to 69)	71	(64 to 76)	62	(56.5 to 69.5)	
Gender, *n* (%)							
Male	34	(38.2)	51	(64.6)	15	(55.6)	
Female	55	(61.8)	28	(35.4)	12	(44.4)	
Race, *n* (%)							
Chinese	76	(85.4)	68	(86.1)	25	(92.6)	
Malay	3	(3.4)	4	(5.1)	1	(3.7)	
Indian	9	(10.1)	6	(7.6)	1	(3.7)	
Others	1	(1.1)	1	(1.3)	0	0	
Median scores (IQR)							
PSQI (Sleep quality)	4	(3 to 6)	3	(2 to 5)	6	(3.5 to 9)	0.004[a]
ESS (Excessive Daytime Sleepiness)	5	(3 to 9)	5	(2.5 to 8)	4	(3 to 8)	0.959[a]
PHQ-2 (Depression screen)	0	(0 to 1)	0	(0 to 1)	0	(0 to 1)	0.251[a]
Poor sleep quality, *n* (%) (PSQI>5)	30	(33.7)	17	(21.5)	17	(63.0)	<0.001[b]
ESS Severity, *n* (%)							0.334[c]
Mild (ESS≤9)	70	(78.7)	69	(87.3)	21	(77.8)	
Moderate (ESS 10-14)	14	(15.7)	8	(10.1)	6	(22.2)	
Severe (ESS≥15)	5	(5.6)	2	(2.5)	0	(0)	
Possible depression, *n* (%) (PHQ-2>2)	7	(7.9)	13	(16.5)	1	(3.7)	0.089[b]
Glaucoma severity of better eye, *n* (%)							0.821[b]
Mild (MD<6)		-	50	(64.1)	17	(70.8)	
Moderate (MD 6-12)		-	13	(16.7)	3	(12.5)	
Severe (MD>12)		-	15	(19.2)	4	(16.7)	
Mean MD of better eye (SD)		-	-5.89	(7.0)	-6.33	(7.9)	0.791[d]

IQR: Interquartile range; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; PHQ-2: Patient Health Questionnaire 2; MD: Mean deviation; SD: Standard deviation. [a]Kruskal-Wallis test; [b]Pearson Chi-square test; [c]Fisher's exact test; [d]Independent samples *t*-test.

Table 2 Comparison of sleep quality amongst controls and glaucoma patients (adjusted for age, gender and possible depression)

Poor sleep quality (No/Yes: PSQI>5)	OR	95%CI	*P*	Full model adjusted OR	95%CI	*P*
Age, y [at most 60 (ref)]						
More than 60	0.58	0.31-1.11	0.099	0.637	0.32-1.28	0.205
Gender						
Male (ref)						
Female	1.30	0.71-2.37	0.390	1.12	0.57-2.18	0.748
Group, control (ref)						
POAG	0.54	0.27-1.08	0.081	0.86	0.25-3.02	0.819
PACG	3.34	1.36-8.19	0.008	5.60	1.37-22.8	0.016
Possible depression (PHQ-2)						
No (ref)						
Yes	3.13	1.24-7.88	0.015	5.067	1.86-13.82	0.002

OR: Odds ratio.

amongst glaucoma patients. VA is a measure of central VA and poor VA can be due to several factors, such as the presence of cataracts or glaucomatous damage affecting central vision. Several studies have found similar observations of sleep dysfunction amongst the visually impaired[8-9]. Lockley *et al*[8] found that most blind people with no perception of light experience continual circadian desynchrony through a failure of light information to reach the hypothalamic circadian clock, resulting in cyclical episodes of poor sleep and daytime dysfunction. Wee and van Gelder[31] found that optic nerve disease amongst the blind led to increased daytime sleepiness. Population studies in the United States, Korea, South Africa

Table 3 Comparison of sleep quality amongst controls and glaucoma patients, adjusted for visual acuity

Poor sleep quality (No/Yes: PSQI>5)	OR	95%CI	*P*	Full model adjusted OR	95%CI	*P*
Visual acuity of better eye						
VA 6/12 or better (Ref)						
VA 6/15 or worse	2.10	0.41-10.70	0.373	2.31	0.42-12.79	0.337
Group						
Control (ref)						
POAG	0.54	0.27-1.08	0.081	0.53	0.26-1.06	0.074
PACG	3.34	1.36-8.19	0.008	3.32	1.35-8.16	0.009

Table 4 Univariate and multivariate analysis of predictive variables for sleep quality between glaucoma patients and controls

Poor sleep quality (No/Yes: PSQI>5)	OR	95%CI	*P*	Full model adjusted OR	95%CI	*P*
Visually significant cataract(s) in better eye						
No (ref)						
Yes	0.64	0.13-3.24	0.59	0.06	0.004-1.09	0.057
Beta blocker/combination in better eye						
No (ref)						
Yes	1.06	0.46-2.44	0.88	0.98	0.27-3.61	0.978
Alpha agonist in better eye						
No (ref)						
Yes	1.72	0.62-4.75	0.30	2.79	0.66-11.81	0.164
Group						
Control (ref)						
POAG	0.54	0.27-1.08	0.081	0.56	0.10-3.11	0.511
PACG	3.34	1.36-8.19	0.008	12.8	1.69-97.04	0.013
Visual acuity of better eye						
VA 6/12 or better (ref)						
VA 6/15 or worse	2.10	0.41-10.70	0.373	5.79	0.23-143.48	0.284
Possible depression (PHQ-2)						
No (ref)						
Yes	3.13	1.24-7.88	0.015	2.71	0.39-18.93	0.314
Glaucoma severity of better eye						
Mild: 1≥-6						
Moderate: 2=-6 to 12	2.10	0.71-6.21	0.18	1.5	0.31-7.27	0.611
Severe: 3≤-12	2.73	1.02-7.33	0.047	1.62	0.35-7.45	0.537

OR: Odds ratio.

Table 5 Comparison of sleep quality amongst glaucoma patients adjusted for glaucoma severity of better eye

Poor sleep quality (No/Yes: PSQI>5)	OR	95%CI	*P*	Full model adjusted OR	95%CI	*P*
Glaucoma severity of better eye						
Mild: 1≥-6						
Moderate: 2=-6 to 12	2.29	0.74-7.09	0.151	3.11	0.90-10.8	0.074
Severe: 3≤-12	2.14	0.74-6.20	0.161	2.74	0.85-8.88	0.092
Group						
POAG (ref)						
PACG	6.20	2.40-16.0	<0.001	7.18	2.53-20.4	<0.001

and Japan[32-35] have also reported poor sleep quality amongst the visually impaired, of which could be related to increased mood disturbances and stress from the loss of independence as a result of poor vision, as well as possible decrease exposure to bright lights due to reduction in outdoor activities from the poor vision.

In addition, this finding of glaucoma patients having poorer sleep quality is consistent with previously published studies, showing that glaucoma is associated with dysregulation of the circadian system[10,12-13] and higher incidence of sleep disorders[11,36]. In the human brain, the primary circadian pacemaker is the suprachiasmatic nucleus (SCN), and we know that light plays an important role in synchronizing the circadian system[37-38]. The light intensity seems to influence melatonin secretion, which in turn modulates sleep and the circadian rhythm. The SCN receives photic input from ipRGCs, which contain the pigment melanopsin[6-7]. Their input synchronizes the SCN to the solar day, which keeps the human circadian rhythm close to a 24-hour cycle by driving the nocturnal synthesis of the pineal hormone melatonin and by inducing the circadian phase and sleep. As mentioned, Singapore is a country located near the equator which receives a constant amount of sunshine throughout the year[30]. Despite so, we still found that glaucoma patients are being affected in their sleep quality. Recent studies have demonstrated that patients with glaucoma lose a large percentage of their RGCs, including the loss of ipRGCs[39], which compromises the circadian rhythm[40].

Univariate analysis of predictive factors for poor sleep quality did not find any statistical significance. However, the role of visually significant cataracts in affecting sleep quality has been discussed in previous studies[41-42]. At present, there are no studies which investigate the association of ophthalmic beta blocker use with sleep quality. Review of the literature does show an increase in EDS and decrease in sleep quality for patients on systemic beta blockers[43-44]. This is due to blockage of pineal beta 1-adrenoreceptors, which synthesise melatonin, by systemic beta blockers. It is unclear if ophthalmic beta blockers have the same effect. Brimonidine eyedrops are known to cause daytime somnolence[45-46] and hence is a possible confounding factor in this study. Univariate analysis did not find a statistically significant association between the use of brimonidine eyedrops and sleep quality or daytime sleepiness in our study.

We did not find increased daytime sleepiness when comparing glaucoma patients and control subjects based on assessment using the ESS instrument. The studies[13-14] examined ESS as well, and they found a positive correlation between EDS and glaucoma. The same investigators also found that POAG patients have poorer sleep quality *via* polysomnography despite the mean MD being better than our POAG cohort (-9.44 *vs* -14.7). EDS can arise from multiple factors and the difference in findings could be due to other confounding reasons affecting daytime sleepiness not included in our study. In a cohort study done in Norway, Sivertsen *et al*[47] found that lifestyle habits such as greater cigarette use and less exercise; psychological states such as anxiety and depression, self-reported somatic symptoms, as well as pain were strongly associated with insomnia at baseline. The study showed that there were other confounders which we could have considered when evaluating our patients. It is important to point out that these confounders were not taken into consideration as well[13-14]. Nonetheless, previous studies have found that PSQI and ESS are weakly correlated, and that subjective questionnaires do not correlate directly to polysomnography measurements and thus may be less effective[48].

Our study had its limitations. First, all the methods used in evaluating sleep quality and daytime sleepiness were done *via* subjective questionnaires. Participants have variable educational levels and hence understanding of the questions by the participants could have been affected, leading to possible inaccurate responses. Previous studies have also noted that people with insomnia tend to overestimate the time awake and underestimate the time asleep when compared to polysomnography readings[49-50]. Unfortunately, it was not possible for us to perform objective measurements such as polysomnography for our subjects. Second, the number of PACG subjects in this study was much lesser than the other groups, which could have led to a sampling error and thus a false positive in proving our hypothesis (Type 1 error). Hence, while our study noted poorer sleep quality in PACG patients, this outcome might have been more robust with a larger data set. Third, as mentioned earlier, there are other confounders for sleep quality unaccounted for in this study. This would also include medical conditions such as hypothyroidism and obstructive sleep apnea which none of the patients self-declared but might have been undiagnosed. Last, we were not able to achieve the desired sample size for both our PACG and POAG patients. In spite of that, even though the desired sample size was not attained for PACG subjects, we were still able to obtain a power of 0.75 for the comparison between controls and subjects with PACG in our study. With the included sample size, we were expected to detect a similar proportion of sleep quality disturbances as compared to Wang *et al*[11]. For the POAG group, the power attained using our sample size was not ideal and higher patient recruitment would have allowed us to detect sleep quality disturbances better.

In conclusion, this study set out to investigate whether glaucomatous damage-with its associated loss of ipRGCs can affect sleep quality in an equatorial South-East Asian population with heavy disease burden. We found that PACG patients, have poorer sleep quality but not excessive daytime sleepiness. Circadian function is one aspect that is not well evaluated in daily clinical practice, but it can interfere with the quality of life of these patients. Concerns about sleep

disturbances in patients with PACG can possibly be included in clinical evaluations to provide more holistic care.

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