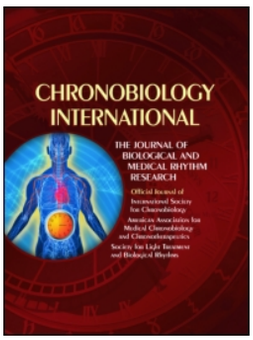

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Progressive retinal ganglion cell loss in primary open-angle glaucoma is associated with temperature circadian rhythm phase delay and compromised sleep

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ABSTRACT

Advanced primary open-angle glaucoma (POAG) is characterized by progressive retinal ganglion cell complex (RGCC) damage that may cause subsequent disruption of the circadian rhythms. Therefore, we evaluated circadian body temperature (BT) rhythm and sleep characteristics of 115 individuals (38 men and 77 women) diagnosed with POAG. GLV (global loss volume; %), a measure of RGCC damage, was estimated by high-definition optical coherence tomography, and RGC functional ability was assessed by pattern electroretinogram amplitude (PERGA). Depending on dynamics of POAG progression criteria, two groups were formed that were distinctively different in GLV: Stable POAG group (S-POAG; GLV = 5.95 ± 1.84, n = 65) and Progressive POAG group (P-POAG; GLV = 24.27 ± 5.09, n = 50). S-POAG and P-POAG groups were not different in mean age (67.61 ± 7.56 versus 69.98 ± 8.15) or body mass index (24.66 ± 3.03 versus 24.77 ± 2.90). All subjects performed 21 around-the-clock BT self-measurements during a 72-h period and kept activity/sleep diaries. Results showed pronounced disruption of circadian physiology in POAG and its progression with increasing severity of the disease. The daily mean of BT was unusually low, compared to age-matched controls. Moreover, our results revealed distinctive features of BT circadian rhythm alterations in POAG development and POAG progression. S-POAG is associated with lowered BT circadian rhythm robustness and inter-daily phase stability compared to controls. In the P-POAG group, the mean phase of the circadian BT rhythm was delayed by about 5 h and phases were highly scattered among individual patients, which led to reduced group mean amplitude. Circadian amplitudes of individuals were not different between the groups. Altogether, these results suggest that the body clock still works in POAG patients, but its entrainment to the 24-h environment is compromised. Probably because of the internal desynchronization, bedtime is delayed, and sleep duration is accordingly shortened by about 55 min in P-POAG compared to S-POAG patients. In the entire POAG cohort (both groups), later sleep phase and shorter mean sleep duration correlate with the delayed BT phase ($r = 0.215$; $p = 0.021$ and $r = 0.322$; $p = 0.0004$, respectively). An RGCC GLV of 15% apparently constitutes a threshold above which a delay of the circadian BT rhythm and a shortening of sleep duration occur.

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Primary open-angle glaucoma; retinal ganglion cells; circadian rhythm; circadian disruption; temperature; sleep; chronotype; pattern electroretinogram (PERG)

Introduction

In mammals, including humans, circadian rhythms are generated by a central pacemaker system located in the suprachiasmatic nuclei (SCN) (Weaver 1998). The main synchronizer, which entrains the endogenous rhythms to the 24-h environment is the light-dark (LD) cycle. The photic information is perceived by a subpopulation of retinal ganglion cells (RGCs), namely by intrinsically photosensitive RGCs (ipRGCs) (Berson et al. 2003; Panda et al. 2003, 2002). The axons of these neurons form the retinohypothalamic tract (RHT), the main afferent pathway to the SCN (Freedman et al. 1999; Golombek and Rosenstein 2010; Markwell et al. 2010). Any damage of these neurons leads to an impairment of photic synchronization. Such circadian disruption has consequences for subjects´ performance and wellbeing and may cause several diseases (Escobar et al. 2011; Waterhouse and DeCoursey 2004; Vaze and Sharma 2013).

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Primary open-angle glaucoma (POAG) is a progressive optic neuropathy, one of the most common forms of glaucoma and the leading cause of irreversible blindness, estimated to affect 70 million people worldwide (Weinreb et al. 2014). POAG affects predominantly urban residents; its incidence is growing steadily and is expected to increase further (Tham et al. 2014). Though pathophysiology of POAG is not fully understood, mechanical stress due to elevated intraocular pressure (IOP) is related to progressive RGCs damage, dysfunction and death (Weinreb et al. 2014). Numerous studies have shown that glaucoma may affect also the number and the function of ipRGCs (Drouyer et al. 2008; Feigl et al. 2011). This mean that not only image forming vision is impaired in glaucoma patients, but also the transmission of the photic synchronizing signal to the central pacemaker, which has adverse consequences for photic synchronization and masking (Drouyer et al. 2008; Girardin et al. 2008; Göz et al. 2008).

It is hypothesized that high IOP-induced ipRGCs damage causing circadian disruption (Agorastos and Huber 2011; Girardin et al. 2008; Golombek and Rosenstein 2010) also compromises sleep (Guo et al. 2017). Indeed, decreased ipRGCs function due to glaucoma associates with reduced sleep quality, assessed by polysomnography (Gracitelli et al. 2015). U-shaped association between duration of sleep and the prevalence of glaucoma, with higher prevalence among those who slept <5 h or ≥9 h is present in an overweight population in Korea (Lee et al. 2016). Glaucomatous damage of ipRGCs also associates with higher daytime sleepiness (Graticelli et al. 2016). The higher prevalence of sleep disturbance, assessed by PSQI integral score was found in POAG and in primary close-angle glaucoma compared to controls: however, no correlation with higher IOP was reported (Wang et al. 2013).

Chronically high IOP, however, is not the only or primary factor causing RGCs/ipRGCs damage in glaucoma (Vidal-Sanz et al. 2017). Impaired IOP circadian rhythm and altered IOP variability could per se be factors for RGC damage: unstable IOP and compromised circadian rhythm of ocular perfusion may lead to mild reperfusion injury (Flammer and Mozaffarieh 2007). Vascular dysregulation (Flammer and Mozaffarieh 2007) and oxidative stress (Sacca and Izzotti, 2008) are other inter-related key mechanisms that may share pathogenic mechanisms. Also, there are numerous similar features among age-dependent neurodegenerative diseases (i.e. Alzheimer's and Parkinson's disease, including glaucoma) connecting RGCs damage and disrupted circadian physiology (La Morgia et al. 2017a, b).

Whatever the leading POAG factor is, detecting RGCs loss in the macula is crucial both for early glaucoma detection and for the evaluation of circadian rhythm alterations, their causes and consequences. RGCs complex global loss volume (GLV) is consistently shown to be the most sensitive measure of RGCs loss and glaucoma detection (Arintawati et al. 2013; Naghizadeh et al. 2014; Tan et al. 2009). Optical coherence tomography (OCT) is a useful tool and modern approach to diagnose the numerous aging-associated neurodegenerative pathologies beyond glaucoma (Doustar et al. 2017; La Morgia et al. 2017b). This is important since these pathologies have many common consequences in terms of circadian rhythm alterations (Gubin and Weinert 2015, 2016; Gubin et al. 2016b; La Morgia et al. 2017a). In addition to GLV, clinical electrophysiological tests allow the noninvasive assessment of macular RGCs function (Robson et al. 2018). Reduction of PERG amplitude is predictive with respect to the assessment of glaucoma development (Ventura et al. 2005) and a useful tool to stratify the risk of glaucoma progression (Ventura et al. 2005, Wilsey and Fortune 2016).

Overall, assessment of circadian disruption in glaucoma, and in POAG especially, is still in its infancy. For example, there are few data investigating circadian activity and sleep-wake rhythms in patients with glaucoma (Gracitelli et al. 2015; Lanzani et al. 2012); we have not found any human studies that characterized circadian marker rhythms like BT in such patients. Accordingly, this study aims to fill some of the existing gaps and focuses on the assessment of circadian disruption in POAG patients; our study provides insight into alterations of the circadian temperature rhythm and sleep associated with glaucoma-progression/RGC-loss. It is part of a more extensive survey on disrupted circadian physiology in glaucoma.

Methods

Data reported herein are part of a broader regional survey on glaucoma, POAG in particular, that incorporated 1,182 patients, including 716

patients with stable and advanced POAG and 406 controls (ophthalmologic patients with non-glaucomatous pathology), obtained in cooperation with 60 ophthalmologists.

POAG diagnosis and progression criteria

All patients were diagnosed and supervised at the State Autonomous Health Care Institution, Tyumen Regional Ophthalmological Dispensary. To determine the progression criteria in the group of patients with POAG, the index characterizing the state of retinal photosensitivity according to Static Automated Perimetry (SAP) – mean deviation (MD) (Aptel et al. 2015) and the dynamic index of the RGC loss, GLV, according to OCT (Bussel et al. 2014) were used. Dynamics of visual functions were assumed to be stabilized in individuals with a change in the MD index by no more than 0.5 decibels (dB) per year and a decrease in GLV by no more than 2% per year (Stable POAG group, S-POAG): in other cases, the process is progressive (Progressive POAG group, P-POAG).

Depending on the dynamics of glaucoma progression criteria, MD (dB) and GLV (%) at the beginning of 2014 and at the end of the 2016 follow-up, all patients were divided into 2 groups: S-POAG (n = 289) and P-POAG (n = 427). The classification considered the data on the worst eye with the worst stage of POAG.

115 age-matched patients with stable (S-POAG, n = 65) or advanced POAG (P-POAG, n = 50) were selected for the investigation of RGCC damage and function, 72-h ambulatory BT self-measurements and sleep behavior. These groups were different in terms of GLV: S-POAG; GLV = 5.95 ± 1.84, P-POAG; GLV = 24.27 ± 5.09. No difference was found between S-POAG and P-POAG patients in terms of mean age (67.61 ± 7.56 versus 69.98 ± 8.15) or body mass index (24.66 ± 3.03 versus 24.77 ± 2.90), Table 1. The exclusion criteria were: primary open-angle end-stage glaucoma, the presence of other types of glaucoma, pronounced cicatricial changes in the cornea, the presence of inflammatory or hereditary eye diseases in history, occlusion of the central artery or central retinal vein, dystrophic eye diseases: degenerative myopia of a high degree, severe cataract, cataract surgery, central age-related retinal degeneration, acute coronary or cerebral blood flow disorders, heart rhythm disorders, oncological and mental diseases, including alcoholism, neurodegenerative diseases: Alzheimer's disease, Parkinson's disease, multiple sclerosis. The study excluded patients with diabetes and thyroid disease, as well as patients working in the night shift or crossing time zones at least once per month.

All participants were recommended to eat 3 meals a day. More stringent restrictions were not advised, as such could make artificial adjustments to the natural daily routine characteristic of a group.

All patients were instructed about the techniques of self-measurements and asked to keep a diary, reflecting self-estimation of health, physical and emotional activity, food intake, medications, time of going to bed, and time of awakening.

RGC function and damage assessment

Retinal Ganglion Cell Complex (RGCC) damage was measured by means of high definition optical computer tomography (HD-OCT), *Cirrus HD-OCT, Carl Zeiss, Germany*. Average amount GCC loss over entire GCC map, GLV (GLV, %) and average amount of localized thinning over the entire GCC map, FLV (focal loss volume, %) were estimated.

RGC functional ability was assessed by means of pattern electroretinogram amplitude (PERGA). Pattern electroretinogram, PERG, is a predictive method to assess glaucoma development (Ventura et al. 2005) and a useful tool to estimate the risk of glaucoma progression (Ventura et al. 2005, Wilsey and Fortune 2016). In our study, PERG was assessed at three different times of the 24-h cycle on three consecutive days (at 8:00, 14:00 and 20:00). For the present paper, each patient's mean value of these three measurements was used for analysis. PERG was assessed by electroretinography "Tomey EP 1000" (*Tomey, Japan-Germany*) using electrodes-cups, fixed on the lower eyelid according to standard methods in accordance with the recommendations of the International Society for Clinical Electrophysiology of Vision (ISCEV) (Marmor and Zrenner 1999). The results were evaluated in accordance with the electrophysiological standards of the ISCEV.

Temperature circadian rhythm assessment

Measurements of axillary BT were taken seven times per day (at 8:00, 11:00, 14:00, 17:00, 19:00, 23:00 and

Table 1. Number, age, gender, retinal ganglion cell complex Global Loss Volume (GLV), focal loss volume, Intraocular Pressure (IOP), Body Mass Index (BMI), Chronotype Score (CS) and Mean Actual Sleep Duration (MASD) of the Participants.

GROUP	S – POAG (n = 65)		P – POAG (n = 50)	
Gender, n	*Men 19*	*Women 46*	*Men 19*	*Women 31*
Age	67.61 ± 7.56		69.98 ± 8.15	
	66.84 ± 7.54	67.93 ± 7.63	71.26 ± 7.57	69.19 ± 8.51
BMI	24.66 ± 3.03		24.77 ± 2.90	
	24.80 ± 2.50	24.61 ± 3.23	25.31 ± 2.42	24.41 ± 3.17
GLV	**5.95 ± 1.84**		**24.27 ± 5.09*****	
	6.68 ± 1.57	**5.65 ± 1.87**	**24.06 ± 3.75 *****	**24.40 ± 5.81*****
FLV	**3.20 ± 1.84**		**10.81 ± 2.37*****	
	3.69 ± 1.77	**3.00 ± 1.98**	**11.03 ± 2.31 *****	**10.67 ± 2.44*****
IOP (OD/OS)	**16.24 ± 2.96/16.16 ± 3.51**		**21.93 ± 3.60***/25.19 ± 3.27*****	
	15.78 ± 3.34/ 14.53 ± 4.30	**16.43 ± 2.80/ 16.83 ± 2.93**	**21.86 ± 4.24***/ 24.64 ± 3.31*****	**21.97 ± 3.23***/ 25.53 ± 3.26*****
HO CS	**60.52 ± 13.50**		**66.22 ± 14.44***	
	58.71 ± 14.13	61.20 ± 13.35	66.70 ± 17.28	65.90 ± 12.50
MASD	**7.22 ± 0.74**		**6.30 ± 0.93*****	
	7.35 ± 0.72	**7.17 ± 0.76**	**6.26 ± 0.72*****	**6.33 ± 1.07*****
BT MESOR	35.85 ± 0.36		35.77 ± 0.43	
	36.06 ± 0.36	35.76 ± 0.32	**35.69 ± 0.44****	35.81 ± 0.42

S-POAG – Stable Primary Open Angle Glaucoma; **P-POAG –** Progression Primary Open Angle Glaucoma

BMI – body mass index; **GLV** – retinal ganglion cell complex global loss volume (%); **FLV** – retinal ganglion cell complex focal loss volume (%) (*Mean values of 2 eyes are indicated*);

IOP OD/OS – intraocular pressure of the right and the left eye (*oculus dexter/oculus sinister*), 72-h mean value; **HO CS –** Horne-Ostberg Chronotype Score (Horne and Ostberg 1976)**; MASD –** Mean Actual Sleep Duration, hours**; BT MESOR –** 72-h Body Temperature MESOR

* **p < 0.05; ** p < 0.01 *** p < 0.001 –** between S-POAG and P-POAG groups; Mean values and Standard Deviations are indicated.

3:00 h) on three successive days (72 h) according to the Tyumen protocol that was previously applied in several studies (Gubin et al. 2006, 2016a, 2017a, b). BT was measured by mercury thermometer, *Amrus AMTD, Amrus Enterprises Ltd.*, USA. Measurements at 03:00 (or other time points, when subjects were asleep) were carried out with the participation of family member, avoiding interruption of sleep and without turning on the external lighting in the room. Axillary BT measurements provide temperature phase estimates that are close to core rectal temperature phase estimates (Edwards et al. 2002).

To compare BT circadian rhythms in POAG, 72-h self-measurement data from age-matched peers (ophthalmologic patients with no signs of glaucomatous retinal damage – a control group, n = 89, age range 50–88; mean age 68.11 ± 10.57) were used.

Sleep assessment

Though detailed assessment of sleep parameters was beyond the main scope of the current study, we considered that having additional objective information on individual sleep habits would be helpful. Thus, individual diaries provided information on the time of going to bed and time of awakening. The difference between the time of going to bed and the time of awakening was considered to reflect sleep duration, and the mid-time of this span was used as sleep phase. Values of three successive days of the survey were then averaged to obtain mean Actual Sleep Duration and mean Actual Sleep Phase. The present study is only a first step and the quality of sleep should be estimated by more sophisticated methods in the future.

To obtain information about individual chronotype score (CS), CS was assessed by the Horne-Ostberg Morningness-Eveningness questionnaire (Horne and Ostberg 1976).

Data analysis

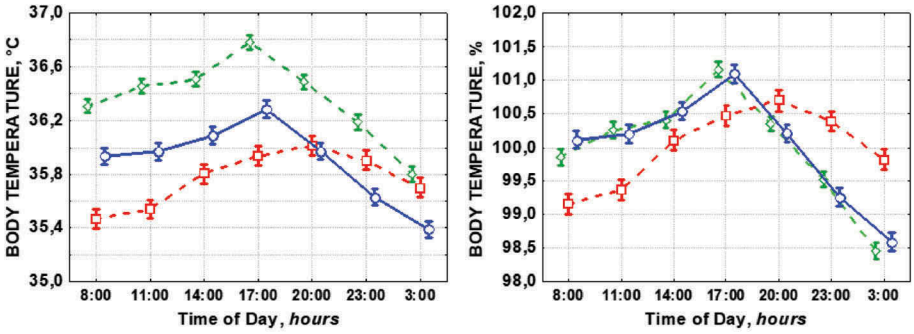
As RGCs estimates from the right and left eyes (OD/OS) were different, circadian parameters were correlated using three different approaches, based on separate estimates of OD/OS, on the estimate from the better eye, and on the mean estimate of both eyes, to determine which approach is most closely related to the circadian rhythm parameters.

One-way analyses of variance (ANOVA), correlation analyses, and tests for statistical differences were performed using the software packages Excel, STATISTICA 6 and SPSS 23.0. Shapiro-Wilk's W-test was applied to check for normal distribution. When variables were normally distributed (W-test's p-value >0.05), 1-way ANOVA with post hoc correction for multiple testing using Tukey or Bonferroni-Dunn was used. Otherwise, the Kruskal–Wallis and the Mann–Whitney post hoc tests were used. The level of statistical significance was set at 5%. Exact p-values have been given in the text and tables. The MESOR, amplitude and acrophase of the 24-h rhythms were assessed for each patient by single cosinor analysis (Cornelissen 2014). Population-mean cosinor analysis was used to assess within group mean values and confidence intervals of 24-h rhythm amplitudes and phases and gauge inter-individual cohesion (Cornelissen 2014). The population-mean rhythm parameters were compared by Bingham's parameter tests (Bingham et al. 1982).

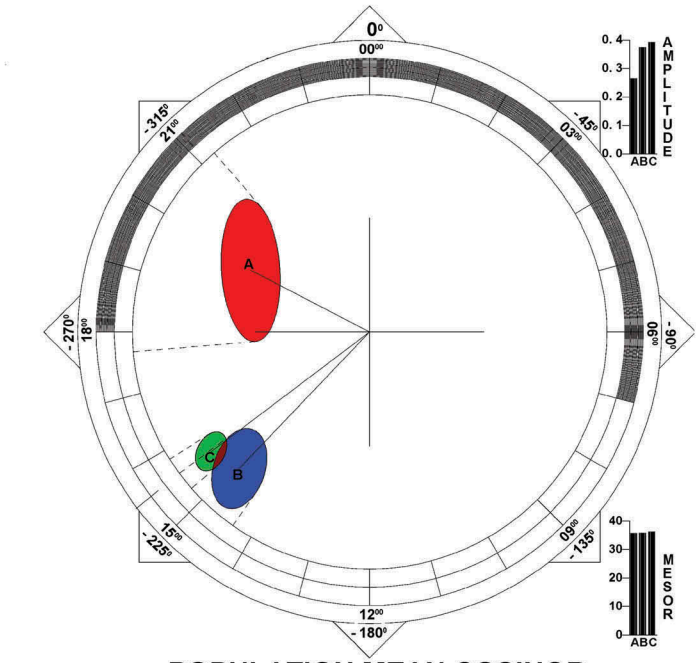
Results

Temperature circadian rhythm parameters of POAG patients differ from those of age-matched healthy peers in specific features. Figure 1 shows daily patterns of control and POAG groups. POAG patients have low BT values throughout the day and accordingly a lower 24-h mean and MESOR compared to healthy controls (MESOR P-POAG: 35.77 ± 0.43; S-POAG: 35.85 ± 0.36; Controls: 36.31 ± 0.12; $p < 0.0001$ between both Controls and S-POAG, or Controls and P-POAG; the difference between POAG groups was not significant; $p = 0.256$), Figure 1. In male patients, however, the BT MESOR was even lower with disease progression; the difference between S-POAG and P-POAG patients was significant, Table 1.

Expression of BT values as percentages of individual daily means illustrates their differences in their daily patterns ignoring the different mean values, Figure 1b. A visual evaluation of the daily patterns shows similarity between the Control and S-POAG groups. Further analyses, however, revealed compromised intra-individual robustness (gauged by BT percentage rhythm, BT%) and phase stability (gauged by phase standard error, BT phi se) of the circadian BT



A B



POPULATION MEAN COSINOR

GROUP	P	N	PR	MESOR+-SE	AMPLITUDE *	ACROPHASE/(0) *
A P POAG	<. 001	50	45	35. 674 . 059	0. 266 (. 190 . 364)	-296° (-263 -318)
B S POAG	<. 001	65	46	35. 802 . 044	0. 373 (. 297 . 450)	-224° (-215 -233)
C CONTROL	<. 001	89	66	36. 258 . 013	0. 392 (. 353 . 431)	-233° (-229 -238)

C

S-POAG (n=65); P-POAG (n=50); control (n=89)

Figure 1. Body temperature (BT) in the individuals with diagnosed primary open angle glaucoma and distinct circadian patterns of the three groups (Stable Primary Open Glaucoma, S-POAG; Progressive (*Advanced*) Primary Open Glaucoma, P-POAG and Controls). BT circadian phase delay associates with P-POAG. a) Temperature circadian patterns differ among the three groups; 2-way ANOVA Time*Group interaction $F_{(12,\ 4263)} = 30.700$, $p < .0001$. Both POAG groups have lower body temperature versus controls throughout the day ($p < 0.001$), except for 3:00 of the P-POAG group; b) Averaged data expressed as % of the individual 3-day means to exclude bias from inter-individual variability, 2-way ANOVA for Time*Group interaction $F_{(12,\ 4263)} = 52.431$, $p < .0001$. 2-way ANOVA for Time*Group interaction between S-POAG and P-POAG, $F_{(6,\ 2401)} = 56.173$, $p < .0001$. Though phase characteristics of the S-POAG group are similar to Controls, circadian patterns are still significantly different; 2-way ANOVA for Time*Group interaction between S-POAG and Controls $F_{(6,\ 3220)} = 5.544$, $p = .00001$. Mean values with corresponding standard errors for each time point are depicted at Figure 1a,b. c) Group (Population) Cosinor analysis with concomitant parameter-test (Bingham et al. 1982) confirms that BT circadian rhythm in P-POAG exhibits both a phase-delay (~5 h, from 14:56 to 19:48, $F_{(1,113)} = 43.28$; $p < .0001$) and an amplitude decrease (−0.11°C; $F_{(1,113)} = 17.88$; $p < .0001$). *Amplitude decrease, however, is merely a consequence of the greater mean phase position heterogeneity/phase instability due to inter- and, mainly, intra-individual phase scattering in P-POAG; as individual amplitude estimates does not significantly differ between S-POAG and P-POAG groups, see also* Figure 2.

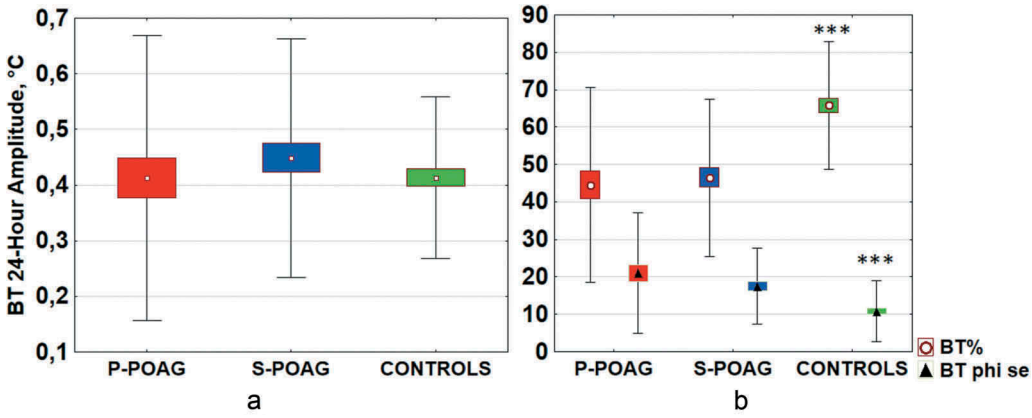
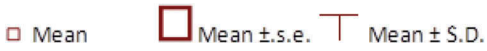


Figure 2. Inter-daily robustness and phase stability, but not the amplitude of the circadian temperature rhythm is reduced in POAG patients as compared to age-matched controls. a: Mean values of individual amplitudes. No significant differences were found among groups (KW-H (2;204) = 1.714; p = 0.424). b: Rhythm robustness (gauged by 24-h % Rhythm, BT%) is lower in POAG patients compared to Controls (Kruskal–Wallis KW-H (2;204) = 44.95; p < 0.0001) because of a decreased inter-daily phase stability. No differences were found, however, between the S-POAG and P-POAG groups (p = 0.655). Intra-individual inter-daily phase instability (gauged by 3-day phase standard error, BT phi se) is increased in POAG: Kruskal-Wallis KW-H (2;204) = 52.95; p < 0.0001), though not between S-POAG versus P-POAG (p = 0.400). Note: Within POAG patients' cohort (both POAG groups), phase instability (higher phase se) also correlates with a higher GLV% (r = 0.237; p = 0.011).*** p < 0.0001 (Figure 3b) for differences Controls versus S-POAG and P-POAG groups (both BT% and BT phi se; Mann-Whitney U-test). Differences between S-POAG and P-POAG are not significant.



rhythm in S-POAG patients, Figure 2b. A putative further decrease of rhythm robustness and phase stability could not be verified. The values obtained for P-POAG and S-POAG groups were not different statistically. However, with POAG progression a considerable BT phase delay and a larger dispersion of individual phases occurred, probably due to different severity of the disease within P-POAG patients. The daily BT pattern of the P-POAG group was shifted to later daytime and had smaller circadian amplitude compared to the S-POAG group, Figure 1. Bingham's parameter tests (Bingham et al. 1982) yielded significant differences in population estimates of the circadian BT rhythm. The P-POAG as a whole shows a phase delay of ~5 h (from 14:56 to 19:48, $F_{(1,113)} = 43.28$; $p < 0.0001$) and a circadian amplitude reduced by 0.11°C ($F_{(1,113)} = 17.88$; $p < 0.0001$), Figure 1c. However, the decreased amplitude was due to inter-individual phase differences as verified by a larger dispersion of phase estimates in P-POAG (F-test for equality of phase variability between S-POAG and P-POAG groups, p = 0.0002). Individual estimates of the circadian BT amplitude were not different between S-POAG and P-POAG patients, Figure 2a. Since the population-mean cosinor estimate of the amplitude is "phase-weighted", it is reduced in the presence of a large dispersion of individual phases.

In the P-POAG cohort the strongest correlation was found between BT circadian rhythm phase delay and focal loss volume (FLV) and Global Loss Volume (GLV). Using the mean value of both eyes (OS/OD mean FLV/GLV) led to a stronger correlation with the BT circadian acrophase, compared to using each eye's FLV separately, or using FLV/GLV of the better eye, Figure. 3a–b. Among electrophysiological variables, the strongest correlation of BT circadian phase was with the mean PERGA of both eyes, Figure 3c. Altogether, these data show that progressive loss of RGC (higher GLV) and compromised RGCC output function (dampened PERG A) do correlate with later circadian phase, i.e. with an impaired photic synchronization of the BT rhythm.

The progressive RGC loss in POAG was connected with an impaired sleep. Notably, sleep duration was shorter, whereas sleep phase did change only modestly (Figure 4). Mean Sleep Duration was markedly reduced in the P-POAG group ($p < 0.00001$) (Figure 4a) and strongly correlated with measures of RGC damage (GLV) ($r = -0.464$, $p < 0.00001$), Figure 4b and an estimate of RGC function, PERGA ($r = 0.463$,

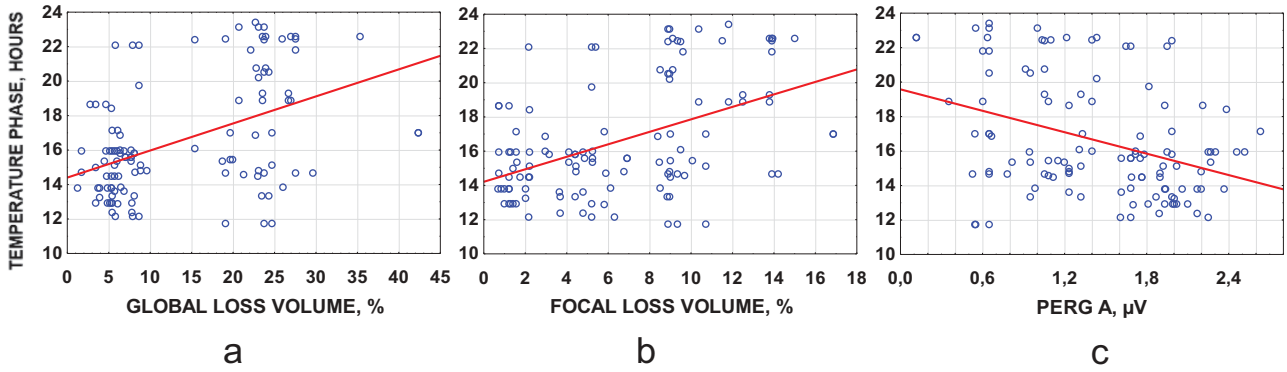


Figure 3. Temperature circadian phase position has strong correlation with indices of retinal ganglion cells (RGCs) damage and dysfunction being progressively delayed with increased RGCs damage and dysfunction. a) Global loss volume (GLV), r = −0.458, p < 0.00001; b) Focal loss volume (FLV), r = −0.470, p < 0.00001; and with c) Pattern electroretinogram amplitude (PERGA), r = 0.367, p < 0.00001,Correlations with mean GLV/FLV/PERGA estimates of the two eyes are depicted since 2-eye means consistently showed the highest correlation with BT circadian phase position.

p < 0.00001), Figure 4c. Mean Sleep Phase did change modestly in P-POAG patients, p = 0.002, Figure 4d, correlated with borderline significance with GLV, r = 0.169; p = 0.071, Figure 4e and not significantly with PERGA (r = −0.138; p = 0.142), Figure 4f. However, Mean Sleep Phase obviously became more scattered in the P-POAG group and with increasing GLV, Figure 4e. Furthermore, between-group comparison of standard deviation of the 3-day Mean Sleep Phases (SD MSP), assessed in each patient, demonstrates that in P-POAG sleep phase became increasingly unstable, p < 0.0001. Also, Mean Sleep Phase only modestly correlates with BT phase in the pooled POAG cohort (r = 0.215; p = 0.021). On the other hand, there is a strong correlation between Mean Sleep Duration and BT phase in the pooled POAG cohort (r = 0.322; p = 0.0004). This correlation can be accounted for by the observation that mean bedtime is shifted by about 55 min to the later hours in P-POAG versus S-POAG patients (23h:04min versus 22h:09 min, p < 0.0001), presumably due to a BT phase delay, while mean Waking Time remained unchanged (5h:28 min versus 5h:22 min, p = 0.574). This difference between sleep habits obviously cannot be explained by chronotype, since the P-POAG group consisted of more morningness-prone individuals and had a higher chronotypes score; p = 0.033, Table 1. It cannot be an age effect either, even though there is a strong trend with age for earlier self-reported bedtime (entire POAG cohort: r = −0.377; p = 0.0003) and waking time (the entire POAG cohort (r = −0.647; p < 0.0001). However, patients´ age was not different between the two groups (Table 1).

Discussion

Our results showed that POAG-progression-associated RGC loss and impaired RGC function is coupled with several manifestations of disrupted circadian physiology.

Already at early stages of POAG, disturbances of the circadian BT rhythm were manifested. This mainly concerned weakened intra-individual and inter-daily phase stability measured as a higher phase standard error of the S-POAG patients compared to controls. Since mean single-day estimates of neither 24-h Amplitude, nor Percentage rhythm were different, it was the inter-daily phase stability but not the waveform of the BT rhythm that was compromised in POAG patients, suggesting that endogenous clock function was preserved, though synchronization with external photic time cues was already altered.

With POAG progression, no further signs of reduced circadian BT rhythm robustness is detected; however, an about 5-h BT phase delay became obvious. This phase delay was accompanied by an increased inter-individual phase scatter of the BT circadian rhythm and with compromised sleep quality. Sleep duration was reduced in P-POAG patients mainly because of a 1-h later bedtime what closely correlated with RGC GLV and PERG amplitude.

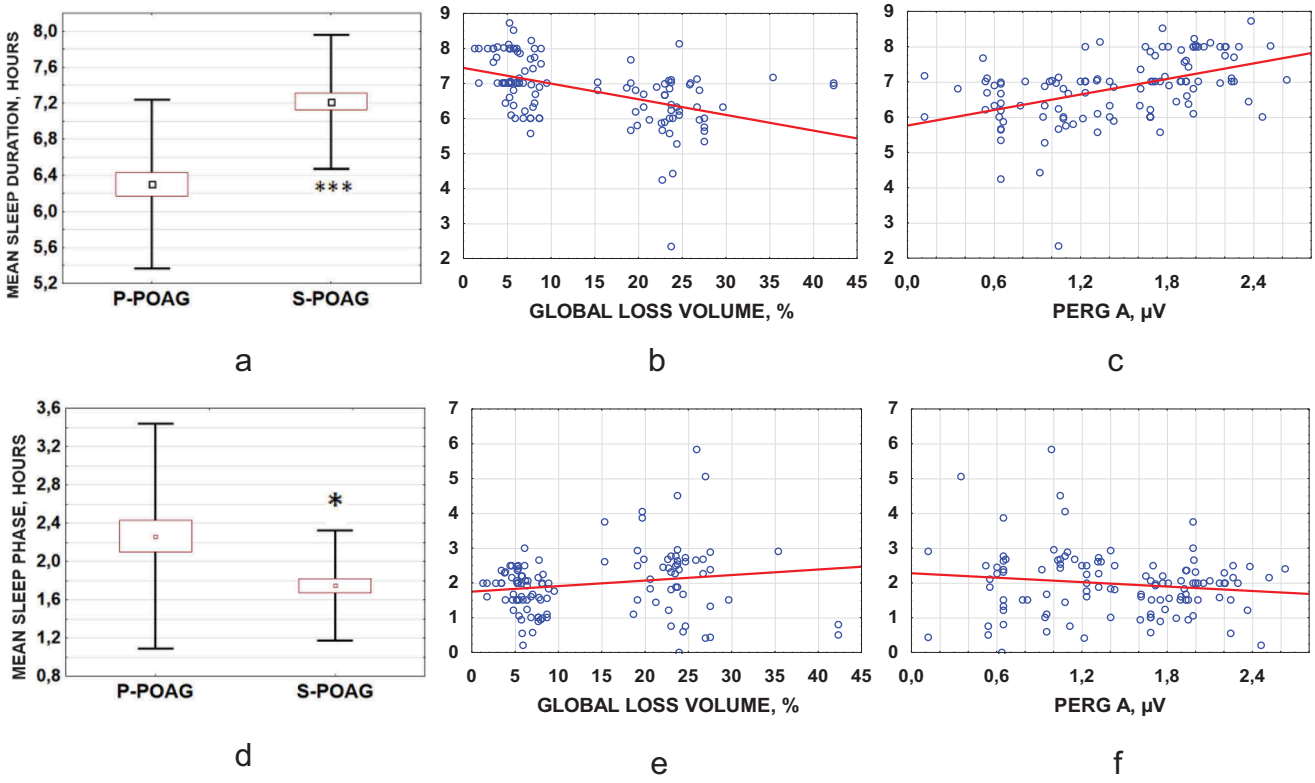


Figure 4. Sleep characteristics (3-day mean sleep phase and duration) in stable and progressive primary open angle glaucoma (S-POAG versus P-POAG) depending on estimates of retinal ganglion cell complex (RGCC) damage, global loss volume (GLV) and RGCs functional ability, pattern electroretinogram amplitude (PERGA). Mean Sleep Duration is markedly reduced in P-POAG group ($p < 0.00001$) (a); strongly and equally correlates with measures of RGCs damage (GLV), $r = -0.464$, $p < 0.00001$ (b); and RGCs functional abilities (PERGA), $r = 0.463$, $p < 0.00001$ (c).Mean Sleep Phase changes relatively modestly in P-POAG ($p = 0.002$) (d), has borderline correlation with GLV ($r = 0.169$; $p = 0.071$) (e) and no correlation with PERGA ($r = -0.138$; $p = 0.142$) (f). However, Mean Sleep Phase obviously became more scattered in P-POAG group and with increasing GLV (e, f).*** $p < 0.001$ (Figure 4a); *: $p < 0.05$ (Figure 4d) for differences between S-POAG and P-POAG groups (Mann-Whitney U-test).GLV/PERG A 2-eye mean estimates are depicted. Note: 2 clusters of GLV (below 10 and above 15) values at figures b and e correspond to the groups S-POAG and P-POAG, respectively.

These results show that, even in advanced POAG, stable circadian BT rhythm was generated. Individual amplitudes were not reduced, though photic synchronization was diminished.

Interestingly, an increased inter-daily phase variability prior to phase advance was previously found to occur during the aging process in mice (Weinert 2010). In the case of glaucoma, increased BT circadian phase instability can be proposed as a supplementary, early diagnostic tool, while BT circadian phase delay may serve as a test for POAG progression linked with RGC loss exceeding a certain threshold (see below for further details).

We found no previous studies of circadian temperature rhythms in POAG, though other authors reported compromised sleep efficiency and duration in advanced glaucoma patients, while no phase changes of the circadian activity rhythm were evident (Lanzani et al. 2012). Our results indicate that increased RGCs damage and dysfunction in POAG progression associates with substantial decrease in sleep duration, obviously a consequence of circadian disruption. That circadian disruption may have adverse consequences for sleep quality has been shown repeatedly (Touitou et al. 2017, 2016).

The shorter sleep duration in P-POAG patients was due to an about 1 h later self-reported sleep time whereas the waking time did not change. We considered the possibility that the latter could be driven by a social need to wake up in proper time. However, data do not provide support for this assumption: most POAG patients were at retirement age;

moreover, there was a strong trend for an even earlier waking time with increasing age both in the entire POAG cohort and within the P-POAG cohort. Since a strong trend with age was preserved both for earlier bedtime and time of awakening, we hypothesize that POAG progression will cause an aggravating conflict between age-associated phase advances and phase delays due to RGCs loss.

RGCs perceive photic synchronizing signals for the circadian system. Particularly intrinsically photoreceptive RGC (ipRGCs) or melanopsin-expressing RGCs (mRGCs) are essential for non-visual signal transduction to the central clock, the SCN. (Berson et al. 2003; Panda et al. 2003; Paul et al. 2009). We have shown that the number of RGCs decreases with progressing POAG. A recent study demonstrated histologically that this concerns particularly melanopsin-expressing RGCs. In mild staged glaucoma, the mRGCs/ipRGCs density is comparable to age matched control whereas at severe stages a 3-fold loss was observed (Obara et al. 2016). As a consequence of the increasing damage of ipRGCs in POAG, the SCN receive weaker signals from the retina. According to the two models of photic synchronization this would lead to an impaired synchronization with the 24-h environment (Golombek and Rosenstein 2010) The LD difference perceived by the retina is decreased, i.e. the non-parametric light effect would be low and being insufficient to induce enough phase changes to compensate for the daily phase delay caused by the long endogenous period length. Therefore, the circadian rhythm will be phase delayed. The same consequence one might expect considering the parametric effect. According to Aschoff's rule, in diurnal species such as humans, dimmer light induces a lengthening of the intrinsic period. In nocturnal species on the other hand, the endogenous period should shorten as a consequence of RGC damage leading to a phase advance. Indeed, indirect evidence could be found in experiments on a murine transgenic model of Alzheimer disease (3xTgAD – mice) since mRGC damage is typical for Alzheimer disease (AD). The circadian temperature rhythm was advanced in these animals (Knight et al. 2013). In humans on the other hand, AD is characterized by phase delay of the circadian BT rhythm (Harper et al. 2005; Satlin et al. 1995; Volicer et al. 2001).

Possibly, a minimal number of intact ipRGCs is necessary to enable an adequate circadian signaling and data published recently do favor this concept (Zhang et al. 2017). Even though we did not assess the ipRGCs loss specifically, our results indicate that there is a threshold of RGC GLV (~ 10–15%) above which distinct phase and amplitude changes of the circadian temperature rhythm occur. The two POAG groups of the present study differed distinctively in their degree of RGC damage, gauged by GLV) and FLV. In none of the S-POAG individuals, the 2-eye mean RGC GLV was above 10%, while all P-POAG patients had a mean RGC GLV > 15%. Whereas in S-POAG subjects only the phase stability was decreased, in P-POAG patients the phase was delayed. Accordingly, our results suggest that a RGCC GLV value of 10–15% represents a threshold linked to phase change of the circadian temperature rhythm and a shortening of sleep duration via delaying bedtime without affecting waking time.

However, there is another point casting this hypothesis into doubt. It stems from a major discrepancy of circadian phase behaviour – a phase advance in the aging process *per se* (Carrier et al. 2002; Duffy et al. 2015; Gubin et al. 2016b) and a phase delay in aging-related pathologies such as POAG and AD (see above). mRGCs loss is found in advanced age both in rats (Lax et al. 2016) and humans (Esquiva et al. 2017). However, analysing phase changes in aged organisms, one has to consider not only the RGC damage but also putative Tau changes, which may lead to phase advances (Gubin and Weinert 2015, 2016, Gubin et al. 2016b).

Another factor that may cause a disruption of the circadian BT rhythm in glaucoma patients is impaired local (retinal) or systemic melatonin production. However, current results on melatonin rhythms in POAG patients are contradictory (Alkozi et al. 2017a, b, Chiquet et al. 2006) or contain some methodological flaws, i.e. data obtained only in the morning (Ma et al. 2018). There is clear evidence, however, that the suppression of melatonin by light is reduced (Perez-Rico et al. 2010). Resulting higher daytime level may produce a vasodilatory effect leading to increased peripheral heat loss, which in turn would lead to a decreased core BT, as observed in the current study.

To investigate melatonin and particularly the function of melatonin receptors in glaucoma patients is essential as several studies suggest they

may be involved in the regulation of IOP (Tosini and Boatright 2013). Mice lacking MT_1 receptors have both high IOP during the night and a reduced number of RGCs. Thus, dysfunctional melatonin signalling is a possible risk factor in the pathogenesis of glaucoma (Tosini and Boatright 2013). Deficit of melatonin's free-radical scavenging property can also lead to elevated retinal oxidative stress, which in turn might be involved in glaucomatous cell death. There are numerous papers substantiating the proposition that melatonin should be beneficial in glaucoma patients (c.f. Agorastos and Huber 2011; Aranda et al. 2017; Lundmark et al. 2007; Tosini et al. 2012, Tosini and Boatright 2013).

It was noticed that ipRGCs may have higher resistance than other RGCs to certain factors. For example, ipRGCS are resistant to ischemic insult (González Fleitas et al. 2015), to excitotoxicity induced by N-methyl-d-aspartate (Wang et al. 2018) and optic nerve trauma (Sánchez-Migallón et al. 2018). However, ipRGCs population is heterogenic in morphology and physiology and consists of presumably five subpopulations, each with a specific response to light stimuli, electrophysiological characteristics and distinct brain projections (Schmidt et al. 2011). Certain ipRGCs are more resistant to injury than the general population of RGCs (Cui et al. 2015). Also, the resistance to chronic intraocular hypertension is different (Li et al. 2006). Indeed, in some forms of glaucoma, especially in normal-tension glaucoma and POAG, high intraocular pressure is not likely a primary factor for RGC loss. On the other hand, mRGCs damage is evident in neurodegenerative diseases, such as Alzheimer's disease, AD and Parkinson's disease, PD (La Morgia et al. 2013, 2016, 2017a).

It is not yet clear what the major factor of POAG development and progression are but, it shares numerous common etiological and pathogenic aspects with other neurodegenerative diseases, particularly with AD (Tsolaki et al. 2011).

While thus far circadian rhythm alteration in glaucoma is only poorly studied, considerably more is known about circadian abnormalities in other age-associated neurodegenerative diseases (Hood and Amir 2017; La Morgia et al. 2017a; Musiek 2015, 2017; Musiek et al. 2018; Ramirez et al. 2017; Stranahan 2012). The results of the present paper provide further support to the concept that different age-dependent neurodegenerative pathologies have common principles of circadian dysfunction (Gubin and Weinert 2015, 2016; La Morgia et al. 2017a; Videnovic and Zee 2015). Indeed, many aspects of circadian disruption in POAG resemble alterations in circadian physiology in certain neurodegenerative pathologies. For example, the circadian temperature phase delay and reduced phase robustness in progression POAG are very similar to what was found in AD (Harper et al. 2005; Satlin et al. 1995; Volicer et al. 2001), particularly an about 4.5-h phase delay (Satlin et al. 1995). One has to consider, however, that compromised circadian rhythms could be not only a consequence but also a cause for neurodegenerative pathologies (Bedrosian and Nelson 2012; Musiek 2017; Videnovic and Zee 2015). As has been shown for example, excessive artificial light-at-night or "poor circadian hygiene", which do cause circadian disruption, may promote the development of AD (Kress et al. 2018).

Future studies are necessary to scrutinize primary factors of circadian rhythm alterations that are evident in POAG and are closely coupled with RGC loss and dysfunction. Particularly, the distinct circadian temperature phase delay in POAG progression that was observed also in AD progression but is opposite to the general phase trend in aging, deserves close attention in future research. Moreover, around-the-clock tracking of BT allowing the assessment of its circadian phase can be an easy and simple way to discern early signs of certain neurodegenerative diseases, including POAG. It may also be helpful to reveal the factors causing the discrepancy of temperature phase trend in POAG and other neurodegenerative or neuroinflammation-associated pathologies versus healthy aging.

Conflict of interest

The authors report no conflicts of interest. They alone are responsible for the content and writing of the paper.

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