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Influence of sleep quality on macula and retinal nerve fiber layer in caucasian healthy adolescents: A cross-sectional assessment with optical coherence tomography

Influência da qualidade do sono na mácula e na camada de fibras nervosas da retina de adolescentes caucasianos saudáveis: uma avaliação transversal por tomografia de coerência ótica

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Abstract

Objective: *Poor sleep quality have affect on neuronal structure in central nervous system. We aimed to investigate the effects of sleep quality on the thickness of retinal nerve fiber layer (RNFL), macula, and ganglion cell complex (GCC) obtained by optical coherence tomography (OCT) in healthy Caucasian adolescents.* ***Methods:*** *In this prospective cross-sectional study,100 healthy adolescents were evaluated for determining of sleep quality score by the Pittsburgh sleep quality index(PSQI) and were monitored for detection of sleep efficiency(%) by Sense Wear PRO3 Armband mobile monitor(SWA). The sleep quality is evaluated based on the PSQI score and PSQI ≤5 was defined as "good sleep", and a score >5 was defined as "poor sleep". All subjects were scanned by spectral-domain OCT for the thicknesses of RNFL, GCC, and macular subfields.* ***Results:*** *Thirty nine of the subjects (39%) have poor sleep quality while 61 of them (61%) have good sleep. Inner superior (P=0.017), inner nasal (P=0.007), inner inferior (P=0.025), outer nasal (P= 0.011), and outer inferior (P=0.007) segments of macular thicknesses in the subjects with poor sleep are significantly thicker than those of the subjects with good sleep, whereas average RNFL of the adolescents with poor sleep is significantly thinner (P=0.02). All these parameters and central macular thickness have significant correlations with sleep efficiency and PSQI score (P<0.05).* ***Conclusion:*** *Sleep quality may have effects on macula and the nerve fiber layer of retina in adolescents and poor sleep may be related to decrease in the thickness of retinal nerve fiber layer.*

Keywords: *Sleep quality; Retina; Nerve fibers; Macula; Tomography, optical coherence/ methods; Adolescents*

Resumo

Objetivo: A má qualidade do sono afeta a estrutura neuronal do sistema nervoso central. O objetivo do presente estudo foi investigar os efeitos da qualidade do sono sobre a espessura da camada de fibras nervosas da retina (CFNR), a mácula e o complexo de células ganglionares (CCG) de adolescentes caucasianos saudáveis submetidos a tomografia de coerência ótica (TCO). **Metodologia:** O presente estudo transversal prospectivo avaliou 100 adolescentes saudáveis a fim de determinar o escore de qualidade do sono através do índice da qualidade do sono de Pittsburgh (PSQI); os participantes foram monitorados através do monitor móvel Sense Wear PRO3 Armband (SWA) a fim de detectar a eficiência do seu sono (%). A qualidade do sono foi avaliada com base no escore do PSQI; PSQI ≤ 5 foi definido como "sono de boa qualidade" e valores > 5 foram definidos como "sono de qualidade ruim". Todos os participantes foram submetidos a TCO no domínio espectral para avaliar a espessura dos subcampos CFNR, CCG e macular. **Resultados:** Trinta e nove participantes (39%) apresentaram sono de qualidade ruim, enquanto 61 (61%) apresentaram sono de boa qualidade. Os segmentos interno superior (P = 0,017), nasal interno (P = 0,007), inferior interno (P = 0,025), nasal externo (P = 0,011) e inferior externo (P = 0,007) de espessuras maculares dos indivíduos com sono de qualidade ruim foram significativamente mais espessos do que os de indivíduos com sono de boa qualidade, enquanto a CFNR média dos adolescentes com sono de qualidade ruim foi significativamente mais fina (P = 0,02). Todos esses parâmetros e a espessura macular central apresentaram correlações significativas com a eficiência do sono e com o escore do PSQI (P < 0,05). **Conclusão:** A qualidade do sono pode ter efeitos sobre a mácula e a camada de fibras nervosas da retina de adolescentes; além disso, o sono de qualidade ruim pode estar relacionado à diminuição da espessura da camada de fibras nervosas da retina.

Descritores: Qualidade do sono; Retina; Fibras nervosas; Mácula; Tomografia de coerência óptica/métodos; Adolescentes

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Introduction

Sleep is a physiological process that can affect cognitive functions and behavioral aspects in children and adolescents. During sleep many neurobiological processes take place that regulate physical and cognitive health.[1] In children, sleep disorders prominently affect the social life and school success. It has been clearly defined that children with sleep disorders have cognitive and learning deficits.[2,3]

Poor sleep may also cause loss of neuronal or axonal integrity.[4] MRI studies have linked primary insomnia with reduced volume of the orbitofrontal cortex,[5,6] hippocampus, [6] and precuneus [5] and in a longitudinal MRI study of sleep quality in healthy adults, it was found that cortical atrophy was correlated with sleep quality, and that the relationship increased with age.[7]

Glaucoma is also neurodegenerative disease and it is commonly related with loss of axons and ganglion cells in retina. Previous studies have reported associations between glaucoma and some sleep parameters, such as, shorter sleep duration, longer sleep latency, reduced sleep efficiency, and poor sleep quality. [8-12] Recently, Qui et al. revealed associations between glaucoma and abnormal sleep parameters in a cross-sectional study and they speculated that poor sleep quality may be a risk factor for glaucoma.[13] Poor sleep may destabilize axonal integrity and deteriorate white matter, but white matter pathology and axonal loss can also precede sleep complaints.[14] It was also known that the alterations in axonal density or retinal nerve fiber layer (RNFL) can be precisely detected in-vivo by optical coherence tomography (OCT) in patients with sleep disturbances.[15-17] RNFL is formed by retinal ganglion cell axons, so RNFL thickness is an important parameter to detect any axonal loss. RNLF thinning indicates retinal cell damage. Its thickness can be measured non-invasively using optical coherence tomography (OCT). Many studies have attested to the effectiveness and reliability of OCT measurement. In literature, it is the most commonly evaluated OCT parameter in patients with sleep disorders, especially in obstructive sleep apnea syndrome (OSAS),[15, 16, 18-21] and a decrease in RNFL thickness has been detected in OSAS patients by OCT, especially with severe disease.[15, 18] Although sleep quality is important for neuronal health, there is limited data about the associations of sleep quality with macula and retinal nerve fiber layer (RNFL) in healthy subjects, especially in children and adolescents.

In this prospective cross-sectional study, we aimed to investigate the association between the sleep quality and the thicknesses of macula, RNFL, and ganglion cell complex (GCC) obtained by spectral-domain OCT (RTVue-100; version 6.9; Optovue, Fremont, CA, USA) in healthy adolescents with no clinically diagnosed sleep disorder.

Methods

In this prospective cross-sectional study; 100 of 8th and 9th grade healthy students aged between 13 and 14 years who were living in the central district of Erzincan province were investigated. The study was performed in Erzincan Binali Yıldırım University Hospital between April 2017 and December 2018 and it was carried out in accordance with the Helsinki Declaration. The study was approved by local ethics committee and the Provincial Directorate of National Education. Informed consent was obtained from the parents of the subjects. Informed consent form was received from their families because the patients were under 18 years of age. Patients with the diagnosis or history of any ocular (strabismus, ambylopia, cataract, etc.) or systemic diseases, or sleep disorders were excluded from the study. Subjects with spherical equivalent < -1 diopter or > +1 diopter were also excluded to prevent the bias about the OCT measurements. Before the measurements of OCT and sleep quality, 20 of the 124 subjects were excluded from the study because of different reasons (systemic disease (n=1), ambylopia (n=3), myopia with <-1 diopter (n=16)).

Demographic features of study participants including age, gender; height and weight of the study participants were recorded. All patients are Caucasian geographical origin. Body mass index (BMI) was calculated as Weight/(Height)^2.

Complete ophthalmologic examinations of the subjects were performed. The best corrected visual acuity (BCVA) was determined with the Snellen chart. Intraocular pressure (IOP) was measured with Goldman applanation tonometry; anterior segment and fundus examinations were performed with biomicroscopy. Regarding ophthalmologic examination, IOP, BCVA and central corneal thickness (CCT) were recorded. The IOPs of all subjects were within the normal limits and there was no subject with glaucoma diagnosis or findings, or any glaucoma progression during the study period.

Sleep quality

Sleep quality in the children of the study was evaluated by Pittsburg sleep quality index (PSQI), and Sense Wear PRO3 Armband mobile monitor (SWA) was also used to assess the sleep efficiency to confirm the detection of sleep disturbance in an objective way.

The results of PSQI were recorded.[22] The questionnaire was self-administered during the patient visit in isolated room in which the subject feels free and comfortable when answering the questions. The PSQI is consisted of 19 questions in Turkish that ask for subjective sleep quality, sleep latency, duration, and sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. The sleep quality is evaluated based on the PSQI score which is associated with impaired sleep at elevating levels. A score ≤5 was defined as "good sleep", and a score >5 was defined as "poor sleep".

Sleep efficiency (%) was assessed by Sense Wear PRO3 Armband mobile monitor (SWA) (Body Media, Pittsburg, USA). [23] SWA was placed over the triceps muscle of the right arm, at the midpoint of humerus in all participants during sleep monitoring. The SWA is a portable sensing device and the sensors in the SWA measure skin temperature, galvanic skin response, heat flux from the body, and movement. The SWA accelerometer is similar to wrist actimeter or actigraphy, except for the fact that SWA is worn over the arm and it utilizes a dual axis accelerometer. The accelerometer uses a micro-electro-mechanical sensor device that detects and measures motion.[23] The data obtained from the SWA were analyzed by algorithms using Body Media Inner View Research Software (version 5.1) provided by BodyMedia, Inc.. These physiological data are then processed by advanced algorithms to calculate and report total energy expenditure, metabolic physical activity and sleep efficiency.[24] The parameter of sleep efficiency was defined as the percentage of time in bed when the subject was asleep (100 x total sleep time (minute) / time in bed (minute)) and it was automatically calculated by the software. All participants were monitored by the SWA for 24 hours and the sleep efficiency was recorded for analysis.

Four subject were excluded because of the discordance between PSQI score and sleep efficiency. Two of them had PSQI

score ≤ 5, but sleep efficiency under 80%, while two subjects had sleep efficiency over 80%, but PSQI score over 5.

OCT imaging

All eyes of the subjects were scanned by spectral-domain OCT (RTVue-100; version 6.9; Optovue, Fremont, CA, USA) for the thicknesses of macula and RNFL, and ganglion cell complex (GCC). All scans were performed in the morning between 9:00 and 11.00 am, by same experienced technician in a blind manner.

We performed full thickness-MM5 protocol (6mm) for macular measurements. Device software provides topographic image displayed with numeric averages of the thickness measurements for each of the 9 map sectors as defined by the Early Treatment of Diabetic Retinopathy Study.(25) In order to prevent Type I errors, we also used the thicknesses of inferior, superior, nasal and temporal quadrants in statistical analysis. OCT images were assessed by an examiner masked to the group of the patient. Centralization of the ETDRS plot over foveal center was checked and corrected if decentration was detected. Mean thickness values of each retinal layer in nine ETDRS subfields were recorded.

The GCC scan protocol used a horizontal line with a 7 mm scan length and 15 vertical lines with a 7 mm scan length. The GCC protocol explores parameters within a circle with a 6 mm diameter; the center of the GCC scan was shifted approximately 1 mm temporal to the fovea to improve the sampling of temporal peripheral nerve fibers. The variables generated by the GCC analysis included the average, superior, and inferior hemi-retinas.

The optic nerve head map protocol was applied for RNFL measurements. This protocol generated an RNFL thickness map that was measured along a circle 3.45 mm in diameter and centered on the optic disc. 3D disc protocol was used to register the edge of the optic nerve head. Only good quality images, as defined by a signal strength index > 30, were accepted. RNFL thickness parameters, including average, superior, and inferior RNFL calculated by the original software were used for analysis.

Statistical analyses

Statistical analysis was performed using the SPSS Version 23 (IBM, Inc., Chicago, IL, USA) program. The data about only right eyes of the subjects were used for analysis in the study. The normal distribution of the data was tested with the Kolmogorov Simirnov test. Mann-Whitney U-test was used to compare the parameters between the groups. Spearman's correlation coefficient was used to examine the relationships among the measured variables. P value lower than 0.05 was considered statistically significant.

Results

The number of the adolescents having PSQI score over 5 is 39 (39%) and in this group, the mean of PSQI score and sleep efficiency (%) are 8.46 ± 2.08 and 74.62 ± 6.09, respectively. This group is defined as 'the subjects with poor sleep' or 'the subjects with sleep disturbance'. The number of the adolescents having PSQI score ≤ 5 is 61 (61%) and the mean of PSQI score and sleep efficiency (%) in this group are 2.96 ± 1.34 and 87.89 ± 4.73, respectively. These are defined as 'the subjects with good sleep' or 'the subjects with no sleep disturbance'. When comparing the data of groups having good (PSQI ≤5) and poor sleep (PSQI >5) regarding PSQI score; the mean age, gender, BMI, CCT and IOP of study participants were not significantly different between the groups (Table 1). However, sleep efficiency determined with SWA device were significantly lower in patients with sleep disturbances (P < 0.00001). PSQI score and sleep efficiency detected by SWA have shown significantly high correlation (r = -0.92, P < 0.00001).

The parameters measured by OCT are summarized in table 2. In general, macular thicknesses for all ETDRS segments are higher in adolescents with poor sleep. But, the difference between the groups is statistically significant in inner superior (P = 0.017), inner nasal (P = 0.007), inner inferior (P = 0.025), outer nasal (P = 0.011), and outer inferior (P = 0.007) segments of the macula. The segments of inner superior, inner nasal, inner inferior, outer

Table 1
Comparison of demographic parameters, intraocular pressure (IOP), central corneal thickness (CCT), body mass index (BMI), and sleep efficiency are shown between the adolescents with poor sleep and those with good sleep.

	Subjects with good sleep	Subjects with poor sleep	
	PSQI ≤5 (n:61)	PSQI >5 (n:39)	P value
Age (years)	13.97 ± 0.26	14.0 ± 0	0.32
Gender (F/M)	31 / 30	18 / 21	0.31
IOP (mmHg)	13.94 ± 1.51	14.12 ± 1.63	0.42
CCT (μm)	538.90 ± 33.51	539.14±27.84	0.61
BMI (kg/m2)	20.46 ± 3.68	21.21 ± 3.33	0.13
Sleep Efficiency (%)	87.89 ± 4.73	74.62 ± 6.09	**< 0.00001**

All parameters are shown as mean ± standart deviation.
Mann-Whitney U-test is used for the comparison.
BMI: Body Mass Index; CCT: Central corneal thickness, IOP: Intraocular pressure, PSQI: Pittsburg sleep quality index.

Table 2
Comparison of the macular quadrants and segments, RNFL and GCC thicknesses between the adolescents with poor sleep and those with good sleep.

	Subjects with good sleep PSQI ≤5 (n:61)	Subjects with poor sleep PSQI >5 (n:39)	P value
CMT (μm)	240.37 ± 21.15	245.11 ± 21.41	0.18
Superior MT(μm)	300.11 ± 20.39	303.68 ± 20.33	0.050
Nasal MT(μm)	305.41 ± 16.42	310.87 ± 19.04	0.014
Inferior MT(μm)	287.06 ± 23.90	295.17 ± 25.06	0.003
Temporal MT(μm)	290.47 ± 14.58	292.87 ± 15.04	0.14
Inner Superior MT(μm)	308.83 ± 30.61	314.71 ± 31.31	0.025
Inner Nasal MT(μm)	312.97 ± 15.75	319.76 ± 17.85	0.011
Inner Inferior MT(μm)	307.90 ± 29.80	313.69 ± 37.60	0.007
Inner Temporal MT(μm)	304.07 ± 19.65	306.48 ± 18.63	0.245
Outer Superior MT(μm)	291.4 ± 20.78	292.65 ± 15.77	0.15
Outer Nasal MT(μm)	297.84 ± 21.70	301.97 ± 24.63	0.017
Outer Inferior MT(μm)	266.23 ± 31.65	274.65 ± 22.05	0.007
Outer Temporal MT(μm)	276.87 ± 14.63	279.25 ± 15.42	0.22
GCC-Average(μm)	92.71 ± 6.29	94.64 ± 10.04	0.53
GCC-Superior(μm)	93.22 ± 6.26	96.01 ± 10.16	0.13
GCC-Inferior(μm)	93.64 ± 5.60	95.42 ± 9.85	0.65
RNFL-Average(μm)	110.42 ± 9.26	107.28 ± 9.46	0.02
RNFL –Superior(μm)	114.57 ± 14.24	111.14 ± 15.41	0.06
RNFL – Inferior(μm)	103.68 ± 9.96	100.97 ± 9.26	0.11

All parameters are shown as mean ± standart deviation.
Mann-Whitney U-test is used for the comparison.
CMT: Central macular thickness, GCC: Ganglion cell complex, IOP: Intraocular pressure, MT: Macular thickness, PSQI: Pittsburg sleep quality index, RNFL: Retinal nerve fiber layer.

Table 3
Significant correlations between the sleep parameters and the parameters obtained by OCT in adolescents

	PSQI		Sleep Efficiency	
	r	P	r	P
Average RNFL Thickness	-0.14	0.039	0.15	0.029
Central Macular Thickness	0.16	0.021	-0.17	0.013
Inferior Macular Thickness	0.19	0.006	-0.16	0.020
Nasal Macular Thickness	0.15	0.033	-0.15	0.032
Inner Superior Macular Thickness	0.16	0.024	-0.15	0.035
Inner Nasal Macular Thickness	0.16	0.019	-0.17	0.015
Inner Inferior Macular Thickness	0.18	0.012	-0.16	0.023
Outer Nasal Macular Thickness	0.14	0.047	-0.13	0.046
Outer Inferior Macular Thickness	0.20	0.003	-0.16	0.017

Spearman correlation test were used for the analysis.
OCT: Optical coherence tomography; PSQI: Pittsburgh Sleep Quality Index; RNFL: Retinal nevre fiber layer.

nasal, outer inferior macula and central macular thickness are significantly correlated with PSQI score and sleep efficiency (P<0.05) (Table 3). Additionally, the thicknesses of nasal and inferior quadrants of macula are significantly thicker in subjects with poor sleep than those in the group of good sleep (P = 0.014 and P = 0.003, respectively.) and the thicknesses of the nasal and inferior segments are significantly correlated with PSQI score and sleep efficiency (P<0.05) (Table 3).

Average, superior, and inferior GCC is higher in children with poor sleep but this difference is statistically insignificant (P > 0.05). There is statistically significant difference between the groups for average RNFL (P = 0.02), while there is no difference

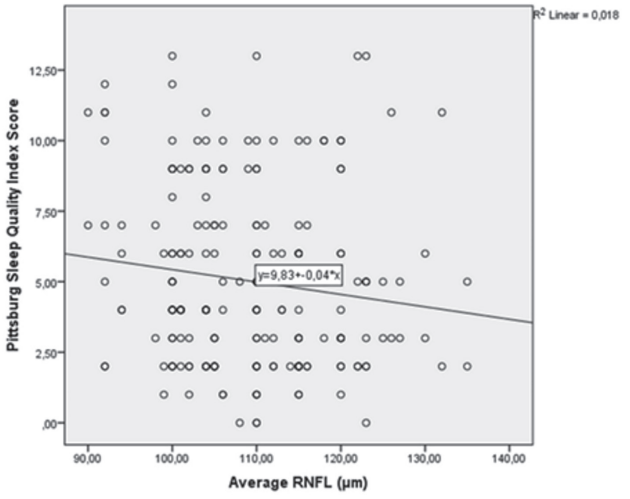

Figure 1. Scattergraph shows the correlation between PSQI score and average retinal nerve fiber layer thickness (RNFL) of the adolescents.

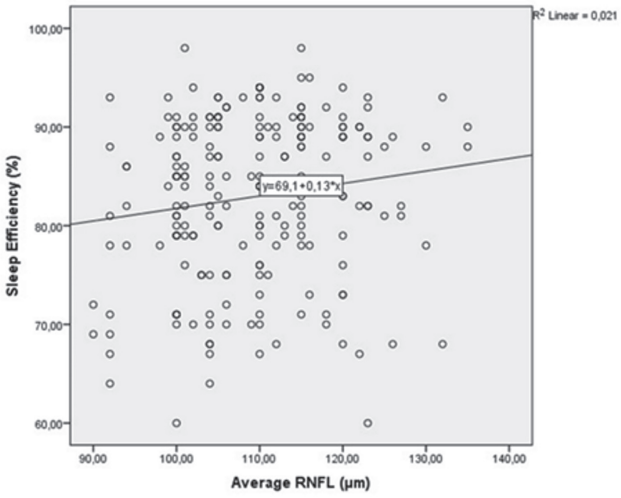

Figure 2. The correlation between the sleep efficiency (%) and average retinal nerve fiber layer thickness (RNFL) of the adolescents is demonstrated on the graph.

for superior and inferior RNFL (P > 0.05). Average RNFL is significantly correlated with PSQI score (r = -0.143, P =0.039) and sleep efficiency (r = 0.151, P = 0.029) (Figure 1 and 2).

Discussion

The exact functions and effects of sleep are unknown, but it was known that sleep is vital for neuronal health.[26] In some imaging studies, cross-sectional associations between poor sleep and microstructural alterations of white matter have been shown in insomnia patients and subjects with reduced sleep quality.[27] Poor sleep may deteriorate axonal function and integrity, white matter pathology and axonal loss can also cause sleep complaints.(14) Although previous studies showed the possible relationship between the sleep disturbances and glaucoma in adults,[8-12, 28, 29] it was not exactly known that whether the poor sleep is one of the main predisposing factors in glaucomatous axonal loss, or it is a consequence of axonal loss.

RNFL is formed by retinal ganglion cell axons, so RNFL thickness may be used for detection of any axonal loss causing by neurodegenerative disease; such as Alzheimer's disease, Parkinsonism, dementia, and glaucoma[30,31]. In literature, RNFL thickness is the most commonly evaluated ophthalmologic parameter in patients with sleep disorders, especially obstructive sleep apnea syndrome (OSAS).[15, 16, 18-21] Wang et al. showed that RNFL of all quadrants are thinner in patients with OSAS compared to controls.[15] Yazgan et al. reported that central macular choroidal thickness and RNFL were significantly thinner in OSAS patients compared with the controls.[19] Similarly, Koskderelioglu et al. also reported a significant thinning in RNFL but without any alterations in GCC thickness in patients with restless legs syndrome.[20] By contrast, Kara et al. found that GCC thickness in OSAS patients is much lower than in healthy population and it showed a significant correlation with the severity of OSAS.[32] In the present study, although the mean thickness of average RNFL in the subjects with poor sleep is significantly thinner than this of the subjects with good sleep, there is no difference between the groups for GCC thickness. So it may be speculated that poor sleep have significant effect on axonal structure and the loss of axonal integrity may be preceded in central nervous system by retrograde trans-synaptic degeneration in subjects with poor sleep quality, or there may be different mechanism for poor sleep unlike the possible mechanisms in OSAS.

OSAS occurs in 1% to 5% of children and polysomnography is needed to diagnose the condition because it may not be detected through history and physical examination alone.[33] In OSAS, one of the possible mechanisms is chronic hypoxia and it may have undesirable effects on neuronal tissue of the patients with OSAS. The duration and the severity of hypoxia may be suggested as the main factors affecting the results of sleep disturbances on IOP and RNFL thickness in OSAS.

We also determine significant correlation between RNFL values and sleep parameters (PSQI score and sleep efficiency) (Figure 1 and 2). Average RNFL thickness decreases as sleep quality and efficiency decrease. This suggests that sleep disturbance may begin to affect the nerve layer of retina in childhood even in children without clinically diagnosed OSAS. Additionally, it may be thought that the subclinical decrease in thickness of average RNFL because of poor sleep in childhood may yield to have risk of clinically significant axon loss or neurodegeneration in later of life.

There is no study investigating the macular thickness in children or adolescents with sleep disturbances. Xin et al. found that the macular thicknesses for all quadrants were thicker in adults with moderate or severe OSAS than the healthy controls.[17] In their study, statistically significant differences were found in only central (P = 0.001) and nasal (P = 0.016) quadrants of macula.[17] Additionally, they showed that OSAS patients have thinner choroidal thicknesses for all quadrants of macula, but, similarly, statistically significant difference was found in only central (P = 0.024) and nasal (P = 0.038) quadrants. They proposed that a sympathetic nervous regulation disorder exists in OSAS patients because of chronic intermittent hypoxia, which is followed by changes in the structure of the normal retina and choroid.[17]

In the study, PSQI subjective assessment was supported by an objective sleep monitoring (SWA) to confirm the diagnosis of poor sleep and we found high correlation between PSQI score and sleep efficiency detected by SWA in adolescents. Shariff et al. reported that SWA is a reliable and non-invasive method for determining sleep efficiency in the patients with OSAS when compared against the gold standard test (polysomnography) and

they suggested that it can be combined with portable sleep studies to determine sleep parameters. [23]

Epidemiologic studies indicate that up to 50% of children experience a sleep problem,[33] and about 4% of them have a formal diagnosis of sleep disorder.[34] In present study, 39 % of the adolescents had poor sleep quality and they were referred to a sleep clinic to be evaluated for sleep disorders and/or improvement of the sleep quality. Because the average RNFL thickness may be associated with sleep quality in healthy adolescents, the relative subclinic decline in RNFL thickness due to poor sleep in childhood or adolescence may be accelerated by aging and may be evident in older ages, they should be followed for these alterations.

The present study has several limitations. PSQI cannot replace the gold standard Polysomnography in assessing sleep quality. PSQI is a practical easy-to-use test. Polysomnography may not be always available and appropriate for the children and adolescents in clinical practice. The number of patients is the limitation of our study. Larger studies with long follow-up period are warranted to confirm the results of our study and determine the longitudinal effects of poor sleep in children and adolescents at different ages.

Conclusion

In conclusion, this study indicated that sleep quality and sleep effciency may have effects on retinal nerve fiber layer and macula thickness in healthy adolescents. Early diagnosis and treatment of poor sleep in children may prevent the premature axon loss and slow down the possible subclinic decline in RNFL thickness by aging in subjects with poor sleep.

Acknowledgements

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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