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Decreased sleep quality in patients suffering from retinitis pigmentosa

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SUMMARY The purpose of this study was to assess the prevalence of sleep disturbance in subjects diagnosed with retinitis pigmentosa (RP), as well as the influence of age and gender. Sleep quality was assessed, by means of the Pittsburgh Sleep Quality Index (PSQI), in people with RP ($n = 177$) and gender-and age-matched normally sighted individuals ($n = 491$). The population was divided, according to their age, in eight decade groups. People on shift-work, with affective disorders or with visual impairment other than RP, were excluded. The influence of cataracts in sleep quality was also studied in non-RP people ($n = 57$), with cataracts significantly impairing visual acuity. Another group of healthy controls ($n = 190$) was studied in different seasons of the year for a possible seasonality in sleep disturbance. Global sleep quality decreased in an age-dependent manner in RP-patients, especially from the second decade of life. Retinitis pigmentosa-patients showed, in relation to age-matched controls: lower subjective sleep quality and efficiency, longer sleep latency, shorter sleep duration, higher daytime dysfunction and a higher use of sleeping medication. No significant differences in sleep quality were found among RP-patients or controls depending either on their gender or on the presence of cataracts. Normal sighted individuals did not show seasonality in their sleep quality. We conclude that the sleep quality of RP-patients decreases in an age-dependent manner and points to the probably degeneration of photoreceptors mediating the photic input to the suprachiasmatic nuclei of the hypothalamus in this disease.

KEYWORDS PSQI, retinitis pigmentosa, sleep disturbance

INTRODUCTION

Current knowledge supports the idea that photic input from the retina to the endogenous clock, located in the suprachiasmatic nuclei of the hypothalamus (SCN), is the main zeitgeber to synchronize endogenous circadian rhythms with the environmental light–dark cycle in mammals (Turek 1985). It has been shown, in some completely blind humans, that several endogenous rhythms (cortisol, melatonin, temperature,…) free-run independently of the environmental lighting conditions (Miles *et al.* 1977; Nakagawa *et al.* 1992; Sack *et al.* 1992; Tzischinsky *et al.* 1991). As one of the rhythms under the control of the SCN is the sleep–wake cycle, it has been proposed that loss of its synchronization is the primary reason for the high prevalence of sleep disorders among the blind community (Czeisler *et al.* 1981; Leger *et al.* 1999; Lockley *et al.* 1999; Tabandeh *et al.* 1998).

Retinitis pigmentosa (RP) is a syndromic degenerative disorder, with a polymorphic hereditary basis, in which there is a primary and progressive degeneration of photoreceptors, rods in the first stage, and later rods and cones, leading to nightblindness (Nyctalopia) and progressive visual field loss (Pagon 1988; Van Soest *et al.* 1999). The prevalence of this disease is of 1 in 4000 people, which indicates that it afflicts about 1.5 million humans worldwide (Nathans *et al.* 1992).

The question of which are the retinal photoreceptors mediating the photic input to SCN responsible for the entrainment of the circadian rhythms is still a subject of study. Some of the specific photoreceptors mediating

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synchronization of circadian rhythms could be affected in RP; furthermore, the reduced visual field could decrease the light input to the SCN in RP patients. Because of these two facts, the overt rhythms (among them the wake–sleep rhythm) in RP affected subjects would be abnormally entrained, poorly entrained (day-to-day instability) or free-run, depending on the degree of retinal impairment, and sleep troubles could be present in these patients. The objective of the present work was to evaluate the prevalence of sleep troubles in patients suffering from RP. The recognition of the sleep disorders of possible circadian origin in RP subjects has an important clinical significance as these patients, in order to improve their sleep quality, could be treated with chronotherapeutic approaches, rather than the unsuccessful attempts at entrainment with conventional medication (Arendt *et al*. 1988; Dijk *et al*. 1995).

METHODS

Subjects

A total of 177 people with RP were included in the study. These subjects were recruited through the local Associations for RP Affected Individuals of different Spanish regions. In all cases patients had been diagnosed with RP by the local services of Ophthalmology in accordance with the consensus criteria of 1982 (Anonymous 1983; Pagon 1988). Subjects were classed according to their age in any of eight decade groups, the first starting at 10-year-old and the last for those over 80. People on shift-work, with psychiatric disorders (evaluated by the Montgomery–Asberg Depression Rating Scale), and those with severe visual impairment other than RP, were not included in the study.

A control group of people without ocular disease ($n = 491$) matched by gender, age, geographical location, employment status and social life, was recruited from people attending the outpatients departments of the University Hospital 'Marqués de Valdecilla' (Santander, Spain), as well as from randomly selected volunteers among the populations of the same regions that RP patients came from.

A group of non-RP people ($n = 57$) but undergoing surgery because of the presence of cataracts which significantly impaired their visual acuity were also included in the trial, in order to study whether the presence of cataracts, with the subsequent decrease of light perception, could disturb sleep quality.

Informed consent was obtained from all patients and control subjects before they entered the study.

Evaluation of the subjective sleep quality

Sleep quality was assessed by means of the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire of 19 individual items generating seven 'component' scores: subjective sleep quality, sleep latency (time needed to fall asleep), sleep duration, habitual sleep efficiency (proportion between total sleep time and time in bed), sleep disturbances (i.e. waking up during night), use of sleeping medication and daytime dysfunction (difficulty to stay awake during the day) (Buysse *et al*. 1989). Each of these 'components' can equally score 0–3 points, to make a global PSQI score with a possible range from 0 to 21. A score ≥5 is usually considered as indicative of subjective sleep disorder (Buysse *et al*. 1989), with higher scoring indicating more sleep problems. Each subject (RP or control) was administered the PSQI questionnaire to assess sleep quality during the preceding month.

The study was carried out over 2 years. During this period, healthy controls (age of 40–59 years; $n = 190$) were recruited and interviewed in spring, summer, fall and winter in order to discard a seasonal pattern in sleep quality.

Statistics

Results were expressed as mean ± SEM and were analysed with the SPSS computer software by using parametric two-ways ANOVA, the ways being: age (eight decade intervals) and case (RP or control). Parametric multiway ANOVA were used to evaluate the interaction of variables such as gender, presence or not of cataracts, and season, with the main variables (age and case). Differences in the frequency of sleep disturbances (PSQI score ≥5) between controls and RP-patients were assessed by means of the χ^2-test.

RESULTS

Figure 1(A) shows the prevalence of sleep disorder, assessed as people scoring 5 or more in the PSQI questionnaire, among subjects affected by RP and controls. The prevalence of sleep troubles was higher in RP patients than in controls, the differences being significant (χ^2-analysis of frequency), when considering case (RP or control), age (eight decade intervals) or subjective sleeping quality (PSQI score lower or higher than 5) ($P < 0.001$ in all cases). As expected, global sleep quality decreased with age in healthy controls ($F = 25.0$, $P < 0.001$), as well as in patients with RP ($F = 14.0$, $P < 0.001$); however, the most important decrease in sleep quality was found for RP patients (Fig. 1B). The two-way ANOVA revealed significant differences depending on age ($F_{7,664} = 29.2$, $P < 0.001$) and on RP condition ($F_{1,664} = 42.1$, $P < 0.0001$), as well as a significant interaction between the main factors (age and RP condition) ($F_{7,664} = 2.2$, $P < 0.05$). The differences in global sleep quality between control and RP patients are evident from the second decade of life, but not before. The individualized analysis of the different items scored in the PSQI, according to age and RP/control condition (Fig. 2), revealed that RP patients have, in relation to age matched controls: lower subjective sleep quality ($F = 8.1$, $P < 0.005$), longer sleep latency ($F = 15.3$, $P < 0.0001$), shorter sleep duration ($F = 15.5$, $P < 0.0001$), lower habitual sleep efficiency ($F = 23.6$, $P < 0.0001$), higher daytime dysfunction ($F = 12.9$, $P < 0.0001$) and a higher use of sleeping medication ($F = 15.9$, $P < 0.0001$); however, no differences were appreciated in sleep disturbances ($F = 3.7$, $P = 0.056$).

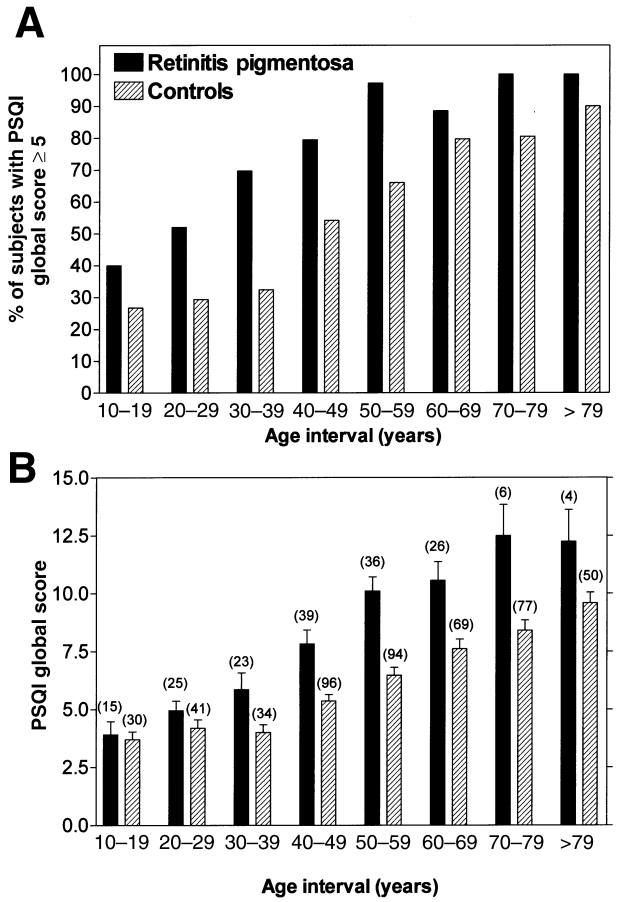

Figure 1. (A) Prevalence of sleep disorders (percentage of subjects with a PSQI score ≥5) among people suffering from RP and healthy controls at different age intervals. The χ^2-analysis of frequency gives significant differences ($P < 0.001$) when considering case (RP or control), age (the eight decade interval), and sleep quality (PSQI score higher or lower than 5). (B) Sleep quality evaluated by the PSQI questionnaire in patients suffering RP and age-matched healthy controls: global scores. Results are indicated as mean ± SEM. The number of cases is indicated in brackets.

We did not find any significant difference in sleep quality according to gender for both RP patients and controls at any of the age intervals studied (data not shown). There were no differences in PSQI value either between healthy controls and those with cataracts or between RP patients with or without cataracts (data not shown). The PSQI value in healthy controls (40–59-year-old) studied throughout the year cycle did not show differences depending on the season of the year in which the analysis was carried out (data not shown).

DISCUSSION

Retinitis pigmentosa (RP) is the general term given to a group of degenerative disorders affecting the outer segment of the retina causing nightblindness and progressive loss of visual field (Pagon 1988). Light is the main synchronizer of the circadian pacemaker located in the SCN which regulates the wakefulness/sleep rhythm (Czeisler *et al.* 1980; Djik and Duffy 1999; Monk 1991). The hypothesis that any degree of visual loss would decrease the light input to the SCN, thus affecting the correct synchronization of the circadian rhythms, implies that persons with severe visual impairment, such as RP people, could show a high prevalence of sleep disorders. Sleep troubles have been described in blind people (Czeisler *et al.* 1981; Leger *et al.* 1999; Lockley *et al.* 1999; Miles *et al.* 1977; Sack *et al.* 1992; Tabandeh *et al.* 1998); however, the prevalence of sleep disturbances in subjects with only a partial loss of vision, such as the RP had not been studied. We achieved this objective by using the PSQI as a validated tool to evaluate the subjective sleep quality (Buysse *et al.* 1989). A global PSQI score higher than 5 yields a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing good and poor sleepers (Buysse *et al.* 1989), this being the reason we used a cut off score of 5 to consider the existence of sleep troubles. Our results show that 76% of the RP-patients have sleep troubles (global PSQI ≥5) and the prevalence rises to 95% when considering people older than 50. Sleep quality has been described as decreasing with age (Djik and Duffy 1999; Myers and Badia 1995). In our study the sleep quality in healthy controls decreases with age although, after the second decade, at each age interval studied, sleep quality always was significantly lower in RP patients. Among the different 'components' of the global sleep quality evaluated with the PSQI questionnaire, the most affected in RP patients were sleep efficiency, sleep duration and sleep latency. The timing of sleep is under the control of the endogenous circadian pacemaker (Dijk *et al.* 1995), and the increase of the sleep latency could be the primary sleep disorder of RP-patients because the reduction in the sleep duration could be subsequent to a combination of the late instauration of the sleep and the socially defined time for waking-up. Daytime sleepiness as well as the greater use of sleeping-pills can also be explained as secondary to the above mentioned factors.

The lack of gender-difference in sleep quality among RP or normal sighted people at all the age intervals studied indicate that menopausal status, or the behavioural changes associated with retirement, do not increase the incidence of sleep disorders. This result agrees with that reported in a recent cross-sectional analysis carried out in 521 women (Owens and Matthews 1998). However, the same authors have found, in longitudinal analyses, that the transition from pre to post-menopausal status was associated with a significant increase in sleep disturbance in women without hormone replacement therapy.

Seasonality in human sleep has been described in previous studies (Honma *et al.* 1992; Kohsaka *et al.* 1992; Wirz-Justice *et al.* 1984). Because the collection of the data for our studies took place over 2 years, we considered it interesting to analyse the existence of a possible seasonal component in the PSQI scores, which could mask the results depending on the time when the questionnaire was administered. We do not, however, appreciate seasonal changes in sleep quality of the 190 normally sighted people studied in the sample. The differences between our experimental design and those of the

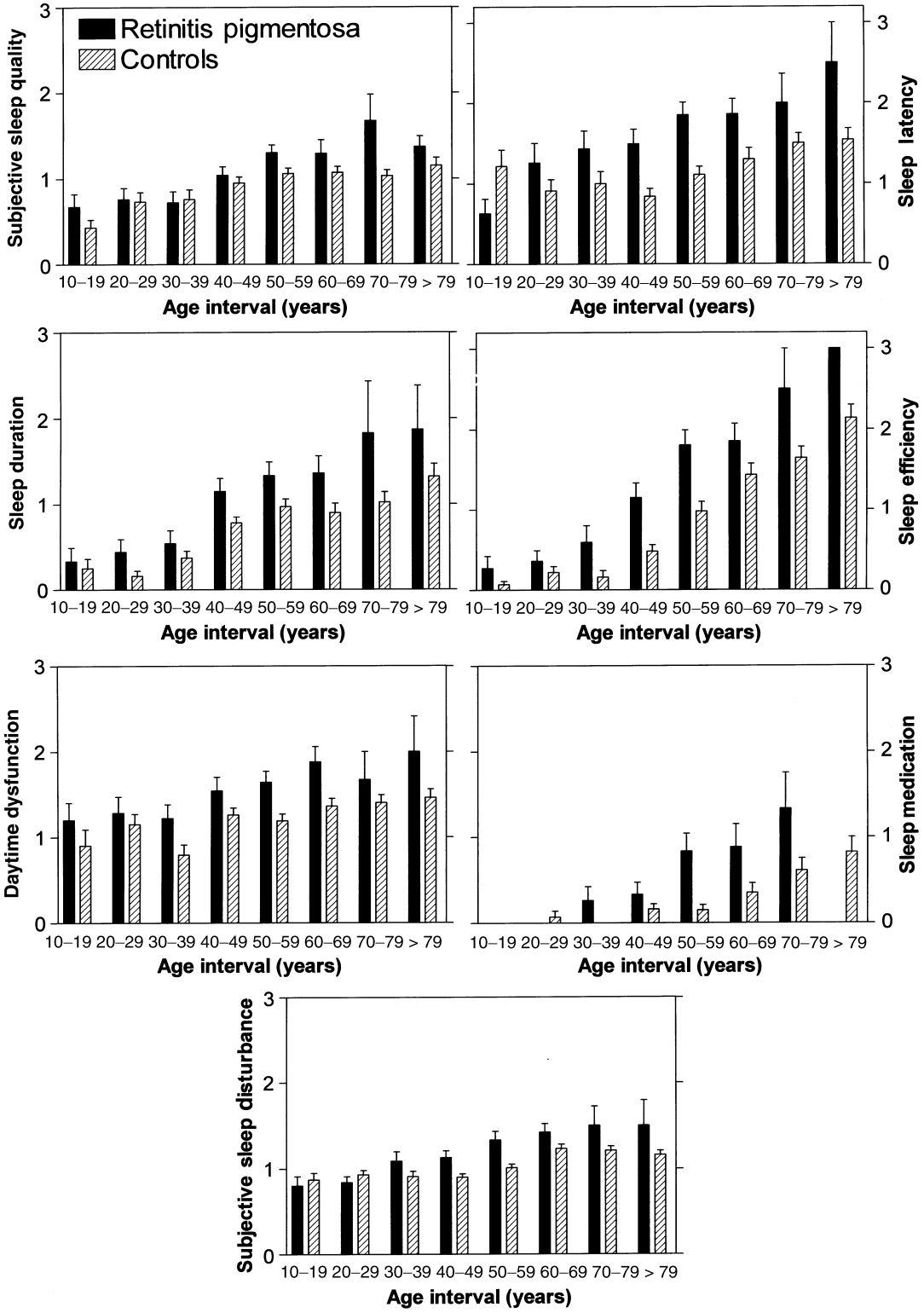

Figure 2. Sleep quality evaluated by the PSQI questionnaire: scores of the seven 'components' of the PSQI in patients suffering RP (black bars) and age-matched healthy controls (hatched bars). Results are indicated as mean ± SEM. The number of cases is indicated in Figure 1(B) and is the same for all the panels. All graphs have been plotted with the same values on the *Y*-axis (3, corresponding to the highest possible score) in order to allow the appreciation of the relative weight of each 'component' in the global score.

above mentioned authors concerning the number of cases included in the trial, the nature of the the study (longitudinal instead of cross-sectional), the age of the subjects, or the general conditions (subject living in community or in isolation, latitude of the laboratory site.), could explain the discrepancy of the results.

The entrainment effect of the light–dark cycle on the sleep-wakefulness rhythm is achieved through complex neurohumoral connections involving basically the SCN (retinohypothalamic and geniculohypothalamic tracts) and the pineal gland (Kohsaka *et al*. 1992; Moore 1992; Myers and Badia 1995; Rusak 1977).The retinal photoreceptors mediating the photic input to the SCN are, however, still unknown. It has been proposed that photoreceptors with cone-like characteristics could be involved in the synchronization of circadian rhythms in mice and hamsters (Foster *et al*. 1991; García-Fernández *et al*. 1995; Nelson and Takahashi 1991; Provencio and Foster 1995). However, a normal trichromatic visual system, which is cone-dependent, does not seem to be necessary for light-mediated neuroendocrine regulation in humans (Ruberg *et al*. 1996). The photoreceptors involved in the entraining of the SCN may not be the same cells mediating the vision (Morin 1994). Recently, a new opsin (melanopsin), which is expressed in the ganglion and amacrine cell layers, has been proposed as the mediator of the nonvisual photoreceptive pathway regulating the circadian rhythms (Provencio *et al*. 2000). The question of which are the retinal lesions in the RP subjects responsible for the alteration of the photic input to SCN and, subsequently, of the sleep troubles, go beyond the objectives of this work. By using the inhibition of melatonin secretion as an indicator of the light input to the SCN and pineal gland, it has been demonstrated that graded responses can be obtained by modulating the light intensity (McIntyre *et al*. 1989). On this basis, the sleep disturbances found in RP subjects could be explained merely by the reduction of the photic input to the circadian system, because of the reduction of visual field. However, retinal degeneration may also be involved because the presence of cataracts, a common feature in all forms of RP (Heckenlively 1982), which could contribute to the loss of light perception, did not influence sleep quality in comparison with RP patients without cataracts. Even among controls, those with cataracts which significantly impair visual acuity showed values of PSQI similar to those without cataracts. In a recent study on a population of blind people with light perception, the authors reported a prevalence of sleep disorders in less than 50% of cases (Tabandeh *et al*. 1998), which contrasts with our results (76% of cases with sleep troubles) and which could be explained because of the specific retinal pathology in RP-patients.

Our study has some limitations that deserve comment. First, sleep problems were assessed by a self-reporting questionnaire and were not confirmed by polysomnographic measurements. However, the PSQI has been largely validated and widely used as a sufficiently precise tool to discriminate between people with or without sleep troubles. The second comment concerns the question of whether the sleep disturbance of RP patients is specifically connected with their retinal pathology or represents a typical form of sleep trouble of patients with chronic illness. The relationship between insomnia and chronic illness is well known (Katz and McHorney 1998), but, however, sleep disturbances in chronic illness are usually related to the specific pathophysiological mechanisms of each disease (pain, gastro-esophageal reflux, nicturia, elevated carbondioxide concentration, dysnea, etc.) and those causes were not present in the RP patients, or at least there was no greater incidence than in matched controls. Finally, whether circadian rhythm disorders, because of alterations in the photic input to the SCN, are the origin of sleep troubles in RP patients would require specific demonstrations. We are now studying in the RP patients the rhythms of cortisol and melatonin in urine samples collected over 2 days of four consecutive weeks, in order to assess whether they are synchronized with the light–dark cycle, at which phase angle, or free running. However, and despite the absence of objective demonstration of circadian rhythm disorders in RP patients, some indirect data from the present work, such as the increased sleep latency and the fact that retinal lesions but not cataracts increased the prevalence of sleep troubles, point towards the above-mentioned etiological hypothesis.

Taken together, our results clearly show that the sleep quality of patients suffering from RP is significantly decreased. The reason for this reduction in sleep quality could be found in the degeneration of photoreceptors mediating the photic input to the SCN in this disease. Recognition of disturbance of sleep in RP patients is also relevant to management, because sleep patterns of these patients could be improved by treatment with chronotherapeutic approaches.

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