ORIGINAL ARTICLE

Actigraphic study of sleep behaviour in sickling patients

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Abstract

Present study was an attempt to evaluate sleep parameters and characteristics of circadian rhythm in rest-activity in sickle cell diseased patients. Rest-activity rhythm was studied on ten patients (6 males and 4 females) non-invasively with the help of wrist actigraphy, and compared with 10 age-matched normal subjects (6 males and 4 females). Several sleep parameters, such as time in bed, assumed sleep, actual sleep time, actual wake time, sleep efficiency, sleep latency, and fragmentation index were recorded by selecting fifteen second epoch length for collection of data. The results of the present study validated a statistically significant circadian rhythm in rest-activity for all subjects with drastic alteration in circadian rhythm parameters in sickling patients. Dichotomy index declined significantly in the group of sickling patients. Results of sleep parameters revealed that sickling patients had lower assumed sleep duration, and exhibited less sleep efficiency as compared to that of the control subjects. More sleep latency and higher fragmentation index indicates deterioration of sleep among sickling patients. In conclusion, the results of the present study document disruption of circadian rhythm and sleep impairment in sickling patients. Alterations of circadian rhythm and deterioration of sleep could be attributed to diseased status.

Keywords: Autocorrelation, Circadian rhythm, Dichotomy index, Rest-activity rhythm, Sickle cell disease, Sleep

Introduction

Alterations in the characteristics of circadian rhythm can influence the sleep- wake cycle and many other aspects of human physiology, such as mood, cognition and alertness. [1-2]

If the timing is altered or lost, performance is suboptimal, which may be manifested as compromised adaptation to stress and illness. Even though it is not obvious whether illness disrupts biological rhythms or disrupted biological rhythms lead to illness, the association between rhythm disruption and illness is well documented by several authors.[3-4] Moreover, sleep wake schedule disorders includes common characteristic of the patients inability to fall asleep and wake up at desired times.[5] Examining an individual's circadian phase is important for designing treatment of various circadian rhythm sleep disorders. Alteration in circadian system function of rest activity rhythm was investigated in subjects suffering from various diseases, such as chronic back pain, insomnia, Alzheimer's dementia, and cancer. [6-10] Several other studies have described sleep problems in mentally retarded persons.[11-13] However, very few efforts have been made to study circadian rhythm in

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patients with sickle cell disease. Sickle cell is a genetic disease, which occurs due to abnormality in red blood cell. It is observed that patients with sickle cell below 5years had Obstructive Sleep Apnea (OSA).[14] In sickle cell, patients face chronic pain problem mainly at nighttime. Enlarged tonsil and adenoids are the biggest contributing factors for OSA resulting in snoring and sleep deprivation. Besides this, a chronic pain crisis occurs mainly at night causing sleep disturbance. However literature in sleep impairment due to chronic pain during sleep is limited. Therefore, an attempt was made to study the rest-activity rhythm and evaluate sleep parameters in sickle cell diseased patients.

Material and methods

Twenty subjects consisting of 10 controls (6 males, 4 females; median age: 32, range 22-39 years; average ± SE of BMI: 21.49 ± 1.12) and 10 patients with sickle cell anemia (6 males, 4 females; median age: 32, range 22-39 years; average ± SE of BMI: 20.01 ± 1.19) contributed their voluntary participation in the present study. They were examined in free-living conditions. Patients were identified as sickle cell diseased after given a confirmed diagnosis of sickling by the doctor. The study was approved by the Ethics Committee of the Pt. J.N.M. Medical College, Raipur. Prior to beginning of data collection, the subjects were explained about the procedure of measurement. Patients did not show any signs of other complications. They were in good health and participated in their usual daily activities. During the study period they were not under the influence of drugs or alcohol. Both patients and control subjects gave a written informed consent.

Assessment of the characteristics of circadian rhythm in rest-activity

The rest-activity rhythm of all the sickling patients was monitored non-invasively by wrist actigraphy (Actiwatch, Model AW64, Mini Mitter Co., Inc., USA) worn on the non-dominant arm over a continuous four-day span. The subjects maintained a daily dairy that contained various types of information, like going to bed time approximate sleep start time, awakening time, getting off the bed time, Actiwatch wearing time and Actiwatch removal time. Fifteen-second epoch length was selected for gathering actigraphy data. In addition, several sleep parameters, such as time in bed, assumed sleep, actual sleep time, actual wake time, sleep efficiency, sleep latency, sleep bouts, wake bouts and fragmentation index were also recorded.

Statistical analysis

The circadian rhythm characteristics, such as Mesor (M), amplitude (A), and peak or acrophase (Ø) were estimated from the log-transformed data.[15] at two different fixed windows, namely t = 24 h and t =12 h. 12-h period was selected since bimodality in activity pattern was perceived in the periodograms/ actograms of most of the subjects. Harmonic means were calculated for M, A, and Ø obtained at both windows. Power Spectrum Analysis software[16] was utilized to determine prominent period (ô). Autocorrelation analyses were also applied to derive the autocorrelation coefficient at t = 24 h, i.e., *r*24, to obtain another measure of the regularity of the activity pattern over 24 h. The dichotomy index, *I<O*, differences in activity distribution between daily activity and rest spans were also computed. The value of this index can vary between 0% and 100%. In the case of a marked circadian rhythm with complete rest at night and high activity during daytime, *I<O* reaches 100%.

Results

Rest-activity rhythm

Actograms of the rest-activity patterns in a sickling patient and a control subject have been shown in Figure 1 (A, B). It was revealed that the sickling patient exhibited marked activity during sleep. The level and intensity of activity were higher in the control subject than sickling patients.

Rhythm detection

Tables 1-2 are the summary of the results of Cosinor rhythmometry of the time series on rest-activity rhythm in sickling patients and control subjects. Results indicate a statistically significant circadian rhythm (ô=24h) in rest-activity in all patients and control subjects. Subjects also exhibited statistically significant 12-h rhythmicity in rest-activity. The harmonic means of the Mesors, amplitudes, and acrophases obtained separately for the 24- and 12-h periods were computed and shown in Table 1-2.

A: SCD Patient

B: Control subject

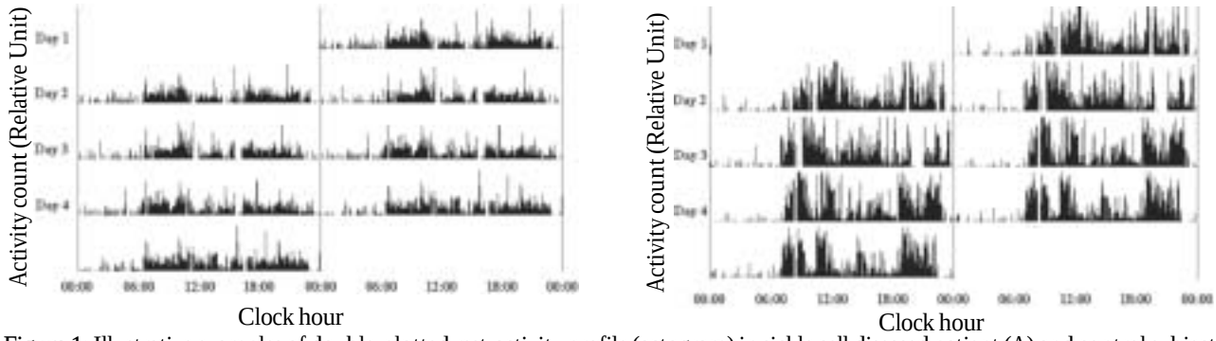

Figure 1: Illustrative examples of double-plotted rest-activity profile (actogram) in sickle cell diseased patient (A) and control subject (B) Abscissa depicts clock hour of the day Each row represents two 24-h spans, ie, for a given day and the following day The height of the black marks in each row indicates the level of activity (counts in relative unit) for the corresponding time in the abscissa Actogram of sickling patient reveal marked activity in the nighttime

Table 1: Cosinor Summary: Characteristics of rest-activity rhythm in sickle cell diseased patients Rhythm parameters were computed at fixed windows with ô = 24 h or ô = 12 h The harmonic means of each parameter obtained at ô = 24 h and ô = 12 h were also calculated

	Fitted period	Data	Rhythm	Mean	Amplitude	Acrophase
S#01	24	7252	< 0001	158 ± 0010	82 (077, 086)	143 (1407, 1448)
	12	7252	< 0001	157 ± 001	062 (057, 066)	85 (839, 868)
	24 + 12[b]			158	070	107
S#02	24	8135	< 0001	164 ± 001	074 (070, 079)	151 (1487, 1531)
	12	8135	< 0001	159 ± 001	064 (059, 068)	84 (826, 853)
	24 + 12[b]			161	069	108
S # 03	24	7161	< 0001	179 ± 001	087 (083, 091)	147 (1453, 1488)
	12	7161	< 0001	179 ± 001	051 (046, 055)	80 (778, 812)
	24 + 12[b]			179	064	103
S # 04	24	7631	< 0001	142 ± 001	083 (079, 087)	136 (1344, 1383)
	12	7631	< 0001	146 ± 001	040 (035, 044)	98 (958, 1003)
	24 + 12[b]			144	054	114
S # 05	24	6761	<0001	167 ± 001	108 (103, 112)	145 (1438, 1466)
	12	6761	<0001	160 ± 001	059 (054, 064)	86 (841, 873)
	24 + 12[b]			163	076	108
S # 06	24	7088	< 0001	159 ± 001	094 (090, 097)	155 (1533, 1563)
	12	7088	< 0001	160 ± 001	039 (034, 043)	89 (867, 911)
	24 + 12[b]			160	055	113
S # 07	24	8984	< 0001	163 ± 001	061 (057, 065)	167 (1640, 1691)
	12	8984	< 0001	164 ± 001	043 (039, 047)	110 (1082, 1119)
	24 + 12[b]			164	050	133
S # 08	24	7137	< 0001	147 ± 001	074 (070, 078)	147 (1447, 1491)
	12	7137	< 0001	147 ± 001	084 (080, 088)	84 (826, 845)
	24 + 12[b]			147	079	107
S # 09	24	4022	< 0001	222 ± 001	028 (025, 031)	149 (1457, 1525)
	12	4022	< 0001	228 ± 001	010 (007, 012)	78 (719, 832)
	24 + 12[b]			225	014	102
S # 10	24	7161	<0001	138 ± 001	057 (053, 061)	1401 (1374, 1428)
	12	7161	<0001	137 ± 001	057 (053, 061)	81 (794, 821)
	24 + 12[b]			137	057	102

Table 2: Cosinor Summary: Characteristics of rest-activity rhythm in control subjects Rhythm parameters were computed at fixed windows with ô = 24 h or ô = 12 h The harmonic means of each parameter obtained at ô = 24 h and ô = 12 h were also calculated

Subject code	Fitted tau Period	Data point	Rhythm detection	Rhythm adjusted mean, (M ± SE)	Amplitude, A (95%CL)	Acrophase, Ø in h (95%CL)
C # 01	24 12 24 + 12[b]	584	< 0001 < 0001	292 ± 003 292 ± 004 292 077	091 (077,104) 067 (052, 081) 1104	151 (145, 156) 087 (083, 091)
C # 02	24 12 24 + 12[b]	600	< 0001 < 0001	298 ± 003 302 ± 003 300 058	062 (051, 073) 055 (044, 067) 997	138 (130, 145) 078 (074, 082)
C # 03	24 12 24 + 12[b]	585	< 0001 < 0001	274 ± 004 274 ± 004 274 067	071 (055, 086) 064 (048, 080) 1137	164 (155, 172) 087 (082, 092)
C # 04	24 12 24 + 12[b]	726	< 0001 < 0001	286 ± 003 286 ± 003 286 043	076 (065, 087) 030 (017, 043) 1064	155 (149,160) 081 (072, 089)
C # 05	24 12 24 + 12[b]	15892	<0001 <0001	150 ± 001 150 ± 001 150 066	091 (088, 093) 052 (049, 055) 147	161 (160, 162) 103 (102, 104)
C # 06	24 12 24 + 12[b]	15841	<0001 <0001	141 ± 001 141 ± 001 141 059	098 (096, 101) 042 (039, 045) 148	163 (162, 164) 103 (101, 104)
C # 07	24 12 24 + 12[b]	551	< 0001 < 0001	271 ± 003 275 ± 004 273 080	111 (098, 124) 062 (046, 079) 973	132 (127, 136) 077 (072, 082)
C # 08	24 12 24 + 12[b]	707	< 0001 < 0001	247 ± 004 246 ± 004 246 064	076 (061, 091) 056 (040, 072) 1297	181 (173, 189) 101 (095, 106)
C # 09	24 12 24 + 12[b]	583	< 0001 < 0001	290 ± 004 290 ± 004 290 087	106 (092, 120) 074 (058, 090) 986	137 (132, 142) 077 (073, 081)
C # 10	24 12 24 + 12[b]	576	< 0001 < 0001	294 ± 003 294 ± 004 294	103 (091, 114) 057 (043, 072) 073	153 (148, 157) 093 (088, 097) 1157

Circadian 24-h average (Mesor)

The averages of Mesors for each group obtained at fixed windows of 24 h, 12 h and their harmonic means are given in Table 3. The results of Cosinor rhythmometry indicated inter-individual differences in the level of 24-h average activity in sickling patients and control subjects (Table 1 and 2). Results showed statistically significant ($p < 0.001$) difference in the harmonic means of the Mesors of the activity rhythm between sickling patients and control subjects (Table 3). This difference was also statistically significantly validated for the data obtained at a fixed window with t = 12 h and t = 24 h (Table 3).

Circadian amplitude

Variation at inter-individual and group circadian amplitudes of the rest-activity rhythm was observed in both groups (Table 1 and 2). The harmonic means of the amplitude of the rest-activity rhythm in the sickling patients were significantly lower ($p < 0.001$) as compared to control subjects (Table 3).

Circadian peak (acrophase)

A statistically significant ($p < 0.001$) difference was noticed for the average timing of the peaks between the

Table 3: Summary of the characteristics of circadian rhythm in rest-activity of sickle cell diseased patients and control subjects. Rhythm parameters were computed at fixed windows with *t*= 24 h or *t* = 12 h. The harmonic means of each parameter obtained at *t* = 24 h and *t* = 12 h were also calculated.

Variable	Mean ± SE Sickle cell diseased Patients	Mean ± SE Control subjects	*t-testdf*, *t*-value, *p* value Sickling patients *vs.* Control
Rhythm parameters at t = 24 h			
24-h average, M	1.64 ± 0.08	2.55 ± 0.19	18, 4.45, <0.001
Amplitude, A	0.51 ± 0.06	0.56 ± 0.04	18, 0.69, 0.25
Acrophase, Ø in h	8.73 ± 0.31	8.87 ± 0.34	18, 0.30, 0.38
Rhythm parameters at t = 12 h			
24-h average, M	1.64 ± 0.08	2.54 ± 0.19	18, 4.47, <0.001
Amplitude, A	0.75 ± 0.07	0.89 ± 0.05	18, 1.59, 0.06
Acrophase, Ø in h	14.80 ± 0.27	15.35 ± 0.47	18, 1.02, 0.16
Rhythm parameters (Harmonic mean)			
24-h average, M	1.58 ± 0.01	2.55 ± 0.19	18, 5.09, <0.001
Amplitude, A	0.43 ± 0.01	0.67 ± 0.04	18, 6.11, <0.001
Acrophase, Ø in h	10.98 ± 0.29	11.24 ± 0.39	18, 0.07, 0.47

two groups. The average harmonic mean of the circadian acrophase of the rest-activity rhythm of the control and sickling patients were witnessed (11.24 ± 0.39) and (10.98 ± 0.29) hours respectively (Table 3).

Dichotomy index (I<O) and Autocorrelation coefficient (r24)

The mean dichotomy index was found to be lower in the sickling patients as compared with the control subjects (Figure 2-A). Further, computation of the autocorrelation coefficients at t = 24 h, the *r*24, for each sickling patient and control subject revealed statistically significantly difference in the value of *r*24 of each subject. However, statistically significant differences were not observed when the means of *r*24 values of the sickling patients and control subjects were compared as a group (Figure 2- B).

Sleep parameters

In Table 4 the means and standard errors of TIB, AS, AST, AWT, SE, SL, and FI of the sickling patients and control subjects have been shown. Result shows that Sickle cell diseased patients had significantly (p<0.05) lower assumed sleep and exhibited statistically significantly (p<0.05) lower sleep efficiency than control subjects. More sleep latency (SL) and higher fragmentation index (FI) were also observed among sickling patients, however it was not statistically significant (Table 4).

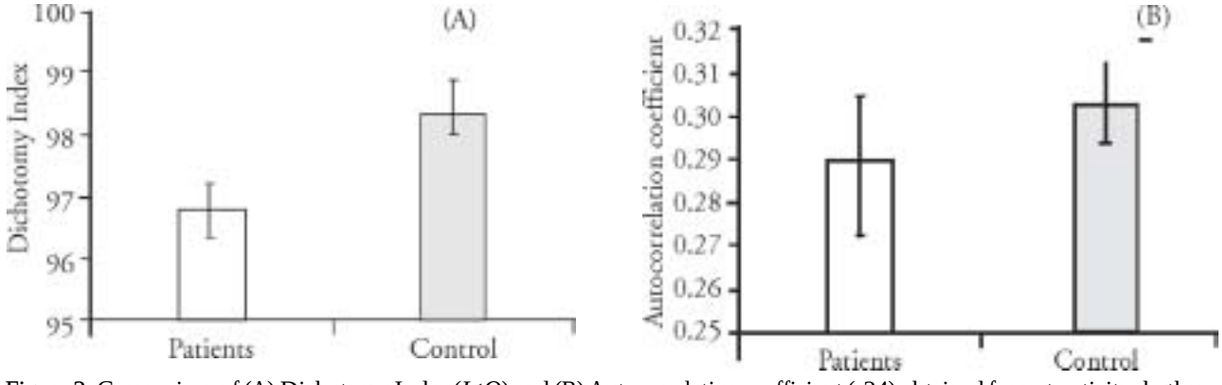

Figure 2: Comparison of (A) Dichotomy Index (*I<O*) and (B) Autocorrelation coefficient (*r*24) obtained for rest-activity rhythm between sickle cell diseased patients and control subjects

Table 4: Mean ± 1 SE of sleep parameters of sickle cell diseased patients and control subjects.

Variable (unit)	Sickle cell diseased Patients Mean ± SE	Control Patients Mean ± SE	t-test df; t value; p-value
TIB (*h*)	7.40 ± 0.35	7.97 ± 0.33	18, 1.18, 0.13
AS (*h*)	6.51 ± 0.32	7.27 ± 0.31	18, 1.70, <0.05
AST (*h*)	5.29 ± 0.38	5.95 ± 0.29	18, 1.37, 0.09
AWT (*h*)	1.45 ± 0.23	1.33 ± 0.13	18, 0.44, 0.33
SE (%)	69.21 ± 2.72	74.56 ± 1.60	18, 1.70, <0.05
SL (*min*)	31.41 ± 4.60	28.25 ± 5.49	18, 0.44, 0.33
FI (%)	42.03 ± 5.88	35.36 ± 2.27	18, 1.06, 0.15

Discussion

A marked difference in the rest-activity pattern was observed between the two groups, i.e., sickling patients and control subjects. The normal day-night variability in sickling patients was drastically impaired as compared with the control group. In contrast, normal subjects (control group) exhibited higher level of activity during the daytime (waking) hours and very low to zero-level activity during the night (rest) hours. The present finding corroborates the earlier report where children with sickle cell disease had disrupted sleep and wake patterns. [17]

Further, Cosinor analysis detected a statistically significant circadian rhythm in both the group. A 24-hr average rest activity rhythm in sickle cell patients suggest that periodicity of the rhythm was not affected by diseased conditions. However, the results of the present study documents disruption of circadian rhythm in rest-activity rhythm of sickling patients characterized by dampening of amplitude, lowering of mean level of activity and advance in acrophase. Dampening of amplitude and lowering of mean level of activity in sickling patients seems to be related with energy status of the patients. Lower level of activity as a compensatory mechanism due to higher demand of resting energy in SCD patients is well documented. [18-19]

Average assumed sleep in sickling patients was found to be significantly less than the control individuals. Further, a significant reduction in sleep efficiency in SCD patients was also observed. Reduced sleep duration, longer sleep latency, higher fragmentation index and significant decrease of sleep efficiency in sickling patients may be ascribed to chronic pain experienced by sickling individuals. The sleep impairment in persons suffering from sickle cell anemia has been reported to be associated with chronic pain and higher stress level. [20, 21]

Nonetheless, dichotomy index was drastically lower in the sickling patients as compared with the control subjects. This could be attributed to sleep disturbances and severity of disease manifestation. In conclusion, the results of the present study document disruption of circadian rhythm and sleep impairment in sickling patients. These alterations of circadian rhythm and deterioration of sleep could be attributed to diseased status.

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