行政院國家科學委員會專題研究計畫　成果報告

有效矯正唐氏症之睡眠呼吸中止能否可改善其動作及心智功能之發展

計畫類別：個別型計畫
計畫編號：NSC92-2314-B-040-012-
執行期間：92 年 08 月 01 日至 93 年 07 月 31 日
執行單位：中山醫學大學醫學系

計畫主持人：丁化
共同主持人：林則彬，張時中
計畫參與人員：鍾璦卉，張淑雲

報告類型：精簡報告

處理方式：本計畫可公開查詢

中　華　民　國 93 年 11 月 2 日

The Sleep Characters in the Children with Down Syndrome

Hua Ting, MD1, Shih-Chung, Chang, MD1, Tzer-Bin Lin, PhD2

1. Department of Physical Medicine and Rehabilitation, Chung Shan Medical University Hospital, Taichung, Taiwan
2. Department of Physiology, Chung Shan Medical University, Taichung, Taiwan

Abstract：

The presence of obstructive sleep apnea is disproportionately higher in pediatric Down syndrome patients than in the general pediatric patient population. We hope to further realize the special sleep characters of Down syndrome children and to investigate the major determinants for their possible sleep fragmentation.

Recruiting eligible registered children (≤ 18 years of age) from the Taiwan Down Syndrome Association and their matched siblings as normal controls, we conduct the overnight polysomnography studies. After two Down syndrome children excluded for poor cooperation, 16 Down syndrome children and their eight siblings are recruited for data analysis. Whereas, the deep sleep (stage 3 and stage 4) in Down's syndrome children is significant less (34.6 ± 2.1 vs 52.1 ± 7.1 % of total sleep time, $p < 0.05$), there were no differences in total recording time, total sleep time, sleep period time, sleep latency, REM latency, and sleep efficiency between two groups.

Additionally, the respiratory distress index (RDI) and hypopnea events (19.6 ± 6.0 vs 5.8 ± 2.3 events /hour, $p < 0.05$ in RDI and 60.5 ± 15.6 vs 22.1 ± 8.8 events/hour, $p < 0.05$, respectively) and substantial greater total apnea events ($p = 0.07$) in Down syndrome group in contrast with control. However, overnight mean oxygen saturation and lowest oxygen saturation are similar in both groups. Down syndrome children appear more awakening (24.4±2.2 vs 3.9 ± 1.4 events, $p < 0.001$) and arousal (80.8 ± 14.5 vs 34.8 ± 4.5 in total arousal, $p < 0.01$; 16.7 ± 3.0 vs 6.7 ± 0.7 events in arousal index, $p < 0.01$), but there were no significant difference in the ratios of arousal and awakening event versus total respiratory events.

In Conclusion, Down syndrome children showed less deep sleep with more respiratory distress, arousal and awakening. However, hypoxia is unlikely responsiblr for their sleep fragmentation and repetitive arousals. Although Down syndrome showed more arousal and respiratory distress, but the respiratory events per se seems not a dominant cause of arousal.

Introduction

Down syndrome is a group of multiple systemic disorders, including psychomotor retardation, caused by chromosomal abnormality with a 1/1000 chance of occurrence. The sleep patterns of these patients have been confirmed as abnormal (e.g., longer sleep time, frequent awakening and snoring). It has been reported repetitively the sleep-disordered breathing, especially obstructive sleep apnea syndrome was highly prevalent in Down syndrome than normal children (31-63% vs. 1-3%)[1-5]. The contributing factors, causing obstructive sleep apnea syndrome in Down syndrome, might include an enlarged tongue, enlarged tonsil and adenoid, soft tissue hypotonia and hypoplasia of skeletal and cartilaginous structures[6]. Although it has been established that sleep disorder or sleep deprivation impairs the cognitive and behavioral function [7-11] in humans, and sleep-disordered breathing might account for children's failure to thrive, cor pulmonale, hypertension, mental retardation and excessive daytime sleepiness, poor learning and attention-deficit/hyperactivity disorder[4, 5, 7-11], but few researchers have precisely described the sleep characteristics [12-15] or been concerned about the impact of the disturbed sleep on cognitive and behavioral function [16].

In this study we conducted a series of researches with Down syndrome children, to determine the sleep characteristics by overnight sleep polysomnographic study, and to find the differences in comparison with their siblings and to long term investigate its possible consequences and comorbilities in comparison with normal children.

Materials and Method

This study will be reviewed for approval by the Institutional Review Board of Chung-Shan Medical University Hospital, in Taichung, Taiwan. All procedures, risks, and benefits will be explained, and informed written consent will be obtained from the subjects' parents or legal caregivers before testing begins.

Subjects

We consecutively enrolled registered Down syndrome children (younger than 18 years of age) from the Down Syndrome Association in Taichung, Taiwan for sleep study after a special conference relevant to topic of " Sleep disordered breathing in Down's syndrome children". Patients' siblings of comparable age will also be recruited as controls. The controls should be free from any cardiovascular, pulmonary, metabolic or neurological diseases. Additionally, they will be excluded if their baseline polysomnography study reveals a meaningful sleep disordered

breathing (apnea/ hypopnea index ≥ 10 events/hr) or a definite O_2 desaturation (O_2 saturation ≤ 90%, 5 events or more /hr) noted.

Polysomnographic (PSG) Evaluation

We conducted overnight PSG study for both Down's syndrome children and their siblings. All the signals were recorded by using a commercial computerized system (Rembrandt, MedCard Diagnostics, Amsterdam, Holland). The PSG monitoring is performed as follows：two electroencephalographic electrodes are applied at the C3 and C4 locations and referred contralaterally to reference electrodes are attached behind the ears in the left (A1) and right (A2) mastoid areas. Two electromyographic electrodes are applied over the submental muscles. Two electrooculographic electrodes are applied 1 cm above the outer canthus of one eye and 1 cm below the outer canthus of the other. The montage arrangement for PSG reading consists of C3-A2 or C4-A1. Nasal and buccal airflow is monitored by a thermistor, thoracic and abdominal movement are monitored by straing-guage electrodes, and hemoglobin oxygen saturation and arterial oxygen saturation pulse wave forms are monitored by pulse oximetry on fingertip.

Sleep architecture was assessed by standard techniques[17]. Obstructive sleep apnea was defined as the absence of airflow with continued chest wall and abdominal movement for a duration of at least two breaths[18-20]. Hypopneas were defined as a decreased in nasal flow of at least 50% with a corresponding decrease in SpO2 of a t least 4 %, an arousal, or both[20]. The respiratory distress index (RDI) was defined as the number of apneas and hypopneas per hour of total sleep time (TST). Children with an RDI of at least 1 but less than 5 per hour of TST were considered to have mild sleep disordered breathing (SDB), while children with RDI of at least 5 per hour of were considered to have obstructive sleep apnea syndrome (OSAS). Since criteria for arousals have not yet been developed for children, arousals were defined as recommended by the American Sleep Disorders Association Task Force report[21] using the 3-second rule, the presence of movement arousal, or both[19]. Arousals were divided into 2 main subtypes: spontaneous arousals and respiratory arousals. In addition, technical arousals and arousals associated with periodic leg movements were conducted and contributed to the total arousal and total arousal index.

Procedures

All subjects, both Down syndrome children and controls, enrolled will complete the questionnaire by their parents or formal caregivers. Personal demography / characters were recorded first and then overnight polysomnography was conducted to

evaluate the sleep related problems and their special sleep patterns. If there are any abnormal sleep related problems such as apnea/hypopnea index higher than 10 events/hr and /or there is significant O_2 desaturation (higher than 5 episodes/hr), the subjects will be excluded from normal control group.

Data analysis

Data are presented as mean ± standard error unless otherwise indicated. Differences between Down's syndrome and control groups in parameters in sleep architectures, i.e. superficial & deep sleep in non-REM, REM sleep; arousals, wakefulness, respiratory events, lowest O_2 saturation; and total arousals/ total respiratory events and total wakefulness / total respiratory events were determined with a 2-tailed non-paired Student's *t* test. Statistical significance was defined as $p < 0.05$.

Result

18 Down syndrome subjects (14 boys, 4 girls, aged 1-11 years in range) and eight normal their siblings (3 boys, 5 girls, aged 4-12 years in range) were recruited in the study. Two Down syndrome subjects (1 boy, 1 girl), who can not accomplish the over night PSG study, were excluded afterward. The demography of the Down syndrome group and normal control group, who can complete over night polysomnographic study, is shown in Table 1. There is no difference in age, body weight and height between the two groups, though more girls in control group.

About sleep architecture (Table 2 and Figure 1), there were no differences in total recording time, total sleep time, sleep period time, sleep latency, REM latency, and sleep efficiency between Down syndrome and control groups. Besides, the deep sleep (Stage 3 and stage 4) in Down's syndrome children is significant less (34.6 ± 2.1 vs 52.1 ± 7.1 % of total sleep time, $P < 0.05$). While, the light sleep and REM percentage were no difference between these groups, though much more stage 1 sleep ($p < 0.005$) in Down's syndrome children. Additionally, the respiratory distress index (RDI) and hypopnea events (19.6 ± 6.0 vs 5.8 ± 2.3 events /hour, $p < 0.05$ in RDI and 60.5 ± 15.6 vs 22.1 ± 8.8 events/hour, $p < 0.05$, respectively) and substantial greater total apnea events ($p = 0.07$) in Down syndrome group (Table 3 and Figure 2) in contrast with control. However, overnight mean oxygen saturation and lowest oxygen desaturation are similar in both groups. Down syndrome children appear more awakening (24.4 ± 2.2 vs 3.9 ± 1.4 events, $p < 0.001$) and arousal (80.8 ± 14.5 vs 34.8 ± 4.5 in total arousal, $p < 0.01$; 16.7 ± 3.0 vs 6.7 ± 0.7 events in arousal index, $p < 0.01$); but there were no significant difference in the ratios of arousal and awakening event versus total respiratory events (Table 4 and Figure 3).

Discussion

Our overnight sleep polysomnographic study showed that Down syndrome children have more light sleep (stage 1, but not in stage 2), less deep sleep (stage 3 + stage 4 sleep) and greater repetitive arousals and awakening from sleep, i.e. more severe sleep fragmentation, compared with control group. This is quite compatible with the family reports by questionare that Down syndrome children frequent awake in the night and with more body movement over night sleep. In previous studies from other authors showed more awakening, body movement, frequent shift to wake state, increased stage 1, and 2 with decreased stage 3, and 4 and REM of Down syndrome groups than control groups[12, 14, 15]. The REM was thought correlated with learning organization and central nervous system plasticity, and in metal retarded subjects it would be abnormal[22]. The authors had reported that the REM latency was increased and the REM sleep decreased in the mental retarded children (include Down syndrome), and the REM sleep and REM density further decreased in older Down syndrome (age > 6 years old). [14, 23]. The REM abnormality was considered due to immaturity of the inhibitory system involving REMs and a disorder of neurotransmitters, and the REM sleep and REM density further decreased at growing older, which was considered as precocious aging. In our study the REM latency and REM sleep were no difference between these groups, it may be due to small number of subjects or too small the age of the group. However, it is still possible that the precipitating factors like repetitively arousals, eliminated deep sleep and absent REM since possibly after birth might affect precocious aging of central nerve system further, besides of genetic impact form trisomy 21.

In our study, Down syndrome group showed significantly more total respiratory events, respiratory distress index, hypopnea events, wakening counts and arousal counts and potentially higher total apnea events (Table 3, 4 and Figure 2, 3) in comparison with control group. While, there is no difference of the mean oxygen saturation and lowest desaturation between these two groups. This might suggest that hypoxia is unlikely the determinant for sleep fragmentation and the actual factor for brain's precocious aging in Down's syndrome children. Even though, we cannot preclude the fast aging processing from repetitive vasoconstriction and its corresponding vasculitis as the result of the repetitive arousals.

Sleep-disordered breathing, especially obstructive apnea had been reported highly occurrence in Down syndrome[1, 2, 12, 24], potentially caused by cranial facial anomaly, hypertrophy of soft tissue and central nervous system anomaly[1, 6, 24].

Moreover, this syndrome should account for children's failure to thrive, cor pulmonale, hypertension, mental retardation and excessive daytime sleepiness, poor

learning and attention-deficit/hyperactivity disorder[4, 5, 7-11]. Besides, the frequent light sleep shifting and sleep fragmentation will causes cognitive and behavioral deficits in children and adults. Therefore, impaired cognitive skills (e.g., visioperceptual skills)[25] in Down syndrome individual, particularly at younger age can be expected to improve after sleep disordered breathing well treated, for example by continuous positive airway pressure application.

Although the RDI and arousal counts were high in Down syndrome group in our study, but when it was divided with total respiratory events there was no significant difference with the control group. Therefore the arousal sensitivity to the respiratory distress events may be no difference between these two groups, or the respiratory distress may be not a predominant cause of arousal. The arousal response to other type of stimuli should be further evaluated. Stebbens, etc.,[1] had demonstrated that Down syndrome with higher respiratory resistance, lower baseline oxygen saturation and longer desaturation episodes, but other authors noted that the arousal of the Down syndrome was only partial related to respiratory events (8.6%) and mostly related to jerk movement (approximately 50%)[12]. The causes of arousal and more awakening during sleep of Down syndrome subjects were thought including genetic factor, developmental factor, sleep deprivation, abnormal sleep/wake schedule, obstructive sleep apnea, gastro-esophageal reflux, seizure or side effect of drugs.

The treatment of sleep-disordered breathing of Down syndrome ever reported include upper airway soft tissue reduction, craniofacial plastic surgery and nasal CPAP[2, 6, 26-28], but there still lack of evaluation of cognitive change after effective treatment of the sleep-disordered breathing. Further research is indicated.

Conclusion

In present study, Down syndrome children showed less deep sleep with more respiratory distress, arousal and awakening. However, hypoxia is unlikely responsiblr for their sleep fragmentation and repetitive arousals. Although Down syndrome showed more arousal and respiratory distress, but the respiratory events per se seems not a dominant cause of arousal. Due to small number of study group, further study for larger subject number should proceed.

References：

1. Stebbens, V.A., et al., *Sleep related upper airway obstruction in a cohort with Down's syndrome.* Archives of Disease in Childhood, 1991. **66**(11): p. 1333-8.
2. Marcus, C.L., et al., *Obstructive sleep apnea in children with Down syndrome.* Pediatrics, 1991. **88**(1): p. 132-9.
3. Southall, D.P., et al., *Upper airway obstruction with hypoxaemia and sleep disruption in Down syndrome.* Dev Med Child Neurol, 1987. **29**(6): p. 734-42.

4. Anders, T.F. and L.A. Eiben, *Pediatric sleep disorders: a review of the past 10 years.* J Am Acad Child Adolesc Psychiatry, 1997. **36**(1): p. 9-20.
5. Marcus, C.L., *Sleep-disordered breathing in children.* Curr Opin Pediatr, 2000. **12**(3): p. 208-12.
6. Lefaivre, J.F., et al., *Down syndrome: identification and surgical management of obstructive sleep apnea.* Plast Reconstr Surg, 1997. **99**(3): p. 629-37.
7. Siegel, J.M., *The REM sleep-memory consolidation hypothesis.* Science, 2001. **294**(5544): p. 1058-63.
8. Kim, H.C., et al., *Sleep-disordered breathing and neuropsychological deficits. A population-based study.* Am J Respir Crit Care Med, 1997. **156**(6): p. 1813-9.
9. Beebe, D.W. and D. Gozal, *Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits.* J Sleep Res, 2002. **11**(1): p. 1-16.
10. Martin, S.E., et al., *The effect of clustered versus regular sleep fragmentation on daytime function.* Journal of Sleep Research, 1999. **8**(4): p. 305-11.
11. Wesensten, N.J., T.J. Balkin, and G. Belenky, *Does sleep fragmentation impact recuperation? A review and reanalysis.* J Sleep Res, 1999. **8**(4): p. 237-45.
12. Levanon, A., A. Tarasiuk, and A. Tal, *Sleep characteristics in children with Down syndrome.* Journal of Pediatrics, 1999. **134**(6): p. 755-60.
13. Diomedi, M., et al., *Sleep abnormalities in mentally retarded autistic subjects: Down's syndrome with mental retardation and normal subjects.* Brain & Development, 1999. **21**(8): p. 548-53.
14. Hamaguchi, H., et al., *Sleep in the Down syndrome.* Brain & Development, 1989. **11**(6): p. 399-406.
15. Clausen, J., E.A. Sersen, and A. Lidsky, *Sleep patterns in mental retardation: Down's syndrome.* Electroencephalography & Clinical Neurophysiology, 1977. **43**(2): p. 183-91.
16. Carskadon, M.A., S.M. Pueschel, and R.P. Millman, *Sleep-disordered breathing and behavior in three risk groups: preliminary findings from parental reports.* Childs Nervous System, 1993. **9**(8): p. 452-7.
17. Rechtschaffen and Kales, *A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects.* 1968: Washington DC: National Institues of health.
18. Marcus, C.L., et al., *Normal polysomnographic values for children and adolescents.* Am Rev Respir Dis, 1992. **146**(5 Pt 1): p. 1235-9.
19. Mograss, M.A., F.M. Ducharme, and R.T. Brouillette, *Movement/arousals. Description, classification, and relationship to sleep apnea in children.* Am J

Respir Crit Care Med, 1994. **150**(6 Pt 1): p. 1690-6.

20. *Standards and indications for cardiopulmonary sleep studies in children. American Thoracic Society.* Am J Respir Crit Care Med, 1996. **153**(2): p. 866-78.
21. *EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association.* Sleep, 1992. **15**(2): p. 173-84.
22. Zucconi, M., *Sleep disorders in children with neurological disease*. Sleep and breathing in children: A developmental approach, ed. G.M. Loughlin, J.L. Carrloll, and C.L. Marcus. Vol. 147. 2000: Marcel Dekker, Inc. 363-375.
23. Diomedi, M., et al., *Sleep abnormalities in mentally retarded autistic subjects: Down's syndrome with mental retardation and normal subjects.* Brain Dev, 1999. **21**(8): p. 548-53.
24. Ferri, R., et al., *Respiratory patterns during sleep in Down's syndrome:importance of central apnoeas.* J Sleep Res, 1997. **6**(2): p. 134-41.
25. Andreou, G., et al., *Cognitive status in Down syndrome individuals with sleep disordered breathing deficits (SDB).* Brain Cogn, 2002. **50**(1): p. 145-9.
26. Guilleminault, C., et al., *Home nasal continuous positive airway pressure in infants with sleep-disordered breathing.* J Pediatr, 1995. **127**(6): p. 905-912.
27. Marcus, C., et al., *Use of nasal continuous positive airway pressure as treatment of childhood obstructive sleep apnea.* J Pediatr, 1995. **127**(1): p. 88-94.
28. Hultcrantz, E. and H. Svanholm, *Down syndrome and sleep apnea--a therapeutic challenge.* International Journal of Pediatric Otorhinolaryngology, 1991. **21**(3): p. 263-8.

Table 1. Demography of the Down syndrome and Control groups

	Down syndrome (n=16)	Control (n=8)	P value
Age (Yr)	7.6 ± 0.7	7.5 ± 1.0	NS
Weight (Kg)	27.6 ± 2.1	25.7 ± 2.8	NS
Height (cm)	115.5 ± 4.0	121.5 ± 5.6	NS

NS, non-significance

Table 2 Sleep architectures of Down syndrome and control groups

	Down syndrome (n=16)	Control (n=8)	P value
TRT (min)	360.3 ± 4.3	361.9 ± 2.5	NS
TST (min)	287.0 ± 10.5	308.6 ± 15.3	NS
SPT (min)	345.4 ± 4.0	320.9 ± 14.5	NS
Sleep latency (min)	9.0 ± 2.5	34.0 ± 12.8	NS
Sleep efficiency (%)	81.3 ± 3.2	86.8 ± 3.9	NS
REM latency (min)	150.9 ± 23.4	176.5 ± 17.3	NS
NREM %			
S1	17.3 ± 2.4	7.5 ± 1.7	<0.005
S2	24.0 ± 3.1	28.0 ± 6.3	NS
S3＋S4	34.6 ± 2.1	52.1 ± 7.1	<0.05
REM %	7.3 ± 1.6	8.5 ± 1.6	NS

Abbreviations: TRT, total record time; TST, total sleep time; SPT, Sleep period time; REM, rapid eye movement sleep; NREM %, percentage of non rapid eye movement sleep; S1, stage 1 sleep; S2, stage 2 sleep; S3, stage 3 sleep; S4, stage 4 sleep; REM %, percentage of rapid eye movement sleep

NS, non-significance

Table 3 Respiratory events and corresponding variables of Down syndrome and Control groups

	Down syndrome (n=16)	Control (n=8)	P value
RDI	19.6 ± 6.0	5.8 ± 2.3	<0.05
Apnea			
Obstruction	1.1 ± 0.8	0.5 ± 0.3	NS
Central	6.0 ± 3.2	3.9 ± 1.7	NS
Mixed	26.9 ± 14.4	1.0 ± 0.7	NS
Total apnea events	33.9 ± 14.8	5.4 ± 2.0	= 0.07
Hypopnea	60.5 ± 15.6	22.1 ± 8.8	<0.05
SaO2 %	94.5 ± 1.3	96.7 ± 1.0	NS
L Des	85.3 ± 1.7	88.5 ± 1.6	NS

RDI, respiratory distress index; SaO2 %, mean oxygen saturation; L Des, lowest oxygen desaturation

NS, non significance

Table 4 Arousal, Awakening events of Down syndrome and Control groups

	Down syndrome (n=16)	Control (n=8)	P value
Awakening	24.4 ± 2.2	13.9 ± 1.4	<0.001
Arousal			
Total count	80.8 ± 14.5	34.8 ± 4.5	<0.01
Index	16.7 ± 3.0	6.7 ± 0.7	<0.01
Arousal/TRE	1.8 ± 0.5	8.0 ± 5.6	NS
Awaken/TRE	0.7 ± 0.2	3.0 ± 2.0	NS

Arousal/TRE, total arousal counts divided by total respiratory events

Awaken/TRE, number of awakening divided by total respiratory events

Figure Legend

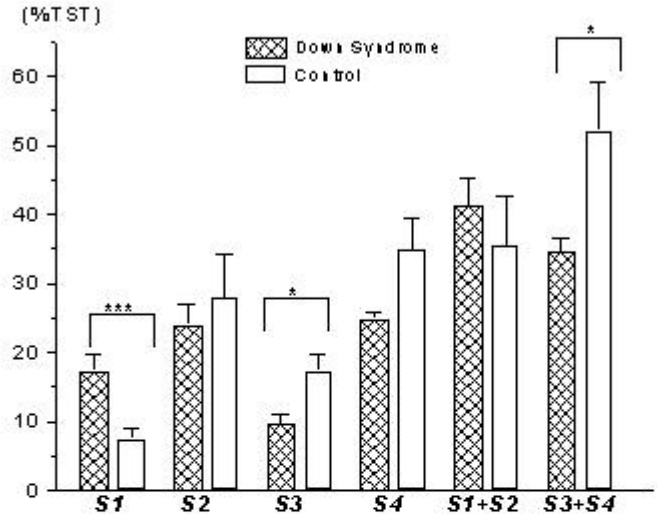

Figure 1. Comparison of Non-REM sleep stages between Down syndrome and normal groups *p < 0.05, *** p < 0.005 between Down syndrome and normal groups.

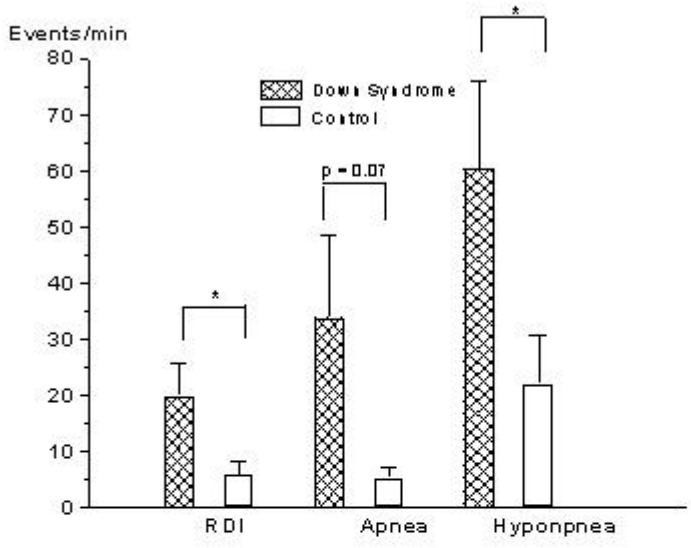

Figure 2. Comparison of respiratory events during sleep between Down syndrome and normal groups *p < 0.05 between Down syndrome and normal groups

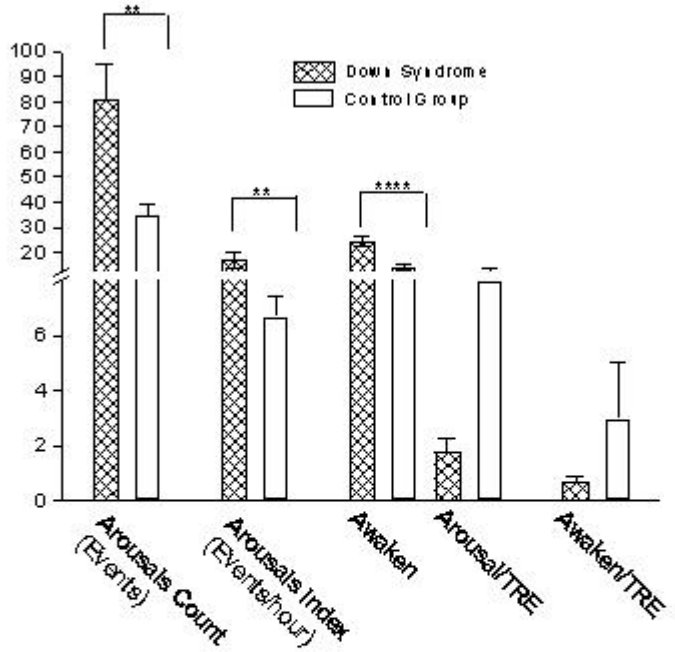

Figure 3. Comparison of arousals and awakenings events and their ratios versus total respiratory events during sleep between Down syndrome and normal groups **p < 0.01, ****p < 0.001 between Down syndrome and normal groups