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The Cortical and Subcortical Arousals were not Lowered in Children with Down's Syndrome than Those with Allergic Rhinitis or Adenotonsillar Hypertrophy

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

Down's syndrome have a high incidence of obstructive as well as central sleep apnea syndrome due to the congenital abnormalities in upper airway structure. Besides, brainstem abnormalities may be responsible for impaired control of respiration during sleep. The aim of our current study is to investigate that Down's syndrome children have worse cortical and subcortical arousal in terms of similar respiratory events during sleep than those with allergic rhinitis, adenotonsil hypertrophy.

It was found that longer total sleep time, better sleep efficiency and longer stage 2 or percentage of non REM sleep in adenotonsillar hypertrophy (n =11) than in Down's syndrome (n =11). Besides, respiratory distress index (RDI) was wide range in both Down's syndrome and adenotonsillar hypertrophy; however the former is greater than the later. Further, allergic rinitis children (n =10) significantly had higher RDI than normal control. Without difference on EEG arousals (cortical arousals) among these three groups, they significantly had greater EEG arousal than normal control (n = 5). At focusing on subcortical arousals, it is significantly less in adenotonsillar hypertrophy than Down's syndrome, particularly in stage 2 and total non REM sleep. The heart rate was found lower at wake and none-REM sleep than those in Down's syndrome children. Finally, after being normalized by RDI, there're still no differences for cortical and subcortical arousals among these four groups. We concluded that Down's syndrome children, although characterized with chromosomal abnormality, was not lowered in cortical and subcortical arousals during sleep.

INTRODUCTION

Regarding respiratory pattern during sleep, children with Down's syndrome have a high incidence of obstructive sleep apnea syndrome (OSAS) due to many predisposing factors such as midfacial and mandibular hypoplasia (36), macroglossia,

glossoptosis and hypoplastic trachea (37), tonsil and adenoid hypertrophy (38,39), obesity, and hypotonia. Recently, Ferri et al. emphasized the finding of central as opposed to obstructive apneas (89.4% versus 9.4 %) in a series of ten Down's syndrome subjects without obesity or upper airway pathology (43). The authors hypothesized that brainstem abnormalities (ascribed to the specific syndrome and not to mental retardation or sleep disturbing factors) may be responsible for the centrally impaired control of respiration during sleep. This theory is supported by the existence of abnormalities in brainstem auditory evoked potentials in Down's syndrome children, suggesting a common brainstem dysfunction. However, few study had related to "spontaneous arousals" evoked during sleep in children with Down's syndrome.

Children with allergic rhinitis may have both nasal congestion and rhinorrhea with significant circadian rhythm and hydrostatic dependent. Without constant high resistance over upper airway, however, the adults with allergic rhinitis eventually had repetitive microarousals associated with abnormal breathing. On the other hand, obstructive sleep apnea in children is related to adenotonsillar hypertrophy. From the previous study before and after tonsillectomy and adenoidectomy, it was postulated that besides of disadvantage structure properties, impaired neuromotor control for upper airway patency might be responsible for collapsibility during sleep.

It is well documented (9, 10, 11) that arousal is not an important mechanism in the termination of respiratory events in both infants and children and that electroencephalographic criteria are not essential to determine the clinical severity of obstructive sleep apnea (OSA). In deed, school and behavior problems (12, 13, 14, 15) similar to those observed in children with attention-deficit/hyperactive disorder have been repeatedly reported in children with sleep disordered breathing (SDB). Besides, cortical EEG arousals and respiratory disturbances do not correlate very well with daytime sleepiness, whereas subcortical reflex increases in sympathetic activity triggering autonomic responses. Alternatively, the pulse transit time (PTT) is a reliable noninvasive blood pressure elevation indicator and PTT arousals (or subcortical arousals) (16) are a more sensitive measure of obstructive events than visible EEG arousals.

Given the contribution of congenital muscular hypotonia and possible central nervous system impairment as well as disadvantage structure of upper airway for patency during sleep, we hypothesized that Down's syndrome children might have worse cortical and subcortical arousal in terms of similar respiratory events during sleep in comparisons to those with allergic rhinitis, adenotonsil hypertrophy or normal.

Therefore, we recruited children with Down syndrome, allergic rhinitis, adenotonsil hypertrothy and normal sleep habit from Taiwanese Association for Down

syndrome Children, the ENT clinic in Chung Shan Medical University Hospital and community, respectively.

MATERIAL and METHOD

Three groups of symptomatic patients between 5 and 12 years of age were recruited: 1) children with Down's syndrome recruited from Down's Syndrome Association in Taichung, Taiwan, 2) children who was impressed as allergic rhinitis with typical symptoms such as sneezing, pruritus, rhinorrhea, and nasal congestion (7) 3) children with a tonsil hyperplasia with scale 3 or 4 in size by physical examination. Where, the last groups of participants were referred from ENT department of our hospital. In addition, a control group of from the community who fulfilled all of the following: l) no history of snoring; 2) no significant medical conditions, including heart disease; 3) normal physical examination; and 4) taking no medications.

All patients underwent a complete history and physical examination focusing on clinical evidence of OSAS and possible etiologic factors. Patients with conditions known to affect sleep or breathing such as craniofaclal dysmorphism, mental retardation, cerebral palsy, and previous otolalyngologic surgery and those taking medications known to affect sleep were excluded. Signed, informed consent was obtained from the parent and assent from children >5 y of age. The study was approved by the institutional review board at our hospital.

Sleep Studies

The overnight sleep studies were conducted at the Sleep Center of Chung Shan Medical University Hospital, Taichung, Taiwan. All persons were requested to arrive at the sleep laboratory between 8:00 pm and 9:00 pm and underwent one night polysomnography. Polysomnography included continuous measurement of esophageal manometry and beat-to-beat PTT. A parent throughout the night accompanied children. Studies were scored using standard pediatric techniques (17, 18). Details of our PSG montage and event definitions have been published elsewhere (19). In brief, EEG (C3-A2, C4-A1, C1- A2); right and left electrooculogram; submental EMG; tibial EMG; ECG; chest and abdominal wall motion by respiratory inductance plethysmography (Respitrace, Ambulatory Monitoring, Inc., Ardsley, NY, U.S.A.); oronasal airflow (three-plonged thermistor); PetCO2, measured at the nose by infrared capnometry (Nellcor N-1000, Van Nuys, CA, U.S.A); SaO2 by pulse oximetry (Nellcor N-1000); and oximeter waveform were measured. Subjects were also monitored and recorded on videotape, using an infrared video camera, and were continuously observed by a polysomnography technician. The studies were performed with a computerized system (Alice 3, Healthdyne, Marietta, GA, U.S.A.) and a Windaq data acquisition system (Dataq Instruments, Akron, OH, U.S.A.). An obstructive apnea was defined as the presence of chesty abdominal wall motion

associated with a reduction in the thermistor tracing 2:80% of baseline, a loss of Pet CO2 wave- form. An obstructive hypopnea was defined similarly, except that the reduction in thermistor was 50-80% of baseline, and was associated with a drop in SaO2 more than 4% anchor arousal. Apneas were considered mixed if they had both a central and obstructive component. All obstructive events were validated with esophageal manometry by demonstrating large negative pressure excursions during the event that terminated by a sudden change in pressure to a less negative level at the end of the event. The RDI was defined as the total number of obstructive and mixed apneas per hour of total sleep time (TST). Microarousals were identified according to the definition of the American Sleep Disorders Association (20). The EEG arousal index was defined as the number of arousals and awakenings per hour of TST.

The PTT was measured on a beat-by-beat basis using a commercially available device derived from an Ohmeda oximeter and ECG (Stowood Scientiac Instruments, Oxford, U.K.). (method) In the Rembrand software from Medicare modular tools are provided to measure both EKG and finger pulse signals and calculate the PTT. The PTT values are calculated per beat by measuring the time between the occurrence of the R-wave and the point at 50% of the rising slope of the plethysmogram. Tracings were carefully analyzed for artifacts caused by inadequate oximeter pulse waveform or ECC. Only artifact-free FW waveforms were used for analysis. A PTT arousal was then defined as a decline in the averaged signal of an15 ms, lasting at least 5 s (21). The PTT arousal index was defined as the number of PTT arousals per hour of TST.

Statistics and Data analysis.

All data in these four groups are expressed as mean ± SD. The group means were compared using a non-paired Student t tests. A value of $p < 0.05$ was considered statistically significant.

RESULTS

We had finally recruit eleven children with Down's syndrome, who had complete overnight sleep polysomnography. For age and body mass index matching, ten and eleven children with allergic rhinitis, adenotonsillar hypertrophy as well as five children normal control were enrolled

Demographically, there is no difference in age, body mass index and waist width among these four groups (Table 1). However, Down's syndrome children appeared significantly shorter in statue and potentially wider in neck circumference than allergic rhinitis and adenotonsillar hypertrophy groups, respectively.

At focusing on sleep architecture (Table 2), better the total sleep time, sleep efficiency and longer stage 2 or percentage of non REM sleep in adenotonsillar hypertrophy than in Down's syndrome. Plus, versus allergic rhinits had greater percentage of stage 4 than Down's syndrome. Finally, both Down's syndrome and

allergic rhinitis children had shorter stage 3 than normal control.

Respiratory distress index was wide range in both Down's syndrome and adenotonsillar hypertrophy, however the former is greater than the later. Further, allergic rinitis children significantly had higher RDI than normal control. Without difference on EEG arousals (cortical arousals) among these three groups, they significantly had greater EEG arousal than normal control.

At focusing on subcortical arousals (PTT dropping) (Table 3), it is significantly less in adenotonsillar hypertrophy than Down's syndrome, particularly in stage 2 and total non REM sleep. Nevertheless, high variety in subcortical arousals were found in all these four groups, leading to no significant differences in all various sleep stages among normal, Down's syndrome, and allergic rhinitis groups. Furthermore, the heart rate was found lower at wake and none-REM sleep than those in Down's syndrome children. Finally, after being normalized by RDI, there're still no differences for cortical and subcortical arousals among these four groups.

While there were no differences on mean SaO2 lowest desaturation and duration of SaO2 less than 90 % among these four groups, the desaturation index in Down's syndrome appeared higher than that in normal and allergic rhinitis groups.

DISCUSSION

The findings of current study are 1) great heterogeneity of sleep quality in terms of respiratory events and O2 desaturation in Down's syndrome children, 2) In comparison with adenotonsillar hypertrophy group, Down's syndrome children had more frequent subcortical arousals, although similar in cortical arousals, and 4) after being normalized by respiratory events during sleep, there are no differences among these four groups.

Daytime sleepiness, poor cognitive functioning and poor sleep quality is presumably caused by sleep fragmentation (22). An adequate quantification of sleep fragmentation to investigate the relation with daytime functioning is, however, difficult. Cortical EEG arousals and respiratory disturbances do not correlate very well with daytime sleepiness (23). Also, alerting arousals may not cause a cortical response, but they may result in a reflex increase in sympathetic activity triggering autonomic responses. Beat-to-beat risen in blood pressure have been described as sensitive indices of transient autonomic arousals When blood pressure rises the arterial walls become stiffer and the pressure wave travels faster, resulting in a shorter PTT. In this way, PTT gives an indirect measure of change in blood pressure with every heartbeat (21). Interestingly, there is greater subcortical arousal in Down's syndrome children than adenotonsillar hypertrophy group. To be a typical obstructive sleep apnea model, adenotonsillar hypertreophy children had been well documented that a dynamic process resulting from a combination of structural and neuromotor

abnormalities (24, 25), rather than from structural abnormalities alone in obstructive sleep apnea children. These neuromotor factors include sleep state, chemoreceptor input (26) and upper airway pressure receptors (27). The literature suggests that the upper airway response to both CO2 and subatmospheric pressure is a centrally mediated reflex (28). Although many predisposing factors driving Down's syndrome children to suffer sleep breathing disorders, it is possible that the neuromotor abnormality might be not as severe as that in adenotonsillar hypertrophy kids. Furthermore, there are no any relationship between cortical and subcortical arousal frequencies in these three studies and even normal control groups. It might consistent with the finding in previous studies that subcortical arousal rather than RDI or cortical arousal might be the determinant for behavior change during the daytime.

To be honesty, without (8) CO2 or subatmospheric pressure application, it is difficult for this study to tell the difference of central-nervous-system augmented upper airway neuromotor tone for Down's syndrome and other groups of children.

In allergic rhinitis kids, (29) both nasal congestion and rhinorrhea exhibit statistically significant circadian rhythms, with peak congestive effects occurring during the early morning hours, increasing their deleterious effects on sleep. Moreover, the increase in nasal airway resistance was caused in part by nasal mucosal swelling secondary to a recumbency-induced increase in hydrostatic venous pressure. It was reported that (30) microarousals (cortical arousals) were 10 times higher in patients with rhinorrhea and congestion due to AR than in healthy controls. We can just find higher but similar frequency in cortical and subcortical arousal, compared with normal control. The nonallergic season for measurement might be the major confounding factor. On the other hand, significant lower heart rate at non REM and wake stages versus Down's syndrome kids might demonstrate that relatively dominant parasympathetic tone (31) was the result of less desaturation at similar cortical/ subcortical arousals and respiratory events than in Down's syndrome children. Besides (32), several of the mediators involved in allergic rhinitis have been implicated in the pathophysiology of sleep disorders.

This is a pilot study for Down's syndrome children by using cortical and subcortical arouals noninvasively to investigate the effect of a combination of structure and chromosome related neuromotor reflex during sleep. Probably, due to small number of participants, wide variety in sleep characters of Down's syndrome and an inappropriate timing (allergic season or not) for measurements, we did not find significant differences in cortical and subcortical arousal over the night sleep.

However, for purposes of prognostic prediction, treatment strategy and perhaps special diagnosis further study for this topic in children might be warranting.

In summary, in comparison to normal, healthy children and children with allergic

rhinitis and adenotosillar hypertrophy, Down's syndrome children, although characterized with chromosomal abnormality, was not lowered in cortical and subcortical arousals during sleep.

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Table 1. Demography for Normal Control Children and Children with Down Syndrome, Allergic Rhinitis and Adenotonsillar Hypertrophy

	Normal	Down Syndrome	Allergic Rhinitis	Tonsil Hyperplasia
No	5	11	10	11
Age(y)	7±3	8.3±2	7.8±2	7.4±1
Male	2	9	7	6
Height(cm)	122.2±9.3	119.77±3	130.9±10.7#	127.7±14.0
Weight(kg)	27.4±8.9	27.8±5.9	31.2±9.6	31.7±18.0
BMI	16.9±2.7	19.5±4.0	17.9±4.1	18.2±15.2
Neck Circumference(cm)	28.4±2.4	30.3±2.1	29.4±3.1	28.0±3.1#(0.06)
Waist Width(cm)		65.6±6.4	66.3±12.7	65.5±15.9

*p<0.05, * *p<0.01, * * * p<0.005 v.s.Normal ; # p < 0.05, p<0.01##, p < 0.005 ### , v.s. Down Syndrome

Table 2. Sleep Structures for Normal Control Children and Children with Down Syndrome, Allergic Rhinitis and Adenotonsillar Hypertrophy

	Normal	Down Syndrome	Allergic Rhinitis	Tonsil Hyperplasia
ESS		4.8±4.2	3.0±2.1	5.1±4.4
TST(min)	312.3±48.2	281.5±44.2	291.9±59.3	328.6±13.6###
Sleep Efficincy	86.6±12.5	78.8±12.7	82.5±15.7	92.3±3.6###
Stage1%	9.18±4.4	14.9±9.3	7.5±5.2#	10.5±4.0
Stage2%	27.6±14.8	24.4±12.9	33.3±13.6	40.8±8.7###
Stage3%	16.4±6.1	9.8±5.0 *	9.6±3.0 *	12.2±5.7
Stage4%	36.3±13.2	23.9±4.3 *	30.8±8.7#	25.5±9.0
NREM%	92.9±4.7	89.7±8.3	90.9±6.4	92.6±4.8
REM%	6.7±4.5	8.3±6.5	8.4±6.2	7.1±4.7
Stage1(min)	31.2±17.7	52.1±32.5	25.1±17.7#	36.1±14.3
Stage2(min)	88.3±51.2	84.4±45.3	93.3±42.8 *	139.9±32.5 *###
Stage3(min)	53.5±23.6	33.7±16.9	32.1±10.4 *	41.7±19.2
Stage4(min)	118.6±52.2	82.6±14.6 *	102.3±29.7	86.8±30.7
NREM(min)	291.6±57.3	252.8±48.4	261.3±43.4	304.5±21.8###
REM(min)	20.7±11.5	28.7±21.8	28.8±21.8	24.1±15.5

*p<0.05, * *p<0.01, * * * p<0.005 v.s.Normal ; # p < 0.05, p<0.01##, p < 0.005 ### ,v.s. Down Syndrome

Table 3. Sleep Quality Variables for Normal Control Children and Children with Down Syndrome, Allergic Rhinitis and Adenotonsillar Hypertrophy

	Normal	Down Syndrome	Allergic Rhinitis	Tonsil Hyperplasia
ESS		4.8±4.2	3.0±2.1	5.1±4.4
TST(min)	312.3±48.2	281.5±44.2	291.9±59.3	328.6±13.6###
Sleep Efficincy	86.6±12.5	78.8±12.7	82.5±15.7	92.3±3.6###
Stage1%	9.18±4.4	14.9±9.3	7.5±5.2#	10.5±4.0
Stage2%	27.6±14.8	24.4±12.9	33.3±13.6	40.8±8.7###
Stage3%	16.4±6.1	9.8±5.0 *	9.6±3.0 *	12.2±5.7
Stage4%	36.3±13.2	23.9±4.3 *	30.8±8.7#	25.5±9.0
NREM%	92.9±4.7	89.7±8.3	90.9±6.4	92.6±4.8
REM%	6.7±4.5	8.3±6.5	8.4±6.2	7.1±4.7
Stage1(min)	31.2±17.7	52.1±32.5	25.1±17.7#	36.1±14.3
Stage2(min)	88.3±51.2	84.4±45.3	93.3±42.8 *	139.9±32.5 *###
Stage3(min)	53.5±23.6	33.7±16.9	32.1±10.4 *	41.7±19.2
Stage4(min)	118.6±52.2	82.6±14.6 *	102.3±29.7	86.8±30.7
NREM(min)	291.6±57.3	252.8±48.4	261.3±43.4	304.5±21.8###
REM(min)	20.7±11.5	28.7±21.8	28.8±21.8	24.1±15.5

*p<0.05, * *p<0.01, * * * p<0.005 v.s.Normal ; # p < 0.05, p<0.01##, p < 0.005 ### ,v.s. Down Syndrome