Breathing abnormalities in sleep in achondroplasia

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Abstract

Overnight sleep studies were performed in 20 subjects with achondroplasia to document further the respiratory abnormalities present in this group. Somatosensory evoked potentials (SEPs) were recorded in 19 of the subjects to screen for the presence of brainstem abnormalities, which are one of the potential aetiological mechanisms. Fifteen children aged 1 to 14 years, and five young adults, aged 20 to 31 years were included. All had upper airway obstruction and 15 (75%) had a pathological apnoea index (greater than five per hour). Other sleep associated respiratory abnormalities, including partial obstruction, central apnoea, and abnormal electromyographic activity of accessory muscles of respiration, also showed a high prevalence. SEPs were abnormal in eight (42%), but there was no correlation between abnormal SEPs and apnoea during sleep, either qualitatively or quantitatively. A high prevalence of both sleep related respiratory abnormalities and abnormal SEPs in young subjects with achondroplasia was demonstrated. However, the sleep related respiratory abnormalities do not always result in significant blood gas disturbances or correlate with abnormal SEPs in this group.

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Achondroplasia is an autosomal dominant syndrome of short limbed short stature and is the most common type of chondrodysplasia. The bony abnormalities present in achondroplasia result in a characteristic phenotype, but the specific underlying defect is not yet known. The distinctive abnormalities of achondroplasia that may predispose to upper airway obstruction in sleep include a short cranial base, and associated with this, a relatively hypoplastic middle third of face. Respiratory control centres can also be affected in this disorder, when there is compression of the brainstem at the level of the foramen magnum,^{1 2} secondary to significant bony stenosis of the foramen magnum.

Recently a number of studies have suggested that sleep apnoea occurs commonly in those individuals with achondroplasia.^{3 4} A range of sleep disordered breathing is recognised, the commonest being the upper airway obstructive variety associated with snoring. The mechanisms that cause apnoea are still uncertain, although structural abnormalities described

above, with subsequent narrowing of the upper airway, is considered to be an important or even dominant cause of adult apnoea.

The reports of apnoea in achondroplasia include central apnoea (apnoea where there is cessation of diaphragmatic activity and airflow) and apneustic breaths. The occurrence of this type of apnoea is suggestive of abnormal reflex control of breathing in sleep. Because achondroplasia can be associated with stenosis of the foramen magnum and brainstem compression, it has been suggested that the apnoea in achondroplasia is the result of damage to brainstem reflexes.⁴ In the infant, life threatening apnoea is thought to be the result of critical stenosis at the craniocervical junction, with compressive damage to the respiratory control centres.

The purpose of our study was to measure and characterise the type of apnoea in achondroplasia, and to measure somatosensory evoked potentials (SEPs) to see if they correlated with the type of apnoea. We provide a detailed description of the types of respiratory abnormalities present in sleep in achondroplasia. This helps to interpret further the sleep disordered breathing in achondroplasia, on the basis of either the limited upper airway dimensions or the neurological abnormalities, secondary to bony malformations.

Patients and methods

In the total study group there were 10 males and 10 females. This included 15 children, eight boys and seven girls, aged 1 to 14 years, and five young adults, two male and three female, aged 19 to 31 years.

The subjects were usually enrolled by contact at the time of their regular review in our skeletal dysplasia clinic. Two patients of 22 who have been approached to date have declined participation. The main reason given in both cases was the parents' desire to limit the number of investigations and procedures their children underwent. Three young adults were recruited through the Little People's Association, where the research study was discussed, and one participant was contacted through a sibling.

Overnight sleep studies were performed in all patients. A clinical history with specific questioning regarding symptoms of obstructive sleep apnoea, apnoea of infancy, and other sleep disordered breathing was obtained. Clinical examinations were performed in each, with specific attention to the presence of either peripheral neurological or cranial nerve abnormalities. The studies subsequently took

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place, overnight, in an established sleep unit, during the period of the subjects' normal night time sleep. Polysomnography included recordings of sleep staging using electroencephalogram (EEG) (C_3-A_2), (O_2-A_1), electro-oculogram (EOG), and chin electromyogram (EMGgg) or sternomastoid electromyogram (EMGsm) via surface electrodes. Respiratory variables included inductance plethysmography (Respirtrace) of chest and abdomen (uncalibrated), nasal airflow (pressure wave), and diaphragm EMG (EMGd). An electrocardiogram (ECG) was recorded using chest leads and oxygen saturation (SaO_2) using a finger probe (Ohmeda Biox 1000). Transcutaneous carbon dioxide ($TcCO_2$) was recorded using the TINA (Radiometer, Copenhagen) monitor. All studies were performed without sedation and recorded on a Grass Model multi-channel recorder.

Sleep studies were staged and scored by two of the authors (KAW or FE) using the staging criteria of Rechtschaffen and Kales.⁵ Results were recorded for apnoea index, total apnoea, central apnoea, and obstructive apnoea times. The apnoea index is the total number of apnoeas during sleep divided by the total number of hours of sleep recorded. An obstructive apnoea is one where there is absence of airflow, but persistent respiratory effort, indicated by EMGd activity and chest and abdominal movements (Respirtrace). Central apnoeas are those where the absent airflow is accompanied by absent diaphragmatic activity and lack of thoracic and abdominal respiratory movement.

The criteria used to define a respiratory event were arousal or a change in SaO_2 ($>3\%$) on transcutaneous measures or a disruption of the regular pattern of respiration (for example, a pattern of repetitive central apnoea). As a result of this, apnoea duration varied quite markedly across the age range of our patients. In a 12 month old infant an apnoea covering three normal breath intervals, but lasting only three seconds and resulting in a 4% oxygen desaturation would be included. We included hypopnoeas (half average respiratory excursions) only if this occurred in association with an arousal and subsequent return to baseline respiratory excursions. The hypopnoeas were not usually associated with measured oxygen or carbon dioxide changes and as a result many minor events were not included in the score. Other respiratory abnormalities were noted in the results, but did not affect the scoring procedure.

The measurement of SEPs was used as an index of brainstem dysfunction. SEPs were usually recorded within 24 hours of the night time sleep study. A transcutaneous stimulus was adjusted to motor threshold (indicated by a toe twitch). A stimulus range of 4–9 mAmp was used, for 200 μ sec, at 2.1 Hz and applied over the posterior tibial nerve at the ankle. The potential was recorded at the lumbar spine (referred to the iliac crest) and the cortical response was recorded at CZ1 referred to FPZ (ground plate of leg). The data were analysed using the Nicolet Compact Four evoked

potential system. Sensitivity set at 25 μ V, and filter 30–3000 Hz were used. Studies were performed without sedation; chloral hydrate (single dose 25 mg/kg) was used in two cases where the subjects were toddlers and unable to cooperate.

The patient's height, leg length, and latency values from the lumbar and cortical responses were used to calculate conduction velocity. For the purpose of this study, the results were divided into four groups. The criteria used were (i) presence of a definable response, (ii) clarity of the cortical response, and (iii) central velocity of conduction in relation to normal values.^{6,7} The four groups were defined as: grade 1=normal; grade 2=present, not delayed, but poorly defined; grade 3=present but delayed; and grade 4=absent.

These group classifications were used to correlate the SEPs with the respiratory scores of apnoea index, total apnoea, central apnoea, and obstructive apnoea times. We also attempted to correlate the absolute time of the occurrence of the evoked response with the apnoea indices.

Results

CLINICAL HISTORY AND EXAMINATION

All the subjects had a history of snoring in sleep, and those with a history of witnessed apnoea had obstructive apnoea sufficient to warrant intervention. Not all of the subjects later shown to have repetitive apnoea had a history of witnessed apnoea. Even in the most severe case, a 21 year old man, symptoms of excessive daytime somnolence and witnessed apnoea were not volunteered as they were chronic and considered a part of having achondroplasia. In the group with respiratory abnormalities not thought to require treatment, the history did not indicate the severity of the abnormality present, and auxiliary symptoms such as restlessness in sleep, sweating, and loud snoring were not discriminatory. None of these individuals had sought medical attention for these symptoms, which on specific questioning included excessive daytime somnolence and witnessed apnoea.

Clinical examination did not discriminate which subjects would have obstruction. None of the group had any evidence of bulbar dysfunction to clinical examination, and all of the group had brisk tendon reflexes of the lower limbs. Only one of the adults had symptoms of headache and upper limb pain that had been diagnosed as secondary to cervical spinal canal stenosis; there were no associated upper limb neuromuscular abnormalities. Two of the subjects had a history of lumbar claudication, and one of these had obstructive sleep apnoea, the other had repetitive cycles of mixed apnoea.

SLEEP STUDIES

Results of all of the studies are presented in the table. A total of 20 individuals with achondroplasia were included. An apnoea index of greater than five per hour⁸ was

recorded in 15 studies. The majority had other respiratory abnormalities during sleep including several disorders ranging from snoring, abnormal EMG activity of the accessory muscles of respiration during sleep (EMG reference), and periodic cycles of apnoea.

All of the subjects snored during the period of their study, and therefore had some degree of partial upper airway obstruction.⁹ The evidence for partial upper airway obstruction on the recorded sleep study was increased EMGgg activity (and EMGsm where this was also measured) indicating use of accessory respiratory muscles during inspiration. Other indicators included acute carbon dioxide retention associated with onset of either sleep, or a particular sleep stage, a characteristic 'flow limited' pattern on the airflow trace (fig 1A), and active expiration on EMGd. These findings were most pronounced in slow wave sleep, and were severe in six (40%) of the 15 children. Respiration during slow wave sleep in these six children was characterised by the presence of all of these components together, in each period of slow wave sleep, and were

not affected by posture. This pattern of obstruction in slow wave sleep was associated in all six cases with carbon dioxide retention of up to 17 mm Hg (2.27 kPa) recorded on TccO₂.

Twelve of the children (80%) demonstrated a pattern of phasic EMGgg in rapid eye movement sleep (fig 2A). This sleep stage was associated with a notable diminution of the tonic EMGgg activity (fig 2B, at change of sleep state) but the children demonstrated partial obstruction, without apnoeas, in the presence of this increased hyoid and sternomastoid activity, a phenomena not seen in adults. All other features were unequivocal of rapid eye movement sleep during these intervals with low amplitude high frequency EEG, phasic eye movements, and reduced EMG activity. In five children no rapid eye movement period was free of this phasic EMGgg activity.

A pattern of repetitive central/mixed apnoea was seen in nine children (60%). These periods were characteristic of the occurrence of regular central apnoeic events, interrupted by brief periods of apparently normal breathing. The number of epochs of repetitive apnoea and the total duration of the combined epochs is included in the table. These cycles were of variable duration, extending up to 25 minutes in a 7 year old boy. In five children this pattern occurred during rapid eye movement sleep. Isolated central apnoeas may be normal, but not repetitive.¹⁰

Complete obstructive apnoea, with complete cessation of airflow despite continuing respiratory effort, was observed in a total of seven (35%) of the group. This led to active intervention in those where there was either an apnoea index of greater than 20 per hour, repetitive blood gas changes (as measured using transcutaneous monitoring) of greater than 10% desaturation and greater than 10 mm Hg (1.33 kPa) carbon dioxide retention, or an arousal index of greater than 20 per hour. Four children were diagnosed with severe obstructive apnoea, and all demonstrated repetitive obstruction associated with oxygen desaturation and carbon dioxide retention. This occurred predominantly in rapid eye

Figure 1 (A) Upper airway obstruction in slow wave sleep. Sleep study tracings showing slow wave sleep with EEG waveforms of high amplitude and low frequency. Surface EMG activity of genioglossus and diaphragm show phasic inspiratory (EMGgg) activity. Expiratory EMG activity on the trace EMGd shows expiratory activity from abdominal muscles. Airflow signal is measured as an airflow wave and shows a flattened inspiratory (flow limited) waveform (1 cm=7.6 secs). (B) Carbon dioxide retention in slow wave sleep (SWS). Sao₂ and TccO₂ levels are recorded simultaneously but on a slow recorder output. There is a phase delay between the output of these signals caused by a combination of pen position and signal response time of the measuring device. There is acute carbon dioxide retention during the period of slow wave sleep, with return to baseline during light sleep. The normal range of carbon dioxide variation is 7 mm Hg (0.93 kPa) throughout the night.

Summary of sleep study abnormalities

Apnoea index (per hour)	Mean (SD) 18.2 (14.8) (range 0-57)
Sleep respiratory abnormalities	
Total	20
(A) Accessory EMG*	12
REM	10
NREM	11
(B) Cyclic apnoea†	12
Duration (min)	32.3 (15.7)
Mean % total sleep time	7.4 (3.9)
No of episodes (total)	10.5 (4.9)
(C) Apneustic breaths	6
SEP grade	
1	11
2	3
3	1
4	4

*Accessory EMG=phasic activity of EMG of accessory muscles, sternomastoid, chin, +/- abdominal.
†Cyclic apnoea=periodic apnoea (not obstructive); values shown are mean duration (SD). REM=rapid eye movement; NREM=non-rapid eye movement sleep.

movement sleep. There was concurrent evidence of severe obstruction in slow wave sleep in only one of these cases.

Three young adults had repetitive apnoea and hypopnoea. This pattern was predominantly in the wake to sleep transition state, and recurred throughout the night in light sleep stages. This resulted in marked sleep disruption, without significant oxygen desaturation or carbon dioxide retention. One 30 year old woman had no apnoea, but hypopnoeas associated with very high arousability, resulting in high sleep disturbance.

SOMATOSENSORY EVOKED POTENTIALS

SEPs were performed in 19 subjects. They were not measured in the 12 month old infant,

as we had no normal values to correlate with the results, making such results uninterpretable. Results are shown in the table. Eight subjects had abnormal SEPs with four having absent responses. Notably, all of these four had substantial apnoea. However, the subjects with normal responses had a wide range of apnoea from none to clinically significant. There was no clear correlation between either the incidence, type (central or obstructive), or duration of apnoea and abnormalities found on the studies of SEPs. There was also no correlation between the absolute delay of the evoked response and the severity of the apnoea (apnoea index or apnoea duration). The child with the most central apnoea had normal SEPs. Only one of the young adults treated for obstructive apnoea and hypopnoea also had abnormal SEPs. All the subjects with abnormal SEPs had abnormal sleep study results, but the presence of an abnormal sleep study (by any of our criteria) was not associated with abnormal results of the SEPs.

Discussion

Our study of 20 subjects with achondroplasia, who were not selected on clinical criteria, has shown that sleep apnoea and sleep disordered breathing are extremely common in this condition. All of our subjects demonstrated variable degrees of upper airway obstruction, and in seven subjects the extent of the apnoea was sufficiently severe to require treatment with either adenotonsillectomy or nasal continuous positive airway pressure (CPAP). Previous studies have reported a high prevalence in clinic patients with achondroplasia. The probable reason that our study showed a higher level of obstructive sleep apnoea is that we used full overnight sleep studies and more recently accepted scoring criteria for use in children.

Stokes *et al* found a 10% incidence of severe respiratory abnormalities in their clinic patients.³ In the study by Nelson *et al* 34% of patients had abnormal polysomnographic studies.⁴ In this study, upper airway obstruction was demonstrated and all of the respiratory abnormalities demonstrated can be accounted for by upper airway obstruction. Possible reasons for the different incidence of significant sleep obstruction include either different patient selection or that our study utilised full overnight sleep studies. Furthermore, the adult scoring criteria used in other studies^{2,4} to define significant apnoea would exclude some of our clearly illustrated examples of sleep disordered breathing in children and young adults. If we were to use the requirements of desaturation >10%, bradycardia to 50% of baseline, or apnoea greater than 10 seconds, we would not consider three of our young adults to have sleep apnoea. These patients had multiple apnoeas/hypopnoeas without oxygen desaturations, resulting in frequent arousal, significant sleep disturbance, and daytime somnolence. The presence of such sleep disturbance in these cases has led us to commence nasal CPAP, with marked clinical improvement.

Figure 2 (A) Phasic EMGgg in rapid eye movement sleep. Sleep record showing rapid eye movement sleep, as indicated by phasic eye movements on the EOG (divergent signals), high frequency low amplitude EEG, and reduced EMGg activity. Phasic inspiratory activity of EMGgg is seen, and mixed hypopnoeas showing reduced EMGd, reduced Respiration (sum of chest and abdominal movement), and markedly reduced airflow. (B) Phasic EMGgg in rapid eye movement sleep, persisting but with augmentation in light sleep; arrow indicates change of sleep state. This figure includes a sleep state transition, from rapid eye movement sleep to light sleep at the arrow pointer. There is loss of phasic eye movements and appearance of sleep spindles in the EEG signal. EMGgg activity is phasic throughout, but is augmented after the transition to light sleep. This clearly shows that genioglossal activity is reduced, but not lost, and remains phasic during rapid eye movement sleep. (In (A) and (B) 1 cm=10 secs.)

There are no adequate data on the prevalence of apnoea in the various age ranges covered by our patients, so it is uncertain if the abnormalities are coincidental. In recent prevalence estimates in the age and sex group clinically thought to dominate sleep apnoea (men aged 40 to 65), the prevalence has been estimated to be up to 10%.¹¹ All of our patients were younger than this known high risk group, and half were female. Clearly, on any of these criteria it is highly likely that sleep disordered breathing occurs much more commonly in subjects with achondroplasia.

Obesity is a known contributing factor in adult sleep apnoea. Our subjects varied in physiognomy from thin to solid, but none appeared obese in the familiar context of adult obstructive apnoea. The body mass index measurement was of limited value as there was no basis for comparison in dwarves.

This particular group provided a unique opportunity to compare the responses of children to that of (young) adults. The characteristic physiological picture of adult sleep apnoea is repetitive upper airway obstruction associated with arousal at the cessation of the apnoea. The typical patient profile is an overweight middle aged male drinker, with women being affected only in the postmenopausal period. Children, in contrast, 'sleep through' upper airway obstruction, and their responses to upper airway obstruction differ qualitatively from our experience of adult apnoea. These children progressed through all sleep stages (including rapid eye movement) without arousing, despite significant upper airway obstruction.

Unlike adults, the infants maintained EMGgg activity during obstructed breathing in rapid eye movement; possibly this EMGgg response allowed the normal sleep stage to progress without arousal. Complete obstruction and apnoea appear to be prevented by maintaining upper airway tone, so forestalling arousal and consequent disruption of rapid eye movement sleep (fig 2). Clearly, the partial upper airway obstruction caused a reduction in alveolar ventilation and the consequent blood gas changes activated chemoreflexes leading to activation of expiratory muscles and EMGgg. Other potential mechanisms include upper airway sensory reflexes resulting in increased upper airway tone^{12 13}; reflexes that this study suggests are more active in children or are maintained in rapid eye movement sleep in the paediatric population where they activate this phasic muscle activity. This phasic EMG response to obstruction is not seen in adults. The difference may simply lie in the ability of children to respond to these reflexes, with specific phasic increase of muscle activity, despite general loss of muscle tone in rapid eye movement sleep. While adults may compensate for their upper airway obstruction in slow wave sleep with phasic upper airway muscle (EMGgg) activity, this activity did not extend to rapid eye movement sleep. Rapid eye movement sleep was markedly disrupted in the adults in the presence of obstruction, consistent with the results of other studies of adult sleep apnoea.¹¹

These young adults also demonstrated an apparently heightened arousal response to obstruction in light sleep, resulting in significant sleep disruption. Two premenopausal women aged 19 and 30 years respectively, had repetitive hypopnoea leading to arousal, without any demonstrable blood gas changes on transcutaneous measures. Presumably, reflexes other than chemoresponses, for example originating in the upper airway¹³ caused arousal in these subjects. The combined effect of these responses to obstruction resulted in sleep disturbance sufficient to cause marked abnormalities of both daytime function and documented sleep records. There was a clear response to treatment with nasal CPAP in both these parameters. The abnormalities described are not detectable without a full overnight sleep recording as used in this study, and premenopausal women would usually be considered at very low risk of developing sleep apnoea.

These results may simply represent the evolution of sleep apnoea, by cross sectional survey of a population at high risk, and therefore be applicable to populations without achondroplasia. Three of our patients have demonstrated the typical picture of sleep apnoea and the associated blood gas disturbances. In affected children, we describe apnoeas being most marked in rapid eye movement sleep, but associated with new findings of sleep not disrupted, despite significant blood gas fluctuations with obstructive episodes. A 21 year old man demonstrated classic obstructive sleep apnoea on the polygraphic recording, but with atypical features of no oxygen desaturation to less than 90% and yet carbon dioxide retention (confirmed on a morning arterial blood gas).

Such a rise in TccO₂ without a corresponding fall in SaO₂ will occur when the initial arterial oxygen tension has been high, because the relatively small change in partial pressure of oxygen does not alter the saturation at this high level. In fig 1B, the saturation has fallen approximately 3% during the period corresponding to that of slow wave sleep and carbon dioxide retention. A time lag occurs between the changes in SaO₂ and TccO₂ on our recording because of technical differences in the methods of measuring and recording the two variables. Acute desaturations do occur in association with more rapid carbon dioxide retention. We were careful to obtain blood gas cross checks of our TccO₂, in order to confirm trends indicating significant carbon dioxide retention. We believe that the apparent discrepancy sometimes seen, of carbon dioxide retention without a corresponding fall in SaO₂, is in the inaccuracy of the oximeter in its high ranges. For example, it does not truly and reliably record saturation in the 90% range and therefore we would not rely on this at these high values. Our blood gases have confirmed the key point that some of these subjects develop carbon dioxide retention.

Both Reid *et al*² and Hecht and Butler¹⁴ have postulated that the brainstem compression in achondroplasia is the principle cause of

the sleep disordered breathing. Nelson reports a fall in apnoea index after decompressive surgery, on follow up sleep studies in four of eight patients. The average apnoea index for that particular group was 11.6 per hour, and fell to 7.2 per hour.⁴ Our results showing a high incidence of sleep breathing disorders support the possibility that brainstem compression is an important contributing factor. The high frequency of central apnoea in our study group could argue in support of brainstem dysfunction disrupting respiratory control. Another feature supporting the hypothesis is apneustic breaths¹⁵; this was seen only in six of our subjects. However, it is also possible that airway/midfacial dimension abnormality is an important factor.

In the available literature, the most common presentation for SEP values is of absolute delay in msec. Because of the wide range of ages in the patient population studied here, we felt that this measurement was too vulnerable to the effects of development and growth in height, to be valid across the entire group. Normal values for SEP velocities have been provided by studies in normal Japanese school-children, and so we felt that the classification of normal or abnormal would be more accurate on these criteria. This choice of classification has affected the decision to call the values normal or abnormal but seems to be the most accurate. Using the criteria of absolute delay in msec, all of the subjects in this group would have been classified as having abnormal SEP results. While this fits with our finding of all subjects have respiratory abnormalities, there was still no qualitative relationship of severity between the two abnormalities.

Our subjects as a group had clear evidence of abnormal SEPs but we showed no simple correlation between these and the respiratory abnormalities. The presence of absent SEPs did correlate with the presence of disordered breathing in sleep. But, the presence, type, or severity of the respiratory abnormalities for either individuals or the group as a whole did not relate to abnormal SEP responses. Clearly the abnormal SEPs reflect dysfunction at the cervicomedullary junction, and it is probable that more subtle damage is involved in other brainstem reflex systems such as respiratory centres and upper airway muscle control. Decompression of the foramen magnum (posterior cranial fossa) has been proposed and used as a treatment for sleep apnoea on the basis that brainstem dysfunction underlies the upper airway obstruction. We do not undertake this surgical form of treatment in achondroplasia because we remain uncertain of whether the aetiology of the apnoea is neurological or in the structure of the upper airway (or a combination of both). Rather, we believe that the presence of these brainstem

and neurological problems potentiates the upper airway obstruction that is common in this disorder, but an abnormal upper airway is still the primary cause.

CONCLUSION

Upper airway obstruction occurs in a significant proportion of individuals with achondroplasia, and this proportion is only determined accurately when overnight studies are undertaken.

While cases of typical obstructive sleep apnoea occur with oxygen desaturation, and carbon dioxide retention do occur, there may be other respiratory disturbances present that will result in significant sleep disruption without alteration of blood gases (on transcutaneous measurement).

With the high frequency of airway obstruction seen in this and other groups of people with achondroplasia, airway obstruction must be considered an integral part of the syndrome rather than an occasional complication, and full sleep studies are required to demonstrate the abnormalities present. SEPs are not an appropriate screening test for the presence of respiratory abnormalities.

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