Sleep apnoea in Scheie's syndrome

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ABSTRACT An 18-year-old student presented with a two-year history of daytime sleepiness and noisy breathing during sleep. Both he and his brother, aged 25 years, had Scheie's syndrome, a mucopolysaccharidosis characterised by small stature, micrognathia, corneal clouding, hepatosplenomegaly, raised urinary mucopolysaccharides, and undetectable levels of α -L-iduronidase assayed in cultured fibroblasts. Both brothers had sleep apnoea (apnoea index, 59 and 35 respectively) during which there was a significant fall in heart rate and arterial oxygen saturation. One brother had EEG changes suggestive of cerebral hypoxia and the other had ventricular extrasystoles at the end of several episodes. Tracheostomy in the younger brother produced a dramatic symptomatic improvement and reduced the number and severity of apnoeic episodes (post-tracheostomy apnoea index 2.4).

Sleep apnoea is increasingly recognised in association with daytime sleepiness, and patients with a sleep disorder may develop cor pulmonale, impotence, morning headaches, difficulty in concentration or even die during sleep. Sleep apnoea has now been clearly defined as cessation of airflow at the nostrils and mouth lasting for at least 10 seconds. The occurrence of 30 such episodes in seven hours' nocturnal sleep constitutes a sleep apnoea syndrome.¹

This syndrome may occur in apparently normal people² or be secondary to disorders affecting the respiratory centre or upper airways. Sleep apnoea may affect patients with the Shy-Drager syndrome,³ muscular dystrophy,⁴ bilateral cordotomy,⁵ myxoedema,⁶ obesity,¹ mandibular malformations⁷ including the Pierre-Robin syndrome⁸ and bird-like face syndrome,⁹ laryngeal stenosis,¹⁰ enlarged tonsils and adenoids,¹¹ and Ondine's curse.¹²

Gastaut *et al*¹³ have distinguished three types of sleep apnoea. Central apnoea is defined as cessation of airflow at the nose and mouth, accompanied by absent respiratory movements. In obstructive apnoea there is absent airflow at the nose and mouth despite persistent respiratory effort. Mixed apnoea consists of cessation of airflow and an absence of respiratory movement early in the episode followed by resumption of unsuccessful respiratory effort in the later part of the episode. In obstructive apnoea, which is the most common, the patient usually seeks medical advice because of

loud snoring and daytime sleepiness whereas the patient with predominantly central apnoea has insomnia.¹

In this report we describe severe sleep apnoea in two brothers with Scheie's syndrome, a rare mucopolysaccharidosis similar to, but milder than, Hurler's syndrome.¹⁴

Patients

Patient LM, an 18-year-old college student, presented with a two-year history of daytime sleepiness and loud snoring at night. At the age of 3 years he developed pain and stiffness of his hands and subsequently developed difficulty with vision and shortness of breath on exertion. On examination he showed the typical features of Scheie's syndrome. He was small (144 cm) and had abnormal facies, corneal clouding, and micrognathia. Oropharyngeal examination revealed macroglossia and indirect laryngoscopy was impossible as the tongue was closely applied to the posterior pharyngeal wall. His hands were fixed in a clawlike deformity. There was limited expansion of his chest and low pitched wheezes throughout both lungs. There was a pansystolic murmur suggestive of mitral incompetence and an echocardiogram showed deformity of the mitral valve. The abdomen was protuberant with hepatosplenomegaly and an umbilical hernia.

His elder brother, GM, aged 25 years, had musculoskeletal deformities of a similar nature. Examination showed the features of Scheie's

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Table 1 Lung function of patients LM and GM (% predicted for age, sex, and height) derived from Cotes¹⁵

	Patient LM	Patient GM
Forced expiratory volume in one second (FEV ₁) l	0.99 (32%)	1.32 (38%)
Vital capacity (VC) l	1.38 (39%)	1.71 (44%)
Residual volume (RV) l	1.74 (217%)	1.17 (97%)
Total lung capacity (TLC) l	3.11 (72%)	2.87 (55%)
Transfer factor (DCO) mmol min ⁻¹ kPa ⁻¹	4.7 (54%)	6.0 (65%)
Transfer per unit volume of lung (KCO) mmol min ⁻¹ kPa ⁻¹ l ⁻¹	2.1 (109%)	2.5 (134%)
Membrane diffusion (DM) mmol min ⁻¹ kPa ⁻¹	7 (46%)	8 (49%)
Pulmonary capillary volume (Vc) ml	67 (119%)	99 (155%)
Ratio of expiratory to inspiratory flow at 50% vital capacity derived from a flow volume loop (n < 1.5)	1.6	0.5
Blood gases pH (normal range 7.38 – 7.42)	7.42	7.38
PACO ₂ (kPa) (normal range 4.5 – 6.1)	4.8	3.8
PAO ₂ (kPa) (normal range 12 – 15)	9.2	9.2

syndrome. Oropharyngeal examination again revealed macroglossia with the tongue in close apposition to the posterior pharyngeal wall but indirect laryngoscopy was possible and a normal larynx was seen.

Investigations

BIOCHEMICAL STUDIES

Biochemical investigation of both brothers showed raised urinary mucopolysaccharides, the predominant being dermatan sulphate. Culture of skin fibroblasts showed absent α -L-iduronidase activity. Routine blood count and biochemistry was normal. Results of lung function studies and arterialised capillary blood gases are shown in table 1. Expiratory flow and lung volumes were reduced in both brothers apart from the residual volume which was normal in GM and raised in LM. A flow volume loop was compatible with upper airways obstruction in LM. Arterialised capillary blood gases in both brothers showed neither marked hypoxaemia nor hypercapnia.

SLEEP STUDIES

Sleep studies were carried out overnight in a quiet darkened room. No drugs were given before the study. Simultaneous recordings were made of airflow at the nose and mouth, thoracic and abdominal movement, electrocardiogram (ECG), ear-oxygen saturation, submental electromyogram (EMG),

electro-oculogram (EOG), and electroencephalogram (EEG).

Airflow at the nose and mouth was measured with thermocouples mounted on nasal prongs, abdominal movement by a strain gauge (Department of Biomedical Engineering, North Staffordshire Hospital Centre), and chest wall movement by thoracic impedance (Apnoea monitor, Air Shields Ltd). Continuous ear-oxygen saturation was measured with an Atlas Universal Oximeter. Sleep stage was assessed by eight channels of electroencephalogram (one frontal, three fronto-centro-parietal and two mid- and postero-temporal electrodes on each side, bipolar recording), electromyogram (by two submental electrodes), and electro-oculogram (by two electrodes outside each outer canthus, one slightly above the other). All the physiological variables were recorded on a 16 channel EEG recorder (Special Laboratory Equipment) for later analysis. Each trace was assessed by two observers independently and sleep stage classified according to standard criteria.¹⁶ The results were analysed using paired or unpaired *t* tests where appropriate.

Results

The overnight sleep record in patient LM showed that the time to sleep onset was nine minutes. During the subsequent sleep period of six hours one minute the sleep pattern was disturbed and he was awake for a total of 32 minutes. There were two main cycles of sleep, the first episode of rapid eye movement (REM) sleep occurring after 88 minutes and the second after 154 minutes of sleep. Thereafter there was no normal cycling. Overnight LM had a total of 320 apnoeic episodes giving an apnoeic index (number of apnoeic episodes per hour) of 59. The mean length of apnoea was 35 seconds (SD $\pm$ 16 s). During apnoea there was a mean fall in heart rate of 35 beats/minute (SD $\pm$ 16 beats/min, $p < 0.001$) and a mean fall in arterial oxygen saturation of 24% saturation (SD $\pm$ 9%, $p < 0.001$). Of the apnoeic episodes, 97% were obstructive (fig 1) and 3% were mixed. There were no episodes of central apnoea alone. Details of the apnoeic episodes during the five stages of sleep are given in table 2. The fall in arterial oxygen saturation was significantly greater in sleep stage 1 than in stage 4 ($p < 0.05$) and REM sleep ($p < 0.05$) although apnoea was more frequent in sleep stages 3 and 4. However, sleep scoring in patient LM was very difficult as apnoea was associated with bursts of paroxysmal rhythmic bifrontal and bisynchronous delta wave activity suggestive of cerebral hypoxia (fig 2) and

Sleep apnoea in Scheie's syndrome

Fig 1 Typical example of the end of an obstructive apnoeic episode in patient LM. The arterial oxygen saturation is shown with a calibration signal (top 100% saturation, bottom 0% saturation) which occurs every 10 seconds. Beneath are the traces of chest and abdominal movement and nasal and buccal airflow. EMG=electromyogram, EOG=electro-oculogram. Two channels of an EEG tracing are shown: F4-C4=right frontal to right central electrodes and F3-C3=left frontal to left central electrodes (bipolar recording). TC=time constant. Note absent airflow but persistent respiratory movements.

these episodes resembled stages 3 and 4 sleep.

In an attempt to overcome the problems of sleep apnoea a dental prosthesis was designed to make a patent channel to the oropharynx. Sleep studies were repeated with the prosthesis in position but showed no improvement in the frequency or severity of apnoea. Patient LM therefore underwent elective tracheostomy under local anaesthetic. After the tracheostomy he stated that his sleep had become satisfying and there was a dramatic improvement in the daytime sleepiness. The stages of sleep in a post-tracheostomy sleep study were much easier to score and more clearly defined. The study showed a reduction in the duration and number of apnoeic

episodes. During the study there were four apnoeic episodes (apnoeic index 2.4). All were central. The mean duration of apnoea was 15.7 seconds ($SD \pm 2.6$ s) with a fall in heart rate of 11 beats/min ($SD \pm 8$ beats/min) and a fall in arterial oxygen saturation of 2% saturation ($SD \pm 2.3$ %).

The overnight sleep record in patient GM showed that the time to sleep onset was 60 minutes. During the subsequent five hours six minutes he was asleep for two hours 18 minutes and awake for two hours 48 minutes. There were four main cycles of sleep. The first episode of REM sleep occurred after 70 minutes. Patient GM was less severely affected by apnoea than his brother with a total of 58 apnoeic

Table 2 Sleep study in patient LM before tracheostomy

Sleep stage	Number of episodes of apnoea	Mean length of apnoea (s) $\pm$ SD	Apnoea index (number of apnoeic episodes per hour)	Mean fall in heart rate during apnoea (beats/min) $\pm$ SD	Mean fall in arterial oxygen saturation during apnoea (%) $\pm$ SD	Type of apnoea		
						Obstructive	Mixed	Central
1	24	36 $\pm$ 22	36	37 $\pm$ 21	29 $\pm$ 13	23	1	0
2	88	36 $\pm$ 18	42	36 $\pm$ 17	24 $\pm$ 10	85	3	0
3	105	35 $\pm$ 15	67	34 $\pm$ 14	24 $\pm$ 8	105	0	0
4	95	34 $\pm$ 14	84	36 $\pm$ 11	22 $\pm$ 8	91	4	0
REM	8	30 $\pm$ 9	48	38 $\pm$ 6	19 $\pm$ 8	8	0	0
Total	320	35 $\pm$ 16	59	35 $\pm$ 16	24 $\pm$ 9	312	8	0

Fig 2 Obstructive apnoeic episode in patient LM. Two extra channels of EEG are included. Fp2-F4=right prefrontal to right frontal electrodes and Fp1-F3=left prefrontal to left frontal electrodes. The EEG shows bisynchronous delta activity suggestive of cerebral hypoxia.

episodes (apnoea index 35). Sleep scoring was more straightforward in patient GM, and apnoeic episodes tended to waken him, in contrast to his brother in whom they produced a transient arousal only. The mean duration of apnoea was 23 seconds (SD $\pm$

5 s). During apnoea there was a mean fall in arterial oxygen saturation of 8% saturation (SD $\pm$ 5%, $p < 0.001$). Of the apnoeic episodes 24% were obstructive, 33% were mixed, and 43% were central. A typical example of a central apnoeic

Fig 3 Typical example of a central apnoeic episode in patient GM showing the beginning and end of apnoea. Note absence of both airflow and respiratory movements.

Table 3 Sleep study in patient GM

Sleep stage	Number of episodes of apnoea	Mean length of apnoea (s) $\pm$ SD	Apnoea index (number of apnoeic episodes per hour)	Mean fall in heart rate during apnoea (beats/min) $\pm$ SD	Mean fall in arterial oxygen saturation during apnoea (%) $\pm$ SD	Type of apnoea		
						Obstructive	Mixed	Central
1	10	23 $\pm$ 3	108	18 $\pm$ 8	10 $\pm$ 7	1	1	8
2	29	22 $\pm$ 6	24	16 $\pm$ 9	8 $\pm$ 6	2	15	12
3	7	24 $\pm$ 7	42	12 $\pm$ 7	8 $\pm$ 5	6	0	1
4	4	25 $\pm$ 3	7	18 $\pm$ 9	7 $\pm$ 2	3	1	0
REM	8	23 $\pm$ 4	23	26 $\pm$ 8	7 $\pm$ 4	2	2	4
Total	58	23 $\pm$ 5	35	18 $\pm$ 9	8 $\pm$ 5	14	19	25

episode is shown in fig 3. Details of the apnoeic episodes are given in table 3. There was no significant difference in the severity of apnoea between the sleep stages. At the end of several apnoeic episodes patient GM had ventricular extrasystoles.

Discussion

Both of the patients described had the characteristic clinical and biochemical features of Scheie's syndrome.^{14 17 18} Abnormalities of the respiratory system have not been described in detail in this condition. Patients with Hurler's syndrome have a reduction in all subdivisions of lung volume apart from the residual volume, which is normal or increased, suggesting decreased chest wall compliance.¹⁹ Similar abnormalities were demonstrated in our two patients with Scheie's syndrome and in addition they had a raised pulmonary capillary volume. The micrognathia and macroglossia present in both brothers and similar to that described in Hurler's syndrome²⁰ caused narrowing of the upper airways. In addition abnormalities of bronchial cartilage are found in Hurler's syndrome,²¹ and probably also occur in Scheie's syndrome.²²

Disorders of sleep have not been described previously in Scheie's syndrome. Both patients reported here showed clear evidence of a sleep apnoea syndrome. It is interesting that the pattern of sleep apnoea was different in the two brothers. Patient LM had predominantly obstructive apnoea, which might be expected in view of the abnormalities of his oropharynx, whereas his brother (GM) showed all three types of apnoea, obstructive, mixed, and central with the latter predominating.

The anatomical abnormalities of the upper airways are present in these patients during waking and sleeping but periods of obstructive apnoea were recorded only during sleep. This indicates that the critical event is a functional disturbance related to sleep. Two different mechanisms have been proposed

for the development of obstructive apnoea.²³ In the first, obstruction may occur because of partial collapse of the airway during inspiration from a combination of loss of abductor muscle tone and negative airways pressure. The second possibility is that there is active constriction of the airway as a result of muscle contraction. There is evidence that the first mechanism may operate during non-REM sleep when there is decreased EMG activity and tone of the upper airway muscles associated with reduced ventilatory drive.²⁴ Phillipson²³ has suggested that the second mechanism may operate during what he classifies as the phasic stages of REM sleep. Both mechanisms may result in periods of obstructive apnoea, especially in patients who already have narrowing of the upper airways.

In patients with obstructive apnoea it has been shown that the ventilatory response to changes in arterial PCO₂ may be impaired,²⁵ suggesting that there is also an abnormality of the respiratory centre. Defects of central respiratory control may lead to central apnoea, and it is therefore not surprising that patients with predominantly obstructive apnoea also have central apnoea and vice versa.²³ This may explain why patient GM had central, mixed, and obstructive apnoea.

Abnormalities of clinical significance were found during sleep in both brothers. In LM the arterial oxygen saturation fell markedly on many occasions and this fall was accompanied by cyanosis and EEG changes suggestive of cerebral hypoxia. Patient GM had milder sleep apnoea but did have ventricular extrasystoles at the end of several apnoeic episodes. Guilleminault *et al*¹ have followed 27 patients with obstructive apnoea without treatment and found that three patients died during sleep within six months of diagnosis. Of the remainder, seven patients had progressive worsening of symptoms; one had a myocardial infarction during sleep and two became bed-bound because of cardiac failure. For these reasons an attempt was

made to prevent apnoea in patient LM.

The initial trial of a dental prosthesis with a channel to the oropharynx failed to reduce the severity of sleep apnoea. Drug therapy with respiratory stimulants—for example, medroxyprogesterone and clomipramine—has little effect even in patients with central apnoea.¹ We therefore performed a tracheostomy on patient LM to prevent the long-term sequelae of sleep apnoea. This treatment, described by Coccagna *et al*²⁶ and more recently by Hill *et al*,²⁷ is effective in preventing obstructive apnoea although some patients continue with mild central apnoea. In addition Guilleminault *et al*¹ found that all patients had a subjective resolution of symptoms after tracheostomy. After tracheostomy patient LM had a marked symptomatic improvement and a sleep study confirmed normal sleep patterns with an absence of obstructive apnoea, although there were a few short episodes of central apnoea.

Because of the other multisystem abnormalities of Scheie's syndrome both brothers are also being considered for fibroblast transplantation, a procedure under investigation in other mucopolysaccharides,²⁸ in the hope that further tissue accumulation of mucopolysaccharides will be prevented.

Awareness of the sleep apnoea syndrome is important because of its clinical implications. Initial investigation can be undertaken easily using a Holter-type ECG monitor.²⁹ A marked sinus arrhythmia present only during sleep is characteristic of this syndrome. Further investigation by polygraphic sleep monitoring indicates the severity and nature of the sleep disorder. The sleep apnoea syndrome carries a significant morbidity and mortality but tracheostomy appears to be an effective treatment.

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