in the production of extrarenal erythropoietin in rats, and Cannon and Pennington¹¹ and Gordon *et al*¹² reported erythropoietin secretion by primary liver tumours in man. Possibly the erythrocytosis of acute viral hepatitis¹³ is also mediated by erythropoietin, though that remains to be investigated.

Other workers have noted increased haemoglobin concentrations in uraemic patients with HBsAg hepatitis.⁶⁻⁷ Our findings show that drug-induced liver cytolysis also increases red-cell production in uraemia. We have documented elsewhere the unsuspected number of hepatotoxic drugs that are prescribed in uraemia,¹⁴ which may explain the reportedly beneficial effects of androgens¹⁵⁻¹⁶ and intravenous iron¹⁷ on the anaemia of chronic renal failure.

Interestingly our patients in group 2 showed an apparent correlation between persistently raised haemoglobin concentrations and biopsy evidence of chronic hepatitis.¹⁴ If this is confirmed a sustained improvement in anaemia after liver cytolysis could be used as additional evidence in tests for persisting liver damage.

Finally, possibly some forms of liver extracts could be utilised for treating renal anaemia.

Requests for reprints should be sent to Dr Alain Meyrier.

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Sleep apnoea in acromegaly

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Summary and conclusions

Daytime somnolence or excessive snoring, or both, occurred in five out of 11 patients with acromegaly. All five had episodes of sleep apnoea, and three had the sleep apnoea syndrome. Growth hormone concentrations were higher ($p < 0.025$) in these patients than in the six patients without these symptoms. One patient with daytime somnolence and one asymptomatic patient had flow loop evidence of upper airways obstruction. Two of the patients with the sleep apnoea syndrome had cardiomegaly.

Sleep apnoea appears to be common and clinically

important in acromegaly, and it may be central, obstructive, or mixed. Polygraphic nocturnal monitoring is indicated to assess these patients properly.

Introduction

Upper airways obstruction may be a complication of acromegaly owing to enlargement of the soft tissues of the oropharynx.¹ Upper airways obstruction from many causes may be associated with daytime somnolence and repeated episodes of sleep apnoea.² Sleep apnoea³⁻⁴ and daytime somnolence⁵ in acromegaly have been reported. The daytime somnolence may remit rapidly after the acromegaly has been treated,⁵ suggesting that it is not solely due to anatomical abnormalities of upper airways. We have studied 11 patients with acromegaly to determine the relation between upper airways obstruction, daytime somnolence, and sleep apnoea and the prevalence of these features.

Patients and methods

We studied 11 patients (five men and six women); table I gives clinical details. Acromegaly had been confirmed in all cases by the finding of raised growth hormone concentrations that did not fall after a glucose load. Two patients (cases 8 and 9) were newly diagnosed

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and had not received treatment, and one (case 7) had recently finished a course of radiotherapy. The remainder had been treated with surgery or radiotherapy, or both. One patient (case 10) had evidence of cerebral arteriosclerosis and mild Parkinsonism, and one (case 11) had had congestive heart failure that responded to treatment.

Two patients (cases 1 and 3) had developed hypopituitarism as a result of their treatment for acromegaly but were receiving adequate replacement treatment with hydrocortisone and thyroxine. The other patients had normal hypothalamic-pituitary-adrenal axes as judged by the cortisol response to insulin hypoglycaemia, except for one patient (case 10), who was not tested in this way but showed a normal cortisol response to tetracosactrin (Synacthen). Two patients (cases 7 and 10) had impaired responses of serum thyroid stimulating hormone to thyrotrophin releasing hormone, but all 11 patients had normal thyroxine concentrations.

The patients were questioned about daytime somnolence, and their bed partners asked if they snored excessively. Fasting growth hormone concentration was measured near the time of the sleep record by a double antibody radioimmunoassay with the MRC 66/214 reference preparation. The fasting concentration corresponded closely ($R=0.99$) to the mean concentration of the hormone in six blood samples taken either during a standard glucose tolerance test with a 50 g oral load or at intervals during the day. Spirometry was performed with a low-resistance spirometer with the patient seated, and the total lung capacity estimated by using a closed-circuit helium dilution technique. The cardiothoracic ratio was measured on a standard posteroanterior chest radiograph.

Sleep was studied overnight with the patient in a quiet, darkened room, continuous recordings being made for seven hours. No hypnotic or sedative drugs were given before the study. Simultaneous recordings were made of the airflow at the nose and mouth, thoracic and abdominal movement, electrocardiogram, ear oxygen saturation, submental electromyogram, electro-oculogram, and electroencephalogram. Airflow was measured with thermocouples mounted on nasal prongs; abdominal movement by a strain gauge (department of biomedical engineering); and chest-wall movement by thoracic impedance (Apnoea Monitor, Air Shields Ltd). Oxygen saturation was measured continuously from the ear with an Atlas Universal

Oximeter. Sleep stage was assessed by using an eight-channel electroencephalogram (three frontocentroparietal electrodes and a mid-temporal and posterotemporal electrode on each side, bipolar recording), electromyogram (two submental electrodes), and electro-oculogram (an electrode outside each outer canthus, one slightly above the other). All traces were recorded on a 16-channel electroencephalogram recorder (Special Laboratory Equipment) for later analysis.

Each trace was assessed by two observers independently. Sleep apnoea was defined as cessation of airflow at the nose and mouth lasting for at least 10 seconds.³ Apnoea was categorised as obstructive if abdominal and thoracic movement continued, central if thoracic and abdominal movements were absent, and mixed if there was no movement early in the episode of apnoea and unsuccessful movement later in the episode.³ Sleep stage was classified according to standardised criteria.⁶ The results were analysed statistically with the Mann-Whitney U test for small samples⁷ or the paired *t* test.

Results

Table II shows details of daytime somnolence, excessive nocturnal snoring, lung function, fasting growth hormone concentration, and heart size ranked according to apnoea index (number of episodes of apnoea per hour). Three patients had three or more episodes of daytime sleep, falling asleep after meals, reading, and watching television. One patient (case 7) retired from work because of embarrassing episodes of sleep. The inappropriateness of the daytime somnolence in case 10 was difficult to assess because of the patient's inactivity. One patient (case 11) had fallen asleep at work while standing at a machine. None of these patients had sleep paralysis, cataplexy, or hypnagogic hallucinations. They and two additional patients whose snoring was judged by their bed partners to be excessive were defined as symptomatic. The six remaining patients were defined as asymptomatic.

The sleep studies in all the symptomatic patients showed episodes of sleep apnoea. Three patients had more than 30 apnoeic episodes overnight, thereby fulfilling the criteria for the sleep apnoea syndrome.³ In the other two patients the number of apnoeic episodes overnight was higher than that in the asymptomatic patients but not

TABLE I—Details of 11 patients with acromegaly

Case No	Sex	Age (years)	Weight (kg)	Duration of symptoms of acromegaly (years)	Time from last treatment (surgery or radiotherapy) (years)	Mean growth hormone (highest recorded during GTT) (mU/l)
1	M	49	102	12	2	369
2	F	35	68	8	5	145
3	F	51	65	16	4	26
4	F	31	62	7	5	20
5	F	58	95	38	13	24
6	F	61	60	15	7	32
7	M	59	76	15	0	101
8	M	43	111	1	0	15
9	M	43	83	1	0	89
10	F	69	79	32	2	47
11	M	58	98	11	6	52
Mean $\pm$ SD		51 $\pm$ 12	82 $\pm$ 18	14 $\pm$ 12	4 $\pm$ 4	84 $\pm$ 103

GTT = Glucose tolerance test.

TABLE II—Details of symptoms, lung function, heart size, and fasting growth hormone concentrations in 11 patients with acromegaly ranked in order of apnoea index

Case No	Apnoea index (No of episodes of apnoea/h of sleep)	No of episodes of sleep daily	Snoring judged excessive by bed partner	Lung function			MEFR:MIFR	Cardiothoracic ratio (normal < 50%)	Fasting growth hormone near time of sleep record (mU/l)
				FEV ₁ (% predicted*)	FVC (% predicted*)	TLC (% predicted*)			
1	0	0		136	120	145	1.0	39	21
2	0	0		89	86	88	1.7	42	3
3	0	0		110	108	110	0.8	44	9
4	0	0		115	104	103	1.0	40	5
5	0.3	0		96	102	113	1.0	44	2
6	0.6	0		105	100	117	0.7	43	8
7	1.0	3	Yes	123	141	140	1.0	41	102
8	1.8	0	Yes	107	106	129	0.8	43	15
9	10.6†	0	Yes	93	104	133	0.4	36	74
10	12.4†	3		38	32	56	2.3	62	27
11	31.6†	5	Yes	76	72	79	1.2	59	14
Mean $\pm$ SD				99 $\pm$ 26	98 $\pm$ 28	110 $\pm$ 27	1.1 $\pm$ 0.5	45 $\pm$ 8	25 $\pm$ 32

*Predicted for age, sex, and height.¹⁰

†Patient fulfilled criteria for sleep apnoea syndrome.

FEV₁ = Forced expiratory volume in one second. FVC = Forced vital capacity. TLC = Total lung capacity. MEFR:MIFR = Ratio of mean expiratory to mean inspiratory flow rate.

TABLE III—Duration of each sleep stage and number of apnoeic episodes in each stage over seven hours in 11 patients with acromegaly

Case No	Apnoea index	Sleep stage								Total			
		I		II		III		IV				Rapid eye movement	
		Duration (min)	No of apnoeic episodes	Duration (min)	No of apnoeic episodes	Duration (min)	No of apnoeic episodes	Duration (min)	No of apnoeic episodes	Duration (min)	No of apnoeic episodes	Duration (min)	No of apnoeic episodes
1	0	11	0	127	0	18	0	19	0	25	0	200	0
2	0	34	0	156	0	23	0	11	0	42	0	266	0
3	0	28	0	123	0	16	0	3	0	42	0	212	0
4	0	55	0	132	0	16	0	9	0	34	0	246	0
5	0.3	49	0	97	0	31	0	28	0	26	1	198	1
6	0.6	36	0	126	1	22	0	6	0	24	1	214	2
7	1.0	43	0	181	3	61	2	40	1	77	1	402	7
8	1.8	57	4	97	1	4	0			7	0	166	5
9	10.6	67	3	177	12	14	1	7	0	75	44	341	60
10	12.4	47	7	91	23	64	17	66	12	31	3	300	62
11	31.6	174	126	130	38					51	23	355	187

TABLE IV—Details of the apnoeic episodes experienced by seven patients

Case No	Apnoea index	Type of apnoea			Mean ($\pm$ SD) duration of apnoea (s)	Mean ($\pm$ SD) change in heart rate (beats/min)	Mean ($\pm$ SD) change in arterial oxygen saturation (%)
		Obstructive	Mixed	Central			
5	0.3	0	0	1	14	0	0
6	0.6	1	0	1	16 (12, 20)	-4 (-2, -6)	-5
7	1.0	6	1	0	22 $\pm$ 10	-2 $\pm$ 5	-2 $\pm$ 3
8	1.8	0	0	5	22 $\pm$ 2	-1 $\pm$ 4	-6 $\pm$ 5
9	10.6	44	16	0	19 $\pm$ 5	-14 $\pm$ 9*	-18 $\pm$ 7*
10	12.4	0	0	62	15 $\pm$ 3	+1 $\pm$ 6	
11	31.6	1	76	110	28 $\pm$ 13	-26 $\pm$ 16*	-12 $\pm$ 10*

*P < 0.001 (paired t test).

outside the normal range (less than 25 episodes overnight in men and less than five in women³). Only one of the asymptomatic patients had an episode of sleep apnoea during stage II sleep as opposed to rapid eye movement sleep or the onset of sleep (table III).

Four of the five symptomatic patients were men compared with one of the six asymptomatic patients. The mean fasting growth hormone concentration in the symptomatic patients (three of whom had received treatment) was 46 mU/l (range 14–102 mU/l), which was significantly greater than that in the asymptomatic patients (all of whom had been treated), whose mean concentration was 8 mU/l (range 2–21 mU/l) ($p < 0.025$). The ratio of expiratory to inspiratory flow at 50% vital capacity was raised (normal < 1.5¹) in one symptomatic and one asymptomatic patient. The two patients with the most apnoeic episodes had cardiomegaly.

Table III shows the duration of each sleep stage and number of apnoeic episodes in each stage. All of the symptomatic patients had episodes of apnoea in stage II, III, or IV sleep. Although the patients were studied over seven hours, wakefulness was common in them all. The sleep pattern was abnormal in three patients (cases 5, 10, and 11), with irregular and incomplete sleep cycling.

Table IV gives details of the apnoeic episodes. One patient (case 9), who snored excessively, had predominantly obstructive apnoea during which heart rate and arterial oxygen saturation fell significantly. One patient (case 11) had daytime somnolence and snored excessively, and sleep studies showed both central and mixed apnoea during which heart rate and ear oxygen saturation fell significantly. Another patient (case 10) had daytime somnolence and episodes of central apnoea, yet the heart rate did not change significantly during these episodes (ear oxygen saturation was not measured in this patient).

Discussion

Daytime somnolence or excessive nocturnal snoring, or both (symptoms that may be associated with sleep apnoea³), occurred in five out of 11 patients with acromegaly. All five had episodes of sleep apnoea in stage II, III, or IV sleep, a feature not seen in a series of 20 normal subjects.³ One of the six asymptomatic patients had a single episode of apnoea during stage II sleep.

Guilleminault *et al*^{3,4} have suggested that acromegaly is associated with predominantly obstructive apnoea. Of the three patients in our series who fulfilled the criteria for the sleep apnoea syndrome, only one had mainly obstructive apnoea; one had episodes of central and mixed apnoea and one had episodes of

central apnoea alone. Interestingly, the patient with central apnoea alone did not show excessive nocturnal snoring, a symptom that occurs in all patients with obstructive sleep apnoea,³ but did have daytime somnolence, a symptom not seen in a series of seven patients with mainly central apnoea.³ Sinus bradycardia did not occur during apnoea in this patient, so that 24-hour electrocardiographic monitoring, which is recommended as a screening test for the sleep apnoea syndrome,⁸ would not have detected this patient. Two of the three patients had cardiomegaly, and one had been treated for congestive heart failure. We may speculate that the cardiomegaly was related to the sleep apnoea, as it is a recognised complication of the sleep apnoea syndrome.³ In these two patients, however, other causes of cardiomegaly such as ischaemic heart disease or acromegaly itself cannot be excluded.

Barnes *et al*⁵ studied seven patients with acromegaly. Remission of narcolepsy followed treatment of the acromegaly in three patients. Two further patients did not, however, have a remission, although concentrations of growth hormone fell. Whether any of these patients had the sleep apnoea syndrome is not known, as polygraphic nocturnal monitoring was not undertaken.

In the present study growth hormone concentrations measured near the time of the sleep studies were significantly higher in the symptomatic than the asymptomatic patients, but the symptomatic patients included four who had been diagnosed recently, of whom two had not been treated. In the asymptomatic group we cannot judge whether sleep disturbances were present before the acromegaly was treated. We cannot, therefore, comment on the effect of treatment on sleep apnoea in acromegaly. No relation existed between the duration of symptoms of acromegaly and daytime somnolence or excessive nocturnal snoring. Rees and Ayres⁹ speculate that the upper airways obstruction that occurs in acromegaly¹ may be associated with sleep apnoea. Our studies show that upper airways obstruction as shown by a flow volume loop is not a reliable indicator of the presence or absence of sleep apnoea in acromegaly, as only one symptomatic and one asymptomatic patient had such evidence of upper airways obstruction.

This study suggests that sleep apnoea is common and clinically important in acromegaly. The condition should be expected

when there is daytime somnolence or excessive nocturnal snoring, and to assess it properly requires polygraphic nocturnal monitoring.

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Management of acute illness in infants before admission to hospital

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Summary and conclusions

Parents and family doctors were questioned about the management of 150 infants with acute illness before their admission to hospital. When 108 of the children were first assessed the family doctor did not consider that admission was necessary, but follow-up was arranged in only 14 of these cases. Thus in 94 cases the initiative for recall was left to the parents, who in 44 cases already wanted their child to be admitted. Forty-eight infants were referred because the doctors thought that the parents could not cope. The parents of 31 of the children delayed in seeking help.

As over half the children were ill for more than three days before they were admitted to hospital, regular follow-up could have been arranged. Doctors should normally retain the initiative for this rather than leave it to the parents' discretion.

Introduction

The classical symptoms of the acute life-threatening illnesses seen in infants presenting at hospital for admission are well documented. Less is known about the earlier symptoms, which may alert parents to the onset of their child's illness or to deterioration despite medical advice or treatment. The pre-

liminary results of a multicentre study of postperinatal mortality carried out by the Department of Health and Social Security suggested that almost half the children dying at home had had major symptoms in the last 48 hours of life and that these deaths, although not expected by the families and family doctors, were not necessarily unpredictable from the symptoms described.¹ The illnesses had usually not developed particularly quickly, but many children had not been medically assessed. A minority had been seen—some more than once—by a doctor who had not appreciated the full or potential seriousness of the illness; follow-up had rarely been arranged. As we concluded that some of these children might have survived had the importance of their symptoms been recognised and appropriate medical aid sought and provided, we carried out a study of children who were acutely ill on admission to hospital and survived. We sought to identify the symptoms that had led the parents to seek medical consultations and to examine the management of children referred to family doctors before admission.

Methods

Information about 150 children aged under 12 months who were admitted to hospital while acutely ill and survived was obtained from studies in Sheffield and Gateshead between November 1977 and April 1978. Seventy-two children were from Sheffield and 78 from Gateshead. The Gateshead series comprised consecutive admissions to the Queen Elizabeth Hospital, the only hospital within the area health authority admitting paediatric emergencies. Only one family refused to be interviewed. The Sheffield series was compiled by weekly rotation of interviews between the three hospitals in the city that accepted acute admissions.

During 1977, 228 general practitioners covered the city of Sheffield, which had a mid-year population of 547 400 and in which 5457 births occurred. Ninety-nine general practitioners covered Gateshead, which had a mid-year population of 217 500 and 3264 births.

All the children had major symptoms, defined as those requiring a medical opinion on the same day and continuing close supervision.¹

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