

CLINICAL STUDY

Effect of transsphenoidal surgery on sleep apnoea in acromegalyLisa Sze, Christoph Schmid¹, Konrad E Bloch², René Bernays³ and Michael Brändle

Division of Endocrinology and Diabetes, Department of Internal Medicine, Kantonsspital St Gallen, 9007 St Gallen, Switzerland, ¹Division of Endocrinology and Diabetes, Department of Internal Medicine, University Hospital of Zürich, 8091 Zürich, Switzerland, ²Division of Pneumology, Department of Internal Medicine, University Hospital of Zürich, 8091 Zürich, Switzerland and ³Department of Neurosurgery, University Hospital of Zürich, 8091 Zürich, Switzerland

(Correspondence should be addressed to L Sze; Email: lisa.sze@bluewin.ch)

Abstract

Objective: Sleep apnoea syndrome (SAS) is common in acromegaly and both diseases are independently associated with hypertension and insulin resistance contributing to increased morbidity and mortality. Pituitary surgery remains the principal treatment modality in acromegaly. The aim of this study was to assess the prevalence and risk factors of SAS in acromegaly and to analyze the effect of transsphenoidal adenomectomy on SAS and cardiovascular risk factors.

Subjects and methods: Thirteen consecutive patients (seven women and six men, aged 25–77 years) with newly diagnosed acromegaly were prospectively studied. Biochemical assessment (IGF-I, GH, acid labile subunit, fasting blood glucose (FBG), insulin), overnight respiratory polygraphy, and an Epworth Sleepiness scale score (ESS) were obtained before and 12 weeks after surgery. SAS was defined by an ESS ≥ 10 and ≥ 5 apnoeas/hypopnoeas (central or obstructive) per hour.

Results: Six of the thirteen (46%) patients had SAS. Risk factors were male gender (83.3 vs 14.3% without SAS) and long disease duration until diagnosis of acromegaly (10.2 ± 3.2 vs 4.6 ± 3.6 years, mean \pm s.d.). Ten patients had a homeostasis assessment model score ≥ 4 indicating insulin resistance and one had diabetes mellitus requiring insulin. Seven patients had hypertension ($\geq 140/90$ mmHg). Postoperatively, GH and IGF-I levels decreased, but only five patients were cured. However, SAS resolved in all patients irrespective of whether acromegaly was cured or not. FBG (5.5 ± 1.2 vs 4.8 ± 0.4 mmol/l) and systolic blood pressure (150.8 ± 18.5 vs 130.8 ± 17.5 mmHg) decreased in all SAS patients.

Conclusion: We found a high prevalence of SAS in acromegaly patients, in particular, in men and those with long duration of disease. Importantly, a marked reduction of GH excess by transsphenoidal adenomectomy may cure SAS and improve insulin resistance and hypertension.

European Journal of Endocrinology 156 321–329

Introduction

Sleep apnoea syndromes (SAS) are characterized by sleep fragmentation and daytime sleepiness due to repetitive apnoeas or hypopnoeas with arterial oxygen desaturation during sleep. The obstructive SAS (OSAS) which is associated with sleep related recurrent upper airway obstruction is common in the general population with a prevalence of 2% in women and 4% in men (1). The central SAS (CSAS) is caused by intermittent loss of neural respiratory drive during sleep. Its prevalence has not been well studied.

Acromegaly is a rare disease with a reported incidence of two to four cases per million person years and an estimated prevalence of 36–70 cases per million population (2–4). The prevalences of OSAS and CSAS are markedly higher in this population and lie between 27 and 60% (5–11), depending on the syndrome definition of SAS.

OSAS and acromegaly are independently associated with hypertension and insulin resistance, leading to

increased morbidity and mortality. Approximately 60% of all acromegalic patients die from cardiovascular disease, 25% from respiratory disease, and 15% from malignancies, with hypertension and heart disease being the major negative survival determinants (12). Since the prevalence of SAS in acromegaly is high and potentiates cardiovascular disease, it is important to detect patients at risk.

Mortality can be reduced by control of growth hormone (GH) excess, and post-treatment GH levels seem to be the most predictive survival index regardless of death cause (13, 14). Previous studies suggested that possibly normal insulin-like growth factor-I (IGF-I) (13) and especially GH random or basal concentrations < 2.5 $\mu\text{g/l}$ are associated with a normal life expectancy (15, 16).

Transsphenoidal adenomectomy remains the principal treatment option for GH-secreting tumors and is often used in combination with pharmacological treatment modalities (somatostatin analogues, GH-receptor antagonists or dopamine agonists) in larger or invasive tumors (17, 18).

The aim of the present study was to assess the prevalence and risk factors of SAS in a prospective series of patients with newly diagnosed acromegaly and to analyze the effect of transsphenoidal surgery on sleep apnoea and cardiovascular risk factors.

Subjects and methods

Patients

Thirteen consecutive patients (seven women, aged 33–77 years and six men, aged 25–72 years), referred to the Division of Endocrinology and Diabetes at the University Hospital of Zurich with newly diagnosed acromegaly, were prospectively studied. One patient with diabetes mellitus requiring insulin treatment was excluded from assessment of insulin resistance.

The diagnosis of acromegaly was based on typical clinical findings, elevated IGF-I concentrations, and a non-suppressible GH during a 75 g oral glucose tolerance test (14). Duration of acromegaly was estimated from the occurrence of first symptoms or signs until diagnosis. MRI revealed microadenomas (<10 mm) in three and macroadenomas (≥ 10 mm) in ten patients. Seven showed supra- and/or parasellar extension including two with invasion of the sellar floor. Transsphenoidal adenectomy was performed in all patients as primary treatment. One patient had an additional operation within 6 weeks, since postoperative tumor residuals were considered accessible for further surgical intervention. One woman had hypogonadotropic hypogonadism pre- and postoperatively and one had secondary adrenal insufficiency and hypogonadism postoperatively. All other patients had normal antero-pituitary function before and 12 weeks after surgery. The patients' had had neither pharmacological treatment nor radiotherapy at the time of follow-up.

Measurements

Clinical examination Height, weight, body mass index (BMI), neck circumference, blood pressure, and pulse rate were determined. The neck/height ratio (NHR) in order to adjust neck circumference for height was calculated.

Sleep studies Cardiorespiratory sleep studies were performed at baseline and at follow-up 12 weeks after pituitary surgery. Two patients without sleep apnoea refused sleep studies after surgical intervention. Continuous nocturnal polygraphic recordings were performed in a sleep laboratory and lasted for at least 6 h, usually 8 h from approximately 2200–0600 h. Measurements included calibrated respiratory inductive plethysmography, pulse oxymetry, electrocardiogram, body position (Respirace PT; Noninvasive Monitoring

Systems Inc., Miami Beach, FL, USA), and audiovisual monitoring by an infra-red/low-light camera. Recordings were visually analyzed by review of the raw data on a computer video screen. An episode of apnoea or hypopnoea was defined as a decrease in the sum signal of the respiratory inductive plethysmograph to $\leq 50\%$ of baseline for more than 10 s. We have previously shown that the apnoea/hypopnoea-index (AHI), calculated as the number of apnoeas/hypopnoeas per hour, determined by this technique agrees closely with face-mask pneumotachography (19). Central apnoea was differentiated from obstructive apnoea/hypopnoea by the absence of chest-wall motion during the event (20).

Assessment of subjective sleepiness This was performed with the Epworth Sleepiness scale (ESS) which extends from 0 (lowest level of sleepiness) to 24 points (maximal excessive sleepiness) (21).

Diagnosis of SAS The diagnosis of SAS was established by the simultaneous presence of daytime somnolence, i.e. ≥ 10 points on the ESS (22), and an elevated AHI of ≥ 5 (23). Patients were thereafter divided into a group with SAS and a second group without SAS.

Laboratory investigations All parameters were determined at baseline and at time of follow-up polygraphy 12 weeks after pituitary surgery. Blood samples were drawn after an overnight fast and discontinued medication on the evening before. IGF-I was determined by RIA after the removal of carrier proteins by Sep-Pak[®] chromatography according to the supplier's instructions (Waters Associates, Milford, MA, USA). Acid labile subunit (ALS) was measured by an ELISA for active total ALS, an enzymatically amplified 'two-step' sandwich-type immunoassay (Diagnostic Systems Laboratories, Webster, TX, USA). GH was determined by an immunoradiometric assay (hGH-RIACT; CIS Bio International, Oris Industries, Gif-Sur-Yvette, France) based on a sandwich technique using two monoclonal antibodies prepared against sterically remote antigenic sites on the hGH molecule. Fasting blood glucose (FBG) was measured on a Roche-Hitachi Modular Clinical Chemistry analyzer using commercial tests from Roche Diagnostics. Insulin was determined by a solid-phase RIA (CIS Bio international, Oris Industries); normal overnight fasting range provided by the manufacturer is 30–138 pmol/l. The homeostasis assessment model (HOMA) was used to estimate insulin resistance (24). A HOMA score ≥ 4 has been proposed as cut-off value for insulin resistance (25). Catecholamines in acidified urine were determined using a high performance liquid chromatograph (Detector 16.40, BioRad Laboratories).

Statistical analysis

Data are presented as mean values \pm s.d. Mann–Whitney's *U*-test was performed to compare data between two groups (with versus without SAS), Fisher's exact test was used to analyze categorical variables. Values before and after surgery within the two groups were examined using the Wilcoxon signed rank test. Correlation coefficients between apnoeas/hypopnoeas, IGF-I and duration of disease were assessed with the Spearman's correlation formula. All statistical analyses were performed with WinSTAT for Excel software. *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics and comparison between patients with and without SAS

Six (46%) of the thirteen patients had SAS with ≥ 10 points on the ESS and an AHI of ≥ 5 . Baseline characteristics of all 13 patients, with SAS ($n=6$), and without SAS ($n=7$) are shown in Table 1. There were significantly more men in the group with SAS and more women in the group without SAS respectively ($P<0.05$). No differences between the two groups were found for age, BMI, waist circumference, diastolic and systolic blood pressure, insulin resistance, lipid profile, and smoking status. Neck circumference

(42.3 ± 2.7 vs 38.4 ± 2.5 cm, mean \pm s.d.) but not NHR (0.24 ± 0.02 vs 0.23 ± 0.01) was significantly higher in the patient group with SAS, and NHR did not correlate with the number of obstructive apnoeas/hypopnoeas. Duration of disease (10.2 ± 3.2 vs 4.6 ± 3.6 years) was significantly longer in the SAS group. In eight patients with a history of acromegaly ≥ 6 years, six patients (75%) had SAS; in other terms, all patients with SAS had a history of ≥ 6 years compared with two of seven (28.5%) patients without SAS. There was a significant correlation between duration of disease and AHI ($r=0.77$, $P<0.001$).

GH excess After pituitary surgery, GH, IGF-I (Fig. 1a), and ALS (Fig. 1b) were significantly lower in both groups ($P<0.05$). In patients with SAS, GH decreased from 16.8 ± 16.3 to 2.0 ± 1.8 $\mu\text{g/l}$, IGF-I from 747.7 ± 356.7 to 245.5 ± 41.9 $\mu\text{g/l}$ and ALS from 33.0 ± 11.6 to 20.9 ± 8.0 mg/l. In patients without SAS, GH declined from 27.0 ± 19.3 to 5.7 ± 5.3 $\mu\text{g/l}$, IGF-I from 748.4 ± 364.1 to 410.0 ± 279.7 $\mu\text{g/l}$, and ALS from 36.4 ± 4.4 to 20.1 ± 9.5 mg/l respectively. However, only five patients (38.5%), three with SAS and two without SAS, were cured by pituitary surgery as defined by biochemical criteria, i.e. serum IGF-I concentrations within the reference interval and GH suppressed to <1 $\mu\text{g/l}$ during oral glucose tolerance testing (14).

Table 1 Baseline characteristics and comparison between patients with and without sleep apnoea syndrome (SAS).

	All patients $n=13$	With SAS $n=6$	Without SAS $n=7$	Significance with vs without SAS P value ^a
Males:females (%males)	6:7 (46.1)	5:1 (83.3)	1:6 (14.3)	<0.05
Age (years)	47.9 ± 16.2	50.2 ± 14.4	45.8 ± 18.5	ns
BMI (kg/m^2)	27.9 ± 3.4	29.3 ± 3.1	26.6 ± 3.4	ns
Smokers:non-smokers	6:7	2:4	4:3	ns
Waist circumference (cm)	94.9 ± 7.2	98.2 ± 6.3	92.1 ± 7.2	ns
Neck circumference (cm)	40.2 ± 3.2	42.3 ± 2.7	38.4 ± 2.5	<0.05
Neck-to-height ratio	0.24 ± 0.02	0.24 ± 0.02	0.23 ± 0.01	ns
Duration of disease (years)	7.2 ± 4.4	10.2 ± 3.2	4.5 ± 3.6	<0.05
GH ($\mu\text{g/l}$)	22.3 ± 18.0	16.8 ± 16.3	27.0 ± 19.4	ns
IGF-I ($\mu\text{g/l}$)	748.1 ± 345.4	747.7 ± 356.7	748.4 ± 364.1	ns
ALS (mg/l)	34.8 ± 8.3	33.0 ± 11.6	36.4 ± 4.4	ns
Apnoea/hypopnoea-index	22.3 ± 22.6	41.0 ± 20.5	6.3 ± 4.9	<0.01
Number of central apnoeas	7.7 ± 8.0	12.7 ± 8.5	3.4 ± 4.6	<0.05
Number of obstructive apnoeas	14.6 ± 18.2	28.3 ± 19.3	2.9 ± 2.4	<0.05
Epworth sleepiness scale	7.0 ± 4.5	12.7 ± 3.2	6.3 ± 4.2	<0.05
Systolic blood pressure (mmHg)	139.5 ± 23.7	150.8 ± 18.5	129.7 ± 24.4	ns
Diastolic blood pressure (mmHg)	84.8 ± 13.1	90.3 ± 12.3	80.1 ± 12.8	ns
FBG (mmol/l) ^b	5.7 ± 0.9	5.5 ± 0.9	5.9 ± 1.0	ns
Insulin (pmol/l) ^b	207.6 ± 124.5	160.2 ± 72.3	207.6 ± 124.5	ns
HOMA ^b	7.3 ± 4.4	5.7 ± 3.0	8.5 ± 5.0	ns
Cholesterol (mmol/l)	4.9 ± 0.9	4.5 ± 0.7	5.3 ± 1.0	ns
Triglycerides (mmol/l)	1.08 ± 0.34	0.90 ± 0.18	1.24 ± 0.38	ns
High-density lipoprotein (mmol/l)	1.52 ± 0.26	1.47 ± 0.13	1.57 ± 0.34	ns

^aComparison between group with SAS and group without SAS using Mann–Whitney *U*-Test.

^bOne patient with insulin dependent diabetes mellitus was excluded (with OSAS). Values are expressed in mean \pm s.d.

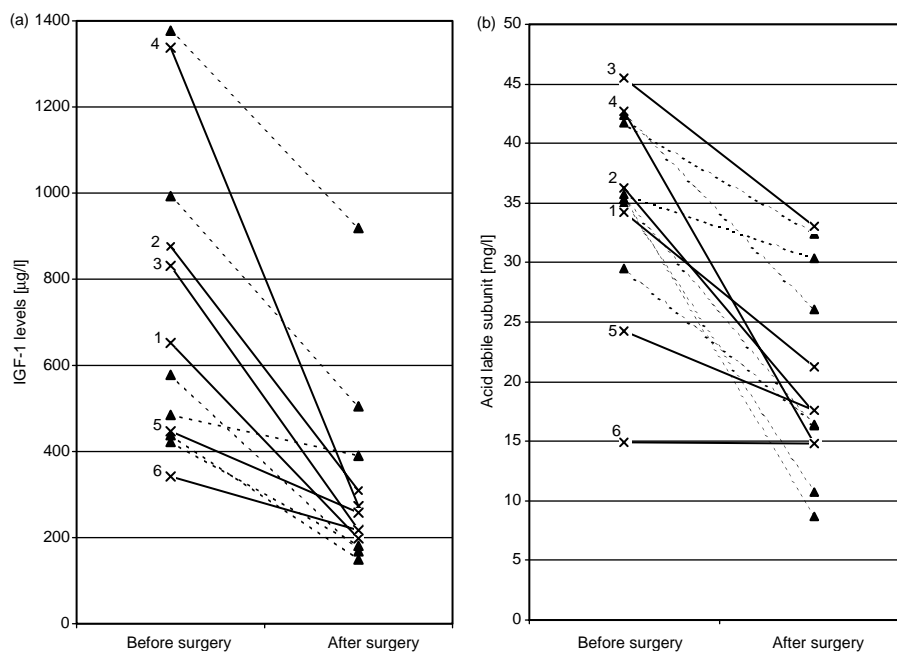


Figure 1 (a) IGF-I before and after surgery. ▲ ..., without SAS; X ..., with SAS (patients 1–6). (b) ALS before and after surgery. ▲ ..., without SAS; X ..., with SAS (patients 1–6).

Patients with sleep apnoea syndrome

Preoperative Among the six patients with SAS, five (83%) had a predominantly obstructive and one (17%) patient had a predominantly central pattern (Table 2). AHI correlated with the duration of disease ($r=0.77$, $P<0.05$). The number of central apnoeas correlated with the IGF-I levels ($r=0.77$, $P<0.05$).

Postoperative After transsphenoidal surgery, SAS resolved in all six patients, irrespective of whether acromegaly was cured or not. All six patients showed normal IGF-I levels, but GH nadir after oral glucose tolerance testing remained non-suppressible (i.e. $> 1 \mu\text{g/l}$) in the three non-cured patients. AHI (41.0 ± 20.5 vs 11.3 ± 13.3), number of central (12.7 ± 8.5 vs 3.0 ± 2.4) and obstructive (28.3 ± 19.3 vs 8.3 ± 13.6) apnoeas/hypopnoeas, and ESS score (12.7 ± 3.2 vs 8.2 ± 3.1) decreased significantly in mean values as well in each patient (Table 2, $P<0.05$ for all comparisons). Furthermore, heart rate (64.7 ± 11.0 vs 57.5 ± 9.1 bpm) and systolic blood pressure (150.8 ± 18.5 vs 130.8 ± 17.5 mmHg) dropped significantly (Table 3). However, no change of catecholamines in the 24-h-urine was found (adrenaline 2.97 ± 0.94 vs 3.29 ± 3.33 nmol/mmol creatinine, noradrenaline 26.0 ± 8.2 vs 19.3 ± 12.1 nmol/mmol creatinine, dopamine 177.0 ± 72.6 vs 148.3 ± 65.9 nmol/mmol creatinine). FBG decreased significantly and HOMA improved in all but one patient leaving no patient with insulin resistance postoperatively. BMI and neck circumference did not change after surgery.

Cardiovascular risk factors

Preoperative Cardiovascular risk factors were assessed in all patients. One patient had known diabetes mellitus requiring insulin treatment. Of the remaining 12 patients, 10 (76.9%) had a HOMA score ≥ 4 and there was a significant correlation between the HOMA score and IGF-I levels ($r=0.57$, $P<0.05$). Seven (53.8%) patients had hypertension ($> 140/90$ mmHg) comprising 5 (71.4%) with SAS; in other terms, 5/6 (83.3%) patients with SAS had hypertension.

Postoperative FBG and HOMA were significantly lower postinterventionally taking all patients into account, with only three patients without SAS remaining insulin resistant, apart from the patient with diabetes mellitus. Improvement in insulin resistance and FBG was not different between the patient group with and without SAS ($P=0.5$ for HOMA and $P=0.8$ for FBG). There was a trend toward lower systolic and diastolic blood pressure in all patients, although the drop of systolic blood pressure was most remarkable and significant in patients with SAS. Two patients with SAS and none of the patients without SAS showed values $\geq 140/90$ mmHg after surgery. Moreover, heart rate decreased significantly in all patients. No significant changes concerning BMI, waist circumference, and lipid profile were found. Finally, there was a significant postoperative increase in serum creatinine levels (78.2 ± 8.0 vs $83.8 \pm 11.2 \mu\text{mol/l}$, $P<0.05$; Table 3).

Table 2 Pre- and postoperative polygraphic findings and growth hormone (GH)/insulin-like growth factor-I (IGF-I)/acid labile subunit (ALS)-levels in patients with sleep apnoea syndrome (SAS).

Case	AHI		Central apnoea		Obstructive apnoea		ESS		GH random (µg/l)		GH nadir, oGTT (µg/l)	IGF-I (µg/l)		ALS (mg/l)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Post	Pre	Post	Pre	Post
1	20	5	8	2	12	3	18	7	17.9	1.03	0.6	652	198	34.2	21.2
2	45	8	28	4	17	4	11	7	20.5	0.45	0.3	876	309	36.3	17.4
3	23	3	11	3	12	0	12	9	4.6	4.9	NA ^a	831	218	45.5	33.0
4	66	10	16	7	50	3	10	5	42.6	0.3	<0.2	1338	273	42.7	14.8
5	28	4	4	0	24	4	15	14	4.9	2.1	2.0	447	258	24.2	17.6
6	64	38	9	2	55	36	10	7	6.2	3.5	1.6	342	217	14.9	14.8
Mean* ± s.d.	41.0±20.5	11.3±13.3	12.7±8.5	3.0±2.4	28.3±19.3	8.3±13.6	12.7±3.2	8.2±3.1	16.8±1.8	2.0±1.8	1.1±0.8	747.7±356.7	245.5±41.9	33.0±11.6	19.8±6.9

*P<0.05 pre- vs postoperative for all parameters using Wilcoxon signed rank test.

^aNot available in the patient with diabetes mellitus.

Table 3 Pre- and postoperative results in patients with and without sleep apnoea syndrome (SAS).

	All patients, n=13			With SAS, n=6			Without SAS, n=7		
	Pre	Post	Signif.	Pre	Post	Signif.	Pre	Post	Signif.
Systolic blood pressure (mmHg)	139.5±23.7	133.0±17.5	ns	150.8±18.5	130.8±17.5	<0.05	129.7±24.4	117.3±18.6	ns
Diastolic blood pressure (mmHg)	84.4±13.1	78.6±8.0	ns	90.3±12.3	77.7±7.8	ns	80.1±12.8	69.2±8.8	ns
Heart rate (beats/min)	71.2±11.9	60.7±8.6	<0.01	64.7±11.0	57.5±9.1	<0.05	76.7±10.0	65.5±5.8	ns
FBG (mmol/l) ^a	5.7±0.9	5.1±1.2	<0.01	5.5±0.9	4.8±0.4	<0.05	5.9±1.0	4.3±1.2	<0.05
Insulin (pmol/l) ^a	207.6±124.5	126.7±44.0	<0.05	160.2±72.3	103.0±18.8	ns	207.6±124.5	126.7±44.0	<0.01
HOMA ^a	7.3±4.4	3.5±1.0	<0.01	5.7±3.0	3.0±0.6	ns	8.5±5.0	3.9±1.1	<0.05

^aOne patient with SAS and diabetes mellitus requiring insulin treatment was excluded (all patients = 12, patient with SAS n=5).

Discussion

In our prospective study of 13 patients with acromegaly, the prevalence of SAS was 46% (6/13), with one patient showing predominantly central apnoea. These proportions lie within the earlier reported ranges of 27–60% for SAS in general, and thereof a CSAS fraction of 0–66% (5–11). As in previous studies, predictive criteria in our patients were male gender (5, 7, 11), long duration of disease before diagnosis (i.e. ≥ 6 years), and large neck circumference (26, 27). The preponderance of men with SAS resembles the trend in non-acromegalic patients. Interestingly, all but one patient with SAS had a neck circumference of ≥ 41 cm, a threshold described by Rosenow *et al.* (27). However, in our study, the NHR which Dancey *et al.* (28) have found to be a significant predictor of OSAS in non-acromegalic patients was not significantly associated with obstructive apnoeas/hypopnoeas. In accordance with the previous findings (5, 8, 27), our data showed no difference in BMI between the two patient groups. We found no correlation between IGF-I levels and the presence of SAS, in line with the report of Grunstein *et al.* As pathophysiologic changes causing SAS are diverse, a simple correlation between disease activity and SAS cannot be expected (5). Our data show that duration of disease is a much more important predictive factor of SAS than biochemical activity of acromegaly. Since most acromegalic patients die from cardiovascular disease, it is crucial to identify and treat patients at risk for SAS, which further potentiates the risk for hypertension and insulin resistance.

OSAS is promoted by anatomical changes induced by GH excess. It leads to tissue hypertrophy and swelling with consecutive collapse and narrowing of the pharynx, macroglossia (29, 30), and prognathia (31). On the other hand, GH and/or IGF-I excess, in the context of an increased respiratory responsiveness to hypercapnia, appears to contribute to the pathogenesis of central apnoeas (5, 6, 32). This assumption was supported by the findings that the degree of GH hypersecretion was related to the central pattern of apnoea. Our data are in accordance with these findings.

Treatment of acromegaly with octreotide improves obstructive SAS by reduction of soft tissue swelling and central SAS by decreasing chemosensitivity to hypoxia (5, 9, 10, 33), usually within the first months. It is not clear if somatostatin analogues also have a direct effect on central apnoea independent of the reduction of GH/IGF-I (34, 35). In spite of the pharmacological treatment modalities, transsphenoidal adenomectomy remains a cornerstone treatment for GH-secreting tumors if performed in experienced centers (18) and it still is the first-line therapy of microadenomas (36). Macroadenomas may often not be treated sufficiently with surgery alone requiring further pharmacological treatment and/or radiotherapy. Previous studies reported postoperative remission in 75–91% of

microadenomas and 48–71% of macroadenomas (13, 15, 37) with inconsistent definitions of disease control. Advantages of surgery are a safe and immediate relief of clinical symptoms and a reduction of mortality (15, 37), elimination of long-term medical treatment and lower costs (38). Nevertheless, the result of transsphenoidal surgery depends on neurosurgeon's skills, tumor size, and preoperative GH levels (13, 15, 37). Primary pharmacological therapy may be preferred in patients with restrictive co-morbidities or unwilling to surgery.

Recent studies have assessed the effect of pituitary surgery on cardiovascular risk factors showing marked improvement (38, 39), whereas only few studies or case reports have examined the effect of adenomectomy on SAS (11, 30, 41–44). These smaller or retrospective studies showed an improvement of SAS after pituitary surgery. However, results have been inconsistent due to limited patient number, different definitions of SAS and cure of acromegaly, and other methodological discrepancies. Some authors found cure or amelioration of SAS after surgery (40–43), while other authors reported persistence of SAS (11, 29, 31). In a retrospective study of 54 acromegalic patients, Rosenow *et al.* (27) found that adenomectomy had been performed less commonly in the group with SAS (52.4%) compared with the group without SAS (93.9%).

We have therefore completed this prospective study, which assessed the effect of transsphenoidal adenomectomy on SAS in a patient group with complete nocturnal polygraphy and biochemical testing. Twelve weeks after transsphenoidal adenomectomy, baseline GH and IGF levels decreased in all patients, although only five patients were cured by strict biochemical criteria. However, SAS resolved in all six patients, irrespective of cured acromegaly including the three patients with non-suppressible GH but normal IGF-I. Our data show that a marked decrease of GH excess and particularly normalization of IGF-I levels by surgery within the same patient led to significant improvement of AHI and cure of SAS within a few months. It remains to be seen whether SAS could reappear in patients with non-suppressible GH and normal IGF-I if GH excess and IGF-I levels re-increase on long-term follow up.

Our results suggest a beneficial effect of pituitary surgery on upper airway soft tissue swelling and central apnoea. It is noteworthy that development of acromegaly with concurrent onset of SAS takes several years, while surgery may cure both conditions within only a few weeks. As our postoperative assessment was performed after 12 weeks, we could not document the exact course of resolution of SAS. However, the patient's partners and nurses usually observed a strikingly fast amelioration of the sleep disorder. Since treatment with somatostatin does not necessarily cure SAS (6, 9), we speculate that adenomectomy may be superior in this respect.

Patients with SAS (83.3%) were more likely hypertensive than patients without SAS (28.6%) before surgery. The prevalence of hypertension in patients with SAS and

acromegaly was higher than the 50–60% found by other authors (5, 11), probably due to our stricter definition of hypertension with a lower threshold (i.e. $\geq 140/90$ mmHg), whereas the prevalence in patients without SAS corresponded to the reported one-third (18). Postoperatively, in patients with SAS, we found a significant decrease in systolic blood pressure and heart rate as well as a trend towards lower diastolic blood pressure. In the group without SAS, all patients became normotensive following successful surgery in accordance to other reports (39, 40). Amelioration of hypertension after pituitary surgery is likely to be linked to the control of GH excess and concurrent improvement of SAS, since somatostatin analogues have shown to have the same effect (45, 46). The pathophysiology of hypertension in acromegaly and in SAS is unclear. In SAS, an association with increased sympathetic activity is well known and has been proposed to play a causative role (47, 48). In our patients, catecholamines in 24-h-urine differed neither between the patient groups nor before and after surgery.

Insulin resistance and impaired glucose metabolism are more prevalent in sleep-disordered breathing (49–51) and associated with hypertension (52). Acromegaly is a known risk factor for impaired glucose tolerance and diabetes mellitus due to an increase in insulin resistance. One of our patients had previous diabetes mellitus requiring insulin treatment and all but two of the remaining patients were insulin resistant before surgery, estimated by the HOMA score. Postoperatively, HOMA values decreased in all but one patient. An improvement of insulin resistance after surgery has been already observed for 30 years (40, 53, 54). This seems to be an advantage over the treatment with somatostatin analogues, which may counterbalance improvement of insulin resistance by their inhibitory effect on insulin secretion (55, 56). Since surgery lowered FBG and insulin resistance irrespective of the presence or absence of SAS, we speculate that reduction of GH excess rather than cure of SAS caused amelioration of glucose metabolism.

A limitation of our study is the relatively small patient number which may skew the results. However, we were limited by the rare occurrence of patients with acromegaly (and SAS) even being a tertiary referral hospital. On the other hand, the strength of our study is its prospective design, assessment of complete overnight sleep studies pre- and postoperatively, and use of currently established definitions of SAS and disease control of acromegaly.

In conclusion, we found a high prevalence of SAS in acromegaly patients, in particular, in men and those with long duration of disease. Importantly, a marked reduction of GH excess by transsphenoidal adenomectomy may cure SAS and improve insulin resistance and hypertension.

Acknowledgements

The authors would like to thank Mrs Cornelia Zwimpfer for the measurement of GH, IGF-I, ALS, and insulin

levels. This study was supported by the Swiss National Science Foundation (Grant 32-46 808.96).

References

- 1 Young T, Palta M, Dempsey J, Skatrud J, Weber S & Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *New England Journal of Medicine* 1993 **328** 1230–1235.
- 2 Alexander L, Appleton D, Hall R, Ross WM & Wilkinson R. Epidemiology of acromegaly in the Newcastle region. *Clinical Endocrinology* 1980 **12** 71–79.
- 3 Mestron A, Webb SM, Astorga R, Benito P, Catala M, Gaztambide S, Gomez JM, Halperin I, Lucas-Morante T, Moreno B, Obiols G, de Pablos P, Paramo C, Pico A, Torres E, Varela C, Vazquez JA, Zamora J, Albareda M & Gilabert M. Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Espanol de Acromegalia, REA). *European Journal of Endocrinology* 2004 **151** 439–446.
- 4 Bengtsson BA, Eden S, Ernest I, Oden A & Sjogren B. Epidemiology and long-term survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984. *Acta Medica Scandinavica* 1988 **223** 327–335.
- 5 Grunstein RR, Ho KY & Sullivan CE. Sleep apnea in acromegaly. *Annals of Internal Medicine* 1991 **115** 527–532.
- 6 Grunstein RR, Ho KK & Sullivan CE. Effect of octreotide, a somatostatin analog, on sleep apnea in patients with acromegaly. *Annals of Internal Medicine* 1994 **121** 478–483.
- 7 Perks WH, Horrocks PM, Cooper RA, Bradbury S, Allen A, Baldock N, Prowse K & van't Hoff W. Sleep apnoea in acromegaly. *British Medical Journal* 1980 **280** 894–897.
- 8 Hart TB, Radow SK, Blackard WG, Tucker HS & Cooper KR. Sleep apnea in active acromegaly. *Annals of Internal Medicine* 1985 **145** 865–866.
- 9 Herrmann BL, Wessendorf TE, Ajaj W, Kahlke S, Teschler H & Mann K. Effects of octreotide on sleep apnoea and tongue volume (magnetic resonance imaging) in patients with acromegaly. *European Journal of Endocrinology* 2004 **151** 309–315.
- 10 Ip MS, Tan KC, Peh WC & Lam KS. Effect of Sandostatin LAR on sleep apnoea in acromegaly: correlation with computerized tomographic cephalometry and hormonal activity. *Clinical Endocrinology* 2001 **55** 477–483.
- 11 Pekkarinen T, Partinen M, Pelkonen R & Iivanainen M. Sleep apnoea and daytime sleepiness in acromegaly: relationship to endocrinological factors. *Clinical Endocrinology* 1987 **27** 649–654.
- 12 Melmed S. Acromegaly and cancer: not a problem? *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 2929–2934.
- 13 Swearingen B, Barker FG, II, Katznelson L, Biller BM, Grinspoon S, Klibanski A, Moayeri N, Black PM & Zervas NT. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 3419–3426.
- 14 Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K & Melmed S. Criteria for cure of acromegaly: a consensus statement. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 526–529.
- 15 Kauppinen-Makelin R, Sane T, Reunanen A, Valimaki MJ, Niskanen L, Markkanen H, Loyttyniemi E, Ebeling T, Jaatinen P, Laine H, Nuutila P, Salmela P, Salmi J, Stenman UH, Viikari J & Voutilainen E. Nationwide survey of mortality in acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 4081–4086.
- 16 Orme SM, McNally RJ, Cartwright RA & Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 2730–2734.

- 17 Abosch A, Tyrrell JB, Lamborn KR, Hannegan LT, Applebury CB & Wilson CB. Transsphenoidal microsurgery for growth hormone-secreting pituitary adenomas: initial outcome and long-term results. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 3411–3418.
- 18 Colao A, Ferone D, Marzullo P & Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocrine Reviews* 2004 **25** 102–152.
- 19 Thurnheer R, Xie X & Bloch KE. Accuracy of nasal cannula pressure recordings for assessment of ventilation during sleep. *American Journal of Respiratory and Critical Care Medicine* 2001 **164** 1914–1919.
- 20 Bloch KE, Li Y, Sackner MA & Russi EW. Breathing pattern during sleep disruptive snoring. *European Respiratory Journal* 1997 **10** 576–586.
- 21 Bloch KE, Schoch OD, Zhang JN & Russi EW. German version of the Epworth Sleepiness Scale. *Respiration* 1999 **66** 440–447.
- 22 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991 **14** 540–545.
- 23 Guilleminault C, van den Hoed J & Mittler MM. Clinical overview of the sleep apnea syndromes. In *Sleep Apnea Syndromes*, pp 1–12. EdsC Guilleminault & WC Dement. New York: Alan R. Liss, 1978.
- 24 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF & Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985 **28** 412–419.
- 25 Ascaso JF, Romero P, Real JT, Lorente RI, Martinez-Valls J & Carmena R. Abdominal obesity, insulin resistance, and metabolic syndrome in a southern European population. *European Journal of Internal Medicine* 2003 **14** 101–106.
- 26 Weiss V, Sonka K, Pretl M, Dostalova S, Klozar J, Rambousek P, Marek J & Haas T. Prevalence of the sleep apnea syndrome in acromegaly population. *Journal of Endocrinological Investigation* 2000 **23** 515–519.
- 27 Rosenow F, Reuter S, Deuss U, Szeliés B, Hilgers RD, Winkelmann W & Heiss WD. Sleep apnoea in treated acromegaly: relative frequency and predisposing factors. *Clinical Endocrinology* 1996 **45** 563–569.
- 28 Dancy DR, Hanly PJ, Soong C, Lee B, Shepard J Jr & Hoffstein V. Gender differences in sleep apnea: the role of neck circumference. *Chest* 2003 **123** 1544–1550.
- 29 Cadieux RJ, Kales A, Santen RJ, Bixler EO & Gordon R. Endoscopic findings in sleep apnea associated with acromegaly. *Journal of Clinical Endocrinology and Metabolism* 1982 **55** 18–22.
- 30 Hochban W, Ehlenz K, Conradt R & Brandenburg U. Obstructive sleep apnoea in acromegaly: the role of craniofacial changes. *European Respiratory Journal* 1999 **14** 196–202.
- 31 Pelttari L, Polo O, Rauhala E, Vuoriluoto J, Aitasalo K, Hyyppä MT, Kronholm E, Irjala K & Viikari J. Nocturnal breathing abnormalities in acromegaly after adenectomy. *Clinical Endocrinology* 1995 **43** 175–182.
- 32 Grunstein RR, Ho KY, Berthon-Jones M, Stewart D & Sullivan CE. Central sleep apnea is associated with increased ventilatory response to carbon dioxide and hypersecretion of growth hormone in patients with acromegaly. *American Journal of Respiratory and Critical Care Medicine* 1994 **150** 496–502.
- 33 Leibowitz G, Shapiro MS, Salameh M & Glaser B. Improvement of sleep apnoea due to acromegaly during short-term treatment with octreotide. *Journal of Internal Medicine* 1994 **236** 231–235.
- 34 Barkan A. Acromegalic arthropathy and sleep apnea. *Journal of Endocrinology* 1997 **155** S41–S44.
- 35 Buyse B, Michiels E, Bouillon R, Bobbaers H & Demedts M. Relief of sleep apnoea after treatment of acromegaly: report of three cases and review of the literature. *European Respiratory Journal* 1997 **10** 1401–1404.
- 36 Burt MG & Ho KK. Newer options in the management of acromegaly. *Internal Medicine Journal* 2006 **36** 437–444.
- 37 Beaugreard C, Truong U, Hardy J & Serri O. Long-term outcome and mortality after transsphenoidal adenectomy for acromegaly. *Clinical Endocrinology* 2003 **58** 86–91.
- 38 Lorenzo-Solar M, Castro A, Peino R, Fernandez-Alvarez J, Dieguez C & Casanueva FF. Can treatment with somatostatin analogs replace neurosurgery? *Journal of Endocrinological Investigation* 2005 **28** 48–52.
- 39 Minniti G, Moroni C, Jaffrain-Rea ML, Esposito V, Santoro A, Affricano C, Cantore G, Tamburrano G & Cassone R. Marked improvement in cardiovascular function after successful transsphenoidal surgery in acromegalic patients. *Clinical Endocrinology* 2001 **55** 307–313.
- 40 Jaffrain-Rea ML, Minniti G, Moroni C, Esposito V, Ferretti E, Santoro A, Infusino T, Tamburrano G, Cantore G & Cassone R. Impact of successful transsphenoidal surgery on cardiovascular risk factors in acromegaly. *European Journal of Endocrinology* 2003 **148** 193–201.
- 41 Main G, Borseley DQ & Newton RW. Successful reversal of sleep apnoea syndrome following treatment for acromegaly, confirmed by polygraphic studies. *Postgraduate Medical Journal* 1988 **64** 945–946.
- 42 Mickelson SA, Rosenthal LD, Rock JP, Senior BA & Friduss ME. Obstructive sleep apnea syndrome and acromegaly. *Otolaryngology-Head and Neck Surgery* 1994 **111** 25–30.
- 43 Piper JG, Dirks BA, Traynelis VC & Van Gilder JC. Perioperative management and surgical outcome of the acromegalic patient with sleep apnea. *Neurosurgery* 1995 **36** 70–74.
- 44 Saeki N, Isono S, Nishino T, Iuchi T & Yamaura A. Sleep-disordered breathing in acromegalics – relation of hormonal levels and quantitative sleep study by means of bedside oximeter. *Endocrine Journal* 1999 **46** 585–590.
- 45 Colao A, Ferone D, Marzullo P, Cappabianca P, Cirillo S, Boerlin V, Lancranjan I & Lombardi G. Long-term effects of depot long-acting somatostatin analog octreotide on hormone levels and tumor mass in acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 2779–2786.
- 46 Ronchi CL, Varca V, Beck-Peccoz P, Orsi E, Donadio F, Baccarelli A, Giavoli C, Ferrante E, Lania A, Spada A & Arosio M. Comparison between six-year therapy with long-acting somatostatin analogs and successful surgery in acromegaly: effects on cardiovascular risk factors. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 121–128.
- 47 Elmasry A, Lindberg E, Hedner J, Janson C & Boman G. Obstructive sleep apnoea and urine catecholamines in hypertensive males: a population-based study. *European Respiratory Journal* 2002 **19** 511–517.
- 48 Somers VK, Dyken ME, Clary MP & Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *Journal of Clinical Investigation* 1995 **96** 1897–1904.
- 49 Reichmuth KJ, Austin D, Skatrud JB & Young T. Association of sleep apnea and type II diabetes: a population-based study. *American Journal of Respiratory and Critical Care Medicine* 2005 **172** 1590–1595.
- 50 Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R & Resnick HE. Sleep Heart Health Study Investigators. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *American Journal of Epidemiology* 2004 **160** 521–530.
- 51 Ip MS, Lam B, Ng MM, Lam WK, Tsang KW & Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. *American Journal of Respiratory and Critical Care Medicine* 2002 **165** 670–676.
- 52 Jaffrain-Rea ML, Moroni C, Baldelli R, Battista C, Maffei P, Terzolo M, Correria M, Ghiggi MR, Ferretti E, Angeli A, Siculo N, Trischitta V, Liuzzi A, Cassone R & Tamburrano G. Relationship between blood pressure and glucose tolerance in acromegaly. *Clinical Endocrinology* 2001 **54** 189–195.
- 53 Sonksen PH, Greenwood FC, Ellis JP, Lowy C, Rutherford A & Nabarro JD. Changes of carbohydrate tolerance in acromegaly with progress of the disease and in response to treatment. *Journal of Clinical Endocrinology and Metabolism* 1967 **27** 1418–1430.

- 54 Moller N, Schmitz O, Joergensen JO, Astrup J, Bak JF, Christensen SE, Alberti KG & Weeke J. Basal-and insulin-stimulated substrate metabolism in patients with active acromegaly before and after adenomectomy. *Journal of Clinical Endocrinology and Metabolism* 1992 **74** 1012–1019.
- 55 Breidert M, Pinzer T, Wildbrett J, Bornstein SR & Hanefeld M. Long-term effect of octreotide in acromegaly on insulin resistance. *Hormone and Metabolic Research* 1995 **27** 226–230.
- 56 Ronchi C, Epaminonda P, Cappiello V, Beck-Peccoz P & Arosio M. Effects of two different somatostatin analogs on glucose tolerance in acromegaly. *Journal of Endocrinological Investigation* 2002 **25** 502–507.

Received 20 September 2006

Accepted 4 December 2006