

CLINICAL STUDY

Influence of disease control with pegvisomant on sleep apnoea and tongue volume in patients with active acromegaly

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Abstract

Objectives: Sleep apnoea has been consistently reported to occur in acromegaly. In uncontrolled patients, the severity of sleep apnoea influences physical activity in the daytime. We investigated the influence of disease activity on tongue volume and sleep apnoea treated with the GH receptor antagonist pegvisomant in poorly controlled patients with acromegaly under octreotide.

Design and methods: A total of 12 patients with active acromegaly (six females; six males; mean age 57 ± 15 years; body mass index 29.4 ± 4.2 kg/m²; mean \pm s.d.) were treated with pegvisomant (13.5 ± 5.0 mg/die) for 6 months. Tongue volume was examined by magnetic resonance imaging, and sleep apnoea was characterized by polysomnography before and after 6 months of treatment with pegvisomant. The mandibular length was determined by lateral X-ray films.

Results: IGF1 levels decreased after 6 months in all patients (407 ± 114 to 199 ± 23 μ g/l; $P=0.0001$). The tongue volume decreased (105 ± 33 to 83 ± 33 ml; $P=0.007$) as well as the apnoea–hypnoea index (23 ± 22 to 18 ± 18 /h; $P=0.0066$). The mandibular length correlated with the initial tongue volume ($r^2=0.6072$, $P=0.0028$).

Conclusion: In conclusion, successful treatment with pegvisomant can decrease tongue volume, which has benefits for coexisting sleep disordered breathing.

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Introduction

Patients with acromegaly have an increased risk of cardiovascular diseases (1–5), cancer (6, 7) and thyroid diseases (8, 9). Sleep apnoea has been consistently reported to occur in acromegaly (10–12). Obstructive sleep apnoea has been attributed to soft tissue hypertrophy of the upper airway, which may predispose to obstruction during sleep either directly by tissue bulk or alteration of pharyngeal collapsibility (13, 14). The relationship between disease activity of acromegaly and sleep apnoea has been controversial with some authors showing a positive correlation between levels of GH and sleep apnoea indices (13, 15), while others did not (10, 16).

The GH antagonist, pegvisomant, has been shown to reduce insulin-like growth factor (IGF)-levels and lead to an amelioration of clinical features of acromegaly such as reduction in soft tissue swelling. Images of magnetic resonance imaging (MRI) are able to calculate the tongue volume and to determine the effect of treatment for acromegaly as described in a previous study by Herrmann *et al.* with octreotide in patients with acromegaly (17). To address this issue, we have

performed a prospective study to characterize the sleep apnoea of patients with acromegaly and the effect of 6-month treatment with pegvisomant.

Patients and methods

Patients

Twelve patients (six females, six males) with a mean age of 57 ± 15 years (range 31–77) with uncontrolled active acromegaly under medical treatment with octreotide were included in the study. They were recruited from the Department of Endocrinology, University of Duisburg-Essen in Germany over a period of 36 months between 2005 and 2008. The diagnosis of acromegaly was made on the basis of physical examination, IGF1 and GH levels after an oral glucose load (75 g) (18). Four patients had microadenomas and eight patients had macroadenomas. All had undergone surgery for pituitary adenoma (7 ± 5 years before starting pegvisomant), and none had defects of visual field assessments. Six patients had TSH deficiency, five patients had ACTH-deficiency and five patients were

LH/FSH deficient. All patients were pretreated with octreotide acetate (Sandostatin LAR, Novartis Pharma GmbH). Owing to elevated IGF1 levels, pegvisomant treatment was started at a dose of 10 mg daily.

Sleep studies polysomnography (PSG) and tongue volume MRI were performed at baseline and after 6 months of treatment. The mean body mass index (BMI) was 28.9 ± 3.9 kg/m² (range 23.2–36.7). Eight patients had arterial hypertension and were treated sufficiently with anti-hypertensive drugs. At baseline, the mean blood pressure was $134 \pm 3/85 \pm 3$ mmHg.

Hormone assays

Serum IGF1 concentrations were measured by an immulite assay, Siemens Medical Solutions, Erlangen, Germany. Intra- and interassay coefficient of variations for low IGF1 concentrations were 2.4 and 5.2% respectively.

Measurement of tongue volume

All examinations were performed in supine position on a 1.5 T MR-scanner (Magnetom Sonata, Siemens Medical Systems) equipped with a high performance gradient system characterized by an amplitude of 40 mT/m and a slew rate of 200 mT/m per ms. A head/neck phased array surface coil was used for signal reception. Tongue volumes were measured by employing a 2 D True-Fisp sequence in sagittal slice orientation without distance factor. A head phased-array surface coil was used for signal reception. In order to avoid motion artefacts, the volunteers were asked not to move their tongue during the examination. Furthermore, all patients also underwent a 3D FLASH MR examination to evaluate the pharyngeal space and underwent a chewing and swallowing examination using a real-time TrueFISP with an oral contrast bolus. Similar examinations were performed in previous studies (19–21). A head and neck phased-array surface coil was used for signal reception. For oral contrast administration, 0.5 ml gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany) was mixed

with 100 ml of normal commercially available vanilla pudding (concentration 1:200). After that, a small piece of banana was mixed into this solution in order to increase the volume and viscosity of the contrast solution. Prior to the examination, all patients were asked to test-chew and swallow a small bolus in supine position outside of the magnet. There were no signs of aspiration in any of the patients with acromegaly. For the examinations, a plastic spoon was used to administer the contrast agent bolus, while the subjects were in supine position and placed in the head coil (Fig. 1).

All images were transferred onto a workstation (Virtuosos, Siemens Medical Systems) and reviewed by a board certified radiologist.

Polysomnography

Complete overnight PSG using the Compumedics System (Melbourne, Australia) was performed between 2200 and 0700 h. Two-channel electroencephalography, electrooculography and chin electromyography were performed using standard methods. Oronasal airflow was recorded by thermistor; thoracic and abdominal respiratory efforts were measured by impedance plethysmography. Oxygen saturation was measured by finger pulse oximetry (ResMed Model 305A, San Diego, CA, USA), and electrocardiography was performed from a precordial lead. Body position was monitored by a position sensor. During PSG, patients were observed by infrared video surveillance. Patients had been instructed to behave during the night as 'normally' as possible. Sleep data were staged manually according to standard criteria (22), and the arousals were scored according to the criteria of the American Sleep Disorders Association (23).

Apnoea was defined as cessation of airflow or reduction in thermistor signal to <10% of the normal flow and lasting for at least 10 s. Apnoeas <10 s were counted if they were followed by either an arousal or an oxygen desaturation of 4% or more. Events were classified as obstructive (clear obstructive or mixed with a clear obstructive component in the event) or

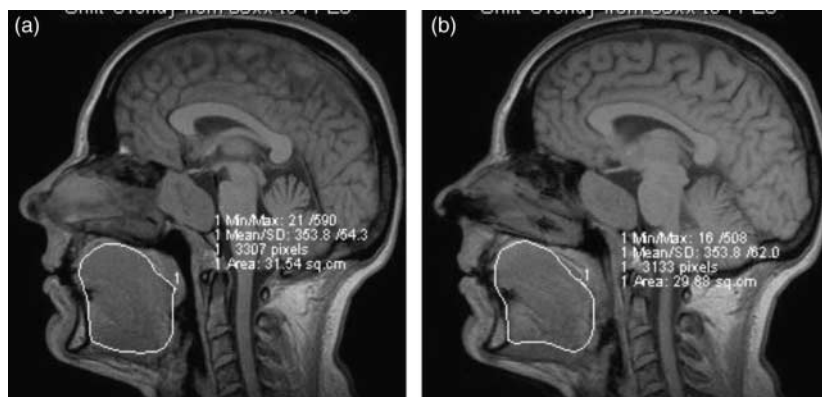


Figure 1 Measurement of the tongue volume by employing a 2-D True-Fisp sequence in sagittal slice orientation with magnet resonance imaging in one patient with acromegaly at baseline (a) and after a 6-month treatment period of pegvisomant (b).

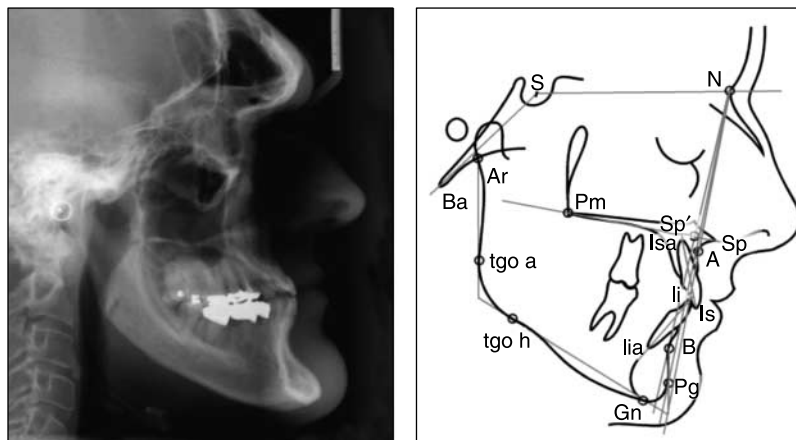


Figure 2 Lateral X-ray film of a patient with acromegaly and landmarks of standardized lateral cephalometric analysis (A, maxillary apical point; B, mandibular apical point; Gn, gnathion; Pg, pogonion; S, sella; N, nasion; Sp, spina nasalis anterior).

central events according to the respiratory effort channels. Hypopnea was defined as a discernible reduction in airflow of at least 10 s duration followed either by arousal or a desaturation of 4% or more.

The respiratory events were scored in accordance with the American Academy of Sleep Medicine Task Force recommendations (23). The apnoea-hypopnea index (AHI) was calculated from the number of all respiratory events per hour of sleep. An AHI shorter than 5 was defined as normal. Sleep-related breathing events were considered mild when AHI was between 5 and 15 events per hour, moderate in cases of AHI between 15 and 30 events per hour, and severe if AHI was >30 events per hour. Clear oxygen saturation (SaO_2) artefacts were excluded manually. Oxygen indices were then calculated by the software from the SaO_2 curve with minimal SaO_2 being the lowest saturation reached during sleep and with average minimal SaO_2 being the mean of all saturation values reached during all respiratory events.

X-ray examinations

Lateral X-ray scans were taken under standard conditions, in centric occlusion with control of head position, to determine the length of the mandible (distance tgo h – Gn, Fig. 2). The patients had their radiographs taken at a constant distance of 1.5 m between the X-ray source and the median plane of the head.

Statistical analyses

The data, if not marked otherwise, represent the mean \pm s.d. Absolute differences between time points (e.g. tongue volume at baseline and after the observation period) were analyzed per group using the paired Wilcoxon signed rank test. All tests were done two-tailed, and P values <0.05 were considered statistically significant. Correlations between mandibular length

and tongue volume were measured by linear regression (P values <0.05 were considered statistically significant). Statistical analyses were performed using GraphPad InStat version 3.02 (GraphPad Software, San Diego, CA, USA).

Results

Four patients received 10 mg, two patients received 15 mg, five patients received 20 mg, and one patient received 30 mg s.c. pegvisomant (Somavert, Berlin, Germany) everyday. Overall, IGF1 levels decreased significantly from 408 ± 114 to 199 ± 80 $\mu\text{g/l}$ ($P < 0.001$; Fig. 3). After treatment with pegvisomant, the age-adjusted IGF1 levels were normalized in all patients. At baseline, 8/12 patients (66%) had moderate or severe obstructive sleep apnoea with a mean AHI of >15/h (range 1–80.2), and no patient had central sleep apnoea.

Effects of treatment on tongue volume

Tongue volume decreased significantly (Fig. 4; 105 ± 33 at baseline versus 83 ± 20 ml, after 6 months,

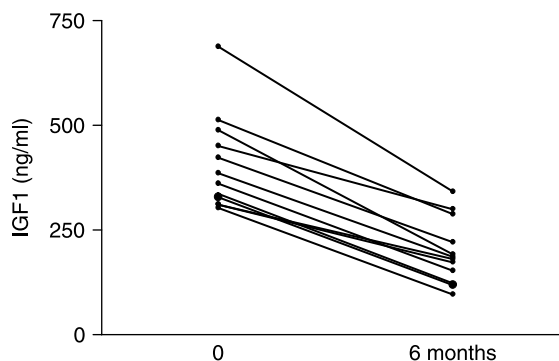


Figure 3 Changes of IGF1 levels of 12 patients with acromegaly before and after treatment with pegvisomant over a period of 6 months.

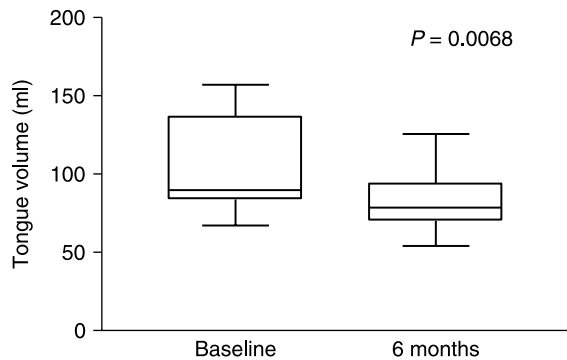


Figure 4 Tongue volume of patients with acromegaly at baseline and after a 6-month treatment period of pegvisomant with normal age-adjusted IGF1 levels ($n=12$).

$P=0.007$). The IGF1 levels at baseline and after treatment correlated significantly with BMI-adjusted tongue volume (Fig. 5; $r=0.40$, $P=0.05$). Moreover, the disease duration correlated with the BMI-adjusted tongue volume ($r=0.71$, $P=0.006$). Mean length of the mandible was 9.0 ± 1.0 cm and correlated significantly with BMI-adjusted tongue volume (Fig. 6, $r=0.78$, $P=0.003$).

Effects of treatment on sleep-disordered breathing

After 6 months of pegvisomant treatment, there was a significant decrease in AHI of $24 \pm 28\%$ (23.4 ± 21.5 vs $17.5 \pm 17.8/h$, $P=0.007$). At baseline, three patients had an AHI $>30/h$, five had an AHI of $15\text{--}30/h$, two had an AHI of $5\text{--}14/h$, and two had an AHI $<5/h$. After treatment, one patient had an AHI $>30/h$, six had an AHI of $15\text{--}30/h$, three had an AHI of $5\text{--}14/h$, and two had an AHI $<5/h$. AHI decreased in 9/12 (75%) of the patients (Fig. 7).

Although a decrease in mean levels of IGF1 and an improvement in mean AHI were seen in the study group, no correlation was noted between the absolute decrease of IGF1 levels and the changes in AHI. AHI did not correlate with BMI ($P=0.24$), BMI-adjusted tongue volume ($P=0.52$) or age ($P=0.24$) but with length of the mandible ($r=0.62$, $P=0.03$). Minimum oxygen saturation did not change significantly ($83 \pm 3\%$ at baseline versus $85 \pm 4\%$ after 6 months).

Discussion

In the present study, we found a prevalence of sleep apnoea syndrome of 83% in patients with active acromegaly, confirming reports from previous studies (17, 24–26). Successful treatment via IGF1 normalization led to a 24% improvement of the AHI. We have shown that soft tissue swelling determined by tongue

size volume by MRI can effectively be reduced by treatment with pegvisomant.

Sleep apnoea is a common complication in uncontrolled acromegaly and is an established additional cardiovascular risk factor potentially increasing morbidity and mortality observed in acromegaly (10, 11, 15, 16). Treatment of obstructive sleep apnoea with nasal continuous airway pressure therapy may result in a significant reduction in cardiovascular complications like hypertension (23, 27, 28).

We confirmed previous studies that suggested obstructive rather than central sleep apnoea being the prevalent form of sleep disordered breathing in acromegaly, as none of our patients had central but all had obstructive sleep apnoea (29, 30).

Regarding predisposing factors, previous studies identified anatomical abnormalities in acromegaly by using lateral X-ray films with cephalometric landmarks and reference lines like dorsocaudal rotation of the mandible, increase in facial height and narrowing of the depth of the bony framework of the nasopharynx (28, 31–33).

Furthermore, soft tissue swelling is a relevant factor in patients with acromegaly for the obstruction of the upper airway (27–29). Studies suggested that upper airway narrowing caused by enlarged uvula and narrowed pharyngeal airway may play a more relevant role in the development of obstructive sleep apnoea in acromegalic patients than skeletal anomalies (14, 28, 31–33). Besides a large uvula, it is pronounced macroglossia narrowing pharyngeal airway space in acromegalics. This was demonstrated in a previous study by Herrmann *et al.* (17) where active acromegalic patients had significantly increased tongue volumes by MRI in comparison to an age-matched healthy control group. MRI, compared with radiographs, has the advantage of more precise delineation of soft tissue and determination of tongue volume. We have adjusted the tongue volume to the BMI, because height and weight are positively related to the tongue volume.

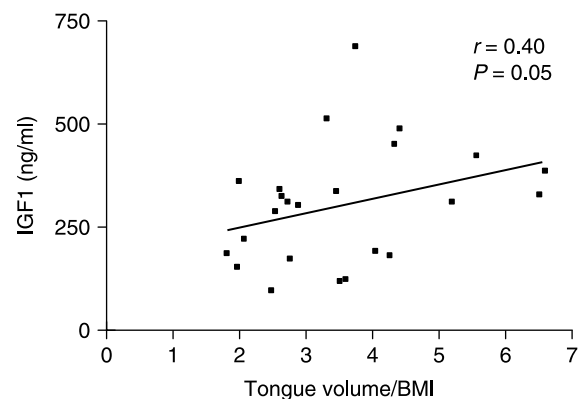


Figure 5 Correlation between IGF1 levels and BMI-adjusted tongue volume in 12 patients with active acromegaly before treatment with pegvisomant over a period of 6 months and after treatment.

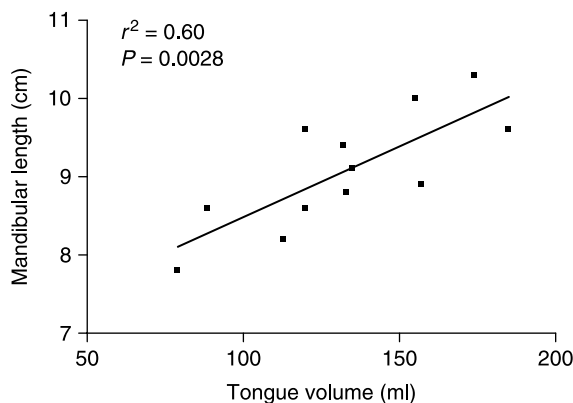


Figure 6 Correlation between mandibular length and BMI-adjusted tongue volume in 12 patients with acromegaly before and after treatment with pegvisomant over a period of 6 months.

As in the study by Herrmann *et al.*, we were able to demonstrate that IGF1 levels were closely correlated to the BMI-adjusted tongue volume (17).

This is the first study evaluating the effect of the GH receptor antagonist pegvisomant on soft tissue swelling of the tongue. There is evidence that IGF1 normalization leads to reduction in soft tissue swelling and is beneficial on acromegalic organ hypertrophy, which has already been shown by Colao *et al.* by the analysis of cardiac size in a similar cohort of acromegalic patients treated for the same time (34). Pegvisomant treatment has been reported to normalise IGF1 levels in more than 90% of acromegalic patients (35). Pegvisomant is a GH receptor antagonist that blocks GH activity by inhibiting functional dimerisation of the GH receptor. Hence, it is blocking its biological activity and inhibiting IGF1 production (36). In our study, we observed reduction in soft tissue swelling by a 22% reduction in tongue volume after 6 months.

Regarding sleep apnoea, the correlation between disease activity and severity of apnoea is controversial, and it is unclear whether and to what extent sleep apnoea subsides after biochemical remission of the disease. So far, this is the only study evaluating the effect of pegvisomant on sleep disordered breathing. Until now, previous studies have only evaluated the effect of surgery or medical therapy with somatostatin analogues on the reversibility of sleep apnoea after IGF1 normalization with conflicting results. Rosenow *et al.* (13) found a relative high frequency of sleep apnoea in patients with treated acromegaly, at least of 21%, with a positive correlation with GH/IGF1 levels, age, as well as neck and index finger circumference as measures of soft tissue hypertrophy. Some studies showed significant improvement or cure after adenomectomy (37, 38), while others found persisting nocturnal breathing abnormalities (39) in patients previously treated with pituitary surgery (25) or only slight to moderate improvement despite normalized or decreased

hormonal levels (40) probably due to the irreversible changes of the craniofacial region and upper respiratory tract (14, 28, 32). Finally, there are many reports of relief during treatment with s.c. or long-acting release octreotide (17, 29, 41), although the sleep apnoea can persist after GH/IGF1 normalization (17, 41).

Although we have seen a significant overall decrease in AHI of 24% after treatment with pegvisomant, this is far from a cure, in particular in patients with severe obstructive sleep apnoea (AHI > 30/h) probably due to the irreversible changes of the upper respiratory tract. Besides obesity, hypertension and hormonal alterations, it could recently have been shown that craniofacial abnormalities have a relevant and irreversible influence on sleep apnoea-related nocturnal hypoxaemia (42, 43). In fact, we have found that tongue volume and apnoeic episodes were affected by the increased length of the mandible in acromegalics. These are irreversible craniofacial changes that together with soft tissue swelling and enlargement of the tongue and uvula are suggested to have a major impact on the obstructive sleep disorders and its complications (17, 28).

Moreover, it has been shown that independent factors like age may influence sleep disorders in patients with acromegaly. Considering the fact that body fat is increased in patients with acromegaly after cure or successful treatment (44, 45), long-term observation of sleep apnoea in acromegalics is recommended. In our study, AHI did not correlate with age or BMI, possibly due to the small number of patients studied. However, some studies have described the BMI-independent effect of age, showing an approximate doubling of AHI every 10 years, probably due to age-related weakening of the upper airway musculature (23).

Although we were able to demonstrate a correlation between the biochemical activity in acromegaly and soft tissue swelling of the tongue, we did not find any correlation between apnoeic episodes and soft tissue swelling of the tongue. This may be due to multifactorial

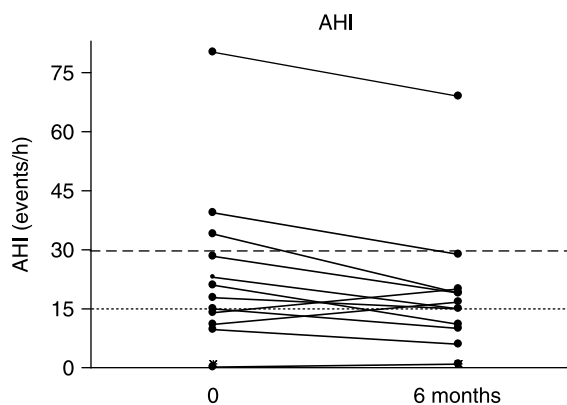


Figure 7 Changes of AHI (apnoea–hypnoea index) of 12 patients with acromegaly before and after treatment with pegvisomant over a period of 6 months.

pathogenesis of sleep apnoea syndrome and to the small number of patients. It could be supposed that periods of disease remission longer than those we observed could be necessary.

In summary, we have shown that treatment with pegvisomant significantly reduces tongue volume and the severity of sleep apnoea. The high prevalence of obstructive sleep apnoea in patients with active acromegaly demonstrates that screening for sleep apnoea should be mandatory in the diagnostic workup of acromegalic patients. Regarding treatment of acromegaly, these findings strengthen the need not only for an early diagnosis of sleep apnoea but for aggressive treatment of the disease.

Declaration of interest

C Berg received German Pfizer grant of the German Endocrine Society for 2004/05 for another project and has received lecture fees from Pfizer Germany, Novartis, and NovoNordisk Germany in the past.

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