

ORIGINAL ARTICLE

Intensity of pituitary adenoma on T2-weighted magnetic resonance imaging predicts the response to octreotide treatment in newly diagnosed acromegaly

Ansgar Heck^{*†‡}, Geir Ringstad[†], Stine L. Fougner^{*†‡}, Olivera Casar-Borota^{§¶}, Terje Nomet, Jon Ramm-Pettersen^{††} and Jens Bollerslev^{*†‡}

**Section of Specialized Endocrinology, Oslo University Hospital, Rikshospitalet, †Department of Radiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway, ‡Department of Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway, §Division of Pathology, Oslo University Hospital, Rikshospitalet, Oslo, Norway, ¶Department of Medical Biosciences, Umeå University, Umeå, **Department of Clinical Pathology and Cytology, Uppsala University Hospital, Uppsala, Sweden, ††Department of Neurosurgery, Oslo University Hospital and ‡‡University of Oslo, Faculty of Medicine, Oslo, Norway*

Summary

Background Primary, preoperative medical treatment is an option in selected patients with acromegaly, but a subset of patients respond poorly. Valid prediction of response to somatostatin analogues (SA) might thus alter treatment stratification. The aims of this study were to assess whether T2 signal intensity could determine long-term response to first-line SA treatment and to assess clinical and biochemical baseline characteristics, as well as histological subtype in relation to the magnetic resonance imaging (MRI) appearances.

Methods In 45 newly diagnosed patients, T2-weighted signal intensity of the tumour was classified into hypo-, iso- or hyperintense. Biochemical and clinical baseline variables for the three groups were compared. In 25 patients primarily treated with long-acting SA for a median of 6 months [interquartile range (IQR):155–180 days], GH and IGF-1 reduction was assessed, and in 34 cases, immunohistochemical granulation pattern was evaluated.

Results The results showed that 12 (27%) adenomas were hypo-intense, 15 (33%) isointense and 18 (40%) hyperintense. Median IGF-1 [ratio IGF-1/ULN; (upper limit of normal)] was 3.5 (2.3–4.9), 2.9 (2.6–3.8) and 1.9 (1.3–2.6), respectively ($P = 0.006$ for difference between groups). Median GH values ($\mu\text{g/l}$) of a 3- to 5-point profile were 17.5 (6.1–35), 9.3 (6.0–32.5) and 4.1 (1.5–8.3), ($P = 0.025$).

Median IGF-1 reduction (% of baseline) after first-line SA treatment was 51 (49–70), 36 (19–74) and 13 (5–42) ($P = 0.03$); median reduction in GH (% of baseline) was 86 (72–94), 78 (62–85) and 46 (1–70) ($P = 0.02$).

T2 hyperintensity was associated with sparse granulation pattern on immunohistochemistry.

Conclusion In patients with acromegaly, T2 signal intensity at diagnosis correlates with histological features and predicts biochemical outcome of first-line SA treatment.

(Received 12 July 2011; returned for revision 10 August 2011; finally revised 29 September 2011; accepted 2 November 2011)

Introduction

Acromegaly is most frequently caused by a growth hormone-producing pituitary adenoma with an incidence of about 3–5/1 000 000/year.^{1,2} In the vast majority of patients, a pituitary tumour can be identified by magnetic resonance imaging (MRI).

Transsphenoidal surgery is a cornerstone in the management of acromegaly, but primary and preoperative medical treatment of growth hormone-producing somatotrope adenomas with somatostatin analogues (SA) has been an option for many years and may improve surgical outcome.^{1,3,4} A subset of patients respond poorly to medical treatment,^{1,5–7} and these may often have sparsely granulated adenomas.^{8,9} In these patients, pretreatment with SA, mainly acting on the somatostatin receptor subtype 2 (sstr2), could delay surgery. Patients with a blunted response to a sstr2 agonist may therefore be candidates for direct surgery or alternative medical treatment, mainly acting on dopamine receptors (D2) or sstr5 receptors.

Predictive tools for stratification to primary medical or surgical treatment are needed, as knowledge of the response to SA may alter treatment stratification. Conflicting results have been reported on the predictive value of the octreotide test for long-term SA response.^{10,11} In contrast to the octreotide test, the histological granulation pattern correlates with long-term SA response as sparsely granulated adenomas are less responsive to SA treatment than densely granulated. These results are of course not available when decisions on primary treatment are taken.^{8,9}

Correspondence: Ansgar Heck, MD, Section of Specialized Endocrinology, Oslo University Hospital, Rikshospitalet, N-0424 Oslo, Norway.
Tel.: 0047 23 07 19 00; E-mail: ansgar.heck@medisin.uio.no

Magnetic resonance imaging appearances, including T2 signal intensity, depend upon various tissue properties, including nuclear/cytoplasmic ratio, content of water, hormones and proteins and the degree of intra- and extracellular compartmentalization.^{12–15}

Magnetic resonance imaging scans with T2 sequences may give additional information on response to SA treatment. On T2-weighted MRI, growth hormone-producing adenomas may present as hypo-, iso- or hyperintense, in contrast to nonfunctioning pituitary adenomas, which commonly are hyperintense.^{14,16} In acromegaly, MRI signal intensity correlates with histopathological granulation pattern as densely granulated adenomas have almost exclusively been reported to be hypointense on T2-weighted MRI.¹⁶

Recently, it was reported that hypointense T2 signal intensity in patients with active acromegaly after pituitary surgery predicts a better response to postoperative SA treatment than a hyperintense signal.¹⁷

The aim of the present study was to assess whether T2-weighted MRI of the pituitary adenoma may determine the response to primary SA treatment in newly diagnosed acromegaly. Secondary aims were to describe the correlation of T2 intensity to clinical, biochemical and MRI baseline characteristics and histological granulation pattern.

Subjects and methods

Subjects

Forty-five treatment naïve patients with active acromegaly diagnosed at Oslo University Hospital in the period 2003–2010 were included in the study. The diagnosis was based on clinical symptoms and confirmed by an elevated age-adjusted IGF-1 level and failure to suppress GH during an oral glucose tolerance test. A pituitary adenoma was identified on MRI in all patients. Forty patients underwent transsphenoidal pituitary surgery. In 34 of them, histological specimens for the analysis of granulation pattern were available, 19 after pretreatment with octreotide long acting release (LAR) monotherapy and 15 of the other patients.

Patients with clinical or radiological evidence of intrapituitary bleeding or pituitary apoplexy were excluded from the study.

The effect of primary medical treatment with SA was evaluated in 25 patients after median 6 months [interquartile range (IQR) 155–180 days]. In most patients, a fixed dose of long-acting octreotide was used (Sandostatin LAR, 20 mg per 4 weeks in 19 subjects; 20 mg start dose increased to 30 mg in five patients; 10 mg start dose and increased to 20 mg in one patient).

Biochemical measurements

Blood samples were drawn after an overnight fast and serum isolated.

Over the years, two methods for serum GH immunoassays were used. When the method was changed, cross-calibration was performed. In the period 2003–2005, AutoDelfia (Walac Oy, Turku,

Finland) was used, and thereafter, (2005–2010) Immulite 2000 (Siemens, Erlangen, Germany) calibrated to the WHO standard IS 98/574. In most patients, GH was estimated as a mean GH level of 3–5 daytime samples. Prior to any treatment, an octreotide test was performed in 41 patients. Three GH values were measured before s.c. administration of 50 µg octreotide and hourly 2–4 hours thereafter. Mean GH values before octreotide injection were compared with mean GH levels measured after injection and the percentage reduction of GH calculated for each patient.¹⁸

Serum IGF-1 was measured by RIA (Nichols Institute, Nijmegen, The Netherlands) until 2005 and thereafter with Siemens Immulite 2000 calibrated to WHO standard IS 87/518. Cross-calibration was performed between the methods. The coefficient of variation (CV) for the latter method was 6%.

IGF-1 was expressed as ratio between the measured value and the age-adjusted upper limit of normal (ULN) as given by the manufacturer (IGF-1/ULN).

MRI evaluation

All patients were investigated with MRI (1.5 Tesla) that included axial and/or coronal T2-weighted images at diagnosis, prior to any treatment. Two neuroradiologists (G.R., T.N.) independently evaluated MRIs in the Picture Archive Communication System (PACS, Sectra®, Linköping, Sweden), as described previously.¹⁷ The T2 intensity of the solid portion was visually compared with the cerebral grey and white matter in the adjacent temporal lobe. Pituitary adenoma tissue was classified as being hypointense, when the MRI signal was equal to or lower than white matter and as hyperintense when the signal was equal to or higher than grey matter. An isointense signal was defined as a signal intensity between white and grey matter.¹⁷ In cases where the adenomas could not be categorized by visual assessment alone, direct measurements of signal intensity on the grey-tone scale in the PACS images were taken to help the radiologists in their decision (Fig. 1). In cases of discrepant results between the radiologists, consensus was achieved after joint review. The radiologists were blinded for clinical and histological data.

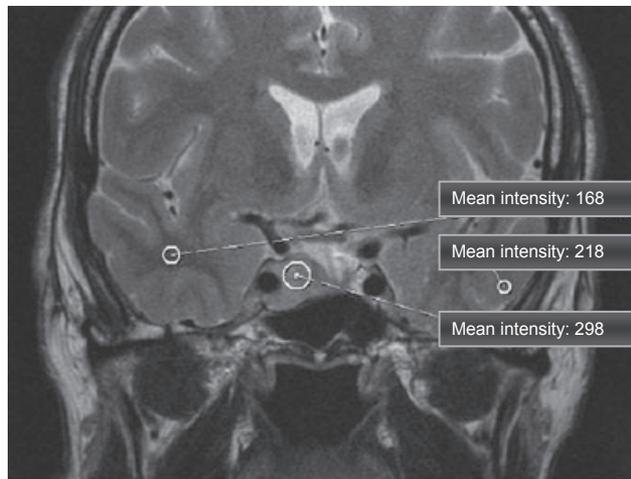
Tumour volume was estimated by the formula width × height × length × 0.5.¹⁹

Immunohistochemistry

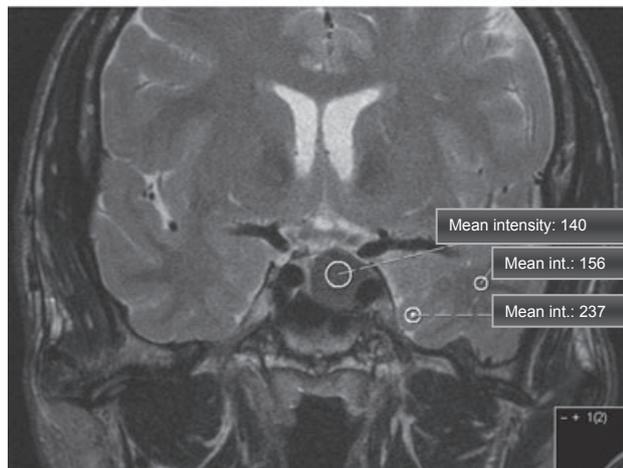
For granulation status, immunohistochemical analyses with a mouse monoclonal cytokeratin antibody (CAM5.2) were performed on whole sections from formalin-fixed, paraffin-embedded tissue blocks from 34 somatotrope adenomas, as described earlier.⁹ Tumours were classified according to Obari *et al.*, as densely, transitional or sparsely granulated.^{9,20}

Statistics

Differences between groups were analysed using nonparametric testing. Kruskal–Wallis test was used to compare differences between groups. Differences in proportions were tested by Pearson's chi-square test and Fisher's exact test as appropriate. Logistic



Hyperintense adenoma



Hypointense adenoma

Fig. 1 Examples for measurement of T2-weighted MRI intensity.

regression analysis was performed for variables possibly predictive for the outcome of medical treatment.

Results are presented as median (interquartile range, iqr), if not stated otherwise. $P < 0.05$ was considered significant. The statistical analyses were performed using SPSS software (version 18.0; SPSS, Chicago, IL, USA).

Ethics

The study was approved by the local ethical committee and conducted according to the Declaration of Helsinki II. Written informed consent was obtained from all patients.

Results

T2 intensity and baseline characteristics

Of the 45 adenomas, 12 (27%) were classified as hypointense, 15 (33%) as isointense and 18 (40%) as hyperintense. In ten cases with discrepant T2 classification between the two radiologists, consensus was reached after joint review. All discrepant cases involved the isointense classification. In other words, no hypointense adenoma was measured as hyperintense by the other radiologist or *vice versa*. Table 1 provides an overview of the demographic and biochemical baseline data according to adenoma intensity group, and representative MRI scans are given in Fig. 1.

There was no difference in sex distribution between the groups ($P = 0.9$). Median age was 54.5 (44.5–63), 46 (37–60) and 46.5 (30.5–56.5) years in the hypointense, isointense and hyperintense group, respectively ($P = 0.2$).

IGF-1 at baseline expressed as median ratio between IGF and of age-adjusted upper limit of normal (IGF-1/ULN) was 3.5 (2.3–4.9), 2.9 (2.6–3.8) and 1.9 (1.3–2.6) (hypointense/isointense/hyperintense; $P = 0.006$). Corresponding median GH values ($\mu\text{g/l}$) at baseline were 17.5 (6.1–35), 9.3 (6.0–32.5) and 4.1 (1.5–8.3) ($P = 0.025$).

The reduction (% of baseline) of GH during the acute octreotide test was 86 (80–90), 87 (66–94) and 60 (8–74) %, respectively ($P = 0.002$). The nadir was not significantly different ($P = 0.64$).

Hyperintense adenomas tended to be larger, but the difference between groups was not significant. The median tumour volume was 1.53 (0.33–3.27), 1.01 (0.50–2.19) and 2.01 (0.78–6.13) cm^3 ($P = 0.26$).

Outcome following primary medical treatment

The effect of primary medical treatment was evaluated in 25 patients after a median of 6 months (172 (155–180) days) with no

Groups, baseline	Hypointense	Isointense	Hyperintense	<i>P</i>
<i>n</i> (<i>n</i> = 45)	12	15	18	
Age at diagnosis (years)	54.5 (44.5–63)	46 (37–60)	46.5 (30.5–56.5)	0.20
Women/men	5/7	7/8	9/9	0.90
Serum GH ($\mu\text{g/l}$)*	17.5 (6.1–35)	9.3 (6.0–32.5)	4.1 (1.5–8.3)	0.025
IGF-1 (mmol/l)	137 (76–148)	125 (89–125)	81 (65–104)	0.053
IGF-1 (Ratio IGF-1/ULN)*	3.5 (2.3–4.9)	2.9 (2.6–3.8)	1.9 (1.3–2.6)	0.006
Tumour volume (cm^3)	1.53 (0.33–3.27)	1.01 (0.50–2.19)	2.01 (0.78–6.13)	0.26
Short octreotide test (<i>n</i> = 41)	10	15	16	
Acute GH reduction (%)*	86 (80–90)	87 (66–94)	60 (8–74)	0.002
Nadir ($\mu\text{g/l}$)	1.1 (0.5–3.1)	0.8 (0.5–4.0)	1.4 (0.7–3.3)	0.64

* $P < 0.05$; Kruskal–Wallis test.

Table 1. Demographic data and baseline characteristics; median (interquartile range)

Table 2. Response to primary medical treatment with somatostatin analogues (SA); median (interquartile range)

Groups	Hypointense	Isointense	Hyperintense	P
Preoperative SA treatment; n = 25	7	9	9	
Time to evaluation (days)	174 (160–180)	172 (159–178)	160 (104–188)	0.82
IGF-1 below ULN (no. of patients)	4 of 7	2 of 9	1 of 9	0.059**
IGF-1 reduction (%)*	51 (49–70)	36 (19–74)	13 (1–42)	0.031
GH reduction (%)*	86 (72–94)	78 (62–85)	46 (1–70)	0.015

ULN: upper limit of normal.

* $P < 0.05$; Kruskal–Wallis test; **Fisher's exact test for comparison between hypointense vs joint iso- and hyperintense Group.

Table 3. Results from linear regression analysis with IGF-1 change (% of baseline) after 6 months treatment with octreotide LAR as dependent variable ($n = 25$). The coefficients for the combined model with octreotide test and T2 intensity as predictors were Beta = 0.62, $R^2 = 0.36$ ($P = 0.019$)

Predictors	Unadjusted estimates					Adjusted estimates				
	Beta	R^2	B	95% CI	P	Beta	R^2	B	95% CI	P
Octreotide test	0.47	0.22	0.41	0.08; 0.74	0.019	0.27	0.07	0.23	-0.10; 0.57	0.167
T2 intensity	-0.58	0.33	-19	-7; -31	0.003	-0.46	0.21	-15	-2; -28	0.022

Beta, standardized regression coefficient (R); R^2 , squared standardized regression coefficient; B, unstandardized regression coefficient.

significant difference in treatment duration between the three intensity groups (Table 2). IGF-1 within reference range was achieved in four of seven, two of nine and one of nine patients in the hypo-, iso- and hyperintense adenomas group, respectively ($P = 0.059$; Fisher's exact test, hypointense vs joint iso- and hyperintense). Median IGF-1 reduction (% of baseline) following primary SA treatment was 51 (49–70) %, 36 (19–74) % and 13% (5–42) ($P = 0.03$); median reduction in GH (% of baseline) was 86 (72–94) %, 78 (62–85) % and 46 (1–70) % ($P = 0.02$).

Linear regression analysis

Baseline parameters that potentially could determine IGF-1 change (in %) were tested in a linear regression model (Table 3). IGF-1 reduction was best predicted by the octreotide test (unadjusted Beta = 0.47, $R^2 = 0.22$, $P = 0.019$) and T2 intensity (unadjusted Beta = 0.58, $R^2 = 0.33$, $P = 0.003$). When combining these two

determinants, the model improved significantly (Beta = 0.62, $R^2 = 0.39$, $P = 0.005$; F -test for improvement: $P = 0.022$).

Histology

Histological specimens were evaluated from 34 patients and classified into densely, transitional or sparsely granulation pattern (Table 4). Twelve adenomas were classified as densely granulated, 14 had a transitional granulation pattern and eight were sparsely granulated. All eight (100%) sparsely granulated adenomas were classified as hyperintense by T2-weighted MRI. Four of 14 (29%) adenomas classified as transitional were hyperintense, and one of the twelve (8%) densely granulated adenomas was hyperintense. Significantly more hyperintense adenomas were sparsely than transitional and densely granulated ($P < 0.001$, Fisher's exact test).

Discussion

In the present study of treatment naïve patients with acromegaly, T2-weighted MRI intensity of the pituitary tumour was correlated with secretory parameters and histological subtype. Hypointensity was associated with a better responsiveness to octreotide than iso- and hyperintensity. The hyperintense tumours had lower baseline GH and IGF-1 and tended to be larger than the hypointense. T2 intensity and granulation pattern were correlated, and all sparsely granulated adenomas were hyperintense.

T2 intensity and baseline characteristics

At baseline, the hyperintense adenomas differed significantly in GH and IGF-1/ULN from the hypo- and isointense group. The

Table 4. T2 weighted MRI signal intensity and granulation pattern; $P < 0.001$ (Fisher's exact test)

Groups	Hypointense	Isointense	Hyperintense
Densely granulated (DG; $n = 12$)	5	6	1
Transitional group (TG; $n = 14$)	5	5	4
Sparsely granulated (SG; $n = 8$)	0	0	8
Total, $n = 34$	10	11	13

absolute IGF-1 values tended to be lowest in the hyperintense group ($P = 0.053$) despite a trend towards younger age and thereby a higher *reference range*. As tumour size tended to be larger in the hyperintense group, the amount of GH secreted per tumour volume (GH index) was lower in the hyperintense adenomas. Further, the response to an octreotide test dose was blunted in these patients. A corresponding trend towards lower GH index and blunted response to octreotide test dose has been described in sparsely granulated adenomas.^{9,20,21} These data indicate that the hypo- and hyperintense tumours might represent biologically different subgroups with a different secretory behaviour.

Silent pituitary adenomas are commonly hyperintense.¹⁶ The lower GH secretion in the hyperintense adenomas may indicate an overlap to patients with clinically silent somatotrope adenomas although clinical parameters of growth hormone excess were not analysed in the present study.²²

Prediction of response to octreotide treatment

The ultimate objective in the treatment of acromegaly is the control of symptoms and normalized long-term survival. Primary and preoperative medical treatment are alternatives to reach this goal in selected patients, and medical pretreatment improves surgical outcome.^{1,3,4,23} However, preoperative medical treatment may delay effective therapy in patients not responding to currently available SAs. As new drugs for treatment of acromegaly become available, the choice of the best suited treatment may become even more challenging.

The value of the octreotide test for clinical decision making is controversial although there is an association between the acute octreotide test and long-term response.^{10,11,24} For patients receiving primary medical treatment, data on prediction of GH and IGF-1 decline and in particular tumour shrinkage are scarce. In a recent study, the octreotide test had only limited predictive value for tumour shrinkage although it was associated with a long-term GH lowering effect.⁶ In an attempt to improve prediction of the octreotide response, we combined T2 intensity and biochemical parameters in a linear regression model. The combination of the octreotide response and T2 intensity fitted best to predict the IGF-1 reduction (Table 3). Despite adjustment for the results of the octreotide test, T2 intensity remained a significant determinant for IGF-1 reduction. On the other hand, the octreotide test was only a borderline significant determinant after adjustment for T2 intensity, which may be due to a type 2 error. According to the regression model in this study, T2 intensity could even be superior to the octreotide test in predicting the antiseecretory effect of SA.

The predictive value of T2 intensity in patients treated with SA after surgical failure was recently reported.¹⁷ Complete response rate (defined as normalized IGF-1) after 6 months of treatment was observed in 70% (14 of 20) of the hypointense group, 56% (5 of 9) of the isointense group and only in 21% (6 of 28) of the hyperintense group, apparently with a similar decline towards hyperintensity as in our present study (Table 2; IGF-1 in reference range). In contrast to our study including

treatment naïve patients, the previous study included patients not cured by surgery. This may explain the lower response rate with regard to normalization of IGF-1 in the present study, as preceding surgical debulking most probably increased the chance of obtaining remission.^{17,25}

Histological classification

Histological granulation pattern correlates with the biochemical response to octreotide.⁸ In a study of 40 patients treated postoperatively with octreotide, dense granulation pattern was the strongest predictor of complete response.⁸ As shown in an earlier and in the present study, there was a correlation between T2 intensity and histological subtype.¹⁶ In a recent study, baseline secretory parameters, adenoma size and response to an octreotide test dose in 141 patients were correlated with the histological classification.²¹ Sparsely granulated adenomas were larger and had a blunted response to an octreotide test dose, in accordance with the present study with classification by T2 intensity. These studies support our findings on octreotide response. In contrast to the histological classification, T2 intensity is in general available in newly diagnosed acromegaly.

The only earlier study correlating T2 intensity and histological subtype demonstrated that hypointense adenomas were almost exclusively densely granulated (15 of 16 adenomas), while all iso- and hyperintense adenomas were sparsely granulated.¹⁶ However, biochemical data were not presented, and no histological intermediate group was defined. Moreover, adenomas were solely classified based on immunoreactivity for GH, whereas our classification in the present study was based on cytokeratin staining (Cam 5.2).

Densely granulated adenomas contain a prominent active Golgi apparatus and numerous secretory granules.²⁶ This compartmentalization should be expected to induce local magnetic field inhomogeneities and thus increase T2 relaxation with reduced T2 signal as a consequence. This may contribute to T2 hypointensity in densely granulated adenomas.

Limitations

As a result of the retrospective study design, the treatment duration varied, but there was no significant difference in this parameter between the groups. GH and IGF-1 were analysed continuously in the clinical routine laboratory and the method varied over time. In individual patients, only GH and IGF-1 analysed with the same method were used to compare IGF-1 before and after SA treatment. IGF-1 values were normalized to the ULN. Thereby, it was attempted to minimize the impact of different methods.

As it cannot be excluded that treatment with SA may change granulation pattern, we tested the distribution of granulation between patients operated directly and patients preoperatively treated with SA and found no difference. Further, in a previous study, granulation pattern in four patients with available adenoma tissue from surgeries both before and after SA treatment did not change.⁹

Patients were selected for medical treatment by clinical judgement and may thereby not be representative of all patients with

newly diagnosed acromegaly. Dosage and dose adjustment of octreotide LAR treatment was not predefined, but most patients were treated at our institution following the same clinical routine. The T2 intensity was evaluated retrospectively on available MRI scans. Therefore, different MRI scanners and protocols were used, and it is unknown whether this may affect the T2 intensity of different tissues. However, we hypothesize that these differences in T2 intensity because of different scanners should not change how the adenoma intensity relates to brain parenchyma in the individual patients and should thus not affect the radiological decision of an adenoma being hyper-, iso- or hypointense compared with white and grey matter.

There might also be a potential for more exact measurements by the quantification of T2 relaxation times; however, robust quantitative techniques are not generally accessible or refined for clinical translation, and we are not aware of reports where T2 relaxation times have been estimated in pituitary disease.

In some cases, T2 intensity varies within the tumour, the white matter or the grey matter. This might have contributed to the different classification of 10 of the 45 adenomas by the two neuro-radiologists. A further subclassification or absolute measurement of T2 intensity related to other calibrants than brain tissue might improve the predictive value.

Change in tumour size and invasiveness was not systematically evaluated in the pretreated patients and is therefore not presented here.

In summary, we have demonstrated the relationship between T2 intensity, biochemical markers of acromegaly, histological subtype and SA responsiveness in the same cohort. T2 hyperintensity correlated with lower GH, IGF-1 and blunted acute octreotide response, features typical of sparsely granulated adenomas.^{8,9,21} Further, T2 intensity correlated with response to SA treatment in treatment naïve patients. As primary and preoperative medical treatment can improve surgical outcome in a subset of acromegalic patients, measurement of T2 intensity may also improve the initial therapeutic stratification and thereby the overall cure rate.

Conclusion

In the present study of patients with newly diagnosed acromegaly, T2 intensity measurement identified biologically and histologically distinct groups of somatotrope adenomas. Further, T2 intensity was predictive for the biochemical outcome of primary octreotide treatment.

Acknowledgement

This study was supported by an unrestricted grant by Novartis.

References

- 1 Carlsen, S.M., Lund-Johansen, M., Schreiner, T. *et al.* (2008) Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenomas increases cure short-term postoperative rates: a prospective, randomized trial. *Journal of Clinical Endocrinology and Metabolism*, **93**, 2984–2990.
- 2 Raappana, A., Koivukangas, J., Ebeling, T. *et al.* (2010) Incidence of pituitary adenomas in Northern Finland in 1990–2007. *Journal of Clinical Endocrinology and Metabolism*, **95**, 4268–4275.
- 3 Mao, Z.G., Zhu, Y.H., Tang, H.L. *et al.* (2010) Preoperative lanreotide treatment in acromegalic patients with macroadenomas increases short-term postoperative cure rates: a prospective, randomised trial. *European Journal of Endocrinology*, **162**, 661–666.
- 4 Melmed, S., Colao, A., Barkan, A. *et al.* (2009) Guidelines for acromegaly management: an update. *Journal of Clinical Endocrinology and Metabolism*, **94**, 1509–1517.
- 5 Bollerslev, J., Fougner, S.L. & Berg, J.P. (2009) New directions in pharmacological treatment of acromegaly. *Expert opinion on investigational drugs*, **18**, 13–22.
- 6 Carlsen, S.M., Svartberg, J., Schreiner, T. *et al.* (2011) Six months preoperative octreotide treatment in unselected, de novo patients with acromegaly: effect on biochemistry, tumor volume, and postoperative cure. *Clinical Endocrinology*, **74**, 736–743.
- 7 Colao, A., Auriemma, R.S., Lombardi, G. *et al.* (2011) Resistance to somatostatin analogs in acromegaly. *Endocrine Reviews*, **32**, 247–271.
- 8 Bhayana, S., Booth, G.L., Asa, S.L. *et al.* (2005) The implication of somatotroph adenoma phenotype to somatostatin analog responsiveness in acromegaly. *Journal of Clinical Endocrinology and Metabolism*, **90**, 6290–6295.
- 9 Fougner, S.L., Casar-Borota, O., Heck, A. *et al.* (2011) Adenoma granulation pattern correlates to clinical variables and effect of somatostatin analogue treatment in a large series of patients with acromegaly. *Clinical Endocrinology*, **76**, 96–102.
- 10 de Herder, W.W., Taal, H.R., Uitterlinden, P. *et al.* (2005) Limited predictive value of an acute test with subcutaneous octreotide for long-term IGF-I normalization with Sandostatin LAR in acromegaly. *European Journal of Endocrinology*, **153**, 67–71.
- 11 Gilbert, J.A., Miell, J.P., Chambers, S.M. *et al.* (2005) The nadir growth hormone after an octreotide test dose predicts the long-term efficacy of somatostatin analogue therapy in acromegaly. *Clinical Endocrinology*, **62**, 742–747.
- 12 Boulby, P. & Rugg-Gunn, F. (2004) T2: the Transverse Relaxation Time. In: P. Tofts ed. *Quantitative MRI of the Brain*. John Wiley & Sons, Chichester, pp. 143–202.
- 13 Iuchi, T., Saeki, N., Tanaka, M. *et al.* (1998) MRI prediction of fibrous pituitary adenomas. *Acta neurochirurgica*, **140**, 779–786.
- 14 Bonneville, J.F., Bonneville, F. & Cattin, F. (2005) Magnetic resonance imaging of pituitary adenomas. *European Radiology*, **15**, 543–548.
- 15 Erdag, N., Bhorade, R.M., Alberico, R.A. *et al.* (2001) Primary lymphoma of the central nervous system: typical and atypical CT and MR imaging appearances. *AJR. American Journal of Roentgenology*, **176**, 1319–1326.
- 16 Hagiwara, A., Inoue, Y., Wakasa, K. *et al.* (2003) Comparison of growth hormone-producing and non-growth hormone-producing pituitary adenomas: imaging characteristics and pathologic correlation. *Radiology*, **228**, 533–538.
- 17 Puig-Domingo, M., Resmini, E., Gomez-Anson, B. *et al.* (2010) Magnetic resonance imaging as a predictor of response to somatostatin analogs in acromegaly after surgical failure. *Journal of Clinical Endocrinology and Metabolism*, **95**, 4973–4978.
- 18 Fougner, S.L., Borota, O.C., Berg, J.P. *et al.* (2008) The clinical response to somatostatin analogues in acromegaly correlates to the

- somatostatin receptor subtype 2a protein expression of the adenoma. *Clinical Endocrinology*, **68**, 458–465.
- 19 Lundin, P. & Pedersen, F. (1992) Volume of pituitary macroadenomas: assessment by MRI. *Journal of Computer Assisted Tomography*, **16**, 519–528.
 - 20 Obari, A., Sano, T., Ohyama, K. *et al.* (2008) Clinicopathological features of growth hormone-producing pituitary adenomas: difference among various types defined by cytokeratin distribution pattern including a transitional form. *Endocrine Pathology*, **19**, 82–91.
 - 21 Bakhtiar, Y., Hirano, H., Arita, K. *et al.* (2010) Relationship between cytokeratin staining patterns and clinico-pathological features in somatotropinomas. *European Journal of Endocrinology*, **163**, 531–539.
 - 22 Wade, A.N., Baccon, J., Grady, M.S. *et al.* (2011) Clinically silent somatotroph adenomas are common. *European Journal of Endocrinology*, **165**, 39–44.
 - 23 Colao, A., Cappabianca, P., Caron, P. *et al.* (2009) Octreotide LAR vs. surgery in newly diagnosed patients with acromegaly: a randomized, open-label, multicentre study. *Clinical Endocrinology*, **70**, 757–768.
 - 24 Halperin, I., Nicolau, J., Casamitjana, R. *et al.* (2008) A short acute octreotide test for response prediction of long-term treatment with somatostatin analogues in acromegalic patients. *Hormone and Metabolic Research*, **40**, 422–426.
 - 25 Colao, A., Attanasio, R., Pivonello, R. *et al.* (2006) Partial surgical removal of growth hormone-secreting pituitary tumors enhances the response to somatostatin analogs in acromegaly. *Journal of Clinical Endocrinology and Metabolism*, **91**, 85–92.
 - 26 Horvath, E. & Kovacs, K. (2006) Pathology of acromegaly. *Neuroendocrinology*, **83**, 161–165.