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Somatostatin receptor imaging in non-functioning pituitary adenomas: value of an uptake index

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Abstract. Somatostatin receptor imaging (SRI) was performed in five patients with known non-functioning pituitary adenomas. To determine whether the pituitary uptake correlates with response to octreotide therapy, an uptake index (UI) was calculated. Pituitary adenomas were detected in all five patients. The UI was, respectively, 15.1, 3.7, 2.2, 2.2 and 2.2 (the UI calculated in 12 normal subjects was between 1 and 1.9). Only the patient with the highest UI (15.1) had a dramatic improvement in tumour volume and visual function in response to octreotide therapy. The UI might be a good predictive parameter of octreotide therapy efficacy in non-functioning adenomas.

Key words: Somatostatin receptor imaging – Pituitary scintigraphy – Non-functioning adenomas – Somatostatin analogues – Indium-111 pentetreotide

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Introduction

Somatostatin receptors have been shown both in growth hormone (GH)-secreting and thyroid-stimulating hormone (TSH)-secreting adenomas and in non-functioning adenomas in vitro and in vivo [1–8]. In addition, octreotide, the somatostatin analogue, may be effective in improving visual defects and occasionally in reducing tumour size in such patients.

Since we have the opportunity to perform somatostatin receptor imaging (SRI), we checked a short series of five non-functioning adenomas which happened to have positive scintigraphic findings and tried to quantify this positivity by establishing an uptake index (UI) in order to investigate the relationship between this index and octreotide treatment efficacy.

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Materials and methods

Patients. Five consecutive patients, whose characteristics are given in Table 1, underwent scintigraphy with indium-111 pentetreotide (^{111}In-DTPA-D-Phe^1-octreotide, Mallinckrodt Diagnostica, Petten, The Netherlands) performed between October 1992 and March 1993. All were women. None had clinical or hormonal evidence of acromegaly, TSH-secreting adenoma, Cushing's disease or prolactinoma.

Patient 1 had GH levels (mean of three values) at 5.1 μg/l (normal < 5 μg/l) but the somatomedin C level was normal at 98 μg/l (normal: 70–380 μg/l). All patients had normal or subnormal gonadotropin and glycoprotein hormone alpha-subunit levels.

Imaging procedure. 111 MBq of ^{111}In-pentetreotide was given as an IV bolus injection. Planar images were obtained with a double-head large field of view gamma camera (DHD Sopha Medical, Buc, France) equipped with medium-energy parallel-hole collimators. The pulse height analyser spectrometer was centered over 173 keV with a window width of 20%.

Digital images were recorded with a Sophy computer. Planar images of the head, both analogue and digital, were obtained 20 min, 4 h and 24 h after injection. Acquisition parameters were as follows: 128×128 word matrix, 10 min/view.

Uptake index. On the 24-h profile view, identical circular regions of interest were placed on the pituitary area and on hemispheric brain (background: mean of five areas). The UI was determined as the ratio of the pituitary activity to the hemispheric activityes (Fig. 1).

In 12 normal volunteers (mean age 44 years), there was no visualization of the pituitary area and the UI was below 1.9 for all subjects (range 1–1.9). The inter- and intra-observer variabiliy of the UI was less than 5%.

Scintigraphy was considered positive if pituitary was visualized and if the UI was above 2. For patients, the inter- and intra-observer variabiliy in the UI was the same as for normal subjects (<5%).

Other parameters. Various other parameters were employed:

1. Visual acuity and fields using a Goldmann perimeter were checked.

2. Tumour volume index (in cm^3) was obtained from contiguous 3-mm sections of magnetic resonance images, at the time of scintigraphy, by multiplying the largest transverse, vertical and anteroposterior diameters in cm^3, as previously described by Lah-

Table 1. Patients' characteristics

Patient	Sex/ year of birth	Clinical signs (year)	Hormone profile	Previous treatment	ICC	Prolactin[a] (μg/l)	Volume index[a]
1	F 1955	A, G (1980) VD (1984) VD (1992)	NF	TS (1984)	GH PRL	1.3	13.9
2	F 1931	A, VD (1959) VD (1965) Epilepsy (1987)	NF	TF (1959) RT (1964) CB (1992)	Not available	3.7	54.4
3	F 1962	A, G, VD (1991)	NF	TS (1991) BC (1992)	Negative	25.4	9.7
4	F 1954	A, G, VD (1992)	NF	None	Negative	60.9	17.9
5	F 1916	Headaches VD (1993)	NF	None	FSH	12.2	14.7

A, Amenorrhoea; G, galactorrhoea; VD, visual defects; TS, transsphenoidal surgery; TF, transfrontal surgery; RT, radiotherapy; BC, bromocriptine; ICC, immunocytochemistry
[a] At the time of scintigraphy

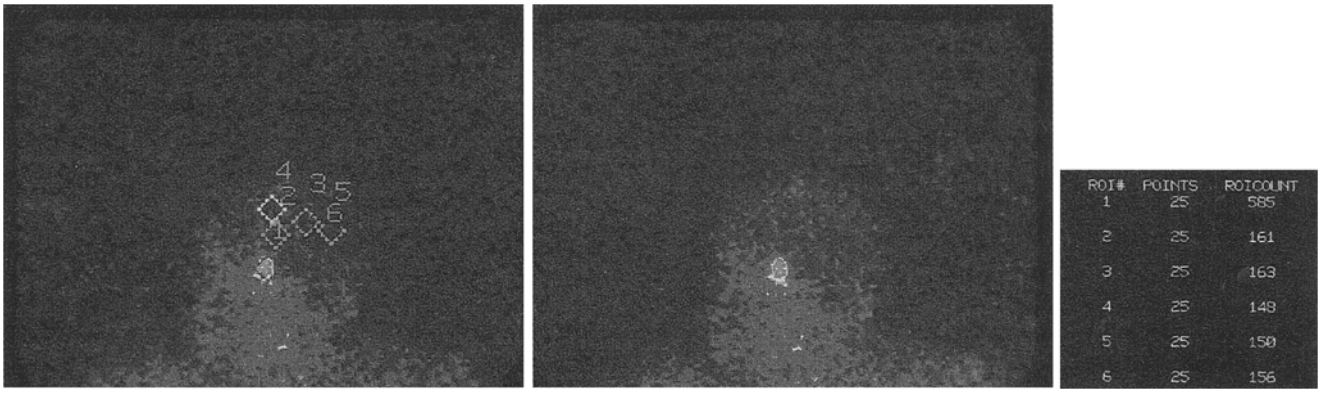

Fig. 1. Example of index uptake calculation in patient 2

lou et al. [9]. During the follow-up, variation in tumour volume was considered significant when it reached 20% or more.

3. In the four available adenomas, immunocytochemistry was performed as stated elsewhere [9].

Octreotide treatment protocol. Patients 1–4 were treated subcutaneously with octreotide 0.1 mg t.i.d. for 2 months, and then with 0.2 mg t.i.d. for 7 months (patient 1), 0.1 mg t.i.d. for 6 months (patients 2 and 3) or 0.05 mg t.i.d. for 1 month (patient 4). Patient 5 was not treated with octreotide, but was operated on.

Results

At baseline the five patients had positive scintigraphic results. Pituitary was always seen as early as 20 min, but visualization was better at 24 h. The UI at 24 h was at least 2.2. However, the imaging signal intensity and the UI differed from one case to another (Table 2).

Within 1 month of octreotide treatment the following results were seen (Table 2): The clinical condition of patient 1 improved dramatically, with a significant decrease in both tumour volume and UI. Patient 3 worsened clinically, with no significant change in either tumour volume or UI. Patient 4 did not improve clinically while the UI decreased. Patient 2 did not improve.

Octreotide treatment was continued in three patients: In patient 1 visual improvement was maintained and there were further decreases in tumour volume (-33% and −36% at 3 and 9 months) and UI (-68% and −72%). There was no significant change in either visual function or tumour volume in patient 2. No further deterioration occurred in the visual function of patient 3, whose tumour shrinkage did not reach (but was close to) significance at 3 months (-19%).

Discussion

Somatostatin analogues labelled with either ^{123}I or ^{111}In allow SRI, which has been reported to be positive in 18 out of 36 cases (50%): 2/8 cases of Faglia et al. [8]

Table 2. Data before (B) and after (A) 1 month of octreotide therapy

Patient	Visual acuity (in tenths)		visual fields	Volume index	Uptake index
	Left	Right			
1 B	04	10	Defective	13.9	15.1
A	08	10	Normalised	9.8 (–23%)	8.3 (–45%)
2 B	10	10	Normal	54.5	2.2
A	Unchanged		Normal	48.7 (–14%)	2.2
3 B	10	10	Defective	9.7	2.2
A	10	08	Left: unhanched Right: slightly worsened	9.4	2.4
4 B	10	09	Defective	10.4	3.7
A	ND	ND	Unchanged	11.8 (+13%)	2.8 (–24%)
5 B	$<10^{-2}$	08	Defective	14.7	2.2

ND, Not done

12/16 cases of Krenning et al. [4] and 4/12 cases of Plöckinger et al. [11]. In this preliminary series of five patients, all had positive SR images.

Octreotide, the somatostatin analogue, has previously been employed in the treatment of non-functioning adenomas [10]. Its efficacy has been evaluated on the basis of visual improvement and tumour shrinkage.

Visual improvement. With regard to patients treated for 1 month or more, an improvement has been reported in 24 [12–19], no change in 29 [12–14, 16, 17, 19] and deterioration in six [15, 16, 19]. Including our four patients, an improvement occurred in 40%, no change in 49% and deterioration in 11% of the cases. However, visual function may be improved by octreotide in patients harbouring tumours not known to have somatostatin receptors [20, 21]. In addition, one patient with negative scintigraphy had visual deterioration during octreotide treatment [14]. On the other hand, our patient 3 had an SRI-positve tumour but showed deterioration of visual function while being treated with octreotide. The visual effect of octreotide thus might not necessarily be mediated by somatostatin receptor involvement but rather might be due to an as yet unknown vascular or neuronal mediation mechanism [21].

Tumour shrinkage. The tumour shrinkage effected by somatostatin analogues is probably due to somatostatin receptor involvement [22]. Shrinkage by at least 20% has been reported in ten cases [8, 11, 15, 16, 19]; no significant change occurred in 52 [8, 11, 12, 14–16, 18, 19, 23] (and there was) an increase in nine [8, 11, 15, 19]. Including the present four patients, shrinkage was achieved in 15%; there was no change in 73%, and tumour growth occurred in 12% of the cases.

Scintigraphy has been used to ascertain tumour size in only 25 patients receiving octreotide therapy, including the present cases. Three of the four tumours which shrank [17], the two adenomas which grew [11, 17] and eight of the 19 tumours which did not change in size [11, 14, 17] were SRI-positive. One SRI-negative adenoma shrank [11], which raises the question of the relevance of scintigraphy, or even of an other mechanism [3] of shrinkage unrelated to somatostatin receptor involvement. The fact that two SRI-positive adenomas grew during octreotide therapy could be due to defective somatostatin receptors or to abnormal post-receptor events since it has been shown that there may be paradoxical responses to somatostatin, such as an increase in the intracellular calcium content of some non-functioning adenomas [7].

On the basis of our short preliminary study with scintigraphy, the UI appears to be promising since the three patients with the lowest indexes did not show any benefit from octreotide treatment, whereas the patient with the highest UI (15.1) had an impressive improvement in both visual defects (within a few days) and tumour volume, which had shrank by 36% after 9 months of octreotide therapy. Interestingly this tumour was a silent GH and prolactin containing adenoma which was not accessible to bromocriptine treatment.

In conclusion, somatostatin receptors of non-functioning adenomas can be easily visualized by scintigraphy with ^{111}In-pentetreotide. Quantifying scintigraphy might be more predictive of octreotide efficacy provided our preliminary data are confirmed by larger series. However, the possibility to tumour growth during treatment with somatostatin analogues cannot be ruled out, and very careful management is required.

References

1. Reubi JC, Heitz PU, Landolt AM. Visualization of somatostatin receptors and correlation with immunoreactive growth hormone and prolactin in human pituitary adenomas: evidence for different tumor subclasses. *J Clin Endocrinol Metab* 1987;65: 65–73.
2. Bertherat J, Brue T, Enjalbert A, et al. Somatostatin (SRIH) receptors on thyrotropin (TSH)-secreting pituitary adenomas: comparison with the inhibitory effects of octreotide upon in vivo and in vitro hormonal secretions. *J Clin Endocrinol Metab* 1992;75: 540–546.
3. Levy A, Eckland DJA, Gurney AM, Reubi JC, Doshi R, Lightman SL. Somatostatin and thyrotropin-releasing hormone response and receptor status of a thyrotropin-secreting pituitary adenoma, clinical and in vitro studies. *J Neuroendocrinol* 1989;1: 321–326.
4. Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WAP, Kooij PPM, Oei HY, van Hagen M, Postema PTE, de Jong M, Reubi JC, Visser TJ, Reijs AEM, Hofland LJ, Koper JW, Lamberts SWJ. Somatostatin receptor scintigraphy with (^{111}In-DTPA-D-Phe^1)- and (^{123}I-Tyr^3)-octreotide: the Rotterdam experience with more than 1000 patients. *Eur J Nucl Med* 1993;20: 716–729.

5. Nocaudie M, Huglo D, Deveaux M, Proye C, Marchandise X. Scintigraphie à l'iode 123-Tyr-3-octréotide et attitudes thérapeutiques. A propos de trois cas. *Médecine Nucléaire, Imagerie fonctionnelle et métabolique* 1993;17: 74–80.
6. Ikuyama S, Nawata H, Kato K, et al. Specific somatostatin receptors on human pituitary adenoma cell membranes. *J Clin Endocrinol Metab* 1985;61: 666–671.
7. Spada A, Reza-Elahi F, Lania A, Del Alamo P, Basetti M, Faglia G. Alterations in receptor status and postreceptor events in human pituitary tumors. In: Faglia G, Beck-Peccoz P, Ambrosi B, Travaglini P, Spada A, eds. *Pituitary adenomas: new trends in basic and clinical research.* Amsterdam: Elsevier Science; 1991: 95–102.
8. Faglia G, Spada A, Beck-Peccoz P, Persani L, Ambrosi B, Colombo P. Clinically nonfunctioning adenomas: advaences and perspectives. In: Faglia G, Beck-Peccoz P, Ambrosi B, Travaglini P, Spada A, eds. *Pituitary adenomas: new trends in basic and clinical research.* Amsterdam: Elsevier Science; 1991: 373–382.
9. Lahlou N, Le Nestour E, Chanson P, et al. Inhibin and follicle-stimulating hormone levels in gonadotroph adenomas: evidence of a positive correlation with tumour volume in men. *Clin Endocrinol* 1993;38: 301–309.
10. Klibanski A, Alexander JM, Bikkal HA, Hsu DW, Swearingen B, Zervas NT. Somatostatin regulation of glycoprotein hormone and free subunit secretion in clinically nonfunctioning and somatotroph adenomas in vitro. *J Clin Endocrinol Metab* 1991;73: 1248–1255.
11. Plöckinger U, Fett U, Bader M, Reichel M, Koppenhagen K, Wolf KJ, Quabbe HJ. Preoperative octreotide therapy of GH-secreting and endocrine inactive pituitary adenomas. Proceedings of the 75th Annual Meeting of the Endocrine Society, Las Vegas, Nevada, 9-12 June 1993 (abstract 75).
12. Warnet A, Timsit J, Chanson P, et al. The effect of somatostatin analogue on chiasmal dysfunction from pituitary adenomas. *J Neurosurg* 1989;71: 687–690.
13. Rünzi M, Jaspers C, Benker G, et al. Dramatische Besserung eines Chiasmasyndromes bei endokrin inaktivem Makroadenom der Hypophyse unter Therapie mit dem Somatostatin-analogon SMS 201-995 [abstract]. *Klin Wochenschr* 1989;67 Suppl 16: 284.
14. De Bruin TWA, Kwekkeboom DJ, Van't Verlaat JW, Reubi JC, Krenning EP, Lamberts SWJ, Croughs RJM. Clinically nonfunctioning pituitary adenoma and octreotide response to long term high dose treatment, and studies in vitro. *J Clin Endocrinol Metab* 1992;75: 1310–1317.
15. Liuzzi A, Dallabonzana D, Oppizzi G, Arrigoni GL, Cozzi R, Strade S, Benini Z, Chiodini J, Chiodini PG. Is there a real medical treatment for "non secreting" pituitary adenomas? In: Faglia G, Beck-Peccoz P, Ambrosi B, Travaglini P, Spada A, eds. *Pituitary adenomas: new trends in basic and clinical research.* Amsterdam: Elsevier Science; 1991: 383–390.
16. Gasperi M, Petrini L, Pilosu R, Nardi M, Marcello A, Mastio F, Bartalena L, Martino E. Octreotide treatment does not affect the size of non-secreting pituitary adenomas. *J Endocrinol Invest* 1993;16: 541–543.
17. Bazzoni N, Farabola M, Arosio M, Casati G, Faglia G. Is the effect of octreotide therapy in patients with functionless pituitary adenomas predictable [abstract]? *J Endocrinol Invest* 1991;14 Suppl 2: 53.
18. Turpin G, Foubert L, Noël-Weckstein S, Kujas M, de Gennes JL. Adénome somatotrope silencieux. Effet anticephalique d'un analogue de la somatostatine (octréotide). *Sem Hôp Paris* 1991;67: 1967–1969.
19. Warnet A, Harris AG, Renard E, James-Didier A, Chaumet-Riffaud P and the French Sandostatin Pituitary Tumor group. Octreotide therapy of nonfunctioning and gonadotroph adenomas.
20. Renard E, Barjon JN, Bringer J, Frerebeau P, Jaffiol C. Efficacité précoce de la sandostatine (SMS 201-995) sur le retentissement visuel des tumeurs hypothalamo-hypophysaires non secrétantes étendues [abstract]. *Ann Endocrinol (Paris)* 1989;50: 260.
21. Losa M, Ducati A, Fava E, Cenzato M, Giovanelli M. Postoperative acute administration of octreotide to patients with tumors of the sellar region can induce improvement of residual defects of visual function [abstract]. *J Endocr Invest* 1991;14 Suppl 4: 214.
22. Lamberts SWJ, Krenning EP, Reubi JC. The role of somatostatin and its analogs in the diagnosis and treatment of tumors. *Endocr Rev* 1991;12: 450–482.
23. Muhr C, Bergström M, Lundberg P, Bergström K, Lungström B. Positron emission tomography for the in vivo characterization and follow-up of treatment in pituitary adenomas. In: Landolt AM, Heïzt PU, Zapf J, Girard J, del Pazoe E, eds. Advances in pituitary adenoma research. Oxford: Pergamon Press; 1988: 163–170.