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An evaluation of the effects of somatostatin analogue therapy in non-functioning pituitary adenomas in comparison to acromegaly

Ocena efektów leczenia analogami somatostatyny nieczynnych hormonalnie gruczolaków przysadki w porównaniu z akromegalią

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Abstract

Introduction: Non-functioning pituitary adenomas (NFPA) are often diagnosed late as invasive macroadenomas. The surgical resection is usually incomplete and about 50% of patients require additional surgery. Recent data suggest that somatostatin analogues (SSA), so important in the pharmacotherapy of acromegaly, can also be effective in the management of NFPA.

Material and methods: We analysed data of patients who had been treated up to 10 years previously with SSA: 40 with acromegaly (23 — primary, 17 — recurrent tumours) and 22 with NFPA (4 — primary, 18 — recurrent tumours). Hormonal profile, dynamics of tumour size change, ophthalmic syndromes, somatostatin receptor (SSTR) scintigraphy, and immunohistochemistry of SSTR subtypes of operated tumours as well as side effects were investigated.

Results: Biochemical cure of acromegaly was achieved in 57.5% of patients, while reduction of tumour size was observed in 37% of patients and it was more frequent in not-operated cases. Regarding NFPA, stabilisation of tumour size was noticed in 68% of patients. Tumour shrinkage was reported in 9% of cases, but in 23% of the study group the adenoma size increased with indication for reoperation.

Conclusions: The efficacy of SSA in NFPA is much lower in comparison to their well-established effects in the treatment of acromegaly. Stabilisation of tumour size, which is observed in the majority of NFPA, is significantly more frequent in comparison to the natural history of untreated NFPA and our previous studies as well. Analysis of SSTR subtypes is an argument in favour of introduction of novel broad-spectrum SSA that may be more effective in the treatment of NFPA. Referring to acromegaly, adenoma size decrease was reported more frequently in primary therapy. Considering recurrent tumours better outcomes were achieved in patients who were pre-treated with SSA before planned surgery. **(Endokrynol Pol 2016; 67 (3): 292–298)**

Key words: *somatostatin analogue therapy; non-functioning pituitary adenomas; acromegaly; somatostatin receptor scintigraphy; immunohistochemistry of somatostatin receptor subtypes*

Streszczenie

Wstęp: Nieczynne hormonalnie gruczolaki przysadki (NFPA) są często diagnozowane późno w stadium inwazyjnych makrogruczolaków. Mają charakter guzów nawrotowych po niedoszczętnych zabiegach operacyjnych i w około 50% przypadków wymagają reoperacji. W ostatnim czasie pojawiają się doniesienia sugerujące, że analogi somatostatyny (SSA), będące podstawą farmakoterapii akromegalii, są również skuteczne w leczeniu NFPA.

Materiał i metody: Analizowano wpływ SSA stosowanych do 10 lat u 40 chorych z akromegalią (23 — guzy pierwotne, 17 — nawrotowe) i 22 chorych z NFPA (4 — guzy pierwotne, 18 — nawrotowe). Badano profil hormonalny, dynamikę zmian wielkości guza, objawy okulistyczne ze zmianami w polu widzenia, scyntygrafię receptorów somatostatynowych (SSTR), podtypy SSTR w badaniu immunohistochemicznym operowanych guzów oraz występowanie objawów niepożądanych.

Wyniki: Biochemiczne kryteria wyleczenia akromegalii uzyskano u 57,5% pacjentów, a redukcję wielkości guza obserwowano u 37,5% chorych i była ona częstsza u pacjentów nieoperowanych. U chorych z NFPA stabilizację wielkości guza i zaburzeń pola widzenia odnotowano u 68% pacjentów, u 9% obserwowano zmniejszenie wielkości gruczolaka, a u 23% doszło do wzrostu guza ze wskazaniem do kolejnej operacji.

Wnioski: Analogi somatostatyny są mniej skuteczne w leczeniu chorych z NFPA w porównaniu z dobrze znanymi efektami leczenia w akromegalii. Stabilizacja wielkości guza dotycząca większości przypadków NFPA leczonych SSA jest obserwowana znacząco częściej w porównaniu z naturalnym przebiegiem nieleczonych farmakologicznie NFPA, jak również w porównaniu z wynikami naszych poprzednich badań. Analiza podtypów SSTR w NFPA przemawia za wprowadzeniem nowych SSA o szerokim spektrum działania receptorowego, które mogłyby być bardziej skuteczne w leczeniu NFPA. W odniesieniu do akromegalii zmniejszenie wielkości gruczolaka w trakcie farmakoterapii jest częściej obserwowane w terapii pierwotnej. W guzach nawrotowych lepsze wyniki uzyskano w przypadkach stosowania SSA przed operacją. **(Endokrynol Pol 2016; 67 (3): 292–298)**

Słowa kluczowe: *leczenie analogami somatostatyny; nieczynne hormonalnie gruczolaki przysadki; akromegalia; scyntygrafia receptorów somatostatynowych; immunohistochemia podtypów receptorów somatostatynowych*

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Introduction

Treatment of non-functioning pituitary adenomas (NFPA) remains a great challenge for endocrinologists. Diagnosed late, usually in a stadium of macroadenomas, frequently with an invasion of the adjacent structures, especially *cavernous sinus*, they regard a complex and multidisciplinary approach. Transsphenoidal surgery, which remains the first-line treatment, is rarely curative. Moreover, tumour residue can regrow in up to 65% of cases during long-term follow-up [1, 2]. Recommendations for postoperative management of NFPA are a debated issue. Some authors suggest "wait and see" attitude, while others indicate a priority of subsequent operation and/or radiotherapy [3, 4]. As far as secondary therapy (i.e. therapy applied after the surgical intervention) is concerned, the use of somatostatin analogues (SSA) is proposed, considering the presence of somatostatin receptors (SSTR) in NFPA [5, 6]. Receptor scintigraphy and possibly immunohistochemistry should be performed for the purpose of SSTR detection [7]. The efficacy of SSA in the treatment of NFPA was evaluated in a few clinical studies [8, 9]. Stabilisation of adenoma size was observed in the overwhelming majority of patients; however, single cases of tumour shrinkage were also noted [10, 11]. It is difficult to draw definite conclusions because of limited clinical data and short duration of therapy.

Conversely to NFPA, SSA are considered a mainstay of the pharmacotherapy of acromegaly. The predominant expression of SSTR2 and SSTR5, through which octreotide and lanreotide act, forms the basis for SSA clinical use in GH-secreting pituitary adenomas [12]. The aim of the therapy is to provide clinical and biochemical control of the disease and tumour shrinkage. Criteria for disease control are defined as an age-normalised serum IGF-1 value and a random GH level < 1.0 ng/mL in oral glucose tolerance test [13]. Full response to somatostatin analogues is also understood as a ≥ 20% decrease in tumour volume in primary as well as in secondary therapy or at least stabilisation of tumour remnant in the case of second-line treatment [14]. Some authors suggest the importance of somatotropinomas pretreatment with somatostatin analogues prior to planned neurosurgery, which can be beneficial, especially in the aspect of tumour debulking [15].

Material and methods

A total of 22 patients (13 women, 9 men) at the mean age of 52.8 ± 14.0 years with diagnosis of NFPA were entered into the database. All tumours represented macroadenomas. The smallest one was sized 13 × 14 × 16 mm. Few giant adenomas were noted with the largest one sized 47 × 47 × 42 mm. *Cavernous sinus* invasion was present in 18 cases. Visual field defects were noted in 12 patients. Eighteen patients (81.8%) were operated, nine of them more than once. Further more, 85% of NFPA were found to be gonadotropinomas in immunohistochemical staining. Four patients with NFPA underwent radiotherapy. Four patients were not operated (disqualified or did not agree). Referring to positive results of SSTR scintigraphy and immunohistochemistry of SSTR subtypes, the decision to treat patients with SSA was made. They received octreotide LAR 20 mg up to 30 mg or lanreotide 120 mg every four weeks and the duration of therapy was 6 months up to 10 years. Moreover, three patients underwent pre-operative treatment with octreotide for at least 6-12 months. Twelve patients were additionally treated with dopamine agonists because of coexisting hyperprolactinaemia.

Concerning acromegaly, 40 patients (28 women, 12 men) at the mean age of 51.9 ± 11.5 years were treated with the same doses of SSA for 2–10 years. Magnetic resonance imaging showed 13 microadenomas and 27 macroadenomas. Seventeen patients (42.5%), in whom only one was with microadenoma, were operated. Two patients underwent neurosurgical procedure twice and one patient received radiotherapy in the postoperative period. In a group of nine patients with macroadenomas SSA was administrated for 6 to 12 months before planned surgery in accordance with the current recommendations of the Polish Society of Endocrinology [16]. SSA was used as a primary therapy in 23 patients (57.5%). Furthermore, eleven patients received dopamine agonists (bromocriptine or cabergoline) due to coexisting hyperprolactinaemia.

The objective of this clinical study is to evaluate the effects of SSA therapy in patients with NFPA in comparison to their well-known effects in acromegaly. The analysis comprises the results of SSA treatment used as primary therapy as well as secondary therapy following surgery. Patient's condition, hormone profile, tumour size, visual field, and undesirable effects were taken into account.

Results

NFPA

Somatostatin receptor scintigraphy was performed in order to qualify patients to the therapy with SSA. Scintigraphy with ^{99m}Tc-HYNIC-TOC or ^{99m}Tc Tektrotyd (740 [MBq]) used to be the first choice investigation for the visualisation of SSTR2 and SSTR5. Only patients with increased tracer uptake were included in the study (Fig. 1).

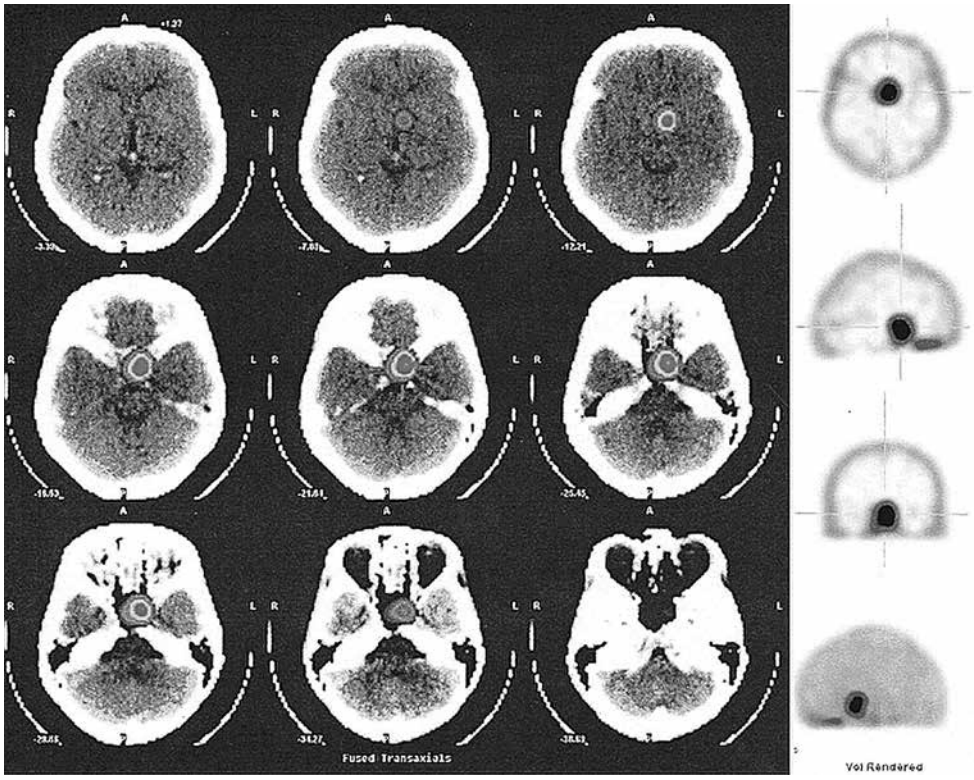

Figure 1. *Somatostatin receptor scintigraphy of representative patient with non-functioning pituitary adenoma — confirmation of strong expression of SSTR in the tumour*

Rycina 1. *Przykład scyntygrafii receptorów somatostatynowych pacjenta z nieczynnym hormonalnie gruczolakiem przysadki — silna ekspresja SSTR w guzie*

Table I. ***Immunohistochemistry of somatostatin receptors in non-functioning pituitary adenomas. Interestingly, the strong expression of SSTR1 is present in the majority of NFPA (66%)***

Tabela I. ***Immunohistochemia receptorów somatostatynowych w nieczynnych hormonalnie gruczolakach przysadki. Zwraca uwagę silny odczyn immunohistochemiczny SSTR1 w większości NFPA (66%)***

The patient's initials	SSTR1	SSTR2a	SSTR2b	SSTR3	SSTR4	SSTR5
W.B.	**Strong**	Moderate	Moderate	**Strong**	Negative	Weak
G.I.	Weak	Moderate	Doubtful	Weak	Negative	**Strong**
K.J.	**Strong**	**Strong**	**Strong**	**Strong**	Doubtful	**Strong**
M.J.	**Strong**	**Strong**	Moderate	Moderate	Negative	Moderate
R.K.	**Strong**	Moderate	Moderate	**Strong**	Negative	Weak
T.M.	Moderate	Moderate	Moderate	Moderate	Negative	Moderate
M.P.	**Strong**	**Strong**	Moderate	Moderate	Negative	Weak
S.S.	Doubtful	Moderate	Doubtful	Non diagnostic	Negative	Moderate
L.J.	**Strong**	Negative	**Strong**	Weak	Negative	**Strong**

Additionally, immunohistochemistry of somatostatin receptor subtypes was performed in part of the surgically removed tumour tissue. Strong or moderate SSTR2 and/or SSTR 5 immunostaining confirmed the decision of SSA therapy (Table I). Interestingly, a strong expression of SSTR1 was present in the majority of NFPA (66%).

SSA therapy alleviated some symptoms of the disease. The reported headaches were less intense and in one case (patient H.G., 66-year-old woman with giant pituitary tumour) even disappeared after three months of SSA therapy. Interestingly, the improvement in headaches was not correlated with a decrease in tumour size. Moreover, no changes in the visual field were observed.

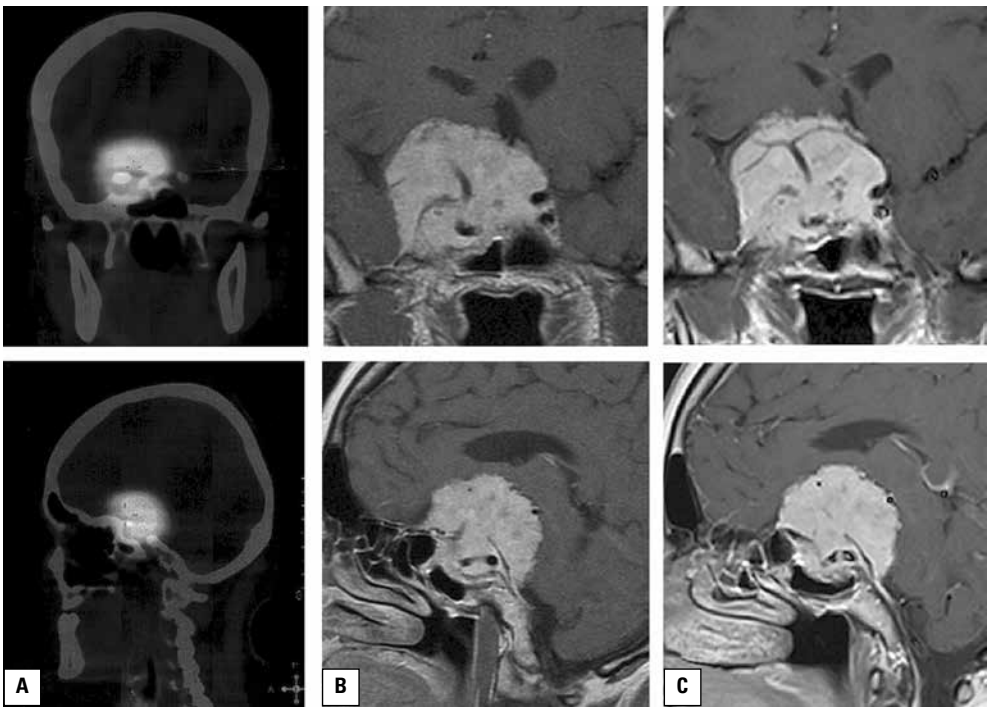

Figure 2. *Giant NFPA (47 × 47 × 42 mm, patient H.G., 66-year-old woman) with high expression of SSTR2, SSTR3, and SSTR5 in receptor scintigraphy (***A.** *22.11.2013). Stabilisation of tumour size in MRI scans during one-year therapy with somatostatin analogues (***B.** *MRI, 4.10.2013,* **C.** *MRI, 2.09.2014). Clinically — significant improvement in patient's headaches three months after introduction of the therapy*

Rycina 2. *Gruczolak olbrzymi NFPA (47 × 47 × 42 mm, pacjentka H.G., 66-letnia kobieta) z silną ekspresją SSTR2, SSTR3 i SSTR5 w scyntygrafii receptorowej (***A.** *22.11.2013). Stabilizacja wielkości guza w obrazach MR podczas jednorocznej terapii analogami somatostatyny (***B.** *MR, 4.10.2013,* **C.** *MR, 2.09.2014). Klinicznie — znaczna poprawa w zakresie bólów głowy u pacjentki trzy miesiące po wdrożeniu leczenia*

Table II. ***Characteristics of patients with non-functioning pituitary adenomas resistant for somatostatin analogue therapy***
Tabela II. Charakterystyka pacjentów z nieczynnymi hormonalnie gruczolakami przysadki opornymi na terapię analogiem somatostatyny

Patient's initials	Age	Sex	Surgery	Pharmacotherapy	Change in tumour size	Time of the therapy
B.M.	56	F	Once	Octreotide + bromocriptine	39 × 32 × 23 mm → volume increase in 2 mm	16 months
J.K.	60	M	3 times + radiotherapy	Octreotide	31 × 32 × 39 mm → 35 × 30 × 39 mm	18 months
K.J.	49	F	3 times	Octreotide	15 × 8 × 8 mm → 18 × 10 × 12 mm	19 months
K.S.	77	M	Not operated	Octreotide	13 × 14 × 16 mm → 18 × 13 × 16 mm	7 months
M.J.	69	F	Once	Octreotide + bromocriptine	26 × 14 × 12 mm → 26 × 20 × 15 mm	7 months

Tumour size remained stable in 15 cases. A representative MRI showing stabilisation of adenoma size in one patient with a giant tumour is presented in Figure 2.

Reduction in tumour size was observed in two patients. These patients were pretreated with SSA before surgery. After incomplete tumour resection the combined treatment with somatostatin analogues and dopamine agonists was initiated. An increase in tumour size in five patients with NFPA was observed (Table II), but there was no deterioration in the visual field. Patient B.M. (Table II) was qualified for reoperation; however, she did not agree to it. Therefore, treatment with lanreotide was initiated. Patient J.K. was advised to start therapy with lanreotide because he was disqualified

Table III. *Comparison of results of somatostatin analogue therapy in acromegaly and non-functioning pituitary adenomas*
Tabela III. *Porównanie wyników leczenia analogami somatostatyny w akromegalii i w nieczynnych hormonalnie gruczolakach przysadki*

Assessed clinical parameters	Acromegaly	NFPA
GH and IGF-1	Diminution in 95% (57.5% normalisation)	–
↓ tumour size ≥ 20%	37.5%	9.0%
	(80% with primary medical therapy)	(100% recurrent tumours)
Tumour size stabilisation	60%	68.0%
↑ tumour size with indication to neurosurgical treatment	2.5%	23.0%
Side effects	25% gall stones	9% gall stones
	7.5% symptomatic cholelithiasis → cholecystectomy	

from neurosurgery. Patients K.S. and M.J. were treated with lanreotide and the therapy resulted in stabilisation (patient K.S.) and slight reduction of tumour size (patient M.J.). Considering patient K.J. we preferred to adopt a "wait-and-see" attitude because the therapy had been stopped for several months due to lack of patient adherence.

SSA were well-tolerated; however, two patients developed asymptomatic cholelithiasis after 20 and 36 months of treatment, respectively.

Acromegaly

More than half of the acromegalic patients noticed that some symptoms improved (headaches, facial features, sleep apnoea) while others were relieved (oedema, sweating).

Biochemical cure of acromegaly was achieved in 23 patients (57.5%); 11 of whom were operated. What is important, biochemical criteria were fulfilled in eight patients who received SSA preoperatively. Biochemical control of the disease was noted in 12 patients who were not operated, and they were treated with SSA as primary therapy (52.2% of all patients with primary therapy). Moreover, criteria of biochemical curre were fulfilled in a shorter time when SSA was used as primary therapy (24.9 ± 13.3 months vs. 33 ± 15 months).

A random GH level > 1.0 ng/mL in oral glucose tolerance test and a decrease of IGF-1 level of at least 50% compared to baseline were observed in 15 patients.

GH and IGF-1 levels increased in two cases. We noticed a temporary increase in IGF-1 level with relatively constant GH level and stabilisation of tumour size in one patient with microadenoma receiving SSA as primary therapy. The second case (B.T.) is a 36-year-old woman with macroadenoma (31 × 31 × 24 mm) after surgery followed by long-term (about five years) combined pharmacotherapy (bromocriptine+octreotide/ /lanreotide). Regardless the therapy, adenoma size increased with a concomitant, significant rise in serum GH and IGF-1 levels.

Adenoma size reduction was noted 15 patients (37.5%): 12 never operated and 3 patients pre-treated with octreotide before neurosurgery. However, increase in tumour size was marked in one patient (B.T. described above).

Criteria for acromegaly remission, defined as biochemical control together with tumour shrinkage, were fulfilled in 10 patients (25%): 7 not operated and 3 patients after neurosurgery.

Common side effects included development of gall stones, which were diagnosed in 25% of patients after approximately two years of the therapy. Three patients required cholecystectomy. Focusing on side effects, persistent gastrointestinal distress was observed in two patients.

A comparison of efficacy of SSA therapy in non-functioning pituitary adenomas and acromegaly is presented in Table III.

Discussion

Considering the main goal of NFPA therapy, which is a decrease in tumour volume, surgery is the current first-choice treatment. With reference to this goal, the use of somatostatin analogues appears to be somewhat controversial as they provide only stabilisation of tumour size in the overwhelming majority of cases (68% in our clinical study). However, stabilisation of tumour size is a remarkable achievement of the therapy, especially concerning the natural history of NFPA, which shows that these tumours regrow and must be reoperated in about 50% of cases [17].

This is the second clinical study to evaluate the long-term efficacy of somatostatin analogues in the treatment of NFPA. The previous one, conducted by Fusco et al., focused only on the use of somatostatin analogues in

secondary therapy after incomplete surgery, and the follow-up period was shorter (37 ± 18 months) [9]. In their group of 26 patients treated with 20 mg of octreotide LAR every 28 days, tumour size increased in 19% of patients. However, comparing to their control group, which consisted of untreated patients with post-operative tumour remnants, the adenoma size increased in 53% of patients. Contrary to our results, no tumour size reduction was noted. Similarly, no changes in visual field were observed. Moreover, Pawlikowski et al. also evaluated the risk of NFPA recurrence and they suggest that it was 45.7% for "pure" gonadotropinomas and as much as 57.1% for other monohormonal types of NFPA [18].

Our results highlight a limited effect of SSA on tumour shrinkage. This can be explained by late diagnosis with the detection of all tumours in a stadium of macroadenoma, frequently with invasion and expansion beyond the confines of the *sella turica*. However, the poorer effect of somatostatin analogues can be also explained by differences in somatostatin receptors expression in non-functioning pituitary adenomas. NFPA are characterised by variable expression of all SSTR apart from SSTR4, while currently available somatostatin analogues (octreotide and lanreotide) bind preferentially to SSTR2 and with lower affinity to SSTR5 [19]. Because of strong immunostaining of SSTR1, which was present in 66% of examined cases of NFPA, we think that introduction of novel broad-spectrum somatostatin analogues would be more effective in the therapy of NFPA [20]. Moreover, considering tumour shrinkage, combined therapy with novel somatostatin analogues and dopamine agonists can presumably be more effective because NFPA are also characterised by the expression of dopamine receptor D2 [21, 22].

As far as postoperative treatment of clinically non-functioning pituitary adenomas is concerned, Ferrante et al. suggested that radiotherapy should be used because it significantly decreases the risk of tumour recurrence or regrowth (18.4% *vs.* 58.4%) [2]. Introduction of new radiation techniques such as Gamma Knife therapy seems to be a safer choice, minimising the risk of side effects [23].

Our observations support the thesis that somatostatin analogues are more effective in primary than in secondary therapy of acromegaly, which has already been suggested by some authors [24, 25].

Furthermore, young (under 40 years old) patients, especially with acromegaly resistant for pharmacotherapy (like patient B.T.), should be tested for AIP gene mutations because deletions of chromosome area 11q13 are often found [26].

Conclusions

Somatostatin analogues are less effective in the treatment of NFPA in comparison to their well known, excellent effects in acromegaly. Stabilisation of NFPA size observed in the majority of patients receiving SSA is significantly more frequent with regard to untreated NFPA, as was documented in our previous studies. Tumour shrinkage, which is the main therapeutic goal, is only marked in single cases. However, strong expression of different SSTR subtypes in NFPA, especially SSTR1, observed in our immunohistochemical studies, argues in favour of introduction of novel broad-spectrum somatostatin analogues. Considering tumour shrinkage, combined therapy of novel somatostatin analogues and dopamine agonists also seems to be more effective.

SSA are undoubtedly effective in the treatment of acromegaly in secondary as well as in primary therapy. Considering the use of somatostatin analogues in secondary therapy, better outcomes are achieved in patients who were pre-treated with SSA before planned surgery. However, our results were better in primary than in secondary therapy. This observation calls into question the current, routine practice of neurosurgery in GH-secreting adenomas.

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