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# "Silent" thyrotropin (TSH) expression in acromegaly and clinically non-functioning pituitary adenomas

## „Cicha" ekspresja tyreotropiny (TSH) w akromegalii i klinicznie nieczynnych gruczolakach przysadki

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## Abstract

**Introduction:** The pituitary adenomas secreting thyrotropin (TSH) are considered the rarest type of hormonally active pituitary tumour. In spite of that, many cases are described in the literature. On the other hand, the observations of the co-expression of TSH with other pituitary hormones (mostly with growth hormone [GH]) and "silent" expression of TSH in clinically non-functioning pituitary adenomas (CNFPA) are rather scarce.

**Materials and methods:** Among 93 examined pituitary adenomas, 22 of them were diagnosed as active acromegaly and 71 as clinically non-functioning pituitary adenomas (CNFPA). All of them were immunostained with antibodies against pituitary hormones, including the anti-TSH antibody. TSH-immunopositive adenomas are immunostained also to detect somatostatin receptor subtypes (SSTR 1-5).

**Results:** TSH immunopositivity was found in 4.2% of CNFPA (3/71 tumours) and in 13.6% (3/22) cases of somatotropinomas manifesting as active acromegaly. All of the examined TSH-immunopositive adenomas expressed SSTR subtypes except SSTR4. The symptoms of hyperthyroidism were not observed in any of the acromegalic patients co-expressing TSH with GH.

**Conclusions:** Our data confirm the relative rarity of TSH expression or co-expression of TSH in pituitary tumours. In most cases TSH is co-expressed with GH in patients with acromegaly and is not accompanied by hyperthyroidism. The "silent" expression of TSH may occur also, although rarely in CNFPA. The strong expression of SSTR in TSH-immunopositive CNFPA ("silent thyrotropinoma") indicates the possibility of the treatment of these tumours with somatostatin analogues. **(Endokrynol Pol 2016; 67 (5): 515–518)**

**Key words:** *acromegaly; clinically non-functioning pituitary adenomas; silent thyrotropinoma*

## Streszczenie

**Wstęp:** Gruczolaki przysadki wydzielające tyrotropinę (TSH) uważane są za najrzadszy typ czynnego hormonalnie guza przysadki. Mimo to w piśmiennictwie opisano liczne przypadki tego rodzaju. Z drugiej strony, raczej nieliczne obserwacje dotyczą ko-ekspresji TSH z innymi hormonami przysadkowymi (zwłaszcza hormonem wzrostu [GH]) i „cichej" ekspresji TSH w klinicznie nieczynnych gruczolakach przysadki (CNFPA).

**Materiał i metody:** Zbadano 93 gruczolaków przysadki, w tym 22 zdiagnozowanych jako aktywna akromegalia i 71 jako klinicznie nieczynne gruczolaki przysadki (CNFPA). We wszystkich gruczolakach wykonano odczyny immunohistochemiczne z przeciwciałami przeciwko hormonom przysadkowym, włącznie z przeciwciałem anty-TSH. W gruczolakach immunopozytywnych dla TSH (za wyjątkiem jednego) przeprowadzono także badanie immunohistochemiczne w celu wykrycia podtypów receptora somatostatynowego (SSTR 1-5).

**Wyniki:** Immunopozytywność dla TSH wykryto w 4,2% CNFPA (3/71 guzów) i 13,6% (3/22) przypadków somatotropinoma manifestujących się aktywną akromegalią Wszystkie badane TSH-immunopozytywne guzy wykazywały ekspresję podtypów SSTR za wyjątkiem podtypu SSTR4. W żadnym przypadku ko-ekspresji TSH z GH u pacjentów z akromegalią ani jego ekspresji w CNFPA nie obserwowano nadczynności tarczycy.

**Wnioski:** Nasze spostrzeżenia potwierdzają względną rzadkość ekspresji lub ko-ekspresji TSH w guzach przysadki. W większości przypadków TSH współistnieje z GH u chorych z akromegalią, czemu nie towarzyszy nadczynność tarczycy. „Cicha" ekspresja TSH może zdarzać się także, jakkolwiek rzadziej, w CNFPA. Silna ekspresja SSTR w CNFPA immunopozytywnych dla TSH („cichych tyrotropinoma") wskazuje na możliwość leczenia także tych guzów analogami somatostatyny. **(Endokrynol Pol 2016; 67 (5): 515–518)**

**Słowa kluczowe:** *akromegalia; klinicznie nieczynne gruczolaki przysadki; cichy tyreotropinoma*

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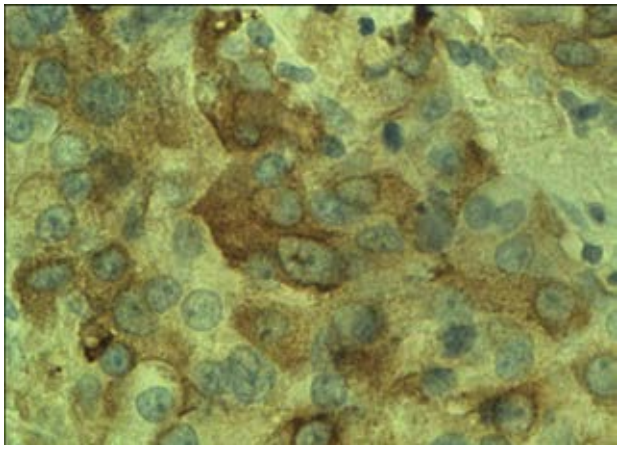

**Figure 1.** *Positive immunostaining for βTSH in clinically non-functioning pituitary adenoma in a 54-year-old man JK*

**Rycina 1.** *Dodatni odczyn na βTSH w klinicznie nieczynnym gruczolaku przysadki u 54-letniego mężczyzny JK*

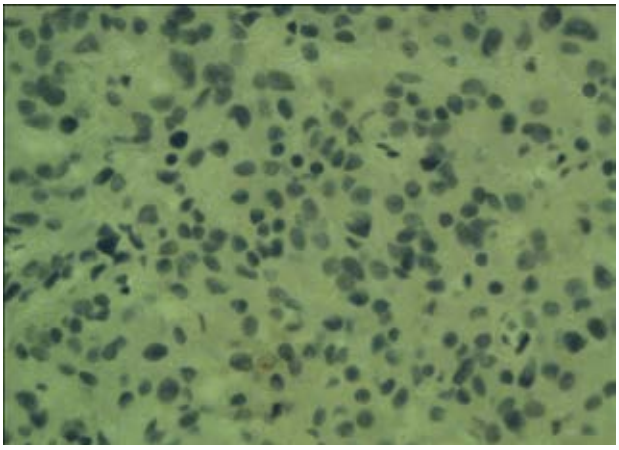

**Figure 2.** *Negative immunostaining for αSU in the same tumour as in Figure 1*

**Rycina 2.** *Ujemny odczyn na αSU w tym samym guzie co na rycinie 1*

## Introduction

The thyrotropin (TSH) expressing pituitary adenoma manifested by inappropriate TSH secretion and subsequent hyperthyroidism belongs to the rarest hormonally active pituitary tumours. Its incidence is estimated approximatively as 2% [1]. In the material of our laboratory, including 184 immunostained pituitary tumours, only one case of active thyrotropinoma manifested by hyperthyroidism was observed (0.54%). This case was described elsewhere [2]. Some reports indicate that sometimes TSH expression of pituitary adenomas is not accompanied by the disturbance of TSH secretion leading to hyperthyroidism [3, 4]. It is also known that GH-secreting tumours in patients with acromegaly are often plurihormonal and express, besides growth hormone (GH), also prolactin and/or TSH [5, 6]. Although nodular goitre is a frequent feature of acromegaly, its appearance is connected more with elevated IGF-I level than with TSH hypersecretion.

## Material and methods

The study includes 92 pituitary adenomas surgically excised. Twenty-two of them were diagnosed before surgery as active acromegaly and 71 as clinically non-functioning pituitary adenomas (CNFPA). All of them were immunostained with antibodies against pituitary hormones, including the monoclonal anti-TSH antibody (Immunotech, France). Detailed data concerning the immunoassays of the pituitary hormones are presented elsewhere [6]. The TSH-positive tumours were also immunostained using rabbit polyclonal antisera raised against specific fragments of human somatostatin receptor subtypes (Gramsch Laboratories, Schwabhausen, Germany). Additionally, SSTR2 and SSTR5 was revealed using the monoclonal antibodies ab109495 and ab134152 from Abcam, respectively. The detailed immunohistochemical procedures of SSTR detection were performed as previously described [8]. The intensity of immunoreaction for specific receptor proteins was scored semiquantitatively using a descriptive scale as follows: strong staining (+++), moderate staining (++), weak staining (+), or negative (0). The study was approved by the Bioethical Committee of the Medical University of Łódź, decision no RNN/335/15/KE.

## Results

In the group of 71 tumours, diagnosed before surgery as CNFPA, only in three cases (4.2%) the positive immunostaining with anti-TSH antibody of tumoural cells was found (Fig. 1). In the group of CNFPA, 18 adenomas expressed positive immunostaining for GH without symptoms of acromegaly (they were qualified as so-called silent somatotropinomas), but none of them showed the expression of TSH. In patients with active acromegaly, TSH immunopositivity was more frequent and concerned 3 cases of 22 examined tumours (13.6%). None of the acromegalic patients with TSH co-expression presented with symptoms of hyperthyroidism. Only one of them (JK) presented neutral nodular goitre. The detailed data on patients with TSH-immunopositive adenomas are presented in Table I. As can be seen there, the majority of TSH-immunoreactive adenomas were plurihormonal. It concerns all cases of acromegaly and one of three cases of non-functioning tumours. In two cases of non-functioning adenomas the expression of the α-subunit (αSU) was lacking (or was below the threshold of the immunohistochemical

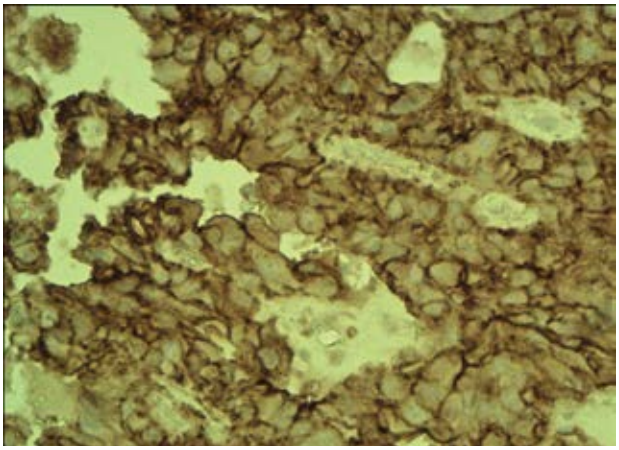

**Figure 3.** *Positive immunostaining for SSTR2 in the same tumour as in Figure 1*

**Rycina 3.** *Dodatni odczyn na SSTR2 w tym samym guzie co na rycinie 1*

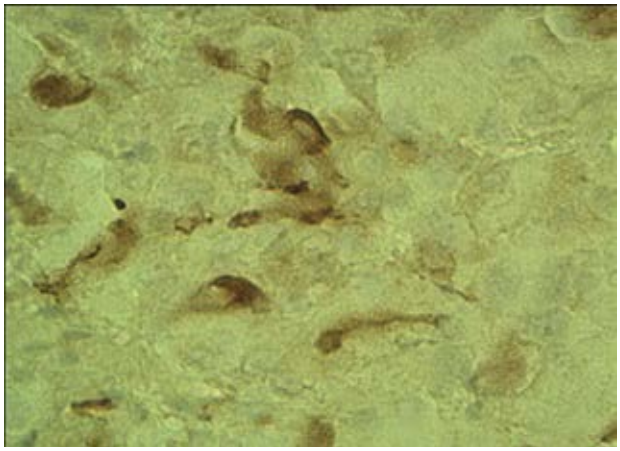

**Figure 4.** *Positive immunostaining for βTSH in pituitary adenoma in a 32-year-old man, LK, with acromegaly*

**Rycina 4.** *Dodatni odczyn na βTSH w gruczolaku przysadki u 32-letniego mężczyzny LK z akromegalią*



**Table I.** *Data of patients with TSH-immunopositive pituitary tumours*

**Tabela I.** *Dane pacjentów z TSH-immunopozytywnymi guzami przysadki*

| Patient | Sex | Age (years) | Clinical diagnosis | Immunohistochemistry |
|---|---|---|---|---|
| BL | M | 23 | Acromegaly | GH PRL αSU LH TSH |
| LK | M | 32 | Acromegaly | GH PRL αSU TSH |
| JM | F | 50 | Acromegaly | GH PRLαSU FSH TSH ACTH |
| MT | F | 42 | NF | αSU TSH |
| AD | F | 31 | NF | FSH βTSH |
| JK | M | 54 | NF | βTSH |

reaction, Fig. 2). We conclude that in these cases only the free β-subunit of TSH was present, and this fact predicted the non-functional character of the tumour. In all the cases of acromegaly and in both examined TSH-immunopositive CNFPA, the presence of SSTR was established by means of immunohistochemistry (Fig. 3). In one case of CNFPA (MT) SSTR immunohistochemistry was not performed, and in one case of acromegaly (BL) it was limited to SSTR2 becauseof the paucity of the sample. The results of immunohistochemical examination of somatostatin receptor (SSTR) subtypes 1–5 are shown in Table II. As can be seen, all of the investigated tumours expressed SSTR subtypes with moderate or strong intensity, except for SSTR4.

## Discussion

The data presented above confirm the rarity of TSH expression of pituitary adenomas. The co-expression of TSH with GH and PRL in acromegaly occurs more often (Fig. 4), which is possibly connected with the fact that the PIT-1 is a common transcription factor involved in differentiation and proliferation of somatotrophs, lactotrophs, and thyrotrophs [9]. Moreover, TSH expression may be observed in relatively rare cases of CNFPA. It is well known that the majority of CNFPA express different pituitary hormones or their free subunits, without the elevation of their levels in blood

**Table II.** *Immunohistochemical examination of SSTR1-5 in TSH-expressing pituitary adenomas. Intensity of immunostaining: 0 negative, + weak, ++ moderate, +++ strong, n.e. — not examined*

**Tabela II.** *Badanie immunohistochemiczne SSTR1-5 na ekspresję TSH gruczolaków przysadki. Intensywność wybarwienia: 0 ujemny, + słaby, umiarkowany ++, +++ silny, N.E. — nie badane*

| Patient | Clinical diagnosis | SSTR1 | SSTR2A | SSTR2B | SSTR3 | SSTR4 | SSTR5 |
|---|---|---|---|---|---|---|---|
| BL | Acromegaly | n.e | +++ | +++ | n.e | n.e. | n.e. |
| LK | Acromegaly | ++ | ++ | ++ | + | 0 | +++ |
| JM | Acromegaly | ++ | +++ | ++ | + | 0 | +++ |
| AD | NF | ++ | ++ | +++ | +++ | 0 | + |
| JK | NF | +++ | +++ | +++ | +++ | 0 | ++ |

and without the clinical symptoms of the pituitary hyperfunction. The most commonly expressed hormones in CNFPA are gonadotrophins FSH and/or LH or their free subunits (50–70%) [10]. The expression of ACTH without the manifestation of Cushing's disease, so-called silent corticotropinoma, or the expression of GH without symptoms of acromegaly, so-called silent somatotropinoma, are less frequent [11–15]. Clinically non-functioning pituitary adenomas expressing TSH without the symptoms of thyroid stimulation might be called, per analogy, silent thyrotropinoma.

It is worth noticing that in our material in two of three tumours examined only the free β TSH subunit was expressed, and this may constitute the cause of the lack of hormonal activity of these tumours. Interestingly, all the somatotropinomas co-expressing TSH and both silent thyrotropinomas immunostained with anti-SSTR antibodies revealed at least moderate immunostaining for all SSTR subtypes, except SSTR4. The treatment with somatostatin analogues is now routine treatment in acromegaly and is also very promising in TSH-secreting tumours accompanied by hyperthyroidism [2, 16, 17]. The attempts to treat TSH-immunopositive CNFPA seem also to be justified.

## Conclusions

Our data confirm the relative rarity of TSH expression or the co-expression of TSH in pituitary tumours. In most cases TSH is co-expressed with GH in patients with acromegaly and is not accompanied by hyperthyroidism. The "silent" expression of TSH may occur also, although rarely in CNFPA. The strong expression of SSTR in TSH-immunopositive CNFPA ("silent thyrotropinomas") gives a good reason for the attempts of their treatment with somatostatin analogues.

## Acknowledgement

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