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'Silent' somatotropinoma

„Cichy" *somatotropinoma*

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Abstract

Introduction: 'Silent' somatotropinomas are defined as GH-immunopositive pituitary adenomas without clinical symptoms of acromegaly and GH elevation in peripheral blood. Such tumours used to be considered as rare. However, recent data has indicated that they are more frequent than previously thought. The present paper shows that pituitary adenomas, diagnosed before surgery as nonfunctioning, often display GH immunopositivity.

Material and methods: Fifty six patients with pituitary adenomas were included in the study. All the patients underwent transphenoidal adenectomy. In 37 patients before the surgery, clinically nonfunctioning pituitary adenomas (CNFPAs) were diagnosed. In 19 patients, acromegaly was diagnosed. All the excised tumours were examined immunohistochemically using the primary antibodies against the pituitary hormones or their subunits.

Results: All the adenomas in the patients with acromegaly were immunopositive for GH. Among the pituitary tumours diagnosed before the surgery as clinically nonfunctioning, 45.9% showed GH immunopositivity. Both somatotropinomas with acromegaly and 'silent' GH-immunopositive adenomas most often co-expressed prolactin, whereas GH-immunonegative nonfunctioning adenomas expressed mainly LH and/or FSH. In three cases of 'silent' somatotropinomas, IGF-1 levels were slightly elevated, suggesting that these patients may present a 'low-symptomatic' acromegaly.

Conclusions: GH-immunopositivity occurs in nearly half of 'clinically' nonfunctioning pituitary adenomas. Because of that, IGF-1 determination in blood before the surgery, and immunohistochemical examination of adenoma for GH after the surgery, should be performed as standard in all patients suffering from pituitary tumours, irrespective of the presence or absence of acromegaly symptoms. **(Pol J Endocrinol 2012; 63 (2): 88–91)**

Key words: *acromegaly, nonfunctioning pituitary adenomas, 'silent' somatotropinoma*

Streszczenie

Wstęp: „Ciche" *somatotropinom*a są GH-immunopozytywnymi gruczolakami przysadki, przebiegającymi bez klinicznych objawów akromegalii oraz podwyższonego stężenia GH we krwi obwodowej. Guzy tego rodzaju do niedawna uważano za rzadkość, jednak nowsze doniesienia wskazują, że są one częstsze niż dotąd sądzono. Niniejsza praca wskazuje, że gruczolaki przysadki rozpoznawane przez zabiegiem operacyjnym jako nieczynne hormonalnie często wykazują dodatni odczyn immunohistochemiczny na GH.

Materiał i metody: Do badania włączono 56 chorych z gruczolakami przysadki. Wszystkich chorych poddano przezklinowej adenektomii. U 37 pacjentów przed operacją rozpoznano klinicznie nieczynne gruczolaki przysadki, a u 19 — akromegalię. Wszystkie usunięte gruczolaki badano immunohistochemicznie z użyciem przeciwciał przeciwko hormonom przysadkowym i/lub ich podjednostkom.

Wyniki: Wszystkie gruczolaki u chorych z akromegalią były immunopozytywne dla GH. W grupie chorych, u których przed operacją diagnozowano je jako klinicznie nieczynne hormonalnie, 45,9% wykazywało immunopozytywność dla GH. Zarówno w przypadkach *somatotropinoma* u chorych z akromegalią, jak i „cichych" *somatotropinoma* najczęściej obserwowano współwydzielanie prolaktyny, natomiast w gruczolakach GH-immunonegatywnych najczęściej obserwowano ekspresję LH i/lub FSH. W 3 przypadkach „cichych" *somatotropinoma* stwierdzono niewielkie podwyższenia stężeń IGF-1, co sugeruje, że ci pacjenci mieli skapoobjawową akromegalię.

Wnioski: Immunopozytywność dla GH występuje w blisko połowie „klinicznie" nieczynnych gruczolaków przysadki. Z tego względu stężenie IGF-1 w surowicy powinno być obowiązkowo badane przed operacją, a badanie immunohistochemiczne na GH powinno być wykonywane po operacji u wszystkich chorych z guzami przysadki, niezależnie od występowania lub niewystępowania objawów akromegalii. **(Endokrynol Pol 2012; 63 (2): 88–91)**

Słowa kluczowe: *akromegalia, nieczynne hormonalnie gruczolaki przysadki, „cichy"* somatotropinoma

Introduction

'Silent' somatotropinomas ('silent' somatotroph adenomas) are defined as pituitary adenomas in patients lacking the symptoms of acromegaly and diagnosed before surgery as nonfunctioning but showing growth hormone (GH) immunopositivity when the excised tumour was examined immunohistochemically [1–5]. Such tumours are not accompanied by elevated GH and IGF-1 levels, but in some cases moderate GH and/or IGF-1 elevation are found [1, 6]. Functional disturbances of GH regulation, such as nonsuppression after glucose

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loading and/or GH response after TRH administration, have also been observed [2].

The causes of a lack of promptly elevated GH secretion, or action in spite of GH expression within the adenoma cells, remain unknown. Moreover, data on the incidence of 'silent' somatotropinomas is scarce. In earlier studies, this type of pituitary adenoma was only recognised sporadically. However, some recent publications have indicated that 'silent' somatotropinomas are not as rare as previously thought [7, 8].

In the present study, we confirm the high incidence of GH immunopositivity in an unselected group of clinically nonfunctioning pituitary adenomas (CNFPAs), and compare these tumours to those obtained from acromegalic patients and patients with GH-immunonegative CNFPA.

Material and methods

We examined 56 patients, 29 women and 27 men, aged from 21 to 73 years. In 37 patients before surgery, clinically nonfunctioning pituitary adenomas (CNFPA) were diagnosed. None of that group presented symptoms of acromegaly. In the remaining 19 patients, acromegaly was diagnosed. All the patients underwent transphenoidal adenectomy, and all the excised tumours were examined immunohistochemically. Paraffin sections of each tumour were immunostained using the primary antibodies against the following pituitary hormones or their subunits: prolactin (PRL, polyclonal, Dako, Denmark), growth hormone (GH, polyclonal, Dako or Immunon, USA), LH (Dako, monoclonal), FSH (Dako, monoclonal), TSH (monoclonal, Immunotech, France), ACTH (polyclonal, Sigma, USA) and alpha-subunit (alpha-SU, monoclonal, Immunotech, France). Visualisation of the immune reactions was done by means of the streptavidin-biotin-peroxidase technique with the use of 3,3'-diaminobenzidine as chromogen. The presence of more than 1% of hormone immunopositive cells was considered as important. The study was approved by the Bioethical Committee of the Medical University of Lodz, decision RNN/183/11/KB, dated 3 March, 2011.

Results

Acromegaly

The group of patients with acromegaly included 14 women and five men (F:M ratio = 2.8:1). The mean age was 47. All adenomas in the patients were immunopositive for GH. In most of them (14/19, 74%) the co-expression of PRL was also found. In 6/19 (32%) LH or free beta-LH subunit, in 2/19 (11%) free alpha-subunit, and in one case TSH, were co-expressed. The mean IGF-1 serum concentration was 1,041.7 ± 470.7 (SD) ng/mL.

GH-immunopositive clinically nonfunctioning pituitary adenomas (silent somatotropinomas)

Among the 37 pituitary tumours diagnosed before surgery as clinically nonfunctioning, 17 adenomas (45.9%) showed GH immunopositivity (Figures 1, 2). The number of women and men in this group was almost equal (nine and eight, respectively). The age of patients was 37–70 years, mean age 57. Almost all the adenomas

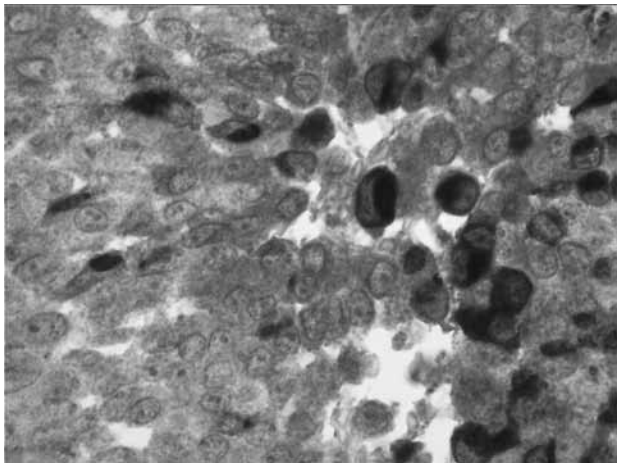

Figure 1. *Immunostaining with anti-GH antibody in 61 year-old male patient (S.J.), diagnosed before surgery as 'clinically' nonfunctioning pituitary tumour. Original magnification 400 ×*

Rycina 1. *Odczyn immunohistochemiczny z przeciwciałem anty-GH u 61-letniego mężczyzny (S.J), u którego przed operacją rozpoznawano „klinicznie" nieczynny guz przysadki. Powiększenie oryginalne 400 ×*

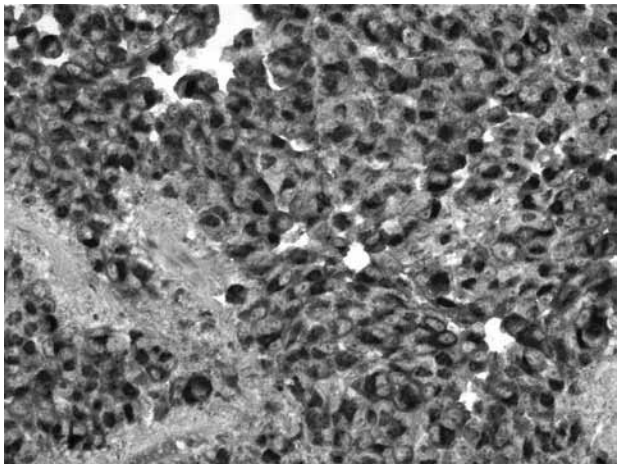

Figure 2. *Immunostaining with anti-prolactin antibody in the same patient as in Fig. 1. Original magnification 200 ×*

Rycina 2. *Odczyn immunohistochemiczny z przeciwciałem antyprolaktynowym u tego samego pacjenta, co na ryc. 1. Powiększenie oryginalne 200 ×*

were plurihormonal; only one tumour expressed solely GH. Most of the adenomas co-expressed PRL (12/17). The second commonest co-expression was of LH or free beta-LH subunit (10/17). FSH was co-expressed in 3/17 cases, free alpha-SU in 2/17 cases, and ACTH in one case. The serum concentrations of IGF-1 were estimated before surgery in ten cases; the mean value was 148.3 ± 102.8 ng/mL. In only three cases did the IGF-1 levels exceed the upper limit of the age-adjusted reference values. However, in one case the IGF-1 value was markedly below the lower limit, suggesting GH deficiency. In the remaining patients, IGF-1 levels were within normal ranges.

GH-immunonegative clinically nonfunctioning pituitary adenomas

The remaining 20 CNFPAs did not show GH immunopositivity. This group showed a prevalence of masculine sex (14 men and six women, M:F ratio = 2.3:1). The age of patients was between 21 and 71 years, mean age 49. Most of the adenomas (12/20) belonged to the gonadotropinoma subtype. LH (8/20) and FSH (8/20) were the hormones most often expressed. The expression of other pituitary hormones was less frequent: PRL in 3/20 cases and ACTH in 3/20. Four adenomas did not show immunostaining for pituitary hormones (null cell adenomas). The IGF-1 concentrations were measured before surgery in seven patients with a mean value of 181.2 ± 106.4 ng/mL.

Discussion

The data presented above confirms recent findings showing that the incidence of 'silent' somatotropinomas within the clinically nonfunctioning pituitary adenomas is relatively frequent. In our study, GH-immunopositivity was found in nearly half of the nonfunctioning adenomas and 'silent' somatotropinomas were in second place in the group of CNFPAs. Gonadotropinomas still remain the most frequent subtype within CNFPA (approximatively 60%, 9). According to Wade et al. [8] 'silent' somatotropinomas represent one third of all somatotroph adenomas.

Since all GH-immunopositive adenomas constitute one third of all surgically treated pituitary adenomas in our material [9], and CNFPA also one third, the incidence of 'silent' somatotropinomas could be calculated as approximatively 10–15% of all pituitary adenomas, and as between a third and a half of all somatotropinomas. These numbers are roughly concordant with the data published by Wade et al. [8], but clearly exceed the values reported earlier by Trouillas et al. (2% of all pituitary adenomas and 7% of all somatotroph adenomas [2]. The majority of them are plurihormonal. Almost all of them co-express PRL or gonadotrophins. In this respect, they did not differ from hormonally active somatotropinomas which are also often plurihormonal [10, 11]. Interestingly, the characteristics of hormones co-expressed together with GH in 'silent' somatotropinomas are identical to the somatotropinomas accompanied by acromegaly. This may suggest that both subtypes of somatotropinomas undergo similar pathways of differentiation. The mean IGF-1 concentration in blood serum in 'silent' somatotropinomas did not differ from that observed in the group of CNFPA lacking GH expression, but was clearly lower than that observed in the patients with acromegaly.

However, in three cases of 'silent' somatotropinomas', IGF-1 levels were slightly elevated. Such cases have also been reported by other authors [2, 6] and it has been suggested that they represent the initial phase of acromegaly. It is well known that the initial stage of this disease is difficult to diagnose, and usually several years elapse between the onset of disease and the formulation of a proper diagnosis.

However, it seems to us unlikely that 'silent' somatotropinomas represent the early phase of acromegaly, because GH hypersecretion is absent or limited in spite of the rather high dimensions of the tumour. The mechanism of this situation remains unclear. Possibly, it is a consequence of an abnormal form of GH molecule with diminished or lacking biological activity, but such a presumption needs further studies to be proven.

Conclusions

Summing up, we conclude that 'silent' somatotropinomas occur in numerous patients with pituitary adenomas. Because of that, IGF-1 determination in blood before surgery, and immunohistochemical examination of adenoma for GH after surgery, should be routinely performed in all patients suffering from pituitary tumours, irrespective of the presence or absence of acromegaly symptoms. The question arises as to what is the importance of GH detection in tumours diagnosed as CNFPA? Obviously, taken together with IGF-1 elevation, it allows the recognition of the 'low-symptomatic' acromegaly. The question as to whether GH-immunopositive CNFPA (silent somatotropinomas) are candidates for treatment with somatostatin analogues or dopamine agonists remains open, and requires further studies.

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