

# A case of growth-hormone staining pituitary adenoma with renal cyst and hepatic cyst: are they related manifestations of a single disease?

Jun MA<sup>1,2</sup>, Pinan LIU<sup>1,2</sup>

<sup>1</sup> Department of Neurosurgery, Beijing Tiantan Hospital affiliated to Capital Medical University, Beijing, China

<sup>2</sup> China National Clinical Research Center for Neurological Diseases, Beijing, China

*Correspondence to:* Pinan Liu, MD.  
Department of Neurosurgery, Beijing Tiantan Hospital,  
Dongcheng District Tiantanxili No. 6, Beijing, China.  
E-MAIL: liupinan@gmail.com

*Submitted:* 2014-06-10 *Accepted:* 2014-07-05 *Published online:* 2014-07-15

*Key words:* **growth-hormone staining pituitary adenoma; insulin-like growth factor-I; renal cyst; hepatic cyst**

Neuroendocrinol Lett 2014; **35**(4):257-261 PMID: 25038593 NEL350414C03 © 2014 Neuroendocrinology Letters • [www.nel.edu](http://www.nel.edu)

## Abstract

Growth-hormone staining pituitary adenoma is a popular disease of the central nervous system. We noticed some patients have accompanying cystic disorders. Several cases of concomitant growth-hormone (GH)-staining pituitary adenoma and other cystic changes have been reported but with no further investigation.

We report a case of adult growth-hormone staining pituitary adenoma with accompanying polycystic changes of multiple systems, as well as hypertension and nephrolithiasis. Preoperative clinical assessment revealed intrasellar tumor, multinodular thyroid disorder, renal cysts, and hepatic cysts, with increased serum growth-hormone level and normal thyroid hormone level. The total tumor resection was performed via endoscopic transsphenoidal approach. The pathologic analysis reported growth-hormone staining pituitary adenoma. The postoperative course was uneventful. The endocrine testing was normal soon after the operation and the patient remained well for a follow-up period of eight months.

This is the fifth report about simultaneous growth-hormone staining pituitary adenoma and polycystic changes of the kidneys and the liver. With review of the literature we speculate that the abnormal growth hormone secretion of the pituitary adenoma may arouse sequential cystic changes of multiple systems through some IGF-I involved pathways.

## INTRODUCTION

Growth hormone (GH)-staining pituitary adenoma is a disorder characterized by GH hypersecretion, multisystem-associated morbidities, and increased mortality. Insulin-like growth factor-I (IGF-I) is a marker of integrated GH secretion. A random serum IGF-I level is an important value

for diagnosis of GH-staining pituitary adenoma and for monitoring the result of therapeutic intervention. Chronic hypersecretion of GH and IGF-I can lead to a myriad of manifestations and accompanying clinical features. But concomitant polycystic changes are seldomly investigated. We report a case of GH-staining pituitary adenoma, with renal and hepatic cysts, nontoxic multinodu-

lar thyroid disorders, and with accompanying hypertension and nephrolithiasis. We try to invest the possible relationship of these multisystem changes with review of literature.

## CASE REPORT

### *Medical history*

A 54-year-old man presented to the Neurosurgery Department of Beijing Tiantan Hospital in July 2013 for progressive blurred vision of six months. His medical history was remarkable. He had hypertension for eight years, and was diagnosed as coronary artery disease one month ago. The maximum blood pressure was 148/92 mmHg. He had hepatic cysts of the right lobule, right renal cysts, and left nephrolithiasis for more than ten years. The patient underwent left thyroid nodule resection under local anesthesia seven years ago and the pathologic examination reported nontoxic benign thyroid nodule. The patient still had bilateral thyroid nodules at the time, with cystic nodules of the left lobe and mixed cystic/solid nodules of the right lobe. The familial history was negative, with no renal cyst, hepatic

cyst, hypertension, nor endocrine disorders of the first grade relatives.

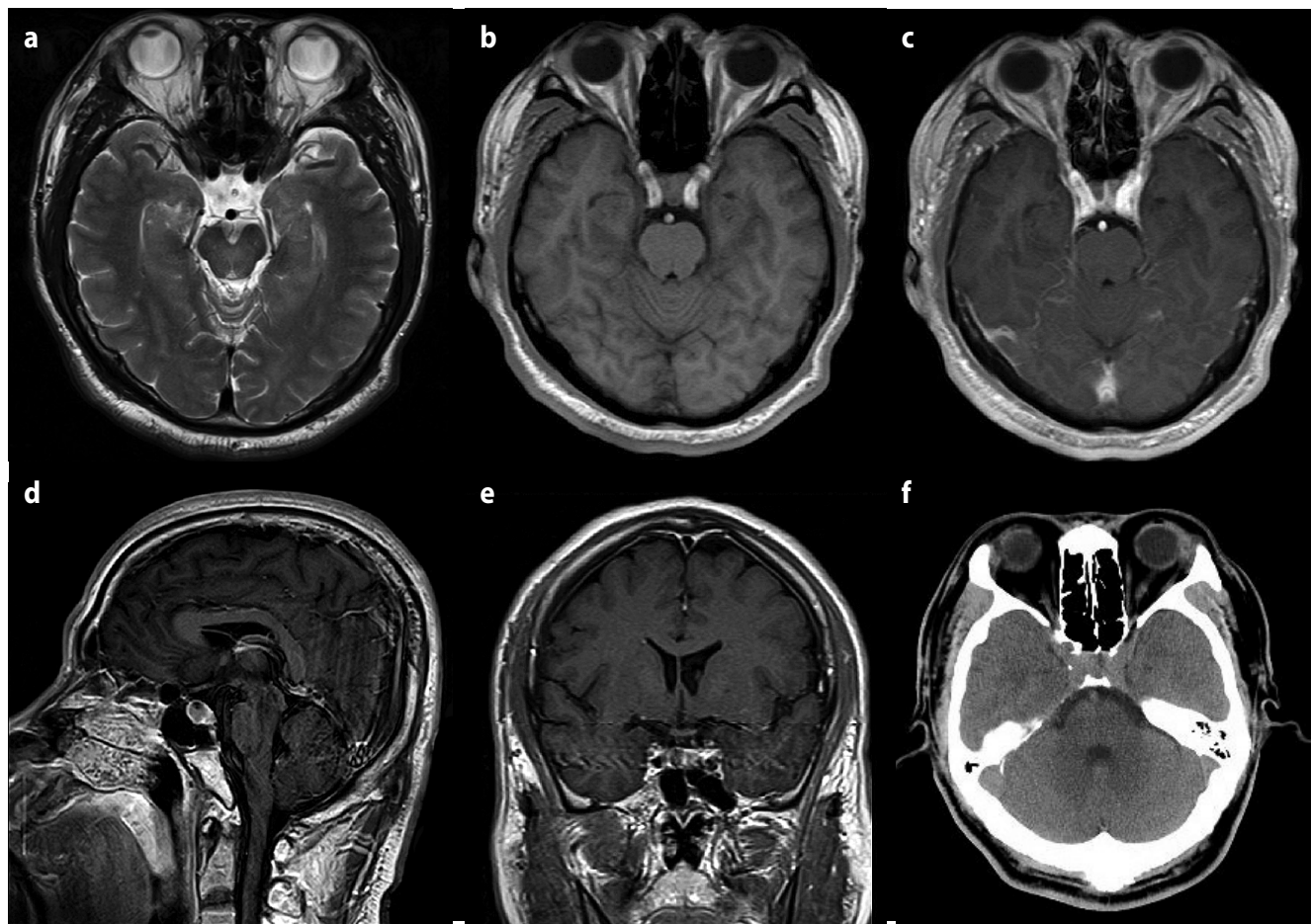
### *Clinical examination*

The vital signs were stable, with the blood pressure of 157/97 mmHg. Physical examination of the central nervous system showed bilateral visual impairment and normal visual field. Baseline assessment of pituitary hormones revealed increased serum growth-hormone (GH) level. The GH nadir after oral glucose dose was 5.46 ng/ml. Other pituitary hormones and the serum adrenocorticotrophic hormone (ACTH), calcitonin, and aldosterone levels were normal.

The patient refused to take related gene analysis for personal reason.

### *Imaging studies*

Cranial MRI showed an intra-sellar mass measuring 13×15 mm, iso- to hypo-intense T1 weighted and hyper-intense T2 weighted, with clear margin. There was slight sellar space enlargement and sellar base depression. The mass was slightly high density on CT scan. The MRA was negative (Figure 1).



**Fig. 1.** Pre-operative MRI images (a transverse, T2-weighted; b T1-weighted; c enhanced-T1 weighted; d sagittal, enhanced-T1 weighted; e coronal, enhanced-T1 weighted) and CT scan (f) of the patient. The lesion locates in the intra-sellar region, is iso- to hypointense T1-weighted and iso- to hyperintense T2-weighted signal, with sharp margin and heterogeneous slightly enhancement. It is slightly hyperintense on CT scan. The pituitary stalk is shifted left.

The ultrasonography and CT scan revealed bilateral thyroid nodules, either cystic or mixed cystic/solid, hepatic cysts of the right lobe, right renal cysts, and left nephrolithiasis. The supra-renal glands were normal (Figure 2).

#### Surgery, pathologic result, and postoperative course

The patient underwent gross total tumor resection of the pituitary mass through endoscopic trans-sphenoidal route on July 24<sup>th</sup>, 2013. The tumor was solid, soft, pale yellow, medium blood-supplied, and was adhesive to normal pituitary gland and the sellar diaphragm. The remote pituitary apoplexy was observed. After tumor resection the sellar diaphragm appeared to be quite thin and was reinforced by self lipid tissue.

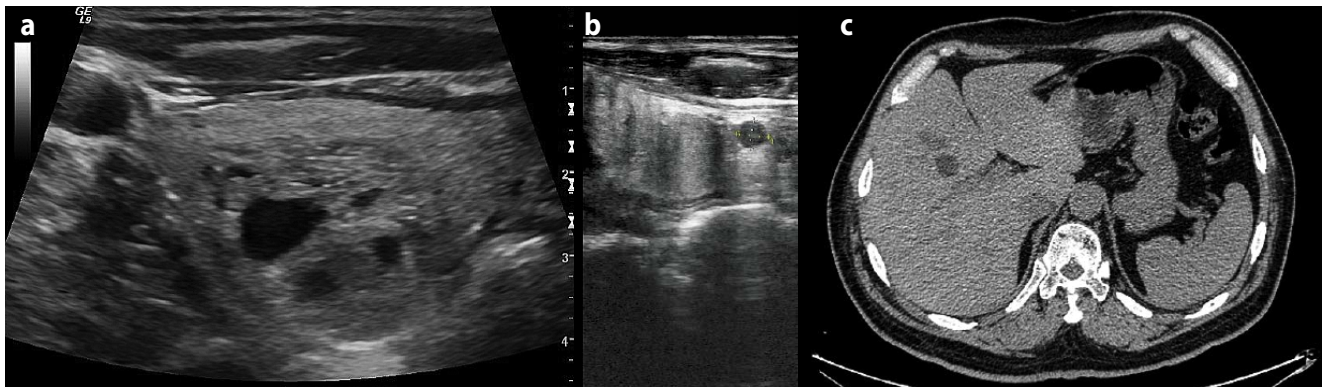
The pathologic examination reported GH-staining pituitary adenoma, with GH+, TSH sparse +, PRL/LH/FSH/ACTH-, CK+, Chromogranin A+, and SYN±.

The patient was discharged seven days after the operation, with balanced daily income versus outcome, normal serum electrolytes levels, and normal hepatic and adrenal functions. The GH nadir reduced to 0.339–0.5 ng/ml. The post-operative MRI was negative. The visual impairment was similar to that of the pre-operative state. The patient recovered well after a follow-up period of eight months (Figures 3 and 4).

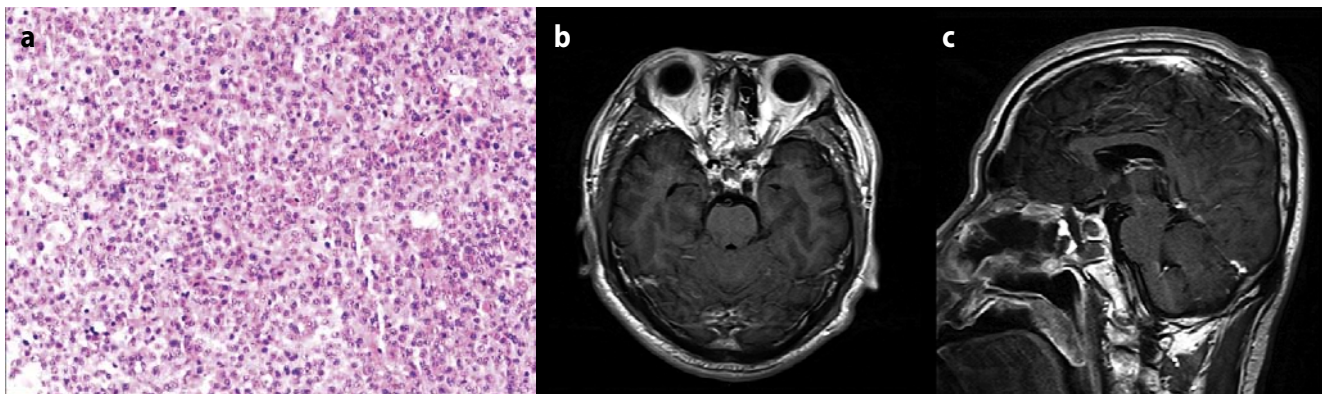
## DISCUSSION

There were several case reports about concomitant GH-staining pituitary adenoma and other cystic changes, including pituitary cyst (Saeki *et al.* 2000), arachnoid cyst (Unalp *et al.* 2007), parathyroid cyst (Kinoshita *et al.* 1986), etc. but with no further investigation. Our patient has concomitant GH-staining pituitary adenoma and renal cyst, as well as hepatic cyst. It is an interesting phenomenon that the concomitant disorders of this patient prone to be “cystic”. Besides the renal and hepatic cysts, the thyroid nodules are mostly cystic. Actually this is not the first time we notice a GH-staining pituitary adenoma patient having concomitant cystic changes, either in the central nervous system or in other system. Is there any relationship of these multiple changes rather than just a coincidence?

GH is produced by the somatotroph cells of the pituitary gland in a pulsatile and diurnal fashion. Its secretion in normal person can also be stimulated by exercise and sleep. In GH-staining pituitary adenoma excessive GH is secreted. Circulating GH stimulates hepatic secretion of IGF-I. IGF-I is a marker of integrated GH secretion. Although serum IGF-I levels are subject to circadian changes to a much lesser degree than GH levels, in general there is a linear relation-

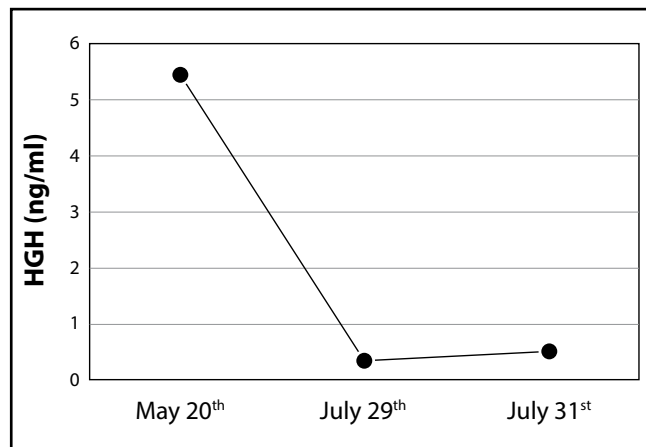


**Fig. 2.** Images of extra-CNS performances. Ultrasonography of bilateral thyroid glands (a, b) showed bilateral cystic or mixed cystic/solid nodules. Abdominal CT scan (c) revealed hepatic cysts of the right lobule. (Further examination showed right renal cysts as well.)



**Fig. 3.** Pathology slice (hematoxylin-eosin stain, original magnification  $\times 100$ ) of the pituitary mass (a). There are large cells with eosinophilic, granular cytoplasm, and a central nucleus with prominent nucleoli. The immunostaining for GH is positive. The diagnosis is GH-staining pituitary adenoma. Post-operative MRI (b, c) showed total resection of the intra-sellar tumor.





**Fig. 4.** The changes of serum GH level (GH nadir after oral glucose dose) of the peri-operative period. The operation was on July 24<sup>th</sup>, 2013. The GH was 5.46 ng/ml before the operation. Five days after the operation the value reduced to 0.339 ng/ml and remained below 1 ng/ml thereafter.

ship between serum GH and IGF-I levels, especially with serum GH levels less than 20 ng/ml. IGF-I levels plateau at serum GH concentrations above 40 ng/ml. A random serum IGF-I level has become a useful value for diagnosis of GH-staining pituitary adenoma and for monitoring therapeutic result.

In normal kidney IGF-I localizes in mesangial cells and principal cells of the collecting duct (Nakamura *et al.* 1992). IGF-I is a multifunctional hormone that has pleiotropic effects on cellular proliferation, apoptosis, hypertrophy, senescence and differentiation. In the physiologic situation IGF-I stimulates gluconeogenesis in renal tubules, and is mitogenic for mesangial cells. The administration of IGF-I can increase glomerular filtration rate (Yoshioka *et al.* 1992).

Multiple lines of evidence suggest that IGF-I plays a role in mediation tubular cell proliferation in the cystic kidney in the polycystic kidney disease (PKD). Early in 1993 Nakamura *et al.* (1992) report increased expression of IGF-I mRNA together with mRNA of other growth factor genes may contribute to the progression of cystic lesions in kidney of murine polycystic kidney disease (DBA/2FG-*pcy* mice). The source of IGF-I mRNA in the kidney of DBA/2FG-*pcy* mouse may be mesangial cells or infiltrated monocyte/macrophages. Song *et al.* (2009) perform global gene profiling on cysts to elucidate the molecular pathways that modulate renal cyst growth in ADPKD. Their data suggest that up-regulation of Wnt/beta-catenin, pleiotropic growth factor/receptor tyrosine kinase, including GF/IGF-IR, G-protein-coupled receptor signaling is associated with renal cystic growth in ADPKD.

Parker *et al.* (2007) find that IGF-I induces PKD cell proliferation, while no effect has been observed in normal tubular cells, indicating that PKD cells are more sensitive to IGF-I compared with normal cells. Haploinsufficiency of polycystin-1 (PC1) deficiency may

lower the threshold for activation of the extracellular signal-regulated protein kinase (ERK) and phosphatidylinositol-3 (PI3)-kinase/Akt pathways by IGF-I via the Ras/Raf cascade. Inhibition of Ras or Raf abolishes the stimulated cell proliferation.

During the research of the mechanism of Thiazolidinediones (TZDs) suppressing polycystic kidney diseases (PKD) development, Liu C *et al.* (Liu *et al.* 2013) find that IGF-I expression increases with the progression of cystic lesions in ADPKD and murine PKD, and cyst-lining epithelial cells are found to be more sensitive to IGF-I compared with normal cells. IGF-I increases the growth of cyst-lining epithelial cells by 15–20% in a dose-dependent manner, while no effect on the proliferation of normal renal cortical tubular epithelial cells (RCTEC) is observed. p70S6 kinase (p70S6K) is an important downstream signaling molecule of IGF-I and is implicated in the regulation of cell cycle progression and cell proliferation. The activity of p70S6K, which is determined by the phosphorylation of p70S6K, is enhanced in the kidneys of ADPKD patients and is important in the pathogenesis of ADPKD. IGF-I induces the phosphorylation of p70S6K in PKD cells. Rosiglitazone, a TZD, is found to inhibit the IGF-I-induced growth of cyst-lining epithelial cells. Moreover, rosiglitazone at the same concentration is shown to inhibit the IGF-I-induced activation of p70S6K. It is speculated that rosiglitazone may inhibit the proliferation-promoting activity of IGF-I in cyst-lining epithelial cells, partially due to the inhibition of IGF-I-induced activation of p70S6K.

On the other hand, the abnormal cells surrounding the cyst may aggravate the imbalance of growth factor pathways, as are discovered in several diseases with cystic changes. Among them the IGF-1 and IGFBP are referred in the pathogenesis of ovarian cyst (Ortega *et al.* 2007; Dyck *et al.* 2001; Kanety *et al.* 1996), breast cyst (Ness *et al.* 1993; Wang *et al.* 1989), cystic craniopharyngioma (Zumkeller *et al.* 1996; 1991), cystic astrocytoma (Zumkeller *et al.* 1993), and even aneurysmal bone cyst (Leithner *et al.* 2001).

There is a bold hypothesis that with genetic predisposition the abnormal hormone secretion of the GH-staining pituitary adenoma may arouse sequential changes of multiple systems through some IGF-I involved pathways. Various signaling pathways may be involved. Further investigation including molecular analysis is critical.

## ACKNOWLEDGEMENTS

This work was supported by the otorhinolaryngology group of the Neurosurgery department, the Radioimaging department, and the Ultrasonography department of Beijing Tiantan Hospital.

**Consent**

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

**Conflict of interest**

The authors have not declared any conflicts of interest. No potential conflict of interest relevant to this article was reported.

## REFERENCES

- 1 Dyck MK, Parlow AF, Sénéchal JF, Sirard MA, Pothier F 2001. Ovarian expression of human insulin-like growth factor-I in transgenic mice results in cyst formation. *Mol Reprod Dev.* **59**(2): 178–185.
- 2 Kanety H, Kattan M, Goldberg I, et al. 1996. Increased insulin-like growth factor binding protein-2 (IGFBP-2) gene expression and protein production lead to high IGFBP-2 content in malignant ovarian cyst fluid. *Br J Cancer.* **73**(9): 1069–1073.
- 3 Kinoshita Y, Nonaka H, Yamaguchi H, et al. 1986. A case of multiple endocrine neoplasia type 1 with growth hormone and prolactin secreting pituitary adenoma, functioning large parathyroid cyst, and Zollinger-Ellison syndrome. *Nihon Naika Gakkai Zasshi.* **75**(4): 512–521.
- 4 Leithner A, Lang S, Windhager R, et al. 2001. Expression of insulin-like growth factor-I (IGF-I) in aneurysmal bone cyst. *Mod Pathol.* **14**(11): 1100–1104.
- 5 Liu C, Zhang Y, Yuan L, Fu L, Mei C 2013. Rosiglitazone inhibits insulin-like growth factor-1-induced polycystic kidney disease cell growth and p70S6 kinase activation. *Mol Med Rep.* **8**(3): 861–864.
- 6 Nakamura T, Ebihara I, Nagaoka I, et al. 1993. Growth factor gene expression in kidney of murine polycystic kidney disease. *J Am Soc Nephrol.* **3**(7): 1378–1386.
- 7 Ness JC, Sedghinasab M, Moe RE, Tapper D 1993. Identification of multiple proliferative growth factors in breast cyst fluid. *Am J Surg.* **166**(3): 237–243.
- 8 Ortega HH, Salvetti NR, Amable P, et al. 2007. Intraovarian localization of growth factors in induced cystic ovaries in rats. *Anat Histol Embryol.* **36**(2): 94–102.
- 9 Parker E, Newby LJ, Sharpe CC, et al. 2007. Hyperproliferation of PKD1 cystic cells is induced by insulin-like growth factor-1 activation of the Ras/Raf signaling system. *Kidney Int.* **72**(2): 157–165.
- 10 Saeki N, Sunada S, Tokunaga H, et al. 2000. Growth hormone secreting adenoma with unusual extension: coexisting pituitary cyst and its clinical significance. *J Clin Neurosci.* **7**(2): 146–147.
- 11 Song X, Di Giovanni V, He N, et al. 2009. Systems biology of autosomal dominant polycystic kidney disease (ADPKD): computational identification of gene expression pathways and integrated regulatory networks. *Hum Mol Genet.* **18**(13): 2328–2343.
- 12 Unalp A, Dizdärer C, Ozturk A, Kalkan S, Asilsoy S 2007. Arachnoid cyst with growth hormone deficiency. *Indian J Pediatr.* **74**(3): 294–296.
- 13 Wang DY, Hamed H, Mockridge CI, Fentiman IS 1989. Radioimmunoassayable insulin-like growth factor-I in human breast cyst fluid. *Eur J Cancer Clin Oncol.* **25**(5): 867–872.
- 14 Yoshioka K, Murakami K, Maki S 1992. Growth factors: a regulator of renal function. *Nihon Rinsh.* **50**(12): 2931–2936.
- 15 Zumkeller W, Sääf M, Rähn T, Hall K 1991. Demonstration of insulin-like growth factors I, II and heterogeneous insulin-like growth factor binding proteins in the cyst fluid of patients with craniopharyngioma. *Neuroendocrinology.* **54**(3): 196–201.
- 16 Zumkeller W, Sääf M, Rähn T 1993. Insulin-like growth factor (IGF)-I, -II and IGF-binding proteins in the cyst fluid of a patient with astrocytoma. *Childs Nerv Syst.* **9**(2): 100–103.
- 17 Zumkeller W, Sääf M, Rähn T 1996. Insulin-like growth factors and IGF binding proteins in cyst fluid from patients with craniopharyngioma prior to intracavitary irradiation with Yttrium and thereafter. *Clin Mol Pathol.* **49**(1): M51–56.