Scientific Research Publishing

Open Journal of Endocrine and Metabolic Diseases, 2024, 14, 179-189
https://www.scirp.org/journal/ojemd
ISSN Online: 2165-7432
ISSN Print: 2165-7424

Bisecreting Pituitary Neuroendocrine Tumors: About 9 Cases at the Abass Ndao Hospital Center in Dakar

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How to cite this paper: Diedhiou, D., Thioye, E.M.M., Ndiaye, M., Sow, D., Ndour, M.A., Ndiaye, F.M., Halim, C.M.A., Dieng, M., Diouf, O.B.K., Diembou, M., Djiba, B., Sarr, A. and Mbaye, M.N. (2024) Bisecreting Pituitary Neuroendocrine Tumors: About 9 Cases at the Abass Ndao Hospital Center in Dakar. *Open Journal of Endocrine and Metabolic Diseases*, **14**, 179-189.
https://doi.org/10.4236/ojemd.2024.1410019

Received: September 8, 2024
Accepted: October 28, 2024
Published: October 31, 2024

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Abstract

Introduction: Pituitary neuroendocrine tumor (PitNET) may present multisecreting forms. Identifying its forms helps to guide management. This management is a real challenge, given the limited resources in our regions. In view of advances in the management of these multisecreting pituitary neuroendocrine tumors and the lack of published data in Africa, and in Senegal particularly, this survey was carried out with the aim of describing the epidemiological, clinical and therapeutic aspects of multisecreting PitNETs. **Patients and Method**: It was a multicenter, retrospective, descriptive and analytical study carried out on files collected from 1st January 2008 to 31 December 2022 in the neurosurgery departments of the Fann and Principal hospitals in Dakar and the endocrinology department of the Abass Ndao hospital in Dakar. **Results**: Of the 242 patients treated for PitNET, 09 presented (the mean age of our patients was 41.7 ± 11 years) with bihormonal PitNET, *i.e.* a proportion of 3.71%. Two types of association were found: 08 tumors with GH (Growth Hormon) + PRL (prolactin) secretion and 01 PitNET with ACTH (Adreno Corticotropic Homon) + prolactin secretion. Clinically, gonadotropic insufficiency was found in all patients (100%). Dysmorphic syndrome was found in 6 patients (66.7%) and tumor syndrome in 7 patients (77.8%). Ophthalmological evaluation revealed a decrease in visual acuity in 66.6% of patients. All had macroadenomas, with extension noted in 02 patients. All patients underwent transsphenoidal surgery with complications such as transient diabetes insipidus (3 patients, 33.3%), followed by cerebrospinal fluid leaks (1 patient, 11.1%). Remission was noted in all 5 patients tested. A comparison between the different secretory forms did not reveal any significant difference in the frequency of postoperative complications. **Conclusion**: Despite the lack of

immunohistochemistry, two types of association were found: ACTH-PRL and GH-PRL. All were macroadenomas, the majority with an associated tumor syndrome. The latter was significantly less frequent in bisecreting PitNETs compared with monosecreting and non-functional forms. However, there was no significant difference in the occurrence of post-operative complications between the three secretory forms of PitNETs.

Keywords

Pituitary Adenoma, Pituitary Neuroendocrine Tumor, Multisecreting Adenoma, Cushing's Disease, Acromegaly

1. Introduction

The term pituitary adenoma is increasingly being replaced by the term pituitary neuroendocrine tumor (PitNET) [1]. Multi-secreting forms are tumors capable of producing two or more different hormones [2]-[4]. Two theories are currently being put forward [5]. The "multiple hit" theory favors the proliferation of different mutated cell types. The other is the transdifferentiation theory, in which cells already present in a pituitary adenoma may differentiate into another cell type. The prevalence of multisecreting PitNETs has been reported to range from 0.01% to 9% and 0.37% to 2.6% respectively in autopsy studies [6] and surgical studies [7].

Functional multisecreting PitNETs are manifested by clinical signs related to hypersecretion [8]. The two most common forms are acromegaly [8] and Cushing's disease [5]. Asymptomatic neuroendocrine tumors (PitNETs) known as non-functional tumors have also been described. They are immunohistochemically positive for one or more hormones or transcription factors. These non-functional PitNETs represent 15% to 30% [9] of all PitNETs and are mainly represented by gonadotrophic PitNETs, *i.e.* 70% to 75% [10] [11].

The sensitivity of magnetic resonance imaging is 85% for the detection of microadenomas [12]. The challenge is then to detect contiguous tumors that appear to be unique, or a macroadenoma dwarfing a microadenoma. To refine the result, 3T MRI or MRI coupled with positron emission tomography (PET-MET/3T MRI) is still decisive [13].

Treatment will depend on the symptoms associated with hypersecreting hormones and any mass effects. When surgery is indicated, transphenoidal resection is the most common way. However, corticotropic and somatotropic PitNETs are more prone to recurrence [14]. The best indicator is Ki67, which correlates with recurrence [15]. In view of these advances in the management of these multisecreting pituitary neuroendocrine tumors and the lack of published data in Africa, and in Senegal particularly, a survey was carried out with the aim of describing the epidemiological, clinical and therapeutic aspects of multisecreting PitNETs.

2. Patients and Method

This was a multicenter, retrospective, descriptive and analytical study. The survey was conducted on files collected from 1st January 2008 to 31 December 2022 (*i.e.* over a period of 14 years) in the neurosurgery departments of the Fann and Principal hospitals in Dakar and the endocrinology department of the Abass Ndao hospital in Dakar. The diagnosis of pituitary neuroendocrine tumor was based on clinical, hormonal, and morphological criteria. Immunohistochemistry, the reference technique, is not yet available in Senegal. Any incomplete file was excluded from the study. The data required for the study were:

- Epidemiological data: age, sex, terrain and antecedents, consultation time.
- Clinical data: hypersecretory syndromes (Cushing, dysmorphic, thyrotropic, amenorrhoea-galactorrhoea), pituitary tumor syndrome (headache and visual acuity or visual field disorders). The visual field was assessed using the Goldmann.
- Pituitary hormone data: baseline pituitary work-up including prolactinemia (norms: 3.46 - 19.4 ng/ml), ACTH (morning norms 5 - 60 ng/L; evening norms: <30 ng/L), midnight cortisolemia (norms: 37 - 194 ng/ml), 24-hour urinary free cortisol (norms: 28 - 138 nmol/24h), plasma GH and IGF1 (age-dependent norms), FSH/LH, testosterone (male norms: 8.7 - 34.7 nmol/l), estrogen (follicular phase: 21 - 251 pg/ml, ovulatory peak: 38 - 649 pg/ml, luteal phase: 21 - 312 pg/ml, menopause: <28 pg/ml), TSHus (norms: 0.35 - 4.94 µIU/ml) and free T4 (norms: 9 - 19 pmol/l). The dynamic tests consisted of a minute braking test with dexamethasone and an oral glucose tolerance test (OGTT) with GH.
- Morphological data had enabled the PitNET to be identified using magnetic resonance imaging.
- Management: this involved medical treatment and its modalities (frenative or substitutive therapy). Surgery was performed by transphenoidal way, guided by endoscopy in the neurosurgery units of Senegal.
- Evolution was assessed based on the secretory syndrome, the pituitary tumor syndrome, the size of the tumor on the follow-up MRI, and the search for surgical complications: breach (leakage of cerebrospinal fluid), meningitis, transient diabetes insipidus, death, etc.

The data collected was entered into Excel 2016. The analysis was carried out using Excel 2016 and R version 4.1.3. For the descriptive analysis, the qualitative variables were described using frequency tables and bar charts. Quantitative variables were described by their position (mean, median) and dispersion (standard deviation, extremes) parameters. For bivariate analysis, the Student's t-test was used for comparisons of means, and the Chi-square or Fisher's t-test for comparisons of proportions. A link or difference is noted if the p is less than 0.05.

3. Results

3.1. Socio-Demographic Data

Of the 242 patients treated for PitNET, 09 were presented with bihormonal

PitNET, *i.e.* a proportion of 3.71%. This proportion was 7.76% of the 116 cases of secretory PitNET. Two types of association were found: 08 tumors with GH + prolactin secretion and 01 PitNET with ACTH + prolactin secretion. The mean age of our patients was 41.7 ± 11 years with extremes of 25 and 59 years. The median age was 45 years. Our study included 5 (55.6%) males and 4 (44.4%) females. The average age of the women was over 45, and most of the men were under 45 (80%). The associated pathologies were diabetes mellitus and high blood pressure in 22.2% each.

3.2. Clinical Data

The mean time to consultation was 24.2 ± 12 months, with extremes of 6 and 36 months. The median was 24 months. The consultation time was longer in women, with an average of 25.5 months, whereas in men the average was 23.2 months. Clinically, gonadotropic insufficiency was found in all patients (100%). Dysmorphic syndrome was found in 6 patients (66.7%) and tumor syndrome in 7 patients (77.8%). Ophthalmological evaluation revealed a decrease in visual acuity in 66.6% of patients and left-sided blindness in one patient. We found no cases of quadranopsia or hemianopsia. Table 1 summarizes the epidemiological and clinical characteristics of patients on admission.

Table 1. Initial clinical characteristics of patients with multisecreting tumors.

Parameters	Results
Epidemiological data	
Population size	9 (100%)
Mean age	41.7 ± 11 years
Average consultation delay	24.2 ± 12 months
Sex ratio	1.25
Diabetes mellitus	22.2%
Hypertension	22.2%
Clinical data	
Tumor syndrome	7 (77.8%)
Amenorrhea-galactorrhea syndrome	9 (100%)
Dysmorphic syndrome	6 (66.7%)
Cushing's syndrome	1 (11.1%)
Diplopia	1 (11.1%)
Reduced visual acuity	6 (66.6%)
Left-sided blindness	1 (11.1%)

3.3. Biological Data

Biological analysis revealed hyperprolactinaemia > 500 ng/ml in all patients, unrelated to pituitary disconnection. This hyperprolactinemia was associated with

ACTH-dependent hypercortisolism in one patient and with elevated GH and IGF1 (Insulin Growth Factor) levels in 8 patients (88.9%).

3.4. Morphological Data

Morphological exploration was performed using magnetic resonance imaging (MRI) in all patients. The results were in favor of pituitary macroadenoma in all patients, with invasion noted in 02 patients. Table 2 summarizes the various paraclinical characteristics of patients on admission.

Table 2. Initial paraclinical characteristics of patients.

Parameters	Results
Hormone data	**9 (100%)**
Mixed secretion (ACTH + Prolactin)	1 (11.1%)
Mixed secretion (GH + Prolactin)	8 (88.9%)
Prolactin levels (average and extremes) (n = 9)	2438 ng/ml (510 - 3843)
GH levels (average and extremes) (n = 8)	112 ng/ml (34 - 150)
IGF1 levels (average and extremes) (n = 8)	618.5 ng/ml (579 - 730)
ACTH levels (n = 1)	97.3 ng/l
Morphological data (MRI)	**9 (100%)**
Macroadenoma	9 (100%)
Tumor invasion	2(22.2%)

3.5. Therapeutic and Evolutionary Data

Of the 9 patients identified, 8 had received treatment with cabergoline (Dostinex®) 0.5 mg/week, *i.e.* a proportion of 88.9%. These were patients with mixed hypersecretion of prolactinemia and GH. The only patient with hyperprolactinaemia associated with Cushing's disease did not receive drug treatment for the hormonal disorder.

Transsphenoidal surgery was performed in all patients. Complications were noted after surgery. These were mainly transient diabetes insipidus, followed by cerebrospinal fluid leaks. We noted one case of death following a post-operative haematoma in a patient with mixed secretion of GH and prolactin. Post-operatively, hormonal monitoring in 5 patients showed remission. Imaging revealed incomplete excision in 2 of the 5 patients who were able to undergo MRI. Ophthalmological symptoms improved after surgery in 7 patients. Table 3 summarizes the evolutionary data after surgical management.

3.6. Analytical Study (Table 4)

We compared 3 different types of PitNETs in their epidemiological, clinical, morphological and surgical aspects. Of all 242 patients followed up for PitNET, we had more non-functioning PitNETs (52.1%), (compared with 44.2% of monosecreting

Table 3. Post-operative evolutionary data.

Evolution data	Population size (frequency)
Post-operative complications	
Transient diabetes insipidus (n = 9)	3 (33.3%)
Cerebrospinal fluid (CSF) leak (n = 9)	1 (11.1%)
Transient diabetes insipidus + CSF leakage (n = 9)	3 (33.3%)
Deaths (n = 9)	1 (11.1%)
Post-operative paraclinical evaluation	
Biological remission (n = 5)	5 (100%)
Complete excision (n = 5)	3 (60%)
Improved visual condition (n = 8)	7 (87.5%)

Table 4. Comparative Table of the different functional forms of PitNETs.

Parameters	Bisecreting PitNETs	Monosecreting PitNETs	Nonfunctional PitNETs	P-value
Epidemiological data				
Population size (n = 242)	9	107	126	
Prevalence	3.7 %	44.2 %	52.1 %	
Female	4 (44.4%)	79 (73.8%)	44 (34.9%)	<0.001
Average age (years)	41.8 ± 11	36.3 ± 11	48.2 ± 14	<0.001
Clinical data				
Average consultation time (months)	24.2 ± 12	27.0 ± 29	14.0 ± 17	<0.001
Tumor syndrome	7 (77.8%)	61 (57.0%)	108 (85.7%)	<0.001
Gonadal syndrome	9 (100%)	81 (75.7%)	13 (10.3%)	<0.001
Dysmorphic syndrome	6 (66.7%)	13 (12.1%)	0 (0.00%)	<0.001
Cushing's syndrome	1 (11.1%)	14 (13.1%)	0 (0.00%)	<0.001
Morphological data				
Macroadenoma	9 (100%)	63 (58.9%)	125 (99.2%)	<0.001
Tumor invasion	1 (11.1%)	13 (12.1%)	8 (6.35%)	<0.001
Surgical and evolution data				
Pituitary surgery	9 (100%)	81 (75.7%)	83 (67.5%)	
Cerebrospinal fluid leak	4 (50.0%)	4 (6.56%)	10 (21.3%)	0.003
Transient diabetes insipidus	6 (75.0%)	46 (75.4%)	30 (63.8%)	0.427
Deaths	1 (12.5%)	9 (14.8%)	8 (17.0%)	0.919
Meningitis	0 (0.00%)	0 (0.00%)	1 (2.13%)	0.474
Remission	1 (20.0%)	13 (15.9%)	10 (13.0%)	0.646

PitNETs and 3.7% of bisecreting PitNETs). Unfortunately, as mentioned above, we did not have immunohistochemistry to better type these PitNETs. We found more women and a younger population in the group of monosecreting PitNETs, with a mean age of 36.3 years. Consultation was earlier in non-functioning PitNETs, with an average delay of 14 months. Among the reasons for consultation, tumor syndrome was significantly more frequent in non-functioning PitNETs than in monosecreting PitNETs. However, when the PitNET was secretive, hypogonadism syndrome was more frequent and was more common in bisecreting PitNETs (100%). Morphologically, there was a lower proportion of macroadenomas in monosecreting PitNETs, but they were significantly more invasive comparing to other types. We did not find any statistically significant difference concerning the morphological data other than a greater frequency of cerebrospinal fluid leak when the operated PitNETs was bisecreting. We also noted that whatever the type of PitNETs, diabetes insipidus was the most frequent complication.

4. Discussion

4.1. Epidemiological Data

In our PitNETs management database, we found a slightly higher proportion of bisecreting PitNETs than in previous studies. [16]. The prevalence was 0.37% in the series by Kontogeorgeos *et al.* [16] with a cohort of three thousand patients. In the study by Magri *et al.* [17] the prevalence was 2.6% in 117 patients operated on for pituitary neuroendocrine tumors. In our series, the prevalence was underestimated due to a lack of immunohistochemical evaluation. Autopsy studies have reported a much higher prevalence, up to 34%. [18]. While some studies have reported cases of triple secreting PitNETs [8] [16], this was not the case in our study. The lack of immunohistochemistry could explain this incomplete diagnostic. There was no clear gender trend [7] [19]-[21]. Our patients were in their forties with a mean age of 41.7 ± 11 years. In the literature, the mean age was 46.5 years in the series by Ogando-Rivas *et al.* [21] 45.7 years in the series by Ho *et al.* [19].

4.2. Clinical Data

Hypertension and diabetes mellitus were found in almost a quarter of cases. These two pathologies, which are cardiovascular risk factors, had not been investigated in many other studies [19] [21]. These were some of the circumstances of discovery in GH (acromegaly) and ACTH (Cushing's disease) secretions. Their secondary nature makes them curable pathologies, depending on how long they have existed. However, the evolution of these cardiovascular risk factors after management of the endocrine pathology was not evaluated in our study. In the literature, the most common endocrine syndromes, in multisecreting PitNETs, were acromegaly, followed by Cushing's syndrome [7] [19] [21]. In our study, the amenorrhoea-galactorrhoea syndrome was more prevalent. This could explain the earlier consultation in younger subjects due to sexual problems. In the study by von Schöning *et al.* [20], the authors found multisecreting PitNETs with no clinical

manifestations. Neurological signs were more common in our study. In the series by Ho *et al.* [19], neurological signs were present in 60% of patients. Among these neurological signs, ophthalmological signs such as visual field abnormalities and reduced visual acuity were the most frequent.

4.3. Morphological Data

We only had MRI available pre- and post-operatively. The other morphological means available for morphological exploration were PET-Methionine coupled to MRI intraoperatively and ultrasound intraoperatively in cases where localisation was difficult [7]. In the literature, discordance between imaging results and surgical findings has been reported. In most autopsy and operative studies, many bi-secreting PitNETs were microadenomas with mean sizes of less than 3 mm [5] [13]. We only had pituitary macroadenomas.

4.4. Therapeutic Data

Medical treatment mainly concerned the management of hyperprolactinaemia when associated [7] [8] [19] [21]. In addition to its inhibitory effect on pituitary hormone secretion, this combined treatment helps to reduce the volume of the PitNETs and therefore facilitates its removal. Dopaminergic agonists reduce tumor size by more than 50% in 80% - 90% of patients, and cabergoline is generally more effective and better tolerated than bromocriptine [22]. In acromegaly, in vivo evidence of the antiproliferative effects of somatostatin analogues has been demonstrated by a significantly lower Ki-67 labelling index in somatotrophic tumor tissue obtained from patients previously treated with octreotide [23]. In addition to this effect on the tumor itself, pre-surgical treatment helps to normalise GH levels, control glycaemia, hypertension and left ventricular hypertrophy. Cabergoline has a limited indication in acromegaly. However, these somatostatin analogues are not available in Senegal. In our study, there was no need for drug treatment of Cushing's disease. Surgery was chosen as first-line treatment [21]. This suggests the low intensity of clinical manifestations in cases with associated Cushing's disease. Surgery was performed via the transsphenoidal route, as in our study. In some cases, intraoperative imaging was necessary to clarify the location of the lesion and allow a more complete resection [5] [9].

4.5. Evolution Data

Numerous postoperative complications have been reported in previous studies [24]. Resection could be complete when the tumor could be located preoperatively and there was no invasion. Thanks to intraoperative exploration, resection rates could reach 96% [25]. In our study, despite the modest resources available, resection was complete in 60% of cases. We might hope to see an improvement in the success rate with the acquisition of a more advanced technical platform and greater awareness of the need for earlier management. Complications mainly resolved spontaneously, apart from one post-operative haematoma which resulted

in death.

Limitations of our study

Our study brought together the largest number of cases in the sub-region. This provides a more accurate picture of the management in our region and within our limited resources. In our study we were unable to distinguish between contiguous bisecreting PitNETs and those that were clearly distinct. Despite the difficulties of accessing certain complementary examinations, the minimum exploration required before and after the operation were performed. An effort still needs to be made to make care available to all. Other points for improvement related to:

- The absence of immunohistochemistry for the diagnosis of non-functional components and the demonstration of contiguous bisecreting PitNETs;
- Lack of evaluation of multiplication indices such as Ki-67 and the search for metastasis;
- The long-term follow-up was not included due to loss of follow-up in some patients.

5. Conclusion

The aim of this study was to describe the epidemiological, clinical and therapeutic aspects of multisecreting PitNETs. Despite the lack of immunohistochemistry, two types of association were found: ACTH-PRL and GH-PRL. All were macroadenomas, the majority with an associated tumor syndrome. The latter was significantly less frequent in bisecreting PitNETs compared with monosecreting and non-functional forms. However, there was no significant difference in the occurrence of post-operative complications between the 3 secretory forms of PitNETs.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Asa, S.L., Casar-Borota, O., Chanson, P., Delgrange, E., Earls, P., Ezzat, S., *et al.* (2017) From Pituitary Adenoma to Pituitary Neuroendocrine Tumor (PitNET): An International Pituitary Pathology Club Proposal. *Endocrine-Related Cancer*, **24**, C5-C8. https://doi.org/10.1530/erc-17-0004

[2] Scheithauer, B.W., Horvath, E., Kovacs, K., Laws, E.R., Randall, R.V. and Ryan, N. (1986) Plurihormonal Pituitary Adenomas. *Seminars in Diagnostic Pathology*, **3**, 69-82.

[3] Kameya, T. and Furuhata, S. (1991) Plurihormonal Adenomas. *Pathology—Research and Practice*, **187**, 574-576. https://doi.org/10.1016/s0344-0338(11)80147-0

[4] McComb, D.J., Bayley, T.A., Horvath, E., Kovacs, K. and Kourides, I.A. (1984) Monomorphous Plurihormonal Adenoma of the Human Pituitary. A Histologic, Immunocytologic and Ultrastructural Study. *Cancer*, **53**, 1538-1544. https://doi.org/10.1002/1097-0142(19840401)53:7<1538::aid-cncr2820530720>3.0.co;2-i

[5] Budan, R.M. and Georgescu, C.E. (2016) Multiple Pituitary Adenomas: A Systematic Review. *Frontiers in Endocrinology*, **7**, Article 1. https://doi.org/10.3389/fendo.2016.00001

[6] Kontogeorgos, G., Kovacs, K., Horvath, E. and Scheithauer, B.W. (1991) Multiple Adenomas of the Human Pituitary. *Journal of Neurosurgery*, **74**, 243-247. https://doi.org/10.3171/jns.1991.74.2.0243

[7] Zieliński, G., Sajjad, E.A., Maksymowicz, M., Pękul, M. and Koziarski, A. (2019) Double Pituitary Adenomas in a Large Surgical Series. *Pituitary*, **22**, 620-632. https://doi.org/10.1007/s11102-019-00996-2

[8] Mete, O., Alshaikh, O.M., Cintosun, A., Ezzat, S. and Asa, S.L. (2018) Synchronous Multiple Pituitary Neuroendocrine Tumors of Different Cell Lineages. *Endocrine Pathology*, **29**, 332-338. https://doi.org/10.1007/s12022-018-9545-4

[9] Raappana, A., Koivukangas, J., Ebeling, T. and Pirilä, T. (2010) Incidence of Pituitary Adenomas in Northern Finland in 1992–2007. *The Journal of Clinical Endocrinology & Metabolism*, **95**, 4268-4275. https://doi.org/10.1210/jc.2010-0537

[10] Kovacs, K., Horvath, E., Van loon, G.R., Rewcastle, N.B., Ezrin, C. and Rosenbloom, A.A. (1978) Pituitary Adenomas Associated with Elevated Blood Follicle-Stimulating Hormone Levels: A Histologic, Immunocytologic, and Electron Microscopic Study of Two Cases. *Fertility and Sterility*, **29**, 622-628. https://doi.org/10.1016/s0015-0282(16)43333-9

[11] Nishioka, H., Inoshita, N., Mete, O., Asa, S.L., Hayashi, K., Takeshita, A., *et al.* (2015) The Complementary Role of Transcription Factors in the Accurate Diagnosis of Clinically Nonfunctioning Pituitary Adenomas. *Endocrine Pathology*, **26**, 349-355. https://doi.org/10.1007/s12022-015-9398-z

[12] Patronas, N., Bulakbasi, N., Stratakis, C.A., Lafferty, A., Oldfield, E.H., Doppman, J., *et al.* (2003) Spoiled Gradient Recalled Acquisition in the Steady State Technique Is Superior to Conventional Postcontrast Spin Echo Technique for Magnetic Resonance Imaging Detection of Adrenocorticotropin-Secreting Pituitary Tumors. *The Journal of Clinical Endocrinology & Metabolism*, **88**, 1565-1569. https://doi.org/10.1210/jc.2002-021438

[13] Ikeda, H. (2013) Demonstration of Improved Surgical Outcome in Patients with Both ACTH and GH Secreting Adenomas Diagnosed by a New Sensitive Method of MET-PET Fusion 3T-MRI.

[14] Langlois, F., Lim, D.S.T., Varlamov, E., Yedinak, C.G., Cetas, J.S., McCartney, S., *et al.* (2017) Clinical Profile of Silent Growth Hormone Pituitary Adenomas; Higher Recurrence Rate Compared to Silent Gonadotroph Pituitary Tumors, a Large Single Center Experience. *Endocrine*, **58**, 528-534. https://doi.org/10.1007/s12020-017-1447-6

[15] Petry, C., Poli, J.H.Z., De Azevedo Dossin, I., *et al.* (2019) Evaluation of the Potential of the Ki67 Index to Predict Tumor Evolution in Patients with Pituitary Adenoma. *International Journal of Clinical and Experimental Pathology*, **12**, 320-326.

[16] Kontogeorgos, G., Scheithauer, B.W., Horvath, E., Kovacs, K., Lloyd, R.V., Smyth, H.S., *et al.* (1992) Double Adenomas of the Pituitary. *Neurosurgery*, **31**, 840-849. https://doi.org/10.1097/00006123-199211000-00003

[17] Magri, F., Villa, C., Locatelli, D., Scagnelli, P., Lagonigro, M.S., Morbini, P., *et al.* (2010) Prevalence of Double Pituitary Adenomas in a Surgical Series: Clinical, Histological and Genetic Features. *Journal of Endocrinological Investigation*, **33**, 325-331. https://doi.org/10.1007/bf03346594

[18] Burrow, G.N., Wortzman, G., Rewcastle, N.B., Holgate, R.C. and Kovacs, K. (1981) Microadenomas of the Pituitary and Abnormal Sellar Tomograms in an Unselected Autopsy Series. *New England Journal of Medicine*, **304**, 156-158. https://doi.org/10.1056/nejm198101153040306

[19] Ho, D.M., Hsu, C., Ting, L. and Chiang, H. (2001) Plurihormonal Pituitary Adenomas: Immunostaining of All Pituitary Hormones Is Mandatory for Correct Classification. *Histopathology*, **39**, 310-319. https://doi.org/10.1046/j.1365-2559.2001.01204.x

[20] Schöning, J.v., Flitsch, J., Lüdecke, D.K., Fahlbusch, R., Buchfelder, M., Buslei, R., *et al.* (2022) Multiple Tumorous Lesions of the Pituitary Gland. *Hormones*, **21**, 653-663. https://doi.org/10.1007/s42000-022-00392-9

[21] Ogando-Rivas, E., Alalade, A.F., Boatey, J. and Schwartz, T.H. (2017) Double Pituitary Adenomas Are Most Commonly Associated with GH and Acth-Secreting Tumors: Systematic Review of the Literature. *Pituitary*, **20**, 702-708. https://doi.org/10.1007/s11102-017-0826-6

[22] Melmed, S., Casanueva, F.F., Hoffman, A.R., Kleinberg, D.L., Montori, V.M., Schlechte, J.A., *et al.* (2011) Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, **96**, 273-288. https://doi.org/10.1210/jc.2010-1692

[23] Selek, A., Cetinarslan, B., Canturk, Z., Tarkun, I., Hanazay, Y., Vural, C., *et al.* (2019) The Effect of Somatostatin Analogues on Ki-67 Levels in GH-Secreting Adenomas. *Growth Hormone & IGF Research*, **45**, 1-5. https://doi.org/10.1016/j.ghir.2019.01.001

[24] Kim, K., Yamada, S., Usui, M. and Sano, T. (2004) Preoperative Identification of Clearly Separated Double Pituitary Adenomas. *Clinical Endocrinology*, **61**, 26-30. https://doi.org/10.1111/j.1365-2265.2004.02055.x

[25] Vitaz, T.W., Inkabi, K.E. and Carrubba, C.J. (2011) Intraoperative MRI for Transphenoidal Procedures: Short-Term Outcome for 100 Consecutive Cases. *Clinical Neurology and Neurosurgery*, **113**, 731-735. https://doi.org/10.1016/j.clineuro.2011.07.025