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PITUITARY ADENOMAS IN ELDERLY PATIENTS

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Abstract Clinical presentation, treatment and its results were evaluated during long-term follow-up of 37 patients older than 65 years with pituitary adenomas. Causes of death were also evaluated. It was a retrospective and cross-sectional study. Prevalence of incidentalomas was 43% (16), macroadenomas 70.3% (26) and giant adenomas 16.2% (6). The most frequent tumor phenotype was the non-functioning adenoma (76%). The prevalence of visual field defects and neurological symptoms was 56% and 57%, respectively. We found normal pituitary function in 54%, partial deficiency in 30% and panhypopituitarism in 16%. Thirty-two patients were treated, 5 were lost to follow-up without receiving treatment. Surgery was indicated in 18. Of those operated by trans-sphenoidal approach, 23% had postsurgical complications and 54% improved the visual field. By trans-craneal approach, 50% had post-surgical complications and 33% visual field improvement. During follow-up (55.1 ± 48.7 months) no tumor regrowth was observed, except in a giant adenoma. Four operated patients died, two due to causes related to tumor. Fourteen were not operated, 11 with non-functioning adenomas and normal visual field were periodically controlled, and 3 with secreting adenomas received medical treatment. No tumor growth was observed during follow-up (43.7 ± 38.1 months). We did not observe tumor progression in elderly patients with non-functioning adenomas and normal visual field, so we suggest watchful approach and periodic control. When there are visual field defects, trans-sphenoidal surgery can be considered safe and effective. In secreting adenomas and depending on the associated comorbidities, medical treatment would be the appropriate approach.

Key words: pituitary adenoma, elderly patients, clinical presentation, treatment, clinical outcome

Resumen ***Adenomas hipofisarios en pacientes añosos.*** Se evaluó la presentación clínica, tratamiento y sus resultados durante el seguimiento prolongado de 37 pacientes mayores de 65 años con adenomas hipofisarios, y sus causas de muerte. El estudio fue retrospectivo y transversal. La prevalencia de incidentalomas fue 43% (16), macroadenomas 70.3% (26) y adenomas gigantes 16.2% (6). El fenotipo tumoral más frecuente fue el adenoma no funcionante (76%). La prevalencia de alteraciones en el campo visual y síntomas neurológicos fue 56% y 57% respectivamente. El 54% tuvo función hipofisaria normal, deficiencia parcial el 30% y panhipopituitarismo el 16%. Fueron tratados 32, 5 se perdieron en el seguimiento sin recibir tratamiento. Indicamos cirugía en 18. De los operados por vía transesfenoidal, el 23% tuvo complicaciones postquirúrgicas y el 54% mejoría del campo visual. Por vía transcraneal el 50% sufrió complicaciones post quirúrgicas y el 33% mejoró el campo visual. Durante el seguimiento (55.1 ± 48.7 meses) no observamos recrecimiento tumoral, excepto en un adenoma gigante. Cuatro pacientes operados murieron, dos por causas al tumor. Catorce no fueron operados, 11 con adenomas no funcionantes y campo visual normal fueron controlados periódicamente y 3 con adenomas funcionantes recibieron tratamiento médico. No observamos crecimiento tumoral durante el seguimiento (43.7 ± 38.1 meses). No observamos crecimiento tumoral en adenomas no funcionantes y campo visual normal, por lo que sugerimos conducta expectante y control periódico. Cuando existe alteración del campo visual, la cirugía transesfenoidal es segura y efectiva. En los adenomas secretantes y dependiendo de las comorbilidades, sería apropiado optar por tratamiento médico.

Palabras clave: adenoma hipofisario, pacientes añosos, presentación clínica, tratamiento, resultados clínicos

Because of longer life expectancy, approximately 7% of pituitary adenomas (PAs) are diagnosed in patients > 65 years. Sixty-five years of age has been usually used as a cut-off for defining "elderly", and patients over 80 years of age are under the very elderly category[1-3].

The diagnosis of PAs in the elderly is often delayed because neurological symptoms and hypopituitarism may be unrecognized and ascribed to age-associated manifestations or co-existing diseases.

While there are extensive series about PAs in younger patients, there are few data in subjects older than 65.

Our objectives were to assess the clinical presentation, to define the safety and efficacy of therapeutic manage-

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ment and to evaluate the clinical outcome in a group of 37 elderly patients with PAs.

Materials and methods

It is a retrospective, cross-sectional study. We studied a consecutive cohort of 37 patients (20 males and 17 women) with PAs, with a mean age at diagnosis of 72 ± 5 years, median age 71 (range: 65-84), followed up in 2 medical centers of the city of Buenos Aires between 1999 and 2014.

We assessed: 1. Clinical presentation: age at diagnosis, tumor size, incidental finding of PAs, visual field defects (VFD), tumor phenotype, neurological symptoms, hyponatremia, hormonal deficiencies, relation between neurological symptoms and tumor size and hormonal deficiencies. 2. Medical treatment, surgery and /or radiotherapy. 3. Long-term follow-up: changes in the visual field (VF), tumor size and development of new hormonal deficiencies in operated and non-operated patients. 4. Causes of death related or not related to PAs.

Data were entered in a database (Microsoft Excel 97) and analyzed using the statistical package Medcalc v12. The frequency distribution and / or percentages for all the variables were established in all the cases. For those measures on a categorical scale or higher, the following statistics were computed: number of cases, minimum value, median, maximum value, arithmetic mean, typical deviation. We performed as tests of significance: Mann Whitney, Wilcoxon test and Chi square test for trend. The significance level was set at alpha 0.05.

Results

Clinical data are summarized in Table 1.

The prevalence of micro, macro and giant adenomas was 13.5% (5), 70.3% (26) and 16.2% (6), respectively.

TABLE 1.– *Clinical data and tumor phenotype*

Clinical data	Cases
Age: mean 71 (65-84)	37 (16*)
Sex	20M/17F
Tumor size	
Micro	5
Macro	26
Giant	6
VF Defects	20 (7*)
Neurological symptoms	22
Hyponatremia	4/14
Hormonal deficiencies	17
NFT	28 (12*)
PRL	3 (2*)
GH	5
GH-PRL	1

VF: visual field; NFT non-functioning adenoma; PRL: prolactinoma; GH: growth hormone
Incidentalomas (*)

The prevalence of VFD was 56% (20/37). Sixteen were non-functioning adenomas (NFTs), 2 prolactinomas, 1 somatotropinoma, and 1 PRL-GH tumor. Out of those 20, seven were incidentalomas (5 NFTs and 2 prolactinomas).

In 22 patients (57%) we found neurological symptoms: headaches, dizziness, vertigo, loss of balance, gait abnormalities, paresthesia, diplopia, palpebral ptosis and disorientation.

In the correlation between tumor size and neurological symptoms, we found that, out of those 22, 16 (73%) macro, 5 (23%) giant and 1 (4%) microadenoma had neurological symptoms ($Chi^2 = 4.695$. GL = 2. p = 0.096). Probably due to the small size of the sample, we did not find a statistically significant association between tumor size and neurological symptoms.

In the assessment of hormonal deficiencies, we observed no hormonal deficiencies in 20 (54%) patients, partial deficiency and panhypopituitarism in 11 (30%) and 6 (16%), respectively. In the correlation between hormonal deficiencies and neurological symptoms, we found that 9/20 (45%) patients without hormonal deficiency, 8/11 (73%) with partial deficiency and 4/6 (67%) with panhypopituitarism had neurological symptoms ($Chi^2 = 2.5$; p = 0.2851). We did not find a statistically significant association between neurological symptoms and hormonal deficiencies.

The most prevalent phenotype was NFT 76% (28/37). The prevalence of prolactinomas was 8% (3/37), somatotropinomas (GH) 13.5% (5/37), mixed PRL-GH 2.7% (1 case); we did not observe any corticotropinomas.

The prevalence of pituitary incidentalomas was 43% (16/37), 87.5% (14/16) were macro (12) and giant adenomas (2). These pituitary tumors were a finding on MRIs performed due to neurological symptoms (Table 2).

Natremia could only be evaluated in 14, of which 4 had hyponatremia.

Out of 37 patients, 5 were lost in the follow-up without receiving the indicated treatment.

We indicated surgery in 18 patients (14 NFTs, 2 GH-secreting, 1 giant prolactinoma and 1 PRL-GH giant tumor). The indication for surgery was due to: chiasmal compression in 9 patients, neurological complications (pituitary apoplexy and hydrocephalia) in 4, large tumor

TABLE 2.– *Symptoms and tumor size of pituitary incidentalomas*

Symptoms	Micro (n = 2)	Macro (n = 12)	Giant (n = 2)
Headache	1		
Neurological	1	10	2
Hearing loss		2	

without VFD in 2, somatotropinoma in 2 and resistance to cabergoline (CAB) in 1 prolactinoma.

Twelve patients underwent trans-sphenoidal surgery (TSS), 5 trans-cranial (TC) and one patient had two surgeries (TSS and TC).

Total or subtotal tumor removal could be performed in 9 patients and partial resection in 9 patients. Post-surgical complications occurred in 3/13 (23%) patients operated by TSS and in 3/6 (50%) by TC (Table 3). Two patients received medical treatment after surgery: octeotride in a somatotropinoma, and CAB and octreotide in a mixed PRL-GH tumor.

Fourteen patients were not operated. Twelve out of 14 did not have VFD: 10 NFTs, 1 GH- tumor and 1 prolactinoma; the other 2 patients had VFD: 1 macroprolactinoma and 1 NFT with minimal defects. In the follow-up of patients with NFT, MRI and VF were periodically performed in order to evaluate tumor growth.

Two patients with prolactinomas were treated with CAB and, one with somatotropinoma was treated with octreotride as unique therapy.

None of the patients received radiotherapy as unique or additional treatment.

We compared the follow-up and evolution of non-operated and operated patients.

The average time of follow-up of the 14 non-operated patients was 43.7 ± 38.1 months (range 8 to 138). The VF remained unchanged in 11 (79%) and became impaired in one (7%). In two patients there was improvement in VF: one with a macroprolactinoma after treatment with CAB and the other one with an NFT who had minimal VFD at diagnosis. The hormonal deficiencies remained unchanged in all these patients and we did not observe tumor growth in any of them.

The average time of follow-up of the 18 operated patients was 55.1 ± 48.7 months (range 1 to 179). In the operated patients by TSS, the prevalence of improvement in the VF was 54% (7/13) and by TC 33% (2/6). One of the 2 patients operated by TC had been previously operated by TSS. The hormonal deficiencies remained unchanged in all of them but one who added a new deficiency of another axis.

In the operated patients there was not tumor regrowth except in one with a PRL-GH giant tumor.

Two patients who were operated died: one because of post-surgery complications, and the other one because of tumor regrowth.

TABLE 3.– *Surgical complications based on the approach*

Complications	TSS (n = 3/13)	TC (n = 3/6)
Transient diabetes insipidus	1	1*
Deterioration of visual field		1
Pure motor hemiparesis	1	
Hydrocephaly		1*
Gait abnormalities	1	1*
Subdural hematoma		2*

TTSS: Transsphenoidal; TC: transcranial
* 1 patient presented all these complications

Discussion

Nowadays PAs in older people are more frequently diagnosed because the number of this population is increasing all over the world. Additionally, as image techniques are more usually performed to investigate age-related neurological illnesses, incidental findings can be expected.

In this study, we present 37 patients older than 65 years with pituitary adenomas. We analyzed the clinical presentation, the therapeutic management and whether there were some differences between operated and non-operated patients in the outcome and evolution during follow-up.

In the general population the prevalence of pituitary adenomas is about 10%[4-6]. However, Ezzat et al. estimated their prevalence about 16.7%[7]. In patients over 65 it is approximately 7%[2, 3] and it is growing because of the improvement of health care and increasing life expectancy[8]. In autopsy studies in very elderly patients it was demonstrated that the prevalence of PAs is approximately 11-14%[9].

In the general population the prevalence of pituitary macroadenomas is approximately 0.2%[10]. In our study, the prevalence of macro and giant adenomas was high in accordance with the literature[11,12]. This situation may be due to the fact that most PAs were NFTs and the symptoms of hypopituitarism are not usually recognized as they can be ascribed to age-associated manifestations or co-existing diseases. Therefore, the diagnosis of PAs is delayed, which may be a reason of the presence of big tumors in this group of patients.

Likewise, there was a higher prevalence of incidentalomas (43%), as it was reported in other series[13,14], and even a higher prevalence of macro-incidentalomas (86%). These pituitary tumors were a finding on brain MRIs performed for neurological reasons. The possibility of finding a pituitary microadenoma in these images is very low and could explain the higher prevalence of macroadenomas as incidentalomas. In a previous study we reported that 63% of pituitary incidentalomas in patients between 16-77 years old were macroadenomas and most of them were NFTs[15].

In the Endocrine Society Guidelines for pituitary incidentalomas they report in a pooled data of 10 series of pituitary incidentalomas that 45% were macroincidentalomas[16].

In this study the prevalence of VFD was 56%. Seven were incidentalomas, which means that these patients with VFD had not perceived these abnormalities. These defects may be misdiagnosed in elderly patients with some ocular diseases more frequent in this age group, such as cataracts, macular degeneration or retinal vascular alterations[17]. Consequently, the diagnosis of a pituitary tumor is delayed in this group, which leads to tumor growth and could explain the higher prevalence of VFD in these patients than in younger ones. This is in accordance with the literature which demonstrated that the severity of VFD and visual loss were related to tumor size[17, 18].

Dizziness, vertigo, loss of balance and gait abnormalities are common in older people, and they can also be present in patients with PAs that is why these symptoms may be unnoticed. We did not find a statistically significant association between tumor size and neurological symptoms probably because of the small sample size.

The most common type of pituitary adenomas observed was NFT, and there was a small percentage of prolactinomas and somatotrophinomas but there were no corticotrophinomas; these findings are in accordance with previous reports[2, 3, 19]. In our patients < 65 years (data not published) the most frequent tumoral phenotype was prolactinoma (53%), the second in frequency NFT (30%), other types were somatotrophinoma (13%) and corticotrophinoma (3%). Liu et al. compared PAs in patients older and younger than 65 years who underwent TSS, and showed that NFTs were more frequent in those > 65 (75.4% vs. 37.4%), while prolactinomas were more frequent in those < 65 (27.1% vs. 0%)[14].

Minniti et al. reported that data about prolactinomas in the elderly were limited to small subgroups of PAs and to single case reports[20].

Although we found the presence of hyponatremia in some patients, the sample size was small, and it was not possible to come to a conclusion. Turner et al. found that hyponatremia was very common as the initial presentation of a pituitary lesion so it should always be considered in older patients[2]. On the other hand, Nishizawa et al. and Lin et al. reported that symptomatic hyponatremia is rarely the clinical presentation of Pas[21, 22]. When hyponatremia is present in patients with hypopituitarism, this is usually due to adrenal insufficiency and age-related changes in vasopressin secretion rather than secondary hypothyroidism[23, 24].

We observed partial hormonal deficiency in 30% and panhypopituitarism in 16%. Because symptoms of hypopituitarism are silent and non-specific, they may go unnoticed in these patients. It was reported that hypopituitarism could be present in up to 50% of all PAs when an in-depth evaluation is carried out[19, 25]. The two patients with macroprolactinomas treated with CAB decreased the tumor size and, the one with VFD improved. In the literature it has been reported that the response to CAB in elderly patients is as effective as in youngsters[20].

Although NFTs usually have a slow growth potential, our decision to indicate surgical treatment was due to VDF or progressive growth of the tumor in the suprasellar space. In acromegalic patients our decision to indicate either medical treatment or surgery depended on their comorbidities. Of the 3 treated patients with acromegaly, only 2 were operated, the other one was treated with somatostatin analogs, his clinical condition improved, and the adenoma remained unchanged during 7 years of follow-up. Van der Lely et al. found that in elderly patients, GH levels tend to be lower and adenomas are more responsive to octreotide, which suggests that this drug can be used as primary treatment in this age group[26]. However, these results might be skewed due to the less aggressive behavior of somatotropinoma in the elderly[20].

Grossman et al. in a retrospective analysis of the Nationwide Inpatient Sample about the surgical risk of PAs in older patients included 8400 subjects of whom only 2.6% were treated by TC and the remaining patients by TSS. They showed that morbidity and mortality rates increase in patients older than 65 years and reported an overall mortality of 3.8%. In this data base the reference about the phenotype and tumor size was not included[27]. In other studies performed in single centers with surgeons with experience in TSS, with appropriate perioperative management and a multidisciplinary team, there was minimal morbidity and mortality was 0%[3,19]. Locatelli et al. demonstrated that the safety and efficacy of TSS in older patients were similar to those reported for the general population[28]. Hong et al. concluded that TSS is the most appropriate approach for elderly patients and that age should not be an obstacle to perform it[3]. Fraioli et al. reported that only in patients with stage 4 and 5 of ASA scale TSS approach is contraindicated because of the high risk of death, and that this approach for removal of adenomas with marked suprasellar extension should be considered safe only for patients with stage 1 or 2 of ASA scale. TC surgery should be reserved only for adenomas with extension to the temporal lobe[11]. In our study, the neurosurgeons made the decision to perform a TC in 5 patients because they had giant adenomas and macroadenomas with neurological complications.

The overall complication rate in our patients who underwent surgery (TSS and TC) was 31.6% (6/19), while for TSS it was 23% (3/13). This is in accordance with Grossman et al. who referred an overall complication rate of 32.6% (26); in other series the complication rate by TSS was 20%, 25% and 37%[3, 17, 12]. Marenco et al. reported that the endoscopic endonasal approach provided better results for CSF fistulae, diabetes insipidus and postoperative pituitary deficits than transsphenoidal microsurgery. They concluded that age as the only factor should not be

a contraindication for surgery, while comorbidities could be[29].

We would like to point out that two patients, one with a giant prolactinoma and the other one with a PRL-GH giant tumor presented resistance to CAB, so we decided to perform surgical treatment. The PRL-GH giant tumor was started on octreotide and CAB treatment after surgery[30].

None of the patients received treatment with radiotherapy because there were neither contraindications to undergo surgery nor postsurgical tumor regrowth, except for one patient with a giant PRL-GH who died as a result of the tumor.

In the follow-up of 10 non-operated patients with NFT and normal VF, tumor size, VF and hormonal deficiencies remained unchanged, except in one patient whose tumor grew, and his VF worsened; another patient who had minimal VFD presented improvement and an intratumoral micro-hemorrhage could be a probable explanation. Deckkers et al. observed the natural course of 28 NFTs: 50% of the patients had tumor growth, and a spontaneous decrease of the tumor size in 29% of them during a follow-up of more than 7 years[31].

In the follow-up of TSS-operated patients the prevalence of improvement in the VF was 53%. In other series, it was demonstrated that 70% of patients showed visual improvement after TSS[3, 19]. Probably our lower rate of improvement in the VF was due to the fact that not all our patients were operated by experienced surgeons in TSS approach. We did not observe improvement in hormonal deficiencies, one patient added a deficiency of another axis. This is in accordance with the literature that suggests that the recovery of pituitary deficiencies in the elderly is less frequent than in younger patients[3, 21]. Webb et al assessed the improvement of pituitary axes post TSS approach in 234 patients whose mean age was 41 ± 15.1 years and showed that almost half of those patients with pituitary insufficiency before surgery improved in the post-surgery period[32].

Two patients with giant adenomas who were operated died: one in the immediate post-surgical period due to pneumonia, and the other one as a result of complications related to tumor regrowth but not to the surgery.

In conclusion, in our group of elderly patients we found a high prevalence of incidentalomas, macro and giant adenomas; and the prevalent phenotype was NFT.

In patients with NFT and without visual abnormalities, a close follow-up of the tumor size and the VF seems to be an adequate conduct. We suggest maintaining a holistic approach and carrying out less aggressive treatments in this age group who usually has co-existing illnesses. Instead, in patients with abnormalities in the VF, the surgical treatment by TSS approach could be considered safe and effective.

In secreting tumors and depending on the associated comorbidities, a medical treatment would be the appropriate approach.

The aim of this study was to show the evolution of PAs in elderly patients who received different treatments and to contribute to the few series that have been published about this age group.

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References

1. Olshansky SJ, Carnes BA, Desesquelles, A. Demography. Prospects for human longevity. *Science* 2001; 291: 1491-2.
2. Turner H, Adams C, Wass J. Pituitary tumours in the elderly: a 20 year experience. *Eur J Endocrinol* 1999; 140: 383-9.
3. Hong J, Ding X, Lu Y. Clinical analysis of 103 elderly patients with pituitary adenomas: transsphenoidal surgery and follow-up. *J Clin Neurosci* 2008; 15: 1091-5.
4. Burrow GN, Wortzman G, Rewcastle NB, Holgate RC, Kovacs K. Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. *N Engl J Med* 1981; 304: 156-8.
5. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. *Ann Intern Med* 1994; 120: 817-20.
6. Molitch ME. Nonfunctioning pituitary tumors and pituitary incidentalomas. *Endocrinol Metab Clin North Am* 2008; 37: 151-71.
7. Ezzat S, Asa S, Couldwell W et al. The prevalence of pituitary adenomas: A systematic review. *Cancer* 2004; 101: 613-9.
8. Antonopoulou M, Sharma R, Farag A, Banerji M, Karam J. Hypopituitarism in the elderly. *Maturitas* 2012; 72: 277-85.
9. Kurosaki M, Saeger W, Ludecke DK. Pituitary tumors in the elderly. *Pathol Res Pract* 2001; 197: 493-7.
10. Nammour GM, Ybarra J, Naheedy MH, Romeo JH, Aron DC. Incidental pituitary macroadenoma: a population-based study. *Am J Med Sci* 1997; 314: 287-91.
11. Fraioli B, Pastore FS, De Caro GMF, Giuffre R. The surgical treatment of pituitary adenomas in the eigth decade. *Surg Neurol* 1999; 51: 261-6; Discussion 266-7.
12. Kurosaki M, Ludecke DK, Flitsch L, Saeger W. Surgical treatment of clinically nonsecreting pituitary adenomas in elderly patients. *Neurosurgery* 2000; 47: 843-8; Discussion 848-9.
13. Del Monte P, Lucca Foppiani L, Ruelle A, et al. Clinically non-functioning pituitary macroadenomas in the elderly. *Aging Clin Exp Res* 2007; 19: 34-40.
14. Liu J, Li C, Xiao Q, et al. Comparison of pituitary adenomas in elderly and younger adults: Clinical characteristics, surgical outcomes and prognosis. *J Am Geriatr Soc* 2015; 63: 1924-30.
15. Fainstein Day P, Guitelman M, Artese R, et al. Retrospective multicentric study of pituitary incidentalomas. *Pituitary* 2004; 7: 145-8.
16. Freda PU, Beckers AM, Katznelson L, et al. Pituitary incidentaloma: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2011; 96: 894-904.

17. Lee J, Park I, Chung Y. The volume of tumor mass and visual field defect in patients with pituitary macroadenoma. *Korean J Ophthalmol* 2011; 25: 37-41.
18. Thomas R, Shenoy K, Seshadri MS. Visual field defects in non-functioning pituitary adenomas. *Indian J Ophthalmol* 2002; 50: 127-30.
19. Ferrante L, Trill G, Ramundo E, et al. Surgical treatment of pituitary tumors in the elderly: clinical outcome and long-term follow-up. *J Neurooncol* 2002; 60: 185-91.
20. Minniti G, Esposito V, Piccirilli M, Fratticci A, Santoro A, Jaffrain-Rea M. Diagnosis and management of pituitary tumors in the elderly: a review based on personal experience and evidence of literature. *Eur J Endocrinol* 2005; 153: 723-35.
21. Nishizawa S, Yokoyama T, Yokota N, Ohta S. Preoperative hyponatremia as a clinical characteristic in elderly patients with large pituitary tumor. *Neurol Med Chir (Tokyo)* 2000; 40: 249-55.
22. Lin SH, Hung YH, Lyn YF. Severe hyponatremia as the presenting feature of clinically non-functional pituitary adenoma with hypopituitarism. *Clin Nephrol* 2002; 57: 85-8.
23. Diederich S, Franzen NF, Bahr V, Oelkers W. Severe hyponatremia due to hypopituitarism with adrenal insufficiency: report on 28 cases. *Eur J Endocrinol* 2003; 148: 609-17.
24. Chanson P. Severe hyponatremia as a frequent revealing sign of hypopituitarism after 60 years of age. *Eur J Endocrinol* 2003; 149: 177-8.
25. Dekkers OM, Pereira AM, Romjin JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. *J Clin Endocrinol Metab* 2008; 93: 3717-26.
26. Van der Lely AJ, Harris AG, Lamberts SWJ. The sensitivity of growth hormone secretion to medical treatment in acromegalic patients: Influence of age and sex. *Clin Endocrinol (Oxf)* 1992; 37: 181-5.
27. Grossman R, Mukherjee D, Chaichana K, et al. Complications and death among elderly patients undergoing pituitary tumour surgery. *Clin Endocrinol (Oxf)* 2010; 73: 361-8.
28. Locatelli M, Bertani G, Carrabba G et al. The trans-sphenoidal resection of pituitary adenomas in elderly patients and surgical risk. *Pituitary* 2013; 16: 146-51.
29. Marenco HA, Zymberg ST, Santos R de P, Ramalho CO. Surgical treatment of non-functioning pituitary macroadenomas by the endoscopic endonasal approach in the elderly. *Arq Neuropsiquiatr* 2015; 73: 764-9.
30. Mallea Gil MS, Cristina C, Perez Millán MI, et al. Invasive giant prolactinoma with loss of therapeutic response to cabergoline: expression of angiogenic markers. *Endocr Pathol* 2009; 20: 25-40.
31. Dekkers OM, Hammer S, de Keizer RJW, et al. The natural course of non-functioning pituitary macroadenomas. *Eur J Endocrinol* 2007; 156: 217-24.
32. Webb S, Riggla M, Wagner A, Oliver B, Bartumeus F. Recovery of hypopituitarism after neurosurgical treatment of pituitary adenomas. *J Clin Endocrinol Metab* 1999; 84: 3696-700.

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