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Research Article

Causes of Hyperprolactinemia in Acromegalic Patients and Clinical Correlations

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Abstract

Hyperprolactinemia in acromegalic patients may result either from co-secretion of growth hormone and prolactin by the tumour or from pituitary stalk compression. The occurrence of both conditions is possible. This study was designed aiming 1) to estimate the prevalence of each cause of hyperprolactinemia and its respective clinical course; 2) to compare the outcomes of patients with tumours staining only for growth hormone against tumours staining for both growth hormone and prolactin. 75 acromegalic patients submitted to transsphenoidal surgery between 1989 and 2018 were included. Patients were divided based on preoperative prolactin levels and immunostaining pattern. Statistical analysis was performed with SPSS version 23.

Hyperprolactinemia was documented in 22 out of 36 patients (61%). Stalk compression was the only underlying cause of hyperprolactinemia in 45% of cases. The levels of prolactin were not associated with the immunostaining pattern for prolactin. Clinical differences were not observed between hyperprolactinemic and normoprolactinemic patients, except for a higher frequency of cavernous sinus invasion (64% *vs* 29%, p=0,064), that reached the level of significance for the subgroup with macroadenomas staining exclusively for growth hormone (p=0,031). In the present series, no clinical differences were noticed between patients with tumours staining only for growth hormone or staining for both growth hormone and prolactin.

Hyperprolactinemia resulting from stalk compression is likely to anticipate a less favourable course of disease, since it is associated with larger tumours and a higher frequency of cavernous sinus invasion. On the contrary, positive immunostaining for prolactin was not a marker of worse prognosis.

Keywords: Acromegaly; Hyperprolactinemia; Immunostaining; Growth-hormone; Prolactin

Introduction

Acromegaly is a chronic disorder resulting from excessive Growth Hormone (GH) secretion. GH hypersecretion stimulates IGF-1 overproduction which in large part mediates the somatic and metabolic effects of GH, leading to a multisystemic disease characterized by somatic overgrowth, multiple comorbidities, premature mortality, and physical disfigurement [1,2]. More than 90% of acromegaly cases are caused by a GH-secreting pituitary adenoma arising from somatotroph cells [2]. Surgery, preferentially through an endoscopic endonasal approach, is recommended as the first line therapy for most patients. However, the optimal treatment approach should be chosen depending on the size, extension of the pituitary adenoma (particularly to the cavernous sinus) and patient characteristics [1,3]. Surgical remission rates can be greater than 85% for microadenomas, however these figures can decrease to 20-30 % for macroadenomas [4-6]. For patients with disease persistence, medical therapy is often indicated with the first-generation Somatostatin Receptor Ligands (SRLs) octreotide and lanreotide. As second-line therapy, both second-generation SRLs such as pasireotide or the GH receptor antagonist pegvisomant are alternatives. Dopamine agonists have a limited efficacy and are likely to be useful in patients with modest elevations of GH and IGF1. Radiosurgery or stereotactic fractionated radiation therapy can also play a role for selected patients [3,4,7]. In a number of patients, a multimodal approach is the most adequate solution.

Hyperprolactinemia has been reported in about 30 to 40% of acromegalic patients. High levels of Prolactin (PRL) can result from co-secretion of GH and PRL by the tumour, from pituitary stalk compression or even from both conditions [8]. Indeed, about 25% somatotrophic adenomas also secrete PRL. These tumours include dimorphous adenomas (mixed somatotroph-lactotroph adenoma) and monomorphous adenomas (mammosomatotroph adenoma) [9]. The aims of the current study were: 1) to estimate the prevalence of each cause of hyperprolactinemia, among a cohort of acromegalic patients from a single center, and follow its evolution after surgery; 2) to compare the clinical presentation and course of acromegalic patients with tumours staining only for GH against tumours staining for both GH and PRL.

Materials and Methods

Study cohort

We retrospectively reviewed medical records of 75 patients with

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acromegaly submitted to transsphenoidal surgery between January 1989 and December 2018 (endoscopic approach, since 2011), at *Hospital de Santa Maria*, in Lisbon, Portugal. Inclusion criteria: pre and post-operative clinical, laboratory and imaging data as well as immunohistochemical study. Exclusion criteria: use of medications likely to induce hyperprolactinemia, radiotherapy prior to surgery and adenomas staining for hormones other than GH and PRL.

Histopathology and laboratory data

Analysis was performed based on the pathology reports included in the patients' files. GH and IGF-1 were measured using an immunometric chemiluminescence assay. IGF1 results were interpreted according to the reference range defined for age and gender. Serum PRL was measured using an electro-chemiluminescence assay and results interpreted according to a reference range adjusted for gender. As a consequence of the retrospective nature of the study, the reference ranges have changed throughout the years. Criteria for biochemical remission were defined as a normal serum IGF-1 for age and gender, as well as a random GH below 1ng/mL [1].

Neuroradiological studies

Pituitary adenomas were classified according to the tumour diameter described on magnetic resonance imaging and/or computed tomography scan. Tumours with diameter <1 centimetre were defined as microadenomas and ≥1 centimetre as macroadenomas [10]. Additionally, cavernous sinus invasion was evaluated.

Statistical analysis

Statistical analysis was performed with SPSS version 23. Chi-square test was used for comparison of categorical variables, whereas Student's T and Mann-Whitney tests were used for continuous variables. Differences were considered statistically significant when p-value was <0.05.

Results

Forty, out of 75 patients, met the study inclusion criteria. The ratio Female/Male was 1,9. Macroadenomas were present in 36 patients. Prior to surgery, PRL was evaluated in 36 patients. Hyperprolactinemia was documented in twenty-two patients (61%), with a median level of 40,3ng/mL. Furthermore, 10 patients (28%) despite presenting hyperprolactinemia did not disclose immunostaining for PRL. All patients in the latter group had macroadenomas. On the other hand, 6 patients, corresponding to 33, 3% of those with positive staining for PRL, had normal values of serum PRL, (Table 1).

Comparative analysis of clinical, laboratorial and imagiological characteristics of patients with hyperprolactinemia versus those with normal values of serum PRL is summarized in (Table 2). No significant differences were noticed.

On a different perspective, categorizing patients based on the immunostaining pattern (GH positive versus GH+PRL positive) did not disclose differences in terms of serum PRL levels between these 2 subgroups, (Table 3).

There was a higher number of patients with serum PRL levels above 40ng/mL among those with GH/PRL staining than among those without PRL staining, although not statistically significant (GH: 22, 2% *vs* GH/PRL: 38, 9%, p= 0,278), (Table 3).

Table 1: Immunostaining and PRL values.

Hyperprolactinemia		
	GH	GH+PRL
Microadenoma	0	1
Macroadenoma	10	11
Normoprolactinemia		
	GH	GH+PRL
Microadenoma	1	1
Macroadenoma	7	5

Table 2: General characteristics-comparative analysis between normo and hyperprolactinemic patients.

Patient Caractheristics[1]	Normoprolactinemia (n=14)	Hyperprolactinemia (n=22)	p-value
Demographics			
Age at diagnosis (years)	50, 6 (±12,5)	42, 9 (±13,3)	0, 074
Gender (Female)	9 (64, 3%)	13 (59, 1%)	0, 755
Immunostaining			
GH	8 (57, 1%)	10 (45, 5%)	0,494
GH/PRL	6 (42, 9%)	12 (54, 5%)	
Biochemical Profile			
Diagnosis			
PRL (ng/mL)	8, 1 (0, 2-15, 6)	40, 3 (18-195, 7)	0, 000
GH (ng/mL)	8, 6 (3-200)	25, 6 (2-200)	0, 120
IGF-1 (ng/mL)	957 (295-2230)	876 (340-1724)	0, 330
Tumor characteristics			
Microadenoma	2 (14, 3%)	1 (4, 5%)	0, 303
Macroadenoma	12 (85, 7%)	21 (95, 5%)	
Cavernous sinus invasion	4 (28, 6%)	14 (63, 6%)	0, 064
Remission			
3 months	4 (28, 6%)	1 (4, 8%) (n=20)	0, 049
1 Year	7 (50%)	10 (45, 5%)	0, 790
Radiotherapy			
Yes	2 (14, 3%)	10 (45, 5%)	0, 053
Medical Therapy			
Yes	4 (28, 6%)	10 (45, 5%)	0, 311
Single	4	6	0, 099
Multiple	0	4	

[1]Data were presented as mean ± standard deviation or median (range) as deemed more appropriated.

There was a trend towards a higher incidence of cavernous sinus invasion among patients with hyperprolactinemia (63, 6% *vs* 28, 6%, p=0,064), (Table 2); this difference reached the level of significance among patients with hyperprolactinemia and immunostaining positive only for GH (GH: n=9, 90%; GH/PRL: n=5, 46%; p=0,031).

Normalization of PRL was not synonymous of remission. Both events occurred in 4 patients. All 10 patients with PRL normalization, despite acromegaly persistence, presented with a macroadenoma, six of them with cavernous sinus invasion; 5/10 had immunopositivity

Table 3: General characteristics-comparative analysis between immunostaining profile.

Patient Caractheristics[1]	GH (n=22)	GH/PRL (n=18)	p-value
Demographics			
Age at diagnosis (years)	48, 1 (±11,5)	44 (±15,1)	0, 084
Gender (Female)	17 (77, 3%)	9 (50%)	0, 072
Biochemical Profile			
Diagnosis			
PRL (ng/mL)	19,4 (0,2–181,2) (n=18)	33,8 (3-195, 7)	0, 334
Hyperprolactinemia	10 (55, 6%)	12 (66, 7%)	0, 494
PRL >40ng/mL	4 (22, 2%)	7 (38, 9%)	0, 278
GH (ng/mL)	17, 6 (4-200)	23,7 (2-200)	0, 530
IGF-1 (ng/mL)	865, 0 (340-1414)	943,0 (295-2230)	0, 329
Tumor characteristics			
Microadenoma	2 (9, 1%)	2 (11, 1%)	0, 832
Macroadenoma	20 (90, 9%)	16 (88, 9%)	
Cavernous sinus invasion	11 (50%)	7 (38, 9%)	0, 502
Remission			
3 months	5 (23, 8%) (n=21)	1 (5, 9%) (n=17)	0,132
1 Year	11 (50%)	8 (44, 4%)	0,761
PRL normalization rate	6 (75%)	8 (72, 7%)	--
Radiotherapy			
Yes	6 (27, 3%)	6 (33, 3%)	0, 677
Medical Therapy			
Yes	7 (31, 8%)	7 (38, 9%)	0, 870
Single	6	4	0, 185
Multiple	1	3	

[1]Data were presented as mean ± standard deviation or median (range) as deemed more appropriated.

for GH and PRL.

Prolactin levels did not correlate with the final outcome. Nonetheless, hyperprolactinemic patients met remission criteria later after surgery, based on results at 3 months and 12 months after the procedure, (Table 2). Among those in whom adjuvant therapy postoperatively was required, the need for radiotherapy and medical therapy with more than one agent trended towards a higher frequency in hyperprolactinemic patients, (Table 2).

Discussion and Conclusions

Acromegaly is a slow progressive disease with significant heterogeneity in both presentation and surgical outcomes. Hyperprolactinemia has been reported in around 30% of acromegalic patients and may result either from the co-secretion of GH and PRL by tumour tissue or from the pituitary stalk compression (stalk syndrome) with impaired dopamine delivery. Previous studies suggested a more aggressive clinical course in acromegalic patients with hyperprolactinemia [8,11]. However, whether this is somehow related to the origin of the hyperprolactinemia is not completely understood. Thus, we started by comparing acromegalic patients with and without hyperprolactinemia. We documented PRL levels above the normal range in 61% of the patients. Differences in the cut-off used to define hyperprolactinemia are a possible explanation for a higher prevalence than observed in other series [8]. In what concerns the immunostaining of hyperprolactinemic patients, only 55% of our patients presented GH and PRL staining, lower than reported by others [12-14].

Similarly to other studies, we also found an association between hyperprolactinemia and tumour invasiveness [8,14]. However, when we compared hyperprolactinemic patients with positive immunostaining for PRL with those with negative immunostaining, the association between elevated PRL levels and tumour extension was only significant for the latter group. Moreover, despite the absence of a significant difference on the final remission rates, early remission rate (3 months after surgery) was significantly lower in hyperprolactinemic patients. Furthermore, the need for adjuvant therapy postoperatively with more than one agent, as well as the indication for radiotherapy also trended towards a higher frequency among hyperprolactinemic patients.

Hence, these findings are in favour of an association of elevated PRL levels with a more aggressive clinical course and less favourable outcome, among those patients in whom hyperprolactinemia is likely to result from stalk compression, usually associated with larger and more invasive tumours [15].

In order to assess the impact of hyperprolactinemia related to co-secretion by the pituitary tumour, we compared acromegalic patients staining positive for just GH with the ones with positive staining for both GH and PRL. Around 45% of our patients had positive immunostaining for both GH, PRL, a number in line with the one reported by Liang et al., although higher than the one reported by Rick et al and Varlamov et al. [16-19].

Comparative analysis of these subgroups did not disclose significant differences. There was a trend towards a lower age and higher levels of GH and IGF-1 in the subgroup staining for GH and PRL. In terms of serum PRL levels no significant differences were noticed. Immunostaining for PRL did not always translate into hyperprolactinemia as observed in 33% of cases. Indeed, when normoprolactinemic patients with and without PRL immunostaining were compared, no differences concerning tumour presentation or final outcome were found. The retrospective nature of our study did not allow to categorize tumours staining for GH and PRL as mammosomatotroph adenomas or somatotroph-lactotroph adenomas and look for differences between these subtypes as performed by others [17,18].

Looking to those patients in whom hyperprolactinemia coexisted with macroadenoma and immunostaining positive both for GH and PRL, 8/11 normalized serum PRL after surgery. However, only 3 reached remission criteria. In the remaining 5, with persistence of disease, debulking of tumour was enough for PRL normalization reinforcing the dominant role of stalk compression for the occurrence of hyperprolactinemia.

The main constraints of this study are its retrospective nature and the number of patients included. Whether a more detailed characterization of the exact lineage profile of the dual staining tumours, namely whether they were monomorphous or dimorphous

adenomas, could add any contribute to final results was far beyond the scope of the study. In conclusion, our results favour a poor outcome for hyperprolactinemic patients, when the underlying cause is stalk compression or, in other words, when the tumours are larger and likely to be more aggressive.

References

1. Katznelson L, Laws ER, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab, 2014; 9911: 3933-3951.
2. Melmed S. Medical progress: acromegaly. New england journal of medicine. 2006; 355: 2558-2573.
3. Muhammad A, van der Lely AJ, Neggers SJCMM. Review of current and emerging treatment options in acromegaly. Netherlands Journal of Medicine. 2015; 73: 362-367.
4. Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JAH, et al. A Consensus Statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018; 149: 552-561.
5. Abu Dabrh AM, Mohammed K, Asi N, Farah WH, Wang Z, Farah MH, et al. Surgical interventions and medical treatments in treatment-naive patients with acromegaly: systematic review and meta-analysis. J Clin Endocrinol Metab. 2014; 99: 4003-4014.
6. Hazer DB, Isik S, Berker D, Guler S, Gurlek A, Yucel T, et al. Treatment of acromegaly by endoscopic transsphenoidal surgery: surgical experience in 214 cases and cure rates according to current consensus criteria. J Neurosurg. 2013; 119: 1467-1477.
7. Ben-Shlomo A, Melmed S. Somatostatin agonists for treatment of acromegaly. Mol Cell Endocrinol. 2008; 286: 192-198.
8. De Marinis L, Zuppi P, Valle D, Mancini A. Retrospective Hormonal and Immunohistochemical Evaluation of 47 Acromegalic Patients: Prognostic Value of Preoperative Plasma Prolactin. Horm Metab Res. 2002; 34: 137-143.
9. Mete O, Lopes MB. Overview of the 2017 WHO Classification of Pituitary Tumors. Endocr Pathol. 2017; 28: 228-243.
10. Ribeiro-Oliveira A, Barkan A. The changing face of acromegaly--advances in diagnosis and treatment. Nat Rev Endocrinol. 2012; 8: 605-611.
11. Cheng JS, Salinas R, Molinaro A, Chang EF, Kunwar S, Blevins L, et al. A predictive algorithm for evaluating elevated serum prolactin in patients with a sellar mass. J Clin Neurosci. 2015; 22: 155-160.
12. Huan C, Cui G, Ren Z. The characteristics of acromegalic patients with hyperprolactinemia and the differences with hyperprolactinemia patients. Pak J Pharm Sci. 2015; 28: 713-718.
13. Van Laethem D, Michotte A, Cools W, Velkeniers B, Unuane D, Andreescu CE, et al. Hyperprolactinemia in Acromegaly is Related to Prolactin Secretion by Somatolactotroph Tumours. Horm Metab Res. 2020; 52: 647-653.
14. Wang M, Mou C, Jiang M, Han L, Fan S, Huan C, et al. The characteristics of acromegalic patients with hyperprolactinemia and the differences in patients with merely GH-secreting adenomas: clinical analysis of 279 cases. Eur J Endocrinol. 2012; 166: 797-802.
15. Karavitaki N, Thanabalasingham G, Shore HC, Trifanescu R, Ansorge O, Meston N, et al. Do the limits of serum prolactin in disconnection hyperprolactinaemia need re-definition? A study of 226 patients with histologically verified non-functioning pituitary macroadenoma. Clin Endocrinol (Oxf). 2006; 65: 524-529.
16. Robert F, Pelletier G, Serri O, Hardy J. Mixed growth hormone and prolactin-secreting human pituitary adenomas: a pathologic, immunocytochemical, ultrastructural, and immunoelectron microscopic study. Human Pathology. 1988; 19: 1327-1334.
17. Lv L, Jiang Y, Yin S, Hu Y, Chen C, Ma W, et al. Mammosomatotroph and mixed somatotroph-lactotroph adenoma in acromegaly: a retrospective study with long-term follow-up. Endocrine. 2019; 66: 310-318.
18. Rick J, Jahangiri A, Flanigan PM, Chandra A, Kunwar S, Blevins L, et al. Growth hormone and prolactin-staining tumors causing acromegaly: a retrospective review of clinical presentations and surgical outcomes. J Neurosurg. 2018; 131: 147-153.
19. Varlamov EV, Wood MD, Netto JP, Thiessen J, Kim J, Lim DST, et al. Cystic appearance on magnetic resonance imaging in bihormonal growth hormone and prolactin tumors in acromegaly. Pituitary. 2020; 236: 672-680.