Giant prolactinomas: experience of a single tertiary center in Mexico

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Abstract

Background: Giant prolactinomas are rare tumors representing only 0.5-4.4% of pituitary adenomas, and 2-3% of prolactin secreting tumors. Clinical presentation is similar than smaller prolactinomas. However, due to the large adenoma size (≥4 cm), the normalization of prolactin levels and reduction of the tumor volume becomes a significant therapeutic challenge and multimodal treatment might be necessary. Methods: Comparative, cross-sectional, observational, retrolective cohort, from January 1988 to December 2017. We included all patients with hyperprolactinemia, those with non-tumoral etiologies were eliminated. Our final sample consisted of 327 patients with prolactinomas. We classified them according to tumor diameter using magnetic resonance imaging (MRI), in microprolactinomas (<10 mm), macroprolactinomas (≥10 mm) and giant prolactinomas with a diameter of ≥4 cm, together with prolactin level > 1000 ng/dl, and no concomitant growth hormone (GH) or adrenocorticotropic hormone (ACTH) secretion. Results: 244 (74.6%) cases had a microprolactinoma, 72 (22%) had a macroprolactinoma, and 11 patients (3.4%) met the selection criteria for giant prolactinomas (9 males). The most common presenting features included headache, impaired vision, and erectile dysfunction. The main hormone deficiency found in men was testosterone (77.8%), followed by Thyroid-stimulating Hormone (TSH) (63%). Mean prolactin (PRL) at presentation was 2,000 ng/mL (IC 95% 1727 - 4374). All patients were treated with dopamine agonists (DA), and only 3 (27%) patients required surgery. Tumor shrinkage for giant prolactinomas with dopamine agonist was 63% on average. All patients had improved visual field defects. Since patients responded well to DA, none required further treatment modalities. Conclusions: Giant prolactinomas are rare tumors with a male predominance. Dopamine agonists are a useful therapeutic strategy, and good response is seen with a similar average dose to those used in smaller prolactinomas. None of our patients required further medical treatment.
Although surgical debulking sometimes is necessary.

Background

Prolactinomas are the most frequent type of secreting pituitary adenomas derived from lactotroph cells and characterized by hypersecretion of prolactin. They represent approximately 60% of pituitary adenomas with a prevalence per year of 44.4 / 100,000 subjects and a yearly incidence of 30/100,000 habitants. Clonal analysis has shown that the origin of pituitary adenomas is mainly monoclonal. Prolactinomas are classified according to their diameter in: microprolactinomas (< 10 mm), macroprolactinomas (> 10 mm), and giant prolactinomas (> 40 mm). A giant prolactinoma is a rare type of pituitary tumor (0.5-4.4%) with very high circulating prolactin levels, generally above 1000 ng/mL. Nevertheless, tumor mass and PRL level may not correlate in some instances because of the hook effect reported in 20% of giant prolactinomas. Giant prolactinomas tend to be more invasive than other smaller prolactinomas. Due to this observation, several markers of proliferation have been investigated. Recently, Soner et al. studied the expression of genetic polymorphisms and the role of CDKN2A gene and C540G (rs11515) polymorphisms in tumor size and behavior of prolactinomas. Results showed that tumors with a high Ki67 index and giant adenomas have higher frequency of C540G polymorphisms. While prolactinomas occur most frequently in 20-50-year-old females, giant forms are much more prevalent in middle aged men, with a male to female ratio of about 9:1 and a similar mean age at diagnosis around 40 years (27-68 years). Giant prolactinomas cause clinical symptoms mainly as a result of its mass effect and to a lesser degree due to hyperprolactinaemia resulting in visual field defects and/or ophthalmoplegia due to compression of the optic chiasm or cranial nerves, as well as headaches.
The most common site of extrasellar extension is into the suprasellar cistern, although large tumors can also have sphenoid sinus extension or laterally into the cavernous sinuses. Rare presentations include invasion of temporal or frontal lobes causing seizures or personality disorders. Skull base infiltration is another rare presentation, that may mimic primary bone dysplasia, as well as irruption of the nasopharynx, which may cause epistaxis. Hyperprolactinaemia typically presents with signs and symptoms such as decreased libido, impotence, infertility, galactorrhea, oligomenorrhea or amenorrhea and gynecomastia. By means of the agonist effect on dopamine receptors, cabergoline (CAB) is the first-line treatment for these tumors, decreasing PRL production and tumor size, even after a few days of treatment. However, due to the large tumor volume, multi-therapeutic approaches are necessary to normalize the serum PRL level and control tumor volume. Finally, a subgroup of prolactinomas exhibits aggressive clinical behavior, which results in a true challenge to control its biochemical function and tumor volume.

Methods
We conducted a comparative, cross-sectional, observational, retrolective study. All patients with hyperprolactinemia confirmed in at least 2 laboratory measurements with a prolactin value for women > 25 ng/mL, and >20 ng/mL for men who attended the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán at Mexico City, Mexico, from 1988 to December 2017, were included for review of their medical records. We excluded cases with an incomplete medical record (n=42), patients with a previously treated prolactinoma showing normal prolactin value (n=65), and those who only had one laboratory value of hyperprolactinemia without any further diagnostic approach (n=84) (Figure 1). Data was retrieved from clinical records by certified medical personnel.
Patients with hyperprolactinemia from non-tumoral etiologies were eliminated (n = 832). Our final sample consisted of 327 patients. We classified them according to their tumor diameter using MRI in: microprolactinomas (<10mm), macroprolactinomas (≥10 mm), and giant prolactinomas. We defined a giant prolactinoma when: 1) a tumor diameter on MRI was equal or more than 40 mm, 2) prolactin levels were equal or more than 1,000 ng/mL, and 3) clinical/neurological symptoms were compatible with hyperprolactinemia and or mass effect. Clinical presentation, laboratory tests, imaging findings, type of treatment, and outcomes were assessed. The Institutional Human Biomedical Research Committee of our hospital approved this study (REF #1740). Exemption of informed consent was requested and achieved by the Research Committee because of the observational and retrolective character of the study based on national legislation. Personal data was previously anonymized, so that the patient identification information was separated from all clinical data used in the present study.

The complete database is available upon request of any reader.

Imaging, biochemical assessment

PRL determination was performed with the Access Prolactin chemiluminescence immunoassay from 2011-2016 (with a detection limit of 0.25-20000 ng/mL). Patients whose prolactin level were performed before 2011 was done with the radioimmunoassay technique (RIA) with a detection limit of (2-133 ng/ml). In these patients, when PRL level had not a direct relationship with tumor size, serum was diluted 1:20 and 1:100 times to check for hook effect. Central hypothyroidism was defined as low free T4 level and low or inappropriate normal TSH concentrations, with negative thyroid antibodies. Central hypogonadism was defined as a serum low testosterone for men, and low estradiol in women, with low or normal LH and FSH. Central hypocortisolism was diagnosed with serum morning cortisol below 3 mcg/dL, or cortisol below 18 mcg/dL after induced-hypoglycemia
or after 250 mcg of synthetic ACTH (Cosyntropin) stimulation test. Growth hormone deficiency was diagnosed with low IGF-1 adjusted for sex and age. Hypopituitarism was diagnosed when two or more hormonal deficiencies were present.

Statistical analysis

Dimensional data with normal or non-normal distribution was expressed with means and standard deviations (SD), or medians and interquartile ranges, respectively. Categorical variables are expressed with frequencies and proportions. Student “t” test or Mann-Whitney U was used to compare prolactin levels before and after treatment. Categorical differences were analyzed with chi square test. Statistical analyses were performed using SPSS 23.

Results

Eleven patients (9 males and 2 females) met the diagnostic criteria for having a giant prolactinoma which resulted in a prevalence of 3.4% among all prolactin-secreting adenomas (n= 327). Mean age at diagnosis was 33 years (25-40). Median follow-up was 6 months (1-12). Baseline patient characteristics are presented in Table 1.

Symptoms and hormonal profile

The most frequent symptoms were headache (n =11, 100%) and impaired visual fields (n=9, 82%). One patient presented with seizures attributed to tumor invasion. In men, hypogonadism presented with erectile dysfunction in 5 patients (55%), decreased libido in 4 (44.4%), and infertility in 1 (11%). Hypogonadism in women presented as oligomenorrhea or amenorrhea. Galactorrhea was present in one female (50%) and 1 male (11%). 6 patients (54%) had hypopituitarism. The most common hormonal deficiency was testosterone, presented in 7 males (77%) whereas hypothyroidism was present in 7
patients (63%). Then, ACTH deficiency was detected in 6 patients (54%), GH deficiency in 4 patients (36%), and low estrogen in 1 woman (50%).

Baseline PRL and MRI findings

Median baseline serum PRL concentration was 2,000 ng/mL (1,727 - 4,374). The mean maximum tumor diameter at diagnosis was 47 mm (42-51) with a mean initial volume of 251 mm$^3$ (183-374). All tumors showed suprasellar involvement at diagnosis, and 9 patients (81%) had optic chiasm compression. Sphenoidal extension of the tumor was present in 5 patients (45%), bilateral cavernous sinus involvement in 3 (27%), and invasion to the carotid artery in 6 patients (54%).

Treatment

All patients received DA as first line therapy. 5 patients (45%) were treated with CAB, and two with bromocriptine (BCT) (18%). In addition, four patients initially received BCT and later switched to CAB (36%). The mean dose of BCT was 12.5 mg/day (8.7-15.6) whereas CAB mean dose was 1 mg/week (0.5-1.87) with a highest dose of 4 mg/week. Three patients underwent surgery (27%), two of them had a transcranial approach due to bitemporal hemianopsia and rapid visual deterioration (case 1 and 8). The third case (case 10) underwent transsphenoidal surgery during childhood because hydrocephaly and amaurosis fugax.

Effects of treatment on serum PRL and tumor size

At follow up, patients had PRL levels of 187 ng/mL (99-340). Prolactin normalization, defined as a PRL level of <25 ng/dl, was achieved in four patients (27%). PRL levels decreased 5 to 10 times of its baseline initial value in 5 cases (54.5%). Follow-up was less than six months in three cases because of lost follow-up (case 3), death of septic shock after liver transplantation due to cryptogenic cirrhosis (case 6), and a recent diagnosed
Median tumor volume decreased from 251 mm$^3$ (183.1-374) to 94 mm$^3$ (10-143), representing a reduction of 62.6%. Similarly, a reduction of tumor size from 47 mm (42-51) to 24 mm (14.5-38.5) was documented, representing a 49% reduction in tumor diameter. (Table 3)

Discussion

We described the clinical presentation, biochemical, and tumor response to DA in patients from a single tertiary center in Mexico diagnosed with a giant prolactinoma. Of all prolactin pituitary tumors in our series, microprolactinomas represented 75%, macroprolactinomas 22%, and giant prolactinomas 3.3%, with a similar prevalence to that reported previously $^7,^8$. Consistent with our results, a higher prevalence was seen in male patients (9 male; 2 female) $^7,^8$. However, our patients were significantly younger at diagnosis (33 years old, 25-40), in comparison with another Mexican series that reported a mean age of 44±14 years (n=47) $^7$. One of our male patients identified at 17-years-old was diagnosed with endocrine neoplasia type 1 (MEN1) syndrome. As referred in literature, pituitary tumors in patients with MEN1 syndrome are larger, more frequently invasive and more symptomatic, prompting early diagnosis in younger patients $^{14}$. The rate of prolactin normalization (<25 ng/dl) was 27% (n=4), considerably lower than previously reported (58/97 cases, 60%) $^7,^8$. However, in our center, a very small dose of CAB was used, emphasizing the importance of recent data suggesting to adjust the CAB dose according to tumor size. Ono, et al. reported a 96.2% rate of prolactin normalization when a dose up to 12 mg/week of CAB was used $^{15}$. Interestingly, although small doses of CAB 1.0 mg/week were used, tumor shrinkage up to 67% was seen in one patient. The
tumor volume reduction achieved in our patients (62.5%) is similar to that found in other series with higher doses of DA 16,17. However, PRL normalization was only seen in 27% of cases, which is not consistent with data reported by S. Yarman of 100% of their cases 18. We attribute the low percentage of normalization of PRL first to the low dose of DA, and secondly to a shorter follow-up. No patient reported adverse events during DA treatment including rhinorrhea, headache, variations in any other pituitary functions, or cerebrospinal fluid rhinorrhea.

The majority of giant prolactinomas respond to DA, nevertheless, some patients require surgical treatment due to its mass effect 8,16,17. In our series, three patients required surgery for tumor debulking and to protect visual fields. It is important to point out that giant and invasive prolactinomas usually cannot be cured by surgery. Therefore, medical treatment is the first line therapy even though visual impairment is present 17. With medical therapy, tumor volume and diameter decreased in 62.6 % and 49 % of our patients respectively, which was enough to decompress optic chiasm. Acharya et al. 19, reported ten giant prolactinomas treated with CAB, with a decrease in mean tumor diameter by 49.28 %. In case of prolactinomas that do not respond to medical therapy, surgery might be an option, in addition to other medical therapy approaches such as temozolamide, a chemotherapeutic agent that has been used in aggressive pituitary tumors including giant prolactinomas 4. It is important to consider that up to 99.3 % of prolactinomas respond to CAB (doses up to 12 mg/week) 15. Therefore, progressively increasing CAB dosage is needed first, in order to confirm a true resistant tumor. In addition, if there is no “prolactinoma” response, a differential diagnosis that may mimic a giant prolactinoma has to be ruled out; such as, craniopharyngioma, Rathke’s cleft cyst, germinoma, giant aneurysm, cavernous sinus meningioma, and sphenoid neoplasms, such
as cell carcinoma, metastases, chordoma and chondrosarcoma.

**CONCLUSION**

We report eleven cases with giant prolactinomas, with a male gender predominance. All patients received dopamine agonists with good response despite low doses. Only three patients required surgery due to tumor-related complications. None of the tumors were resistant to treatment with dopamine agonists, which highlights their efficacy. In general, even though our patients had a short-term follow-up, their response to dopamine agonists was a 63% tumor volume reduction and reduction of 51% in tumor diameter. None of them received radiotherapy or temozolamide.

**Abbreviations**

Growth Hormone (GH)
Insulin-like Growth Factor 1 (IGF-1)
Adrenocorticotropic Hormone (ACTH)
Thyroid-stimulating Hormone (TSH)
Prolactin (PRL), Luteinizing Hormone (LH)
Follcile-stimulating Hormone (FSH)
Dopamine Agonists (DA)
Bromocriptine (BCT)
Cabergoline (CAB)
Magnetic Resonance Image (MRI)
Radioimmunoassay Technique (RAI)
Standard Deviation (SD)

Multiple Endocrine Neoplasia Type 1 (MEN1).

Declarations

Competing Interests:

The authors declare that they have no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval and consent to participate: all procedures involving human patients were approved by our Institutional Human Research Ethics Committee (REF#1740). Exemption of informed consent was requested and achieved by the Research Committee because of the observational and retrolective character of the study and based on national legislation. Personal data was previously anonymized, so that the patient identification information was separated from all clinical data used in the present study.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

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AUTHORS' CONTRIBUTIONS

Research idea and study design: TRT, MCP,

Data Acquisition: TRT, MCP, AV, DAC, FDM, LT, AM, JMH, AP, AL, MAG, FJG

Statistical analysis: TT, MCP, DCR

Data analysis/interpretation: TT, MCP, DCR

Manuscript Drafting: TT, MCP, AV, MAG, FJG, DCR
Supervision and mentorship: DCR

All authors have read and approved the manuscript. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Tables

Table 1. Patients baseline characteristics
### Variable | Giant Prolactinomas (n=11)
--- | ---
Mean age (years) | 32.9 (25-40)
Gender (M: F) | 9/2
Mean weight (Kg) | 82 (74.5-109.5)
Mean BMI (kg/m²) | 28.2 (27.25-39.9)
Time to diagnosis (months) | 6 (2-12)

**Symptoms (%)**

| Symptom | % |
| --- | --- |
| Amenorrhea | 50 |
| Galactorrhea | 18 |
| Infertility | 9 |
| Headache | 100 |
| Impaired vision | 81 |
| Decreased libido | 44 |
| Erectile dysfunction | 55.5 |
| Seizures | 9 |

**Hormonal Deficiency at Diagnosis**

| Hormone | % |
| --- | --- |
| GH | 36 |
| TSH | 63 |
| ACTH | 54 |
| Estrogen | 50 |
| Testosterone | 77.8 |
| Panhypopituitarism | 54.5 |

**Hormonal Profile**

| Median baseline | Value (range) |
| --- | --- |
| prolactin (ng/mL) | 2,000 (1,727.5-4,374) |
| LH (UI/L) | 1.09 (0.47-2.03) |
| FSH (UI/L) | 1.6 (0.5-2.81) |
| Testosterone (ng/mL) | 1.64 (0.45-6.85) |
| T4 | 57.2 (21.5-83.63) |
| TSH (UI/L) | 0.88 (0.46-1.97) |
| GH (ng/mL) | 1.7 (0.32-2.8) |
| ACTH (pg/mL) | 31 (19-37) |
| Cortisol (mcg/dL) | 10.2(1.58-14.4) |

**MRI Characteristics**

| Mean volume (mm³) | 251.32 (183.09-374) |
| Mean max size diameter (mm) | 47 (42-51) |

**Bone Density**

| Bone Density | % |
| --- | --- |
| Osteopenia | 50 |
| Osteoporosis | 18 |

**BMI**: body mass index, **GH**: growth hormone, **TSH**: tirotropin stimulating hormone, **ACTH**: adrenocorticotropic hormone, **LH**: luteinizing hormone, **FSH**: follicle stimulating hormone, **Max**: maximum

**Table 2. Follow-up characteristics of giant prolactinomas.**
| Variable                                                      | Giant-prolactinomas |
|--------------------------------------------------------------|---------------------|
| Mean CAB dose (mg/week)                                      | 1 (0.5-1.87)        |
| Mean BCT dose (mg/day)                                       | 12.5 (8.7-15.6)     |
| Tumor volume shrinkage (%)                                   | 94 (10.4-143.3)     |
| Max tumor diameter post-treatment (mm)                       | 23.8 (14.5-38.5)    |
| Tumor reduction (volume %)                                   | 62.5                |
| Follow-up PRL (ng/mL)                                        | 187 (99.7-340.3)    |
| Follow-up (months)                                            | 6 (1-12)            |
| Surgery (n)                                                   | 3/11                |

*BCT: Bromocriptine, CAB: Cabergoline, Max: maximum, PRL: prolactin*

*Table 3. Characteristics of eleven patients with giant prolactinomas treated with DA*
|   | Gender | Age (years) | PRL at diagnosis (ng/ml) | Tumor size at diagnosis (mm) | Hormone deficiency | Surgery | PRL at last follow-up (ng/mL) | Tumor size at last follow-up (mm) | Maximum dose of DA | Tumor shrinkage (%) |
|---|--------|-------------|--------------------------|-------------------------------|--------------------|---------|-------------------------------|-------------------------------|---------------------|---------------------|
| 1 | M      | 30 - 40    | >2,000                   | 56 x33 x41                   | GH, TSH, ACTH, Test | TC      | 21                           | 23 x37 x40                   | CAB 1/wk            | 40%                |
| 2 | M      | 20 - 30    | >2,000                   | 46 x38 x45                   | ACTH, TSH, Test    | --      | 0.48                         | NA                           | BCT 5mg/d CAB 1/wk    | NA                  |
| 3 | M      | 40 - 50    | 4,000                    | 40 x40 x30                   | TSH                | --      | 535                          | 1 HMI                         | BCT 12.5/d CAB 1/wk   | NA                  |
| 4 | M      | 50-60      | 5,496                    | 43 x37 x25                   | TSH, ACTH,         | --      | 24.4                         | 20 x23 x27                   | CAB 0.5mg/wk         | 36%                |
| 5 | M      | 20 - 30    | 8,133                    | 46 x28                       | GH, TSH, ACTH, Test| --      | 58                           | 38 x 25                      | BCT, 15mg/d          | 17%                |
| 6 | M      | 30 - 40    | >2000                    | 47 x31 x30                   | GH, TSH, ACTH, TSH | --      | --*                          | Recent Dx NA               | CAB 1mg/wk           | NA                  |
| 7 | M      | 30 - 40    | >115                     | 33 x62 x49                   | Test               | --      | 15.42                        | 20 x5                        | BCT 15/d, Cab 1mg/wk  | 67%                |
| 8 | M      | 15-20      | 910                      | 30 x42                       | Test               | TC      | 89.38                        | NA                           | BCT 10mg/d           | NA                  |
| 9 | M      | 30 - 40    | 2157                     | 47 x41                       | Test               | --      | 119                          | 13 x15                      | BCT 12.5 mg/day CAB 3 mg/wk | 68%                |
| 10| F      | 15-20      | +                        | 50 x40 x30                   | GH, TSH, ACTH, E2  | TSS     | 60                           | 13 x16 x17                | CAB 4/wk             | 66%                |
| 11| F      | 20 - 30    | >2000                    | 42 x41 x35                   | NA                 | --      | NA                           | Recent Dx NA               | CAB 0.5/wk           | NA                  |

PRL: prolactin, DA: Dopamine Agonists, M: Male, F: Female, GH: growth hormone, TSH: thyroid stimulating hormone, ACTH: adrenocorticotropic hormone, Test: Testosterone, E2: Estrogens, NA: Not available, Dx: Diagnosis, CAB: Cabergoline, BCT: bromocriptine, MEN1: Multiple Endocrine Neoplasia Type 1, TSS: Transsphenoidal surgery, TC: Transcraneal surgery.

--* Died because of cryptogenic cirrhosis.

+ Modification on prolactin levels because of dopamine agonist treatment.
Figures

Figure 1

Patients with hyperprolactinemia included in the study.