Original Article

Clinical Characteristics of Macroprolactinomas and Response to Medical Therapy

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Abstract

Introduction: The presentation of macroprolactinomas and response to treatment may vary according to age, sex and tumour characteristics. To analyse clinical phenotype, biochemical and radiological characteristics of macroprolactinomas presenting to a tertiary care centre. A retrospective observational study from January 2018 to December 2022. **Methods:** Thirty diagnosed cases (18 females, 12 males) of macroprolactinomas were included and followed up for one year. **Results:** The most common presentation was headache (73%), visual disturbances (50%), galactorrhoea (33.3%) and loss of libido (26.6%) along with menstrual cycle disturbances (94%), and infertility (55%) in females. Duration of symptoms (2.22 ± 2.87 vs 4.61 ± 3.4 years), tumour size (4.8 ± 2.09 vs 2.75 ± 1.24 cm) and prolactin levels (5153.5 ± 4755.3 vs 1803.5 ± 3785.5 ng/ml) were different significantly between males and females. Good response to medical therapy was observed in 84% of the treatment-naive patients. **Conclusion:** Macroprolactinomas in males present with shorter duration of symptoms, larger size, higher prolactin levels and more resistant tumours, emphasizing the need for early diagnosis and aggressive management. Medical therapy remains the treatment of choice irrespective of gender.

Keywords: Gender, macroprolactinoma, medical therapy, pituitary tumours

Introduction

Prolactinomas are the most common anterior pituitary tumours, with an annual incidence of 30 per 1,00,000.[1] Macroprolactinomas (≥1 cm in diameter) account for 10% of all prolactinomas with an equal sex ratio of 1:1.[2] Clinical phenotype and biological behaviour of macroprolactinoma differ according to age and sex. The younger population and males are known to harbour aggressive tumours.[3] The clinical presentation of macroprolactinoma varies depending on the tumour size, mass effects and associated other pituitary hormone involvement. We have sparse data regarding the clinical behaviour and outcomes of macroprolactinomas from India, especially in the northeast region of the country. The present study was undertaken to analyse the clinical phenotype in both genders and different age groups in macroprolactinomas and to assess the response to medical therapy at the end of one year.

Materials and Methods

This was a single-centre retrospective observational study, conducted in the department of Endocrinology at a tertiary care centre in north-eastern India. The records of diagnosed cases of macroprolactinomas presenting between January 2018 and December 2022 and those who completed one year of follow-up were analysed. Diagnosis of macroprolactinoma was made on the basis of serum prolactin >200 ng/ml and evidence of pituitary tumour on magnetic resonance imaging (MRI) pituitary with a maximum tumour size of more than or equal to 1 cm in diameter.[4] Patients were excluded if they had any other condition causing hyperprolactinemia, pregnant and lactating women, and patients with clinical and biochemical evidence of mixed pituitary tumour.

Clinical assessment

All relevant history, including age, sex, loss of libido, headache and visual disturbances, galactorrhoea, menstrual

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disturbances, infertility and hirsutism in females, was recorded. The modified Ferriman Gallwey score was used to score hirsutism. Humphrey's perimetry was used to assess the visual field defects.

Biochemical measurements

Serum prolactin, insulin-like growth factor 1 (IGF-1), thyroid-stimulating hormone (TSH), thyroxine (T4), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone and 8 am cortisol were analysed in all the patients in fasting state between 8 and 9 am by electrochemiluminescence assay using Roche Cobas e411 analyser. Normal prolactin level was defined as 4.6-21.4 ng/ml for males and 6-29.9 ng/ml for females. A 1:100 dilution was done for prolactin measurements if suspecting the hook effect. Prolactin levels were repeated at one month, three months, six months and at the end of one year. Secondary hypogonadism was defined on the basis of FSH and LH values ≤10 mIU/mL along with a history of oligomenorrhoea/amenorrhoea for females and total testosterone less than or equal to 200 ng/dl for males. Secondary hypocortisolism was defined by 8 am cortisol <5 µg/dl, and central hypothyroidism was defined by low T4 along with normal or low-normal TSH. Serum IGF1 and growth hormone suppression test with 75 gram glucose were done to rule out concomitant growth hormone secretion. A growth hormone cut-off level of <1 ng/ml excluded growth hormone excess.

Imaging findings

MRI of the pituitary was performed on a 1.5 Tesla system, including both non-contrast and contrast films. Tumour size was evaluated using the maximum craniocaudal diameter obtained in coronal sections. The Knosp classification system was used to quantify invasion of the cavernous sinus, in which only grades three and four define true invasion of the tumour into the cavernous sinus. Grade 0–2, where the tumour does not extend beyond the lateral margin of the internal carotid artery (ICA), was labelled non-invasive.[5] After starting medical management, MRI was repeated at six months and 12 months. Tumour volume was calculated as 0.52 × height × length × width of the tumour. Tumour shrinkage was evaluated as the reduction of tumour volume >50% compared to the baseline. Tumours larger than 4 cm in diameter were called giant prolactinomas.

Treatment

Medical therapy with cabergoline was started as first-line therapy for macroprolactinoma, as per the treatment protocol at our institution. Cabergoline was initiated with a starting dose of 1 mg in the 1st week and titrated at 4, 12 and 36 weeks depending on the response to hyperprolactinemia, to maintain normal prolactin levels. Resistance to medical treatment was defined as failure to normalize prolactin levels and tumour size reduction by more than 50% on cabergoline doses of up to 2 mg/week for a minimum of 6-month period.[6] Resistance patients were given a trial of cabergoline doses up to 3.5 mg/week. In case of no or inadequate response, patients were offered second-line treatment such as transsphenoidal surgery or radiotherapy. For some patients, transsphenoidal surgery was chosen as the first modality of treatment as per the indications. Those found with pituitary hormone deficiencies were replaced adequately.

Statistical analysis

Qualitative data were represented in the form of frequency and percentage. Association between qualitative variables was assessed by the Chi-square test and Fisher's exact test. Quantitative data were represented using mean ± SD, median, and interquartile range. Association between quantitative variables was assessed using Student's *t*-test. Relationship between quantitative data was assessed using Pearson's correlation if data passed 'Normality test' and Spearman's correlation if the data failed the 'Normality test'. Results were graphically represented where deemed necessary. A *P* value less than 0.05 was considered significant. SPSS version 20 was used for the statistical analyses.

Ethical aspects

Our study was approved by institutional Ethics Committee (EC- 190/2007, 23/06/2023). In view of retrospective study design, informed consent was omitted. The study was conducted in accordance with principles outlined in declaration of Helinski (1964).

Results

A total of 30 diagnosed cases (18 females, 12 males) of macroprolactinomas were analysed between the period of January 2018 and December 2022. The clinical characteristics of these patients are shown in Table 1. The mean age of presentation was 34.6 ± 13.7 years, ranging from 20 to 70 years. Female to male ratio was 1.5:1. Overall, the most common presentation was headache (n = 22; 73.3%), followed by visual disturbances (n = 15; 50%), galactorrhoea (n = 10; 33.3%) and loss of libido (n = 8; 26.6%). Of 18 females studied, additional complaints were menstrual cycle disturbances (n = 17; 94%) and infertility (n = 10; 55.5%). Visual disturbance was one of the major complaints among which optic atrophy (n = 2; 13.5%), bitemporal hemianopia (n = 10; 66.67%) and monocular temporal field defect (n = 4; 26.67%) were found.

Mean prolactin level was 3143.467 ± 4445.56 ng/ml, with values ranging from 290.6 to 18097 ng/ml. As per our predefined criteria, central hypogonadism was seen in 70% (n = 21) patients, secondary adrenal insufficiency in 30% (n = 9) and central hypothyroidism in 10% (n = 3) patients. The mean pituitary tumour volume was 25.16 ± 32.11 cm^3, and the maximum tumour diameter was 3.58 ± 1.9 cm. Cavernous sinus invasion and apoplexy were observed in 36.7% (n = 11) of the patients. Giant prolactinoma was observed in 33.3% (n = 10) of the patients.

Males had a shorter duration of symptoms as compared to females (2.22 ± 2.87 years vs. 4.61 ± 3.4 years, *P* = 0.049). The symptoms in females in decreasing order

Table 1: Sex-wise distribution and characteristics of macroprolactinoma cases

Parameters	Total (*n*=30)	Female (*n*=18)	Male (*n*=12)	*P*
Age (years)	34.6±13.7	30.72±8.85	40.5±17.65	0.096
Symptoms duration (years)	3.39±3.3	4.61±3.4	2.22±2.87	0.049
% of symptoms				
Galactorrhoea (%)	33.3	55.5	0	
Oligomenorrhoea/amenorrhoea (%, females only)	-	94.4	-	-
Infertility (%, females only)	-	55.56	-	-
Loss of libido (%)	26.67	22.2	33.3	0.517
Headache (%)	73.3	72.2	75	0.817
Visual disturbances (%)	50	38.8	66.67	<0.001
Serum prolactin (ng/ml)	3143.5±844.7	1803.5±3785.5	5153.5±4755.3	0.05
MRI findings				
Tumour volume (cm^3)	25.1±32.1	10.89±15.97	50.83±38.36	0.009
Apoplexy (%)	36.7	44.4	25	0.35
Cavernous sinus invasion (%)	36.7	27.7	50	0.036
2° hypogonadism (%)	70	72.2	66.67	0.64

of frequency were menstrual cycle disturbances (94.4%), headache (72.2%), galactorrhoea (55.5%), infertility (55.5%), visual disturbances (38.8%) and loss of libido (22.2%), whereas males most commonly presented with headache (75%), visual disturbances (66.67%) and loss of libido (33.3%). Males had higher serum prolactin values as compared to females (4242 ng/ml (2001- 7035); 625 ng/ml (302.15- 1253.5) ($P = 0.05$). Males harboured larger tumours when compared to females (4.8 ± 2.09; 2.75 ± 1.24, $P = 0.0074$). Ten cases of giant prolactinoma were discovered, which were more common in males (66.6% vs 11.1%, $P < 0.001$) than females.

Compared to young patients (18-35 years old), older group subjects (those above 35 years) had significantly higher tumour volumes (44.83 vs 12.4 cm≥; $P = 0.03$) and higher frequency of giant prolactinoma (50% vs 22.2%; $P = 0.001$) [Table 2]. Serum prolactin levels (822.35 vs 2418 ng/ml; $P = 0.12$) and maximum tumour diameter (3.002 vs 4.44 cm; $P = 0.08$) did not show significant difference between the two age groups. We found a significant positive correlation between serum prolactin levels and the maximum tumour diameter (r = 0.829, $P < 0.001$).

Medical therapy was chosen as the first modality of treatment in 83.3% (n = 25) of patients [Table 3]. At six months, 72% (n = 18) patients showed good response to medical therapy as shown by normalization of prolactin and reduction in tumour size [Figure 1] and were continued with the same doses of cabergoline. Seven patients did not show prolactin normalization. In these cases, cabergoline dose was escalated to a maximum of 3.5 mg/week. At the end of one year, out of these seven patients, three patients showed adequate response, two patients had discordant response that is prolactin was normalized but tumour size did not decrease, and the remaining two patients had persistently raised prolactin without tumour size reduction, who were

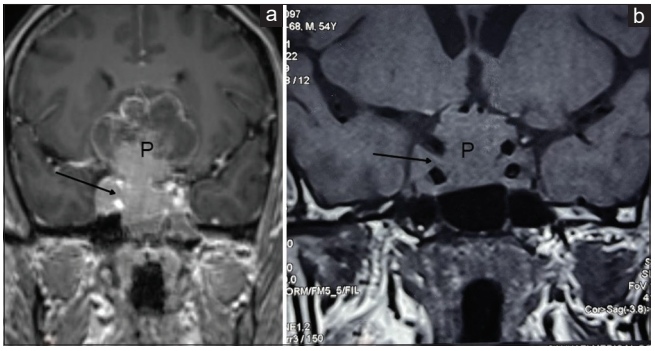

Figure 1: MRI image of a patient with giant macroprolactinoma: (a) Pre-treatment image showing large-sized pituitary adenoma (P) with bilateral Knosp grade IV invasion (black arrow) in the coronal TIW postcontrast image. (b) MRI image 6 months after treatment with cabergoline showing >50% reduction in tumour size (P) but persistent Knosp grade IV (black arrow) invasion

then subjected to transsphenoidal surgery and radiotherapy[1]. Seven patients underwent surgery, the indications being cystic prolactinomas (n = 1), apoplexy (n = 2), personal preference (n = 2), and as second line of treatment in two patients nonresponsive to medical therapy (n = 2). Out of 25 patients undergoing medical therapy, seven patients had resistant prolactinomas (M: F = 4:3), of which two patients had aggressive tumours (both males) (increasing tumour size despite medical therapy).

Menstrual cycle was normalized in all women in the reproductive age group after treatment, implying an improvement in hypogonadism. Additionally, two patients conceived during the treatment. Two out of eight males with hypogonadism had normal testosterone levels after medical therapy. However, during follow-up, patients on levothyroxine (n = 3) and hydrocortisone (n = 9) continued to require the same doses. Visual field assessment on follow-up showed clinical improvement in all cases responding to therapy.

1 "At the end of one year, three patients…"

Table 2: Age-wise distribution and characteristics of macroprolactinoma cases

Parameters	18-35 years (*n*=18)	36-70 years (*n*=12)	*P*
Age (years)	25.55±3.66	48.25±11.72	<0.001
Sex ratio (F: M)	2.6:1	0.83:1	0.392
Symptom duration (years)	3.83±3.57	2.72±2.87	0.355
Serum prolactin	822.35 (440-2745.3)	2418 (312-7118.3)	0.1207
MRI findings			
Tumour volume (cm^3)	12.42±14.12	44.83±41.93	0.03
Maximum tumour diameter (cm)	3.002±1.004	4.44±2.48	0.08
Apoplexy (%)	38.8	33.3	0.576
Cavernous sinus invasion (%)	33.3	41.6	0.538
Giant prolactinoma (%)	22.2	50	0.188

Table 3: Response to therapy

Parameters	Total (*n*=30)	Male (*n*=12)	Female (*n*=18)	*P*
Medical therapy as first line of treatment (%)	83.3	75	88.9	0.277
Surgery as first line of treatment (%)	16.7	25	11.11	0.47
Average cabergoline dose per week (mg/week)	1	1	1	
Treatment modality chosen				
Cabergoline alone (%)	76.7	58.3	88.9	0.01
Cabergoline + surgery + radiotherapy (%)	6.7	16.7	0	
Follow-up at 1 year				
% of patients showing normalization of prolactin	93.3	83.3	100	0.217
% of patients showing >50% reduction in tumour volume	86.7	75	94.4	0.136

Discussion

Macroprolactinomas are tumours of the anterior pituitary lactotrophs secreting prolactin. The usual presentations are due to mass effect (headache, visual disturbances) or hyperprolactinemia *per se*. In concordance with previous studies, in our study, we found headache as the most common presentation followed by visual disturbances. There was a gender difference in the clinical presentation in our study with females mainly presenting with symptoms such as menstrual cycle disturbances, infertility, headache, and galactorrhoea, whereas males mainly presented with symptoms due to mass effect. Previous studies have depicted males to have presented at a more advanced age than females with larger tumour size and higher prolactin levels as compared to females.[4,7] Possible explanation could be that early symptoms of hypogonadism are largely disregarded in males, and medical attention is not sought unless advanced symptoms due to mass effect appear. Also, the male reproductive axis seems more resistant to hyperprolactinemia than the female one, contributing further to the length of the asymptomatic phase.[3,8] Our study revealed similar findings with larger tumour size and higher prolactin levels in males, though we did not find significantly advanced age of presentation in males as compared to females. We found shorter duration of symptoms in males compared to females, owing probably to mass effects due to tumour *per se* and very rapid proliferation potential of tumours in males, as has been discerned in previous studies.[7,9] In our study, the maximum tumour diameter was somewhat larger as compared to that reported in previous studies (3.93 cm in males and 2.49 cm in females) from other parts of India.[4] The reason behind could be socioeconomic factors, lack of education and inadequate diagnostic facilities leading to delayed medical attention. Also, the possible role of genetic and environmental factors cannot be denied. We found pituitary hormone deficiencies in a significant proportion of the patients with the most common being secondary hypogonadism (70%), followed by secondary adrenal insufficiency (30%) and secondary hypothyroidism (10%). The well-known explanation is the inhibitory effect of prolactin on gonadotrophs as well as the compression of gonadotrophs and other anterior pituitary cells by the tumour. Other anterior pituitary hormone deficits did not show a significant difference between the two sexes.

The first line of treatment of prolactinoma is medical therapy with dopamine agonists.[10] Therefore, majority (n = 25, 83.3%) of our patients were treated with cabergoline. Among these, 72% (n = 18) showed a good response to therapy with cabergoline with median dose of 1 mg in both males and females, whereas the rest seven required doses 2-3.5 mg/week. In a study of 122 cases of macroprolactinoma by Delgrange *et al.*,[11] normoprolactinemia was achieved in 94% (n = 115) on cabergoline doses of ≤1.5 mg/week. The another study by Colao *et al.*[12] assessed cabergoline response in 107 patients and found 64% of patients achieved normalization of prolactin levels. However, in an Indian study by Khare *et al.*,[4] a lower response to medical therapy (69.31% (n = 61) was observed in 88 treatment-naïve patients.

As observed in the study by Khare *et al.*,[4] resistant tumours have been observed in a significant proportion of patients (30%), without significant gender differences. We have found a similar response with 28% of patients being resistant to medical therapy. The role of genetic factors in resistance to medical therapy and benefits of debulking surgery has been described.[13]

Prolactinomas in males have been reported to be aggressive. The preponderance of larger prolactinoma in males is not due to longer delay in diagnosis but to high proliferative index in them, which are more frequently invasive and less likely to respond to bromocriptine therapy.[7] Likewise, Nishioka *et al.*[9] described male prolactinomas to exhibit higher proliferative index than females. In our cohort, we had found males having higher tumour size with shorter duration of symptoms; however, proliferative index and other immunohistochemistry markers were not studied. Also, the two cases labelled aggressive were males.

We found correlation between serum prolactin levels and maximum tumour diameter, which has also been reported by other studies.[4,9,12] Contrary to earlier findings, our study observed older age to possess larger tumour volume and more frequent giant prolactinoma though tumour diameter and serum prolactin values did not differ. Moreover, there was no significant difference with respect to clinical phenotype, tumour behaviour and treatment outcomes between younger (18-35 years) versus older (>35 years) subgroups. This could be attributed to referral bias or ethnic and genetic variants.

The limitations of our study were that it was a retrospective study and the sample size was small. We had inadequate immunohistochemistry and genetic study for multiple endocrine neoplasia (MEN1) was not available. Furthermore, large, prospective studies with immunohistochemistry studies and relevant genetic studies are needed to better assess clinical characteristics and proliferative potential of these tumours.

Conclusion

Macroprolactinomas in males are larger, with shorter duration of symptoms, higher prolactin levels and more resistant tumours, necessitating early diagnosis and aggressive management. Older subjects had larger tumour volume, indicating delayed presentation. There was a good response to medical therapy in both males and females, which remains the treatment of choice.

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None.

Authors' contribution

Pooja Tiwari designed research, managed recruitment, wrote manuscript and performed statistical analysis. Uma K Saikia contributed in recruitment, participated in manuscript writing and did proof reading. Abhamoni baro and Ashok Krishna Bhuyan contributed in recruitment and proof reading.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

All data underlying the results are available as part of the article.

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