



Gender differences in macroprolactinomas: a single centre experience

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Abstract

Macroprolactinomas are the most common functional pituitary tumours. Hypotheses proposed to explain predominance of large tumours in males are: i) diagnostic delay, as hyperprolactinaemia remains under recognised in males and ii) gender-specific difference in tumour proliferation indices. Our study objectives are to compare gender differences in clinical, biochemical, radiological features, management outcomes and cabergoline responsiveness in macroprolactinomas. Drug resistance was defined as failure to achieve prolactin normalisation and >50% reduction in tumour volume with cabergoline (3.5 mg/week dose for minimum 6 months duration). The baseline characteristics of 100 patients (56 females and 44 males) with macroprolactinoma were analysed. Drug responsiveness was analysed in 88 treatment naïve patients, excluding 12 post-primary trans-sphenoidal surgery cases. We found that females (30.29 ± 10.39 years) presented at younger mean age than males (35.23 ± 9.91 years) ($P < 0.01$). The most common presenting symptom was hypogonadism (oligo-amenorrhoea/infertility) in females (96.15%) and symptoms of mass effect (headache and visual field defects) in males (93.18%). Baseline mean prolactin levels were significantly lower in females (3094.36 ± 6863.01 ng/ml) than males ($7927.07 \pm 16\,748.1$ ng/ml) ($P < 0.001$). Maximal tumour dimension in females (2.49 ± 1.48 cm) was smaller than males (3.93 ± 1.53 cm) ($P < 0.001$). In 88 treatment naïve patients, 27.77% females and 35.29% males had resistant tumours ($P = 0.48$). On subgrouping as per maximum tumour dimension (1.1–2 cm, 2.1–4 cm and >4 cm), gender difference in response rate was insignificant. In conclusion, macroprolactinomas are equally prevalent in both sexes. Macroprolactinomas in males predominantly present with symptoms of mass effects, as against females who present with symptoms of hypogonadism. Males harbor larger tumours but are equally cabergoline responsive as those in females.

Key Words

- ▶ macroprolactinoma
- ▶ gender differences
- ▶ cabergoline resistance
- ▶ responsiveness

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Introduction

Macroprolactinomas constitute approximately half of all the functioning pituitary macroadenomas (1).

Prolactinoma (majority being microprolactinoma) are usually diagnosed in women aged 20–50 years, with a

female:male ratio of 10:1. This female preponderance is not seen in macroprolactinoma cases (1). Males harbour larger macroprolactinoma at presentation, as compared with females (2, 3). Diagnostic delay owing to subtle symptoms



of hypogonadism in males may lead to late recognition and larger tumour size. Additionally it is proposed that macroprolactinoma in males have higher growth potential, as deduced from studying tumour proliferation markers (3, 4).

The aim of this retrospective analysis was to compare the gender differences in clinical, biochemical, radiological features and management outcomes in patients with macroprolactinoma.

Patients and methods

Medical records of patients with macroprolactinoma presenting to a tertiary care centre in western India between 2001 and 2014 were retrospectively analysed. The diagnosis of macroprolactinoma was based on elevated prolactin level (>200 ng/ml) and evidence of pituitary adenoma on magnetic resonance imaging (MRI) with the largest dimension ≥ 1 cm. Tumours larger than 4 cm were labelled giant prolactinomas. For inclusion in the analysis, a minimum follow-up of 1 year after starting the medical treatment was the prerequisite.

Macroprolactinomas with MEN1 syndrome were not included in this study. The data retrieved from files (at baseline and on serial follow-up) included: clinical features, hormonal investigations, imaging (MRI) details, the management modalities and the outcomes (clinical, hormonal and radiological).

Imaging studies

Patients underwent MRI of pituitary, on a 1.5 T MR system (Sonata Vision; Siemens, Erlangen, Germany) using eight channel circularly polarised head coil. All the images (baseline and follow-up) were reported by a single experienced radiologist in a predefined format. Knosp classification system was used to quantify invasion of the cavernous sinus, in which, grade 3 and grade 4 defined 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) were labeled noninvasive (5). After starting medical management, MRI was repeated at 6 months, 12 months and subsequently as per the response in an individual patient. Tumour shrinkage was evaluated as the reduction of the maximal dimension and tumour volume compared with baseline. Tumour volume was calculated as $\pi/6 \times \text{height} \times \text{length} \times \text{width}$ of the tumour (6).

Visual perimetry

The visual field was assessed by Goldmann–Freidman perimetry at baseline and repeated subsequently as clinically required.

Hormonal assay

The normal range for prolactin was 100–532 mU/l (5–25 ng/ml) for females and 100–425 mU/l (5–20 ng/ml) for males. Prolactin assay is a two-site sandwich immunoassay using direct chemiluminometric technology, which uses constant amounts of two antibodies. Macroprolactin was analysed if clinically indicated. Pituitary hormonal deficiencies were defined as follows: hypocortisolism was defined as 0800 h serum cortisol <137.5 nmol/l (5 $\mu\text{g/dl}$) while the 0800 h serum cortisol levels >275.9 nmol/l (10 $\mu\text{g/dl}$) were considered normal. Corticotropin stimulation test was not done due to unavailability of corticotrophin in India. Central hypothyroidism was defined as low <57.91 nmol/l (<4.5 $\mu\text{g/dl}$) total thyroxine with low/normal (≤ 4 mIU/l) serum thyrotropin levels (7). Patients were considered to have secondary hypogonadism if the follicle-stimulating hormone and luteinising hormone levels were each less than 10 mIU/ml in women with oligo/amenorrhoea and in men with low-serum testosterone <10.4 nmol/l (<3.0 ng/ml). Patients underwent thyroid and cortisol axis evaluation at baseline and then yearly. Evaluation for growth hormone (GH) axis was not done in all the patients due to resource limited set up. All patients were clinically evaluated for evidence of GH excess and whenever it was suspected, insulin-like growth factor 1 (IGF1) levels were done. Patients with raised IGF1 (thus with GH and prolactin co-secretion) were not included in the study.

All hormonal measurements were carried out by chemiluminescence assay (Advia Centaur CP). Intraassay and interassay coefficients of variation were less than 8 and 10% respectively, for all hormonal evaluation.

Treatment and responsiveness

At our institute, medical therapy with cabergoline is the first line therapy for macroprolactinoma. Cabergoline is started at dose of 0.25 mg in the first week and then increased to 0.5 mg/week in the second week. Further dose is escalated (if need be) by 1 mg/week, at 2 monthly intervals. Before labelling patient as cabergoline resistant, patient was exposed to one year of cabergoline treatment which included minimum 6 months of 3.5 mg/week cabergoline treatment. Failure of prolactin normalisation



and >50% reduction in tumour volume with this treatment was defined as resistance. In resistant patients, maximum dose of cabergoline used was 7 mg/week and if still unresponsive, second line therapies were offered. Second line management includes trans-sphenoidal surgery (TSS) by a single experienced neurosurgeon and/or fractional radiotherapy (RT). The technique of RT used was modern high precision three-dimensional conformal RT. Dose delivered was 45 Gy in 25 daily fractions over 5 weeks prescribed to the isocentre of the planning target volume. 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 χ^2 -test with Continuity Correction for all 2×2 tables and Fisher's exact test for all 2×2 tables where P value of χ^2 -test was not valid due to small counts. Adjacent row data of more than 2×2 tables were pooled and χ^2 -test reapplied in case more than 20.0% cells having expected count <5.

Quantitative data were represented using mean \pm s.d. and median and interquartile range.

Relationship between quantitative data will be assessed using Pearson's correlation if data pass 'Normality test' and by Spearman's correlation if data fail 'Normality test'.

Predictiveness of factors for 'Response status' as dependent variable by a set of independent (predictor) variables was assessed using binary logistic regression analysis.

Results were graphically represented where deemed necessary. P value <0.05 was considered significant. SPSS version 13 was used for most analysis.

Results

One hundred patients (56 females and 44 males) with macroprolactinoma, diagnosed from year 2001 to 2014, were analysed. Females presented at a younger age as compared with males (30.29 ± 10.39 vs 35.23 ± 9.91 years, $P < 0.01$). The majority ($n = 33$; 57.1%) of the females presented in the third decade whereas percentage of males presenting in the second, third and fourth decade was 27.3% ($n = 12$), 34.1% ($n = 15$) and 29% ($n = 13$) respectively. Age wise and sex wise distributions of study cohort are depicted in Fig. 1.

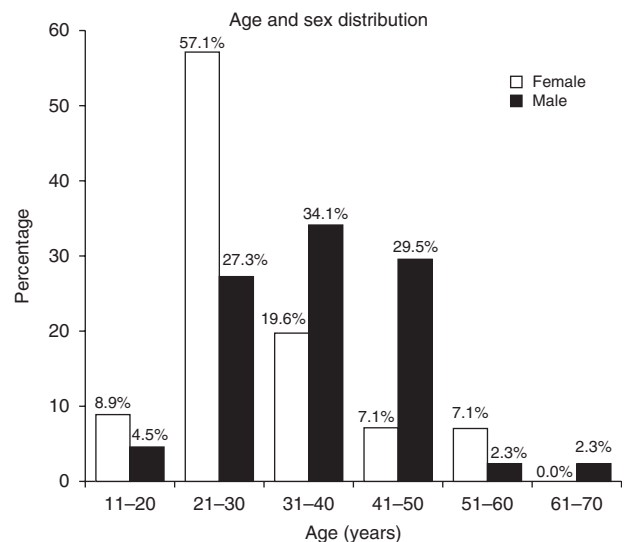


Figure 1

Age and sex distributions (the percentage values are not for the entire cohort but for the males and females separately).

The presenting symptom in females was due to hypogonadism (oligo-amenorrhoea/infertility) in 96.15% (50/52 females; excluding four postmenopausal females), while only 6.81% ($n = 3$) males presented with symptoms of hypogonadism (decreased libido, erectile dysfunction infertility) ($P < 0.001$). The presenting symptoms in males were due to symptoms of sellar mass effect in 93.18% ($n = 41$; headache in 33, visual field defect in 17), while only 12.5% ($n = 7$, visual field defects) females presented with similar complaints ($P < 0.001$). On enquiry 50% ($n = 23$) females had headache and 72.72% ($n = 32$) males had decreased libido, though these symptoms were not their primary concern. Galactorrhea was seen in 53.57% ($n = 30$) females and 6.81% ($n = 3$) males. Other less common symptoms were cranial nerve palsies in four (one female and three males), seizures in three (two females and one male) and cerebrospinal fluid (CSF) rhinorrhoea in two (one female and one male) and epistaxis in one male patient. Baseline prolactin levels were significantly lower in females (3094.36 ± 6863.01 vs 7927.07 ± 16748.10 ng/ml) as compared to males ($P < 0.001$). Baseline biochemical gonadal axis evaluation was available in 72.72% ($n = 32/44$ males) and all of them had secondary hypogonadism. Central hypothyroidism was seen in three patients (two females and one male) and central hypocortisolism was seen in three patients (two females and one male) at baseline.

Females had significantly smaller tumours than males. The mean maximal tumour dimension was 2.49 ± 1.48 cm

Table 1 Comparison of baseline characters in females and males with macroprolactinoma ($n=100$, 56 females, 44 males).

Baseline characters	Females ($n=56$)	Males ($n=44$)	P value
Age at presentation (years)			
Mean (\pm s.d.)	30.23 \pm 10.39	35.23 \pm 9.91	<0.01
Range	15–59	18–62	
Presenting symptom			
Hypogonadism	96.15%	6.81%	<0.001
Symptoms of mass effect	12.5%	93.18%	<0.001
Maximal tumour dimension (cm)			
Mean	2.49 \pm 1.48	3.93 \pm 1.53	<0.001
Range	0–7.2	1.3–7.8	
Tumour volume (cm ³)			
Mean (\pm s.d.)	8.00 \pm 14.4	26.08 \pm 28.1	<0.001
Range	0.396–97.34	0.858–117	
Percentage of invasive tumours by Knosp	26.78%	79.54%	<0.01
Baseline prolactin level (ng/ml)			
Mean (\pm s.d.)	3094.36 \pm 6863.01	7927.07 \pm 16 748.10	<0.001
Range	201–43 165	239–90 000	

in females and 3.93 \pm 1.53 cm in males ($P<0.001$). On applying Knosp scale of pituitary tumour invasiveness, significantly less number of females had invasive tumours than males. Table 1 shows comparison of baseline characters in females and males with macroprolactinoma.

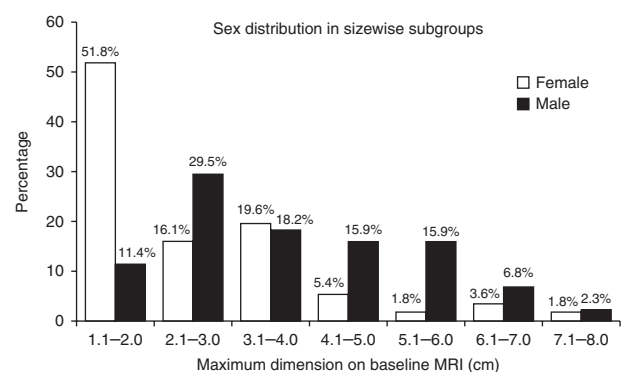
Figure 2 shows sex distribution in tumour size wise subgroups in our cohort. The majority (51.8%) of females had maximum tumour dimension ≤ 2 cm, while 29.5% ($n=14$), 19.6% ($n=8$), 15.9% ($n=7$) and 15.9% ($n=7$) males had tumour dimension between 2.1 and 3 cm, 3.1 and 4 cm, 4.1 and 5 cm and 5.1 and 6 cm respectively. Giant prolactinomas were present in 25 (seven females and 18 males) patients.

The baseline prolactin correlated well with the maximum tumour dimension at baseline ($r=0.57$ for entire cohort; 0.6286 for females and 0.5848 for males) as well as with tumour volume at baseline ($r=0.65$). The baseline prolactin correlated with the maximum tumour dimension at baseline with greater strength ($r=0.7901$ for entire cohort; 0.8064 for females and 0.6923 for males) when the log scale was used (Fig. 3).

Out of 88 treatment naive patients, 69.31% (39/54 females and 22/34 males) were cabergoline responsive. The median dose requirement was 1 mg/week for females and 1.5 mg/week for males ($P=0.127$). On follow-up, 90% females ($n=45/50$) had resumption of regular menses. In the male patients where baseline biochemistry was available, 62.5% ($n=20/32$) had recovery of hypogonadism i.e., normalisation of testosterone. Twelve patients who were referred post-primary TSS had elevated prolactin levels (mean: 2733.292 \pm 4512.032 ng/ml, range: 42.5–12 500 ng/ml) and tumour residue (2.60 \pm 1.44). All these cases responded to cabergoline (median dose: 1 mg

within 1 year. The cabergoline dose was similar to that of drug naive population (cabergoline responders).

Overall the difference in proportion of resistant tumours in females (15/54; 27.77%) and males (12/34; 35.29%) was not statistically significant ($P=0.48$). The difference in proportion of resistant tumours in females and males when subgrouped as per the maximum tumour dimension: 1.1–2 cm (3.5% vs 0%), 2.1–4 cm (47.36% vs 23.52%) and >4 cm (71.42% vs 57.14%) was also statistically insignificant. The difference in proportion of resistant tumours in females and males for noninvasive tumours was statistically insignificant (7.6% vs 11.11%). For invasive tumours, proportion of females ($n=12/15$, 80%) having resistant tumours were significantly more as compared with males ($n=11/25$, 44%). At 1-year follow-up, the mean percentage reduction in maximum tumour dimension was 52.52 \pm 21.09% (females: 49.78%,

**Figure 2** Sex distribution in tumour size wise subgroups (the percentage values are not for the entire cohort but for the males and females separately).

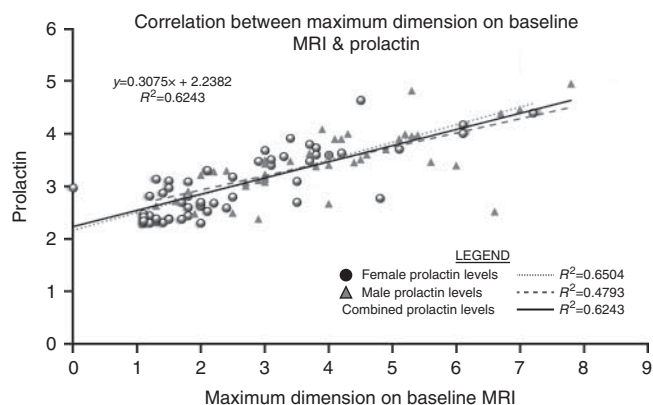


Figure 3
Correlation between maximum dimensions on MRI and prolactin at baseline (log scale).

males: 57.73%; $P=0.18$) in responsive and $29.84 \pm 21.6\%$ (females 21.93%, males 39.74%, $P=0.03$) in resistant patients (Table 2).

Out of 27 resistant cases, nine patients (two females and seven males) responded to high-dose cabergoline (up to 7 mg/week). Remaining resistant cases were subjected to TSS (four females and three males), RT (two females) and combined TSS+RT (six females and three males). Among these resistant cases, five had discordant response i.e., prolactin failed to normalise but there was > 50% reduction in tumour volume. Out of these five cases with discordant response, four responded to higher dose of cabergoline, and one case required TSS+RT in addition.

In seven resistant patients treated with TSS, the post-operative cabergoline requirement decreased (median 2 mg) in all the patients with normalisation of prolactin. In nine resistant patients, RT was given after TSS for persistence of tumour after TSS (six patients) and progressive neurodeficit or regrowth after TSS (three patients). In all these patients except one, there was no further tumour growth and at median duration of 2 years after RT, the prolactin was controlled on median cabergoline dose of 1 mg. One patient had resistant giant prolactinoma which persisted despite TSS (twice), RT and temozolamide therapy and patient succumbed to the disease. Two resistant patients were managed by only RT after high dose cabergoline therapy as they refused TSS. The cabergoline dose requirement decreased with normalisation of prolactin, at 2-year follow-up after RT. Twelve patients who were referred to us after TSS had elevated prolactin levels and significant tumour residue, which responded to cabergoline ≤ 3.5 mg/week within 1 year.

Discussion

Prolactinoma (>90% being microprolactinoma) are usually diagnosed in women aged 20–50 years, with a female: male ratio of 10:1. This female preponderance is not seen in macroprolactinoma, as reported in a series described by Colao *et al.* (1, 8). Our data also reconfirms that macroprolactinomas are equally prevalent in both sexes.

In our cohort, there was a striking gender difference in the clinical presentation. Females presented with symptoms of hypogonadism (amenorrhea and galactorrhea), whereas males presented with symptoms of sellar mass effect (headache and visual compromise). This is in accordance with reported macroprolactinoma clinical presentation. In females, the menstrual dysfunction and/or galactorrhea which set in with rising serum prolactin are identifiable and early medical attention is sought. In males, the symptoms of hypogonadism (loss of libido and/or erectile dysfunction) largely remain unattended, and medical attention is sought later, *per se* due to tumour growth. Also, the male reproductive axis seems more resistant to hyperprolactinaemia than the female one, contributing further to the length of the asymptomatic phase (8, 9).

Overall the observed gender differences in our cohort (younger age at presentation, smaller tumour dimension and lesser serum prolactin levels in female) are coherent with the reported gender differences in macroprolactinoma series (Table 3). Notably, tumour size was the largest in our cohort. The reason behind the larger tumours could be, socioeconomic factors leading to delayed medical attention. Also, possible role of genetic and epigenetic factors need further research.

Table 2 Comparison of resistance in females and males with macroprolactinoma ($n=88$; 54 females and 34 males).

	Females	Males	P value
Resistant tumours (%)			
Overall (F:54, M:34)	27.77	35.29	0.48
1.1–2 cm (F:28, M:3)	3.00	0.00	1
2.1–4 cm (F:19, M:17)	47.36	23.52	0.17
> 4 cm (F:7, M:14)	71.42	57.14	0.65
Invasive (F:15, M:25)	80	44	0.026
Noninvasive (F:39, M:9)	7.6	11.11	0.738
Decrease in maximum tumour dimension (%)			
Overall (F:54, M:34)	42.04 ± 23.8	51.15 ± 22.4	0.078
Responsive (F:39, M:22)	49.78 ± 21.26	57.73 ± 20.3	0.18
Resistant (F:15, M:12)	21.93 ± 17.9	39.74 ± 22.4	0.03

F, females; M, males.

Table 3 Gender differences macroprolactinoma: comparison of our series with literature.

Baseline characters	Our series			(2)			(3)			(4)		
	Females (n=56)	Males (n=44)	P value	Females (n=49)	Males (n=58)	P value	Females (n=27) (macro/micro div not clear)	Males (n=16)	P value	Females (n=51) (15 macro)	Males (n=45) (40 macro)	P value
Age at presentation (years)												
Mean (\pm s.d.)	30.2 \pm 10.3	35.2 \pm 9.9	0.004	36 \pm 14	36 \pm 14	0.9	37 \pm 10	37 \pm 11	NS	28 \pm 1	42 \pm 2	<0.001
Range	15-59	18-62					17-60	19-53				
Maximal tumour dimension (cm)												
Mean (\pm s.d.)	2.4 \pm 1.4	3.9 \pm 1.5	<0.001	1.72 \pm 0.72	2.58 \pm 1.54	<0.001	NA	NA		1.0 \pm 0.1	2.6 \pm 0.2	<0.001
Range	0-7.2	1.3-7.8										
Tumour volume (cm ³)												
Mean (\pm s.d.)	8.00	26.08	<0.001	NA	NA		8.5 \pm 120.2-4.9	16.6 \pm 14	0.009	NA	NA	
Range	0.39-97.3	0.85-117						1-56.3				
Baseline prolactin (ng/ml)												
Mean (\pm s.d.)	3094 \pm 6863	7927 \pm 16 748	<0.001	1132 \pm 2351	2848 \pm 2954	0.001	1286 \pm 1910	1946 \pm 1912	0.035	292 \pm 72	2789 \pm 573	<0.001
Range	201-43 165	239-90 000					98-8700	190-7800				

macro, macroprolactinoma; micro, microprolactinoma; div, division; NA, not available; NS, not significant.

In our series, there was log linear relation between serum prolactin and maximum tumour dimension at baseline. This co-relation was similar in both sexes, when analysed separately. Colao *et al.* (2) have analysed 219 prolactinomas (107 macroprolactinoma) and reported similar correlation ($r=0.86$). Additionally, linear correlation was observed between serum prolactin and tumour volume at baseline in our cohort. Nishioka *et al.* (3) have reported similar correlation between serum prolactin level and tumour volume at baseline from analysis of 43 prolactinoma cases ($r=0.535$).

In our cohort, few patients had central hypocortisolism and central hypothyroidism at presentation, hence gender difference in this regard could not be commented upon. Reported hypopituitarism (other than hypogonadism) in prolactinomas is based on data derived from small number of patients and with nonidentical diagnostic criteria leading to variable conclusions (10). We have used 0800 h serum cortisol to define hypocortisolism, due to nonavailability of adrenocorticotrophic hormone (ACTH) pharmaceutical preparation in India.

As described by Yip *et al.* (11), 0800 h serum cortisol cut-off of <128 nmol/l (4.63 μ g/dl) is sufficient for predicting a post-ACTH value <550 nmol/l (19.93 μ g/dl), and 0800 h serum cortisol levels >266 nmol/l (9.64 μ g/dl) predict peak post-ACTH >550 nmol/l (19.93 μ g/dl), obviating the need for dynamic testing. So, we consider that the defining hypocortisolism using 0800 h serum cortisol values though approximate may be applicable.

In our cohort, around 70% patients were responsive to cabergoline with median dose requirement of 1 and 1.5 mg/week in females and males respectively. In the literature cabergoline response is primarily based on serum prolactin normalisation and tumour size reduction in addition. In general cabergoline dose of 2.0 mg/week has been proposed to define resistance to treatment in macroprolactinomas, and dose escalation beyond 3.5 mg/week does not have additional benefits. In responsive prolactinomas, prolactin usually normalises in initial treatment period (6 months). Tumour size reduction is variably defined and established dose-response relationship regarding tumour shrinkage is still absent. In presence of persistent high prolactin levels, tumour shrinkage has been recorded (12, 13).

We defined resistant macroprolactinoma as failure to achieve prolactin normalisation and >50% reduction in tumour volume with 1-year cabergoline treatment (including minimum 6 months of 3.5 mg/week cabergoline). In responsive patients of our cohort, 56 had responded

to dose ≤ 2 mg/week and only five cases required doses between > 2 and 3.5 mg.

The percentage of resistant tumours in females was more in each subgroup based on size, though the overall percentage of the resistant tumours in females (27.78%) was less than that of males (35.29%). This is explained by the fact that the majority of the females ($n=28$ out of 54) belonged to 1.1–2 cm subgroup as against the males ($n=3/34$). But the subgroup data-based tumour size and invasive tumours point towards the fact that the male macroprolactinomas are at least equally (if not more) responsive than female macroprolactinomas. Colao *et al.* (2) described 107 medically managed macroprolactinoma cases, prolactin levels normalised in 64% (cabergoline dose: up to 2 mg/week; duration 6 months) without any gender difference.

Delgrange *et al.* have postulated that the macroprolactinomas in males are aggressive *per se*. Macroprolactinomas in males ($n=16$) exhibit higher indices of proliferation (Ki-67 and proliferative cell nuclear antigen) than in females ($n=9$) ($P=0.08$). They concluded that the predominance of large prolactinomas in males is not due to a longer delay in diagnosis, but, rather, to the greater proliferative potential of the tumours, which are more frequently invasive and less responsive to bromocriptine therapy (4). In macroprolactinomas where proliferation indices were studied the mean tumour size in female and male subgroup was not specified. Overall mean tumour dimension was 2.6 and 1 cm in males and females respectively, with giant prolactinoma seen in males only. There is plausibility that hypothesised gender difference in biological tumour behaviour is likely to be the reflection of tumour size difference. In the cohort described by Nishioka *et al.*, male prolactinomas exhibited higher positive cell index than those in females. But when $< 1 \text{ cm}^3$ tumours were excluded, there was no difference in the positive cell index (3).

At 1-year follow-up, the mean percentage reduction in maximum tumour dimension was 42.04% in females and 51.15% in males. Similarly, Colao *et al.* (2) reported absence of gender difference in percentage reduction of tumour dimension. The quantum reduction in the tumour dimension after 1 year of cabergoline therapy was more in males as compared with females points towards the fact that macroprolactinomas in males are at least equally (if not more) responsive.

Retrospective nature, nonavailability of genetic testing for MEN1, aryl hydrocarbon receptor interacting protein mutation, IGF1 and GH suppression tests (in all the patients), histopathological proliferation indices, and

sex steroid receptor expression studies in operated patients can be considered as limitations of this study (14). A prospective study with larger sample sizes and with histopathological proliferation indices, genetic analysis of tumours will help to characterise the gender differences in macroprolactinomas further.

Conclusion

Macroprolactinomas have equal prevalent in both the sexes. Macroprolactinomas in males predominantly present with symptoms of mass effects, as against females who present with symptoms of hypogonadism. Males harbor larger tumours but are equally cabergoline responsive as those in females.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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