ORIGINAL ARTICLE

DEMOGRAPHIC CHARACTERISTICS, PRESENTATIONS AND TREATMENT OUTCOME OF PATIENTS WITH PROLACTINOMA

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Background: Prolactinomas are the most common type of functional pituitary tumours. The objective of this study was to determine demographic profile of patients with prolactinomas, and to compare the outcomes in patients treated with Cabergoline versus those receiving Bromocriptine treatment. **Methods**: This descriptive study was conducted at Endocrinology Section, Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan. We reviewed the medical record of 68 patients with prolactinoma. Data about demographic characteristics, clinical presentation and treatment were entered on a pre-designed pro forma. **Results:** Out of the total 68 patients, 36.8% were males and 63.2% were females, with a mean age of 34±10.7 years. The most frequent presenting complaint amongst the patients was of headache, present in 57.4% patients. Galactorrhea, amenorrhea and infertility were next highest reported symptoms. Results of the tumour size on initial MRI showed macroprolactinomas 52.9% (36), microprolactinomas in 33.8% (23), and giant prolactinomas in 13.3 % (9) patients. Decreasing trend of prolactin levels were also seen on follow up visits at 9 months and 12 months. Tumour size was decreased in 48.53% (33) patients and lesion completely disappeared in 16.18% (11) patients after 6 months of treatment and also almost similar trend in tumour size change was seen after one year. There was no significant difference between the two drugs in bringing prolactin to normal range at each follow up duration. **Conclusion:** Most of the prolactinoma patients were females and the common the most frequent presenting complaint was headache. The decreasing trend of serum prolactin and tumour size reduction in patients was noted, suggesting the beneficial impact of medical therapy as it is the first line treatment modality in these patients.

Keywords: Prolactinoma, Prolactin, Tumour size, Bromocriptine, Cabergoline

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INTRODUCTION

Prolactinomas are the most common type of functional pituitary tumours, with predictable incidence of 6–10 cases per million population per year and a prevalence of around 60–100 cases per million.[1,2] According to previous reports, it accounts for 40–45% of pituitary tumours.[3,4] Its occurrence varies with age and gender, developing more commonly in females of age between 20–50 years with the female-to-male ratio of around 10:1.[2] Microprolactinomas are more common in females whereas macroprolactinomas are more common in males. It is not well established what the reason for delayed diagnosis in men is presenting macroprolactinoma rather than microprolactinoma. Is it an actual tumour pathophysiology distinction between the two genders or male present later because, decrease in libido is appreciated later whereas menstrual irregularities are picked up initially in females.[3,5]

Prolactin producing adenomas are classified according to their size as microprolactinoma if the tumour size is less than 1cm, macroprolactinoma if its size is between 1cm and 4cms and giant prolactinomas if its size is greater than 4 cms. Clinical features of prolactinomas appear due to raised serum prolactin levels and the pressure effect of the tumour. The endocrine symptoms include galactorrhea, decreased libido, gynaecomastia, infertility and menstrual irregularities in females and erectile dysfunction in males. Patients experiencing mass effect of tumour such as headaches, visual disturbances and cranial nerve palsies.[3,6] Both sustained hyperprolactinemia and radiographic evidence of pituitary adenoma are mandatory for the diagnosis of prolactinoma, after excluding any secondary cause of hyperprolactinemia.[1] Regarding treatment of prolactinomas, medical treatment is the mainstay. Most are treated medically with drugs such as Bromocriptine or Cabergoline, as first line treatment.[7,8] About 80-90% of patients with microprolactinomas and 70% of patients with macroprolactinomas, can achieve normal prolactin level, reduced tumour size, and restoration of gonadal function with Bromocriptine.[9] It has been observed that results are better with Cabergoline treatment, as 95% of patients with microprolactinomas and 80%

with macroprolactinomas acquired normal prolactin levels after receiving treatment.[9] Surgical treatment has become second option in the treatment of prolactimomas, however surgery is recommended if the tumour is cystic, as cysts will not shrink with dopamine agonist therapy, dopamine agonists intolerance or resistance, haemorrhage within the tumour with mass effect or apoplexy which will not resolve with dopamine agonist therapy and if the patient presents with rapid visual loss even when on dopamine agonist therapy.[3] Radiation therapy is another treatment option. Radiosurgery and external beam radiation therapy are commonly applied treatment methods of pituitary adenomas when medical therapy has been unsuccessful, when surgery results in incomplete excision of tumour or in the situation of tumour recurrence.[10] Many patients benefit from moderate reduction of their prolactin level from radiosurgery even though the endocrine remission rates of prolactinomas are lower as compared to patients with acromegaly and Cushing's disease.[10]

There are many studies on demographic characteristics, presentations and treatment outcomes of patients diagnosed with prolactinoma internationally. However, to our knowledge there is no previous study which has explored the demographic characteristics, presentations and treatment outcomes of patients diagnosed with prolactinoma in Pakistan. Studies conducted previously in the region have highlighted the clinical features and treatment outcomes of all pituitary lesions but not specifically of prolactinomas.[11] Another review article focused on the comparison of demographic features and surgical treatment aspects of pituitary adenomas in Pakistan with that of other developing countries in South Asia again differing from this study in its objective of considering only prolactin-pituitary tumours.[12] Therefore we conducted this study to assess the different aspects of the disease. Our research, thus, allows a look into the prolactinoma which is not sufficiently studied in this region. Our primary objectives included the determination of demographic details of patients with prolactinomas, to identify the signs and symptoms commonly experienced by these patients as well as to know the effectiveness of the treatment modality they received. Secondarily we aimed to compare the outcomes in patients treated with Cabergoline versus those who received Bromocriptine treatment.

MATERIAL AND METHODS

This cross-sectional descriptive study was conducted at the Aga Khan University Hospital (AKUH), section of Endocrinology, Department of Medicine. Records of 68 patients of prolactinoma were reviewed in the time period from August 2013 to January 2014. Patients with both biochemical and radiological evidence of prolactinoma, individuals of Age ≥16 years and having at least one follow up MRI after receiving treatment were included in the review. Patients with co secreting tumours of prolactin and growth hormone and those with other identified causes of hyperprolactinemia such as drug induced hyperprolactinemia were excluded from the review.

Patients meeting the inclusion criteria were enrolled in the study and the information retrieved from their record was entered into a *pro forma* designed before the start of the study. Hospital and clinical charts were reviewed to obtain the demographics details of patients; age and gender. Details pertaining to investigations such as tumour size, serum prolactin levels and treatment modality were recorded. Prolactin at initial visit (before treatment) and in the follow up visits at approximately 3 months, 6 months, 9 months and 1 year after the initial visit were recorded. Signs and symptoms experienced by patients for example decreased libido, galactorrhea, amenorrhea, oligomenorrhea, erectile dysfunction, infertility, headache and visual disturbances were noted.

The statistical analysis was conducted by using SPSS-19. A descriptive analysis was performed for demographic and clinical characteristics. Continuous variables with normal and non-normal distributions were reported as mean±SD and median [inter-quartile range (IQR)], respectively and numbers (percentages) for qualitative variables. To analyse the association of treatment and its outcome, the categorical variables were evaluated using the chi-square test while the means were compared by the t-student test or Wilcoxon sign rank test. A *p*-value of less than 0.05 (<0.05) was considered to be statistically significant.

RESULTS

The total number of eligible patients meeting the definition of prolactinoma were 68, out of the 68 patients, 25 (36.8%) were males and 43 (63.2%) were females. The mean age of patients was 34±10.7 years with a median (Inter quartile range) of 33.5 (26–40). Men were significantly older than women ($p<0.001$).

When different clinical symptoms in the 68 patients were analysed we noticed that only a few patients presented with a single (one) complaint, most however, were experiencing multiple symptoms (two or more). The most frequent complaint was headache, present in 39 (57.4%) patients followed by galactorrhea 28 (41.2%), amenorrhea 24 (35.3%), and infertility 20 (29.4%). On visual field assessment; 9 (13.2%) patients suffered from bitemporal hemianopia. A minority of patients, that is

2 (2.9%) had cranial neuropathy, both with third nerve palsy, and 1 (1.5%) was found to have optic nerve atrophy.

Results of tumour size in the initial MRI confirmed microprolactinomas in 23 (33.8%) patients, macroprolactinomas in 36 (52.9%) patients and 9 (13.3%) patients had giant prolactinomas. Moreover in initial MRIs, microprolactinomas were significantly more frequent in women than men (p=0.001) while giant adenomas occurred mainly in men.

Table-1: Demographic characteristics of study population

	Total (n=68)		Male (n=25)		Female (n=43)		*p*-value
	No	%	No	%	No	%	
Age, in years	34±10.7		40.4±11.3		30.1±8.4		<0.001
Median(IQR)	33.5 (26-40)						
Clinical presentation							
Headache	39	57.4	14	56	25	58.1	0.99
Galactorrhea	28	41.2	2	8	26	60.5	<0.001
Amenorrhoea	24	35.3			24	55.8	
Infertility	20	29.4	7	28	13	30.2	0.99
menstrual irregularities	17	25			17	39.5	
Erectile dysfunction	11	16.2	11	44			
Decreased Libido	7	10.3	6	24	1	2.3	0.008
Oligomenorrhoea	7	10.3			7	16.3	
Gynecomastia	7	10.3	6	24	1	2.3	0.008
Hirustism	4	5.9			4	9.3	
Examination*							
BMI,	28.2±5.3		28.6±5.7		28.2±5.3		0.64
Tumour characteristics							
Microprolactinoma	23	33.8	4	16	19	44.2	0.001
Macroprolactinomas	36	52.9	13	52	23	53.5	
Giant prolactinomas	9	13.2	8	32	1	2.3	

*mean ± SD

Tumour extension was assessed by identifying the involvement of optic chiasma and cavernous sinus and stalk deviation. In the initial MRI, tumours in 25 (36.8%) patients were abutting the optic chiasma, cavernous sinus involvement of the tumour was seen in 27 (39.7%) patients whereas stalk deviation was found to be present in 34 (50%).

According to our results, male patients (n=25) had a significantly higher prolactin level at baseline [Median IQR 695.4(133-8171.7)] as compared to females [210 (101-634)] (p=0.01)

Overall, 66 (97.1%) patients received medical treatment, either Cabergoline or Bromocriptine or both. Cabergoline was given as a first line treatment in 26 (39.4%) patients whereas 18 (27.3%) patients had received Bromocriptine. A number of patients 22 (33.3%) received both drugs at different times in their treatment period (Table-3). Fifteen (22.1%) patients had to be treated surgically, 13 (86.6%) of these were operated via trans-sphenoidal approach and 2 (13.3%) by transcranial. Only 1 (1.5%) patient required radiation therapy showing that radiation is an unpopular treatment modality for prolactinomas.

Out of the fifteen patients treated surgically, the majority (n=13) underwent the operation primarily because of very high prolactin levels and symptoms of mass effect. The indication of surgery, however, in the rest (n=2) was failure of medical therapy. Post surgically, 12 (80%) received medications in order to normalize the raised prolactin level due to the presence of residual tumour. 2 (20%) did not require medical support after surgical intervention. 3 out of the 15 patients who were operated did not respond to medications post surgically and radiation therapy was being considered as a final treatment option for them, but only one received.

The change in serum prolactin in both male and female patients over three monthly follow ups was recorded. At follow up after 3 months of treatment (n=47) prolactin level was seen to normalize in 11 (55%) males and only 8 (29.6%) females, this however was not significantly different in the two genders (p value 0.08). At follow up after 6 months of treatment (n=35) prolactin level became normal in 10 (71.4%) males and 7 (33.3%) females, males having a significantly higher normalization rate than females (p value 0.027). Furthermore, at the end of 9 months and 1 year of treatment the return of prolactin to normal level was not significantly different in the two genders, p-values of 0.141 and 0.275 respectively (table-2).

Table-2: Change in serum prolactin in follow up visits

Duration	Prolactin Level	Gender		*p*-Value
		Male	Female	
Three Months (n=47)	Normalized	11 (55.0)	8 (29.6)	0.080
	Remain elevated	9 (45.0)	19 (70.4)	
Six Months (n=35)	Normalized	10 (71.4)	7 (33.3)	0.027
	Remain elevated	4 (28.6)	14 (66.7)	
Nine Months (n=31)	Normalized	7 (58.3)	6 (31.6)	0.141
	Remain elevated	5 (41.7)	13 (68.4)	
One Year (n=25)	Normalized	4 (57.1)	6 (33.3)	0.275
	Remain elevated	3 (42.9)	12 (66.7)	

The comparison between medical treatment by Cabergoline and Bromocriptine in bringing prolactin to normal level was recorded. We found that 6 (50%) patients treated with Bromocriptine, 9 (47.4%) of those treated with Cabergoline and 4 (25%) of those treated with both drugs achieved normal prolactin after 3 months of treatment, out of available prolactin measurements of 47 patients (n=47). We recorded that 5 (62.5%) Bromocriptine users, 8 (61.5%) Cabergoline users and 4(28.6%)

using both drugs (that is started initially bromocriptine and then switched to cabergoline or vise versa) achieved normal prolactin levels after 6 months of treatment (n=35). Similarly, at 9 months after treatment 3 (50%) patients receiving Bromocriptine and 7 (63.6%) receiving Cabergoline therapy 3(23.1%) using both drugs were seen to have normal prolactin level (n=31) and at the end of 1 year of treatment 2 (33.3%) Bromocriptine users, 6(60%) Cabergoline users and 2 (22.2%) using both drugs had normal prolactin (n=25). Our results showed that there was no significant difference between the two drugs in bringing prolactin to normal range at each follow up duration (table-3). In order to assess the effect of treatment on tumour size the change in tumour size was recorded over 6 monthly follow ups. MRI at 6 months after treatment revealed that a total of 33 (48.5%) tumours decreased, 5 (7.4%) increased, 19 (27.9%) did not show any change in size whereas 11 (16.2%) completely resolved compared to initial reported MRIs. At the end of 1 year of treatment MRI reports of 23 patients (*n*=23) showed that 10 (43.5%) decreased, 2 (8.7%) increased, 6 (26.1%) did not change in size and 5 (21.7%) completely resolved. MRI reports at the end of 18 months of treatment (*n*=12) showed that 4 (33.3) tumours decreased in size, 1(8.3%) increased, 6 (50%) did not change in size and 1(8.3%) completely resolved while those at the end of 2 years of treatment (n=8) revealed that 5 (62.5%) decreased in size and 2 (25%) completely resolved (Table-4).

Table-3: Comparison between cabergoline and bromocriptine in change in prolactin levels

Duration	Prolactin	Type of treatment given		
		Bromocriptine	Cabergoline	Both
Three	Normalized	6	9	4
	Remain elevated	6	10	12
Six	Normalized	5	8	4
	Remain elevated	3	5	10
Nine	Normalized	3	7	3
	Remain elevated	3	4	10
One Year	Normalized	2	6	2
	Remain elevated	4	4	7

Table-4. Effect of treatment on the change in tumour size on follow up visits

Duration	Size Change (Tumour)	Tumour size at baseline			Total
		Micro Prolactinoma	Macro prolactinoma	Giant prolactinoma	
Six Months (n=68)	Decreased	4	22	7	33
	Increased	2	2	1	5
	No change	13	5	1	19
	lesion disappeared	4	7	0	11
	Total	23	36	9	68
One Year (n=23)	Decreased	1	8	1	10
	Increased	1	0	1	2
	No change	1	5	0	6
	No lesion	1	4	0	5
	Total	4	17	2	23
18 Months (n=12)	Decreased	1	2	1	4
	Increased	0	1	0	1
	No change	1	5	0	6
	lesion disappeared	0	1	0	1
	Total	2	9	1	12
Two Year (n=8)	Decreased	1	3	1	5
	Increased	0	0	0	0
	No change	1	0	0	1
	lesion disappeared	0	2	0	2
	Total	2	5	1	8

DISCUSSION

The study is a useful reflection of the demographic characteristics, clinical presentations and treatment outcomes of patients with prolactinoma. We observed the gender difference quoted in literature regarding prolactinoma incidence. Since majority of our patients were females (63.2%), we reached a conclusion that prolactinoma occurrence was more common in females supported by multiple studies such as the one titled 'Epidemiology of prolactinomas' which stated that the female to male ratio is close to 10:1.[2] An article reported a similar result; that certain pituitary adenomas including prolactinomas occur frequently in females.[13] Furthermore, we observed in our study that microprolactinomas were significantly more frequent in women than men whereas macroprolactinomas and giant prolactinomas did not have a significant gender difference. This, too, is supported by a number of previous researches. One example is that of the results of a prospective study to determine the role of gender in hyperprolactinemia state. This study, like

ours, proved that the frequency of microprolactinomas was higher in the female sex while that of macroprolactinomas was equal in both.[5] We failed to prove the statement made by various researches that macroprolactinomas occurred frequently in males, possibly due to limitations such as small sample size. This aspect needs further attention in future research.

Our finding of the mean age (34±10.7) of patients reinforces that of various researches including one that predicted that the usual age of occurrence is between 20–50 years.[2] Similarly, an important consequence of our study; that men were significantly older than women, has also been discussed in the past. Thus, we confirmed, through our study, that women with the disease present earlier and are mostly diagnosed with microprolactinomas possibly because of the difference of symptomatology between the two genders as shown by studies previously.[2,14] In contrast a similar study revealed that men and women with prolactinoma had approximately similar median age.[5]

Clinical presentations, in our study, were divided on the bases of gender. Our finding that the most common complain amongst males is of headache followed by erectile dysfunction and in females common presentations are of galactorrhea, headache and amenorrhea can be compared to previous observations. Galactorrhea was also found to be a significantly frequent in women in the study comparing clinical features in the two genders.[5] An article defining the features of micro and macroprolactinomas in males supported the idea of headache being the most common symptom in males with macroprolactinomas[15] and another discussed that because males have a greater incidence of macroprolactinomas they are more likely to present with symptoms of mass effect including headache.[1] Since, our results did not show a significant difference in the frequencies of macroprolactinomas in males and females, thus we can also see that there is not a significant difference of frequencies of headache experienced by the two groups, highlighting the discussion in literature.

Concerning treatment our study results confirmed that medical treatment is routinely practiced (received by 97.1% patients) as stated in multiple articles. One such study stated that the primary remedy of prolactinomas is achieved by using dopamine receptor agonists.[16] At the same time a study showed that drugs such as Cabergoline and Bromocriptine are initial treatment modalities and the option of surgery is reserved if medical therapy fails.[17] The evidence of this statement is present in our study results because only 22.1% patients were treated surgically and only 1.5% required radiation therapy showing that radiation is an uncommon treatment modality for prolactinomas.

The comparison of treatment outcomes of Cabergoline and Bromocriptine is a topic to international researches. Cabergoline is studied to have a better outcome based on normalization of serum prolactin level, reduction of tumour size, its efficacy and tolerability.[17] While Bromocriptine is effective in about 80–90% of patients with microprolactinomas and 70% of those with macroprolactinomas, Cabergoline is more efficacious because it overcomes hyperprolactinemia state in more than 90% patients with either micro or macroprolactinoma.[9,16] A similar article concluded that Cabergoline was more potent in decreasing prolactin level, offering better efficacy as well as fewer side effects as compared to Bromocriptine. They discovered that 59% patients in the Bromocriptine group achieved normal prolactin levels while a larger number (82%) in the Cabergoline group did so.[18] Thus, our study's result of similar outcome with Cabergoline and Bromocriptine treatment differs from medical literature. This may be because of influence of various limitations in the study such as a small sample size.

The limitations of the study included a small sample size and large dropout of patients in follow up visits. Increasing the sample size could have played a role in producing better results. Furthermore our patients' belonged to a single tertiary care hospital. This may have introduced confounding factors. The compliance to medications was assumed to be 100% during the treatment period and the choice of drug was also based on economic reasons as bromocriptine is cheaper than Cabergoline.

For future research purpose on a similar topic, initiating a prospective study should be considered because it is indeed a better design to confirm some of the findings in our study. We also recommend that a larger study with a bigger sample size as well as including records from different hospitals in the region is the way forward to correctly identify if there is any difference in treatment outcomes of Cabergoline and Bromocriptine in the population.

CONCLUSION

We conclude that the demographic features and clinical presentations of prolactinoma in patients of Pakistan closely match the results of international studies. All commonly reported symptoms were experienced by the study patients, most frequent being headache. There was a decreasing trend of serum prolactin and tumour size reduction in patients suggesting the beneficial impact of medical therapy

as it is the first line treatment modality in these patients.

CONFLICT OF INTRESTS

The authors declare that they have no conflict of interests

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