Original Article

Demographic study of pituitary adenomas undergone trans-sphenoidal surgery in Loghman Hakim Hospital, Tehran, Iran 2001–2013

Farahnaz Bidari Zerehpoosh, Shahram Sabeti, Guive Sharifi[1], Hania Shakeri, Setareh Alipour, Farid Arman

Departments of Pathology, and [1]Neurosurgery, Loghman-Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ABSTRACT

Background: Pituitary adenomas (PAs) are abnormal benign tumors that develop in the pituitary gland. This study aimed to assess the prevalence of different types of PAs with an indication for trans-sphenoidal surgery in a well-defined population referred to Loghman Hakim Hospital during 2001–2013. **Subjects and Methods:** In this retrospective study, the prevalence rate and symptoms associated with pituitary mass and hormone excess in operated patients were investigated. The diagnosis was verified after retrieval of clinical, hormonal, radiological, and pathological data. Demographic data were collected in all cases. Descriptive analysis, *t*-test, one-way analysis of variance and Fischer exacts test were used. **Results:** A total of 278 patients with PAs who underwent surgical interventions were evaluated. Most of the patients were aged 40–50 years with an average of 41 ± 14. The most prominent complaint was pressure effect, which was detected in 153 cases (55.2%). At the second place, hormonal disorders were observed in 125 cases (44.8%). Type of pituitary tumors were: Prolactinomas (29.1%), growth hormone (GH)-producing tumors (25%), nonfunctioning PAs (28.4%), adrenocorticotropic hormone (ACTH)-producing tumors (2.1%), thyroid stimulating hormone (TSH)-producing tumors (0.7%), GH/prolactin (13.6%), GH/ACTH (0.3%), and TSH/ACTH (0.3%). Fifty-seven patients presented with recurrent adenomas. Pituitary apoplexy was found in 11 patients. One case of Sheehan syndrome was recorded among these. The correlations between clinical symptoms and patients, age and sex were not significant. **Conclusion:** The overview of demographic characteristics in Iranian patients with PAs with surgical indication has been discussed in the present investigation. The prevalence of different types of PAs and the most common clinical symptoms have been demonstrated.

Key words: Clinical symptoms, pituitary adenomas, prevalence

Introduction

Pituitary adenomas (PAs) are nonmetastasizing neoplasm which consist adenohypophysial cells. Although they usually occur in the Sella-Turcica, they may occasionally be ectopic.[1] These tumors display a broad range of hormonal and proliferative behaviors.[2] They are relatively common benign neoplasms with different clinical features.[3] According to the WHO classification in 2004, endocrine pituitary tumors are clinically classified as functioning (mainly secrete adrenocorticotropic hormone [ACTH] with Cushing's disease; growth hormone [GH] with acromegaly and prolactin [PRL] with amenorrhea–galactorrhea) and nonfunctioning (mainly – luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) tumors.[4] Considering the small size of many pituitary tumors and their tendency to exist without symptoms, estimation of their accurate prevalence of PAs is challenging in

Corresponding Author: Dr. Farid Arman, Department of Pathology, Loghman-Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail: farid.arman@gmail.com

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.167551

Cite this article as: Zerehpoosh FB, Sabeti S, Sharifi G, Shakeri H, Alipour S, Arman F. Demographic study of pituitary adenomas undergone trans-sphenoidal surgery in Loghman Hakim Hospital, Tehran, Iran 2001–2013. Indian J Endocr Metab 2015;19:791-6.

the general population. Pituitary tumors present with a diversity of clinical manifestations that include symptoms of excessive hormone secretion by the tumor, signs of hormone shortage by the normal pituitary gland and those related to pressure effects due to development of the tumor mass. Tumors that expand more quickly, even if they are hormonally inactive, are more likely to cause signs of an intracranial mass, including visual field disturbances.[5] The main purpose of this study was to present retrospective information on the epidemiology, clinical, and demographic presentation in patients with PAs with the surgical indication. This is the first study which evaluates the epidemiology of operated PA in Iran.

Subjects and Methods

Study design

A retrospective survey of PAs was organized in the Loghman Hakim Hospital, a main teaching and general hospital that is characterized as one of the highly qualified centers for diagnosis and treatment of pituitary tumors in Iran, affiliated to Shahid Beheshti University of Medical Sciences. Data were collected between 2001 and 2013. The study was approved by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences. Each medical record related to a patient with confirmed PA, who underwent surgery between 2001 and 2013 were included and reviewed. Loghman Hakim is a tertiary center and all the patients in this study were referred to this center for surgical procedures.

Main outcome measures

The main inclusion criterion was previously performed trans-sphenoidal surgery. Patients' characteristics including data on demographics, diagnosis, initial symptoms, hormonal profiles, radiological data and applied therapies were gathered from patients' medical records, hospital case information, and other important clinical records. Diagnosed symptoms linked to pituitary mass (e.g., headache and visual disturbance) and hormone excess (gigantism or acromegalia, hyperprolactinemia and Cushing's disease) were investigated and recorded. Basically, baseline assessment included the followings: Clinical review, serum levels of GH, thyrotropin thyroid stimulating hormone (TSH), PRL, LH, FSH, cortisol, and perimetry to assess visual field defects. Definitive diagnosis was made after a histopathological study of tissues obtained by surgery. The circulatory levels of the pituitary hormone were assessed by means of radioimmunoassay.

Statistical analysis

Descriptive analysis was used in which categorical variables are expressed by frequency (percentages), and continuous variables were expressed as mean ± standard deviation (SD). Data were analyzed by SPSS version 21 software (IBM Corp., New York, USA). Fischer exacts' test was used to assess the relationship between categorical variables. Comparison of means between subgroups was performed using independent *t*-test and one-way analysis of variance. $P < 0.05$ was considered as statistically significant.

Results

In this study, 278 patients with confirmed PAs who underwent trans-sphenoidal surgery with a mean age of 41 ± 14 years were included. One hundred and sixty patients (57.5%) were male, and 118 (42.4%) were female. There was no significant difference in mean age between men and women (42 ± 15 and 39 ± 13-year-old in men and women, respectively; *P*: 0.262). The majority of the patients were aged between 40 and 50 years (30% in males and 26.3% in females). The chief complaint was pressure effect due to a pituitary tumor in 153 cases (55.2%) and hormonal disorders in 128 cases (44.8%). In comparison between genders, male patients tended to initially present with mass effect symptoms (66.9%) while hormonal symptoms were the most commonly observed complaints among women (61%). Main symptoms originated from pressure effects of a pituitary tumor were: Headache ($n = 37$, 13.3%), visual field defects ($n = 69$, 24.8%) and coincidence of headache and visual field defects ($n = 44$, 15.8%) [Table 1]. Main symptoms caused by hormonal disorder included: Acromegaly ($n = 72$, 25.9%), symptoms of both acromegaly and galactorrhea ($n = 10$, 3.6%), hypopituitarism resulted after pituitary apoplexy ($n = 5$, 1.8%), and Amenorrhea ($n = 6$, 2.1%) [Table 2]. There was a significant relationship between patients' age and the initial manifestations of the disease. The mean age of patients who presented with hormonal symptoms was 35 ± 10 years while patients with mass effect were significantly older (mean age of

Table 1: Baseline characteristics and the most commonly detected mass effect symptoms in patients with pituitary adenoma with surgical indication

Variable	Subgroup	Frequency (%)
Gender	Male	160 (57.5)
	Female	118 (42.4)
Time interval between initial manifestations and diagnosis	1-6 months	65 (22.6)
	6-12 months	51 (18.2)
	12-24 months	59 (20.8)
	2-10 years	82 (29.14)
	More than 10 years	21 (7.2)
Commonly detected chief complaints among patients presented with mass effects symptoms (*n*: 153)	Visual field defects	69 (45.1)
	Coincidental headache and visual field defects	44 (28.8)
	Headache	36 (23.5)
	Decreased level of consciousness	4 (2.6)

45 ± 15 years old; $P < 0.0001$). The time interval from initial disease manifestations to diagnosis was 1–6 months in 65 cases (22.6%), 6–12 months in 51 cases (18.2%), 1–2 years in 59 cases (20.8%), 2–10 years in 82 cases (29.14%) and more than 10 years in 21 cases (7.2%) [Table 1].

Pituitary tumors were categorized based on whether or not they generate hormones and the sorts of produced hormones (WHO categorization in 2004). The prevalence of different types of PA according to WHO classification, which was observed in this investigation were as follows: Prolactinomas (29.1%), GH-producing tumors (25%), nonfunctioning PAs (NFPAs) (28.4%), ACTH-producing tumors (2.1%), TSH-producing tumors (0.7%), mixed GH/PRL adenomas (13.6%), mixed GH/ACTH adenomas (0.3%) and TSH/ACTH adenomas (0.3%) [Table 3]. While prolactinoma was the most prevalent type in females, NFPA was the most prevalent type of PA in men [Table 3]. Adenoma type showed no significant difference between genders ($P = 0.16$). Pituitary apoplexy was found in 11 patients. Ten of which were male and only one was female. Four of these patients had prolactinoma (36.4%), five had NFPA (45.5%), one had mixed GH/prolactinadenoma (9.1%) and one case had mixed TSH/ACTH adenoma (9.1%). Hormonal disorders found in radio-immunoassays were hyperthyroidism (3.9%), hypothyroidism (8.6%), hyperprolactinemia (41%), high LH (2.5%), high FSH (2.8%), and high cortisol (6.8%).

Moreover, there was a significant difference in size of tumors between genders and adenoma type. Macroadenomas were more prevalent in male patients compared to women ($P = 0.001$). Furthermore, GH producing tumors were mostly microadenomas, while prolactinomas and NFPA's presented as macroadenomas more often ($P < 0.001$).

Considering recurrent adenomas, 57 patients had more than one surgery. Recurrent adenomas with surgical indication occurred mostly among men ($n = 34$, 59.6%). Common types of adenomas which required surgical process included: Prolactinoma (21.1%), NFPA (36.8%), GH adenoma (26.3%), mixed GH/PRL adenoma (12.3%, ACTH adenoma and TSH adenoma (1.8%) [Table 4]. No significant differences were found between the type of adenoma in patients with recurrent and nonrecurrent adenomas ($P = 0.639$). Twenty-four (42.1%) patients with recurrent PA were diagnosed with microadenomas whereas 33 (57.9%) had macroadenomas, and the difference between these groups was not significant either ($P = 0.881$).

Table 2: Prevalence of different signs and diagnosis in patients with hormonal imbalance complaints

Diagnosis	Frequency (%)
Acromegaly	73 (58.4)
Coincidental amenorrhea and galactorrhea	13 (10.4)
Impotency	10 (8.0)
Amenorrhea	6 (4.8)
Hypopituitarism resulted after pituitary apoplexy	5 (4)
Galactorrhea	1 (0.8)
Hypothyroidism	1 (0.8)
Hyperthyroidism	1 (0.8)
Headache and visual field defects	1 (0.8)
Coincidental acromegaly and abnormal uterine bleeding	1 (0.8)
Coincidental acromegaly and amenorrhea	1 (0.8)
Coincidental acromegaly and hypothyroidism	1 (0.8)
Coincidental galactorrhea and abnormal uterine bleeding	1 (0.8)
Coincidental acromegaly and galactorrhea	1 (0.8)
Total	125 (100)

Table 3: Type of adenoma in patients with PA

Adenoma type	Gender		Total frequency (%)
	Men	Women	
ACTH-secreting adenoma	1	5	6 (2.1)
GH secreting adenoma	40	30	70 (25.2)
Mixed adenoma (GH + ACTH)	0	1	1 (0.4)
Mixed adenoma (GH + prolactin)	17	21	38 (13.7)
Mixed adenoma (TSH + ACTH)	1	0	1 (0.4)
Nonfunctional PA	52	27	79 (28.4)
Prolactinoma	47	34	81 (29.1)
TSH secreting adenoma	2	0	2 (0.7)
Total	160	118	278

ACTH: Adrenocorticotropic hormone, GH: Growth hormone, TSH: Thyroid stimulating hormone, PA: Pituitary adenoma

Table 4: Adenoma type in patients with recurrent PAs

Adenoma type	Frequency (%)
Nonfunctional PA	20 (36.8)
GH secreting adenoma	15 (26.3)
Prolactinoma	12 (21.1)
Mixed adenoma (GH + prolactin)	7 (12.3)
ACTH-secreting adenoma	1 (1.8)
TSH secreting adenoma	1 (1.8)
Total	57 (100)

ACTH: Adrenocorticotropic hormone, GH: Growth hormone, TSH: Thyroid stimulating hormone, PA: Pituitary adenoma

Discussion

In this study, the most common types of PAs with surgical indications in Iran have been identified by reviewing medical files of patients during 12 years. Pituitary tumors are known to be the most frequent intracranial neoplasms, affecting 1/1000 of the worldwide population.[6,7] In the present study, the medical records of 278 patients with PA who underwent surgery were reviewed. The registered data (i.e., the symptoms caused by the mass effect and similar presentations of the disorder over time) were analyzed. The majority of patients with PAs with surgical

indications are men with the most prevalent adenoma type of prolactinoma. In a meta-analysis, Ezzat *et al*.[8] reported that the whole estimated prevalence of PAs was 16.7% (22.5% in radiologic studies and 14.4% in autopsy studies). In Iran, a cross-sectional descriptive study was carried out on a total of 485 cadavers to estimate the prevalence of pituitary incidentaloma.[9] Pituitary glands were removed from cadavers and evaluated. Of the 485 investigated cadavers, 61 (12.6%) had concealed pituitary masses. Aghakhani *et al*.[9] did not find any statistically significant difference between the mean age, sex, and body mass index of the cadavers with and without concealed tumors. They estimated the prevalence of the concealed PAs was 12.6%.[9] In a cross-sectional study performed in Iran on 250 patients by Asadi-Lari *et al*.[10] the estimated prevalence of different types of PA was prolactinoma (4.48%). Our study showed that prolactinoma was the most prevalent PA with surgical indication among women and the second commonly observed PA among men which are in line with Asadi's report. Furthermore, acromegaly was reported in about 7% of patients by Asadi-Lari *et al*. Here, since we recruited those patients with surgical indication, the prevalence of acromegaly was much higher and reached 58%. Only 2.5% of patients had Cushing's disease in Asadi-Lari *et al*. investigation.[10] Low prevalence of ACTH-secreting adenomas was also observed in our study. One reason for the low prevalence of ACTH-secreting PA in our study is that we only included those patients who required surgical intervention. In fact, the most common indication for surgical intervention is mass effect symptoms in which the most prevalent type of PA is nonfunctioning adenomas. Given the small size of many pituitary tumors and lack of existence of clinical symptoms in many cases of PA, estimation of the accurate prevalence of PA is challenging. In this regard, another study in Iranian population showed that among 3437 cases who were hospitalized with brain tumors, PA was diagnosed in 488 cases (14.2%).[11] Here, the most prevalent type of PA among those patients with confirmed PA who underwent trans-sphenoidal surgery was assessed. The findings of this study does not illustrate the most prevalent types of PA among the whole population with pituitary tumors, but these outcomes demonstrate that among patient with clinical symptoms of PA probable necessity for surgical intervention, which manifestations of disease are more probable to be observed.

According to Terada *et al*. study, there is usually a female predominance in tumor occurrence, who typically present at a younger age and have a higher incidence of ACTH-secreting tumors and PRL-secreting adenomas, whereas men were likely to present in middle or older age with clinically nonfunctioning tumors.[12] In Sanno *et al*. study,[13] 506 patients with incidentally originated pituitary masses also were included, among which 204 were male, and 292 were female. In a study of Annegers *et al*.[14] in Minnesota in 1978, the investigators reported the incidence of PAs to be as high as 7.1 per 100,000/year in women of child-bearing age, decreasing thereafter, in contrast to men whose PA incidence increased with age. Ferrante *et al*.[15] in a retrospective registration of NFPA patients, reported from 295 patients, 161 were male, and 134 were female. Daly *et al*.[6] in a study that was conducted in several regions of the province of Liège, Belgium, identified 68 patients with clinically related PAs in a population of 71,972 individuals, who were 67.6% female; the mean (±SD) prevalence was evaluated to be 94 ± 19.3 cases per 100,000 population (95% confidence interval, 72.2–115.8). All these literature have shown the probability of the existence of a gender polymorphism when addressing the prevalence of PAs. Our study showed that there is a gender difference in the most prevalent type of PA with surgical indications. In fact, male individuals are more probable to have NFPA, whereas prolactinoma is the most frequently observed PA among women. Moreover, recurrent adenomas were detected among men more often. Our results suggest that gender can be predictive of a specific type of PA or recurrent tumors.

According to present results, the highest incidence of PAs was in the 40–60-year age group. The most common subtype of PAs was the prolactinomas (29.1%) followed by GH-secreting adenomas (25%) and NFPA (24.8%). Considering these findings, the current study is consistent with previous reports. In a population-based study during 1960–1966 in Israel, Leibowitz *et al*.[16] reported the highest incidence of PAs in the 40–69-year age group, which was declined in older ages. Gruppetta *et al*.[17] reported that the most common subtypes of PAs were the prolactinomas (46.2%), NFPA (34.2%) and GH-secreting adenomas (16.5%) with prevalence rates of 34.96, 25.86 and 12.45/100,000, respectively. Prolactinomas have a much higher incidence in these studies, which is due to the fact that most prolactinoma cases are treated medically. Since, our study investigated only those cases with adenomas who underwent surgery, the prevalence of prolactinomas was relatively lower. The same results were reported by Raappana *et al*.[18] and Fernandez *et al*.[7] in which the majority of PAs were prolactinomas. Furthermore, Ezzat *et al*.[8] reported that PAs arisen in pooled autopsy and radiological series have a frequency of 14.4% (range: 1–35%) and 22.5% (range: 1–40%), respectively. Among autopsy specimens that undertook immunohistochemical analysis, 25–41% of cells were PRL positive which is illustrative of the high prevalence of prolactinoma.

The results of this study indicated that the most common mass effect symptom among PAs with surgical indication is visual field defect which is followed by a headache. Consistent with our results, Hennessey and Jackson[19] demonstrated that visual defects and headache are the most common clinical symptoms due to intracranial mass effects of PAs. In line with our study, Gruppetta *et al*.[17] reported that the most common presenting feature in PAs patients was a headache, presented in approximately 40% of cases, followed by menstrual irregularities and visual impairment. According to Ferrante *et al*.[15] study on patients with NFPAs, mass-correlated symptoms, such as a headache (41.4%) and visual deficit (67.8%) were most frequently reported. Visual field changes were observed in the majority of patients and impairment of visual acuity in about one-third. In line with these investigations, our study confirms that major clinical mass effect symptoms are defects of visuals field and headache.

In a study by McComb *et al*.,[20] no adenohypophyseal hormones were identified in 50% of the adenomas, whereas PRL was presented in 42%. In our study, main symptoms caused by the hormonal disorder was acromegaly which contradict with previous studies indicating prolactinoma as the most commonly observed hormonal disorders among patients with PAs.[20] One reason for this discrepancy can be due to differences in the study population. Since the majority of prolactinoma cases are treated medically, the prevalence of prolactinoma was lower in our study, in which only patients with surgical indication were included. In present study, pituitary apoplexy was found in 11 patients; in one case it was occurred during pregnancy, while all other 10 patients were male, which shows a significant dominance of pituitary apoplexy in male patients.

Pituitary apoplexy is an acute clinical syndrome characterized by an array of presenting features including sudden onset of a headache, nausea, vomiting and sometimes altered consciousness.[21,22] The clinical appearance of pituitary apoplexy may be highly variable, and the diagnosis can often be delayed especially given that the majority of apoplectic patients have no knowledge of preexisting pituitary disease.[22,23] Pituitary apoplexy is rare in pregnancy, and only a few cases were published in the previous literature.[24] According to Raappana *et al*. study[18] classical pituitary apoplexy with dramatic general symptoms was a rare occurrence (n = 20 in NFi; 0.17 episodes/100,000/year).

About recurrent adenomas, the present study showed, 57 patients had more than one surgery, which were mostly male. These surgeries were due to incomplete resolution of symptoms in 21 patients, and recurrence of symptoms in 36 cases. (n = 34, 59.6%). The mean age of these patients was 40 ± 12, which did not show any significant difference between patients who were undergone of their first surgery (P = 0.159). No significant differences were found between the type of adenoma in patients with recurrent and nonrecurrent adenomas. Twenty-four patients had microadenomas, whereas 33 had macroadenomas. Laws and Jane showed long-term results of trans-sphenoidal surgery in a series of 4020 patients with PAs treated over three decades.[25] Between their patients with nonfunctioning adenomas, the recurrence rate at 10 years was evaluated to be 16%. Our study showed a recurrence rate of 20% which is similar to the rate reported by Laws and Jane.[25] NFPAs were the most common cause of recurrent PAs in our investigation. Our study shows that nonfunctioning adenomas are more likely to be resistant to medical treatment and therefore, they are more susceptible to become recurrent after trans-sphenoidal surgery.

Conclusion

In conclusion, the data collected in our study provided an overview of the patients with PAs in the case of clinical data. By studying this well-defined population, we confirmed recent findings on the epidemiology of PAs in Iran. This information may help to decrease the time between symptom beginning and diagnosis. We suggest further studies in other centers (especially centers with active endocrinology ward) to confirm the results of this research.

Study Limitations

This study illustrates the prevalence of different types of PAs among patients with the surgical indication. The prevalence of all types of PA (including those without surgical indication) needs to be determined in future investigations. Since this study was a retrospective investigation, the obtained data were limited to those indexed in medical files. Therefore, it is recommended to assess the short- and long-term complications of trans-sphenoidal surgery in the future studies. The data about immunohistochemistry of most of the patients were not available, and we recommend this matter be considered in future studies.

Financial support and sponsorship

The study was financially supported by Shahid Beheshti University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

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