

Frequency of prolactinoma in surgical specimens of pituitary adenoma in patients referred to Alzahra hospital in Isfahan (2012–2019)

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Abstract

Introduction: Prolactinoma is a common subtype of the pituitary adenomas. Epidemiology study of the distribution of this tumor is necessary to assess the burden of the disease.

Objectives: The aim of this study is to describe the prevalence of prolactinoma in pituitary adenoma patients in Isfahan.

Patients and Methods: This retrospective cross-sectional study included all pituitary adenomas patients who underwent transphenoidal tumor resection during 2012–2019. The biopsy samples of these patients were conducted for immunohistochemistry (IHC) staining and were blindly interpreted.

Results: Around 188 eligible patients with mean age of 46.05 ± 9.5 including 96 female patients and 92 male patients were enrolled in the study. Prolactinoma was seen in 76 (40.1%) of patients, with 44 female patients with a mean age of 42.1 years and 32 male patients with a mean age of 51.8 years. Women were significantly younger.

Conclusion: Prolactinoma is a common subtype of pituitary adenoma since this disease is more frequent in female patients. Although the mean age of diagnosis in female patients is lower, the size and intensity are greater in male patients.

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Introduction

Pituitary adenomas are a group of neoplasms originated from pituitary gland in sellar cavity (1). In most cases they are benign and slow-growing (2). Pituitary adenomas are classified by their clinical and biochemical characteristics (3). Tumors which have sign and symptoms of hormone secretion are functional and the others with no clinical sign of hormone secretion are non-functional. Nonfunctioning pituitary adenomas may produce inactive form of α subunit of thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) or hCG (4). Although the majority of these tumors are asymptomatic, the compression effect of tumors on surrounding structures may cause complications such as visual disturbance and headache (5). Furthermore, excessive amounts of hormones are secreted by functional tumors. This would result in specific clinical presentations such as

Key point

The current study highlights the prevalence of prolactinoma as a frequent subtype of pituitary adenomas. The immunohistochemistry studies show that in 40% of pituitary adenomas, prolactin is present. This tumor is more frequent in females.

acromegaly or Cushing's disease based on the origin (6,7). Pituitary adenomas are categorized into two groups based on the size of tumor. Tumors smaller than 10 mm are considered as microadenomas and the ones larger than 10 mm are considered as macroadenomas (8). The prevalence of pituitary adenomas in epidemiologic studies has been reported to be up to 0.1% of the population (9,10). However, most of them will not be diagnosed because of being asymptomatic (11).

Prolactinomas are thought to be the most common type of functional pituitary adenomas (12). Approximately 40%-66% of

all pituitary tumors are prolactinomas with incidence rate of 6–10 new patients per year (13). It is more frequent in 20–50 years old women (14). These tumors are functional and are the most important causes of excess prolactin in the body. Generally, among pituitary adenomas, patients' amenorrhea and visual disturbance are more common in prolactinoma patients (15). Clinical presentations vary between female and male patients of different age groups (16). In women of childbearing age predominantly it presents as microadenomas in this age group and it presents with galactorrhea and gonadal dysfunction (irregular menses and amenorrhea) (17). Accordingly the presentation of the disease in male patients is usually loss of libido, impotence. Due to late appearance, the prevalence of macroadenoma and consequently visual symptoms is higher in men and postmenopausal women (13,16,18).

In contrast to other pituitary adenomas, pharmacotherapy is the treatment of choice for prolactinomas. Surgery is the second line treatment in cases of medical treatment failure (19, 20).

A study in Sweden on pituitary adenoma patients showed the prolactinoma (32%) is the second most common type of pituitary adenoma after non-functional tumors (54%). While a similar study in Iran results in 45% prolactinoma (21).

Studies show that even in many healthy people, pituitary adenoma could be found without any symptoms and the most common subtype in these adenomas is prolactinoma. In a study by Buurman et al, the investigation of autopsies revealed that pituitary adenoma was present in about 10% of them. The immunohistochemistry study of these cases in 39.5% was positive for granulated prolactin (22).

Objectives

Based on these findings, it seems the prevalence of prolactinoma may be different from what is reported. To the best of our knowledge, there are no research regarding this type of tumor in the Iranian population. Therefore, in this study we aimed to investigate the prevalence of this specific type among patients suffering from pituitary adenoma.

Patients and Methods

Study design

This is a cross-sectional retrospective study conducted in Alzahra hospital from 2012 to 2019. Patients who underwent tumor resection surgery were included in the study. Patients would be excluded from the study if the paraffin embedded samples of them were not available or they were reluctant to participate. Written informed consent at the time of admission was taken from each patient after informing the aim of the study to them.

Subjects were diagnosed with pituitary adenoma by endocrinologists. All cases were referred to neurosurgery department in order to perform pituitary resection surgery. This surgery is performed via transsphenoidal

resection technique.

The resected tumor samples were sent to pathology department to confirm the diagnosis. Then, the samples were fixed via formalin 10% and embedded in paraffin. After initial assessments, the paraffin embedded samples have been stored in pathology center bank for further investigation.

The pituitary resection samples from 2012–2019 were restored from the sample bank. The samples are cut into 4 μ m thickness slices. In order to detect prolactin in the samples, a special immunohistochemistry marker (PRL) will be applied to them. After staining experienced pathologist reviewed and interpreted the samples. The presence of prolactin granules and percentage is recorded for each case.

Ethnic issues

The study was in accordance with the Declaration of Helsinki and its later amendments. This research was the MD thesis of Mohammadhatef Sadri, at the Isfahan University of Medical Sciences. Ethics committee of the Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.723) approved this study. All the participants were informed about the study procedure and aims.

Statistical analysis

For statistical analysis, the achieved data were entered into SPSS (statistical package for the social science v25.0, SPSS Inc. Chicago, IL). The prevalence of the prolactinomas and the quantity statistics will be assessed by descriptive analysis. To check the relation between result, gender, age, and prolactin percentage, the Pearson's correlation test and chi-square test were performed ($P < 0.05$).

Results

This retrospective cross-sectional study was performed Al-Zahra hospital, Isfahan. The subjects of this study were patients suffering from pituitary adenoma who underwent pituitary resection surgery. Of 209 patients, only 188 (89.9%) patients participated in this study, other 11 (10.1%) patients were excluded due to missing their paraffin blocks. Therefore, the study was conducted using 188 eligible patients' data.

The patients were aged between 28–71 years old (average; 48.05 ± 9.5 years old). There were 96 female patients with a mean age of 46.62 years and 92 male patients with a mean age of 49.5 years old.

The IHC studies show that prolactin presents in 40.5% of pituitary adenomas. However, the intensity of the staining was different in cases. The presence of prolactin was higher in female patients; however it was not significantly higher than male patients ($P = 0.123$). From the prolactin positive cases 32 patients (42.1%) were male and 44 patients (57.9%) were female (Table 1).

The mean age of PRL positive patients was 42.1 years while in negative patients, it was 51.8 years. The Pearson's

Table 1. Distribution of prolactin among patients

	Number	Mean age	Prolactinoma	Prolactin intensity (%)
Male	92	49.5	32	56.4
Female	96	46.6	44	38.6
Total	188	48	76	46.1

correlation test indicated that prevalence of prolactin secreting PA significantly decreased by age ($P < 0.001$).

The samples with positive results were classified by the intensity of the staining from 5% (weakly positive) to 100% (strongly positive). The average severity of all positive cases was 46.1% (SD = 33.3). The result in male patients was 56.4% which is higher than female patients that were 38.6%. Pearson's correlation analysis reveals that prevalence of prolactin granules in pituitary adenoma is correlated with gender ($P = 0.023$).

Discussion

Pituitary adenoma can arise from different cell types. The presentation of the disease is different based on the origin and the size of tumor. Pituitary adenoma functional tumors are the hormone secreting tumors while some of them could be asymptomatic. The most common functional pituitary tumor is prolactinoma. It can present with menses disorders, loss of libido, visual disturbance. In the current study pituitary adenoma patients' biopsies checked using prolactin specific immunohistochemistry methods.

Of 188 pituitary adenoma patients, 76 patients were positive for prolactin by IHC. The average age of the patients was 42.1 years. We found that pituitary adenoma in younger patients is highly suspected to be a prolactinoma. Although the rate of prolactinoma was higher in female patients, it was not statistically significant. Additionally, in male patients the number prolactin secreting cells was significantly higher. As mentioned prolactinoma presentation in female patients is more evident, which could be the cause of higher percentage in female patients.

Mete et al in 2017 performed a study on 1055 pituitary adenoma patients. They gathered pathology samples of patients who underwent transsphenoidal tumor resection and used specific biomarkers to review them. The outcome of this study revealed 27.8% prevalence of prolactinoma. This tumor is a common tumor among different types of pituitary adenomas (23). This result is confirmatory of our study; however the prevalence is not quite the same. This variety has been repeated in other studies as well. A study conducted in Malta reviewed profiles of 316 adenoma patients since 46.2% (146 patients) were suffering from prolactin secreting adenoma and the majority of the patients were female. Although this result is similar to our study, the selection of cases is different. The diagnosis is made by clinical presentation in PA patients (24).

However, various studies that confirmed the high prevalence of prolactinoma, showed the gender

distribution of this tumor is higher in women. In Sweden Tjornstrand et al in an investigation of PA patients showed, 32% of them were prolactinoma including 68% of female patients and 22 % of male patients (25). The higher prevalence in women has been seen in other communities as well. Another study has been conducted in Iceland on 471 pituitary adenoma patients. They checked the medical records of patients such as radiology and pathology reports and the results showed that prolactinoma was the diagnosis of 39.9% of their patients (26). According to the studies, prolactinoma is one of the most frequent pituitary adenoma tumors; however, the prevalence in different communities is not the same. Additionally, the study methods in these researches are different, while the ethnic diversity is the probable cause of this difference.

In this regard, recent studies reported higher incidences of prolactinoma in women, which it is likely to occur in younger ages (24-26).

Furthermore the size of prolactinoma in male patients are greater than female patients and the prevalence of giant prolactinoma is nine times higher in male patients (27, 28). These finding would support the higher prolactin percentage in our study.

Conclusion

Prolactinoma is one of the most common types of pituitary adenomas. The prevalence of this adenoma varies among different communities. Our study shows that the prolactinoma could be seen in up to 40.5% of pituitary adenoma patients. This disease is more frequent in female patients. Although the mean age of diagnosis in female patients is lower, the size and intensity are greater in male patients.

Limitations of the study

An important limitation of this study was inability to access the medical records of these participants. It would help us compare patients' diagnosis, clinical presentation, and severity of the disease with the pathology results. Also, the results would be much more comprehensive if we could perform a multi-centric study.

Authors' contribution

MD: study design. AA: patient diagnosis and referral. PR, AB, PH, SE, MH, AN, PR: Pathology and IHC review. MS: data collection and analysis. AZ, SF: Writing and editing. AB: Supervised and revised.

Conflicts of interest

The authors proclaim that there were no conflicts of interest. The authors are responsible for the writing and content of the article.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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