ISSN: 2573-9565

Research Article

Journal of Clinical Review & Case Reports

The Incidence of Anterior Pituitary Hormone Deficiencies in Patients with Pituitary Microadenoma and Idiopathic Hyperprolactinaemia. A Retrospective Single Centre Study

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Submitted: 24 Feb 2018; **Accepted**: 02 Mar 2018; **Published**: 15 Mar 2018

Abstract

Introduction: *Patients with microprolactinoma and idiopathic hyperprolactinaemia are not generally considered to be at risk of hypopituitarism and are therefore not routinely screened for this abnormality.*

Aims: *We aimed to establish the frequency and clinical significance of anterior pituitary hormone deficiencies, comparing patients with radiologically proven microprolactinomas and idiopathic hyperprolactinaemia.*

Study Design: *We retrospectively examined the case notes of 242 patients with hyperprolactinaemia from our centre. Patients who did not fit the profile of surgically naïve microprolactinoma or idiopathic hyperprolactinaemia or who had incomplete data were excluded, resulting in a study group of 185 patients.*

Results: *Out of 242 patients, 185 patients were identified with microprolactinoma and idiopathic hyperprolactinaemia. 47 (20 %) were male and 148 (80 %) were female with mean age 35.4 ± 13.7. 87(47%). Four types of hypofunctioning pituitary gland were seen such as panhypopituitarism, secondray hypogonadism, growth hormone deficiency and central hypothroidism and were associated with more frequent normal MRI. Patients with MRI evidence of microprolactinoma were identified, three (3.4%) of whom had one or more anterior pituitary hormone deficiencies. A total of 98 (53%) patients with MRI-negative idiopathic hyperprolactinaemia were identified, twelve (12.2%) of whom had one or more anterior pituitary hormone deficiencies. Patients in the MRI-positive and MRI-negative groups had panhypopituitarism, hypogonadotrophic hypogonadism and growth hormone deficiency that required hormone.*

Conclusion: *The current study shows an increased frequency anterior pituitary hormone deficiency in patients with idiopathic hyperprolactinaemia, not with pitutary microadenoma. A prospective study would be required to assess the underlying cause for these abnormalities, as they suggest a nontumour pan-pituitary process.*

Limitations: *Question of clustering of cases within the study region and limited study sample size.*

Keywords: Anterior Pituitary Hormone Deficiencies, Pituitary Microadenoma and Idiopathic Hyperprolactinaemia

Introduction

Hypopituitarism is a clinical syndrome of deficiency in pituitary hormone, however, only one or more pituitary hormones are often involved, resulting in isolated or partial hypopituitarism [1]. Hyperprolactinemia is an endocrine disorder of the hypothalamic-pituitary axis with elevated prolactin levels in blood which could be physiological, pathological, or idiopathic in origin. The prevalence of hyperprolactinemia ranges from 0.4% in an unselected adult population to as high as 9-17% in women with reproductive diseases [2, 3]. Prolactinomas account for 25-48% of pituitary tumors and are the most frequent cause of hyperprolactinemia [4-7]. The most frequent abnormalities found on imaging are adenomas of the pituitary gland and in most cases, where the tumor size of < 10 mm is labeled as microadenomas. In cases where other causes of hyperprolactinemia have been excluded and no adenoma can be visualized with MRI, the hyperprolactinemia is referred to as "idiopathic".

Patients with microprolactinoma and idiopathic hyperprolactinaemia are not generally considered to be at risk of hypopituitarism and are therefore not routinely screened for this abnormality. No detailed data are available for the prevalence of anterior pituitary hormone deficiencies in patients with pituitary microadenomas and idiopathic hyperprolactinemia [8]. This study aimed to obtain information on the

epidemiology of anterior pituitary hormone deficiencies in patients with pituitary microadenomas and idiopathic hyperprolactinemia in a tightly defined geographical area in Jeddah, Saudi arabia.

Methods

All MRI pituitary records were collected from the radiology department data base between January 2008 and December 2017 at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia. Serum prolactin, MRI pituitary and clinical Records of patients were thoroughly analyzed. Out of the initial screening of 630 subjects, 445 subjects were excluded from the study as they were normal prolactin levels, incomplete clinical records, MRI pituitary were reported pituitary macroadenoma or MRI was repeated for the same patients. The remaining 185 subjects constitute the subject material for the study. Information was collected from two resources such as clinical case records of subjects seen at the endocrinology or other services and the data on hormonal analysis including neurodynamic tests of the subjects. Records were thoroughly reviewed for clinical data and hormonal assays. MRI pituitary radiological findings were reported by our centre radiologists and reports were reviewed. The Pituitary microadenoma were reported according to their size on MRI scan (less than 10 mm in diameter). In cases where other causes of hyperprolactinemia have been excluded and no adenoma can be visualized with MRI, the hyperprolactinemia is referred to as "idiopathic".

Statistical Analysis

Continuous variables were described using means and Standard Deviations. Univariate analysis of baseline demography both between groups, were accomplished using unpaired t-test and Chi square test were used for categorical data comparison. P value <0.05 indicates significance. The statistical analysis was conducted with SPSS version 22.0 for Windows.

Results

Out of 242 patients, 185 patients were identified with microprolactinoma and idiopathic hyperprolactinaemia. 47 (20 %) were male and 148 (80 %) were female with mean age 35.4 ± 13.7. 87 (47%), Table 1. Four types of hypofunctioning pituitary gland were seen such as panhypopituitarism, secondray hypogonadism, growth hormone deficiency and central hypothroidism and were associated with more frequent normal MRI, table 2. Patients with MRI evidence of microprolactinoma were identified, three (3.4%) of whom had one or more anterior pituitary hormone deficiencies. A total of 98 (53%) patients with MRI-negative idiopathic hyperprolactinaemia were identified, twelve (12.2%) of whom had one or more anterior pituitary hormone deficiencies. Patients in the MRI-positive and MRI-negative groups had panhypopituitarism , hypogonadotrophic hypogonadism and growth hormone deficiency that required hormone.

Table 1. Gender and age in correlation to Pituitay microadenoma and Idiopathic Hyperprolactinemia

Parameters		Total	Pituitay microadenoma	Idiopathic Hyperprolactinemia	P value
		185	87 (47)	98 (53)	
Age (years)		35.4 ± 13.7	33.1 ± 9.7	34.3 ± 12.9	0.5
Gender	Male	37 (20.0)	14 (37.8)	23 (62.2)	
	Female	148 (80.0)	73 (49.3)	75 (50.7)	0.2

Data are number (%) and mean ± standard deviation

Table 2. Anterior pituitary hormones in correlation to Pituitay microadenoma and Idiopathic Hyperprolactinemia

Associated pituitary abnormalities	Total	Pituitay microadenoma	Idiopathic Hyperprolactinemia
Panhypopitiuturism	3 (20)	1 (33.3)	2 (66.7)
Secondary hypogonadism	8 (53.3)	1 (12.5)	7 (87.5)
Growth hormone deficiency	3 (20)	1 (33.3)	2 (66.7)
Central hypothyroidism	1 (6.7)	0	1 (100)

Data are number (%).

Discussion

Dedicated pituitary MRI is the preferred diagnostic imaging modality for evaluation of sellar and parasellar tumors, including adenomas. In particular, when functioning adenomas are suspected, a dynamic pituitary MRI, which obtains images within seconds after gadolinium contrast injection, may be more useful because it has higher sensitivity than other imaging modalities for detecting small microadenomas [9]. Small incidental lesions of little or no clinical significance visualized on dynamic pituitary MRI may be misinterpreted as the pathological source of excess hormonal secretion given lower specificity vs. conventional MRI. However, our calculation of the specificity of pituitary MRI is likely limited due to underestimation of true negative values because there are few conditions in which clinicians would obtain pathology results of the pituitary mass when a normal pituitary gland is reported on MRI.

Pituitary adenomas are the most common intracranial neoplasm comprising approximately 5–20% of primary central nervous system tumors, which would translate into a relatively low prevalence [10-12]. The most frequent abnormalities found on imaging are adenomas of the pituitary gland are microadenomas [4]. Epidemiologic studies are limited by their dependence on population-specific registries, which subject them to bias from regional influences such as diagnostic practices, reporting patterns, and case definitions. In general, the incidence of PA is higher in more recent than in older studies, probably due to improved endocrinological and radiological diagnosis, and increased neurosurgical interest in these lesions. In this sample, the mean age of patients was 35 years old. It should be taken into account that PA mostly affect young and economically active individuals in whom diagnostic delay translates into loss of productivity [13]. These data highlight the need for increasing the awareness of these treatable conditions, thereby minimizing the adverse squeal of late diagnosis.

The clinical features of pituitary adenoma vary depending on the location and size of the tumor and its secretory capability. Pituitary adenomas typically appear during early adulthood, and no sex predilection is known. Hormone deficiencies should also be evaluated because hypopituitarism is present in up to 30% of macroadenomas, where our report showed only 3.4 % of microprolactinemia have anterior hormones deficiencies. As evident in our report, the most common pituitary deficit in these patients is hypogonadism [14]. There is no evidence from controlled trials to guide a specific investigative approach, and recommendations are based largely on expert opinion and extrapolation from observational studies [15,16].

Hyperprolactinemia is a common endocrine disorder of the

hypothalamic-pituitary axis. It occurs more commonly in women. The prevalence of hyperprolactinemia ranges from 0.4% in an unselected adult population to as high as 9-17% in women with reproductive diseases [2,3]. Around 40% patients with primary hypothyroidism, 30% patients with chronic renal failure, and up to 80% patients on hemodialysis have mild elevation of prolactin levels. Many patients with acromegaly have prolactin co-secreted with growth hormone. In cases where other causes of hyperprolactinemia have been excluded and no adenoma can be visualized with MRI, the hyperprolactinemia is referred to as "idiopathic". Approximately 16% of patients with idiopathic hyperprolactinemia (negative imaging and no other apparent cause) will develop evidence of microadenomas in follow-up [17-19]. Behan et al reported 42% of whom had one or more anterior pituitary hormone deficiencies which higher than our report (12.2%), likey because of their sample size [8].

Variability in reported positive MRI results was observed for different clinical indications. 84% of MRI scans ordered for hypogonadism did not reveal a pituitary lesion which compatible with us. These results highlight that pituitary MRI is likely not helpful as a screening tool for patients with hypogonadism. Positive pituitary MRI scans observed with hypogonadotropic hypogonadism were typically observed in cases of severe testosterone deficiency in which total testosterone was less than 100 (normal 250-1000 ng/dl). Given the lack of definitive imaging changes in patients screened for hypogonadism, clinicians should use a higher judgment threshold before ordering pituitary imaging for these patients [20-21].

We aimed to identify the clinically apparent pituitary masses in patients with hyperprolactinemia as screened by MRI scans, and this aim was reflective of the clinical setting because not all pituitary masses are formally diagnosed with histological confirmation. Furthermore, due to the retrospective nature of this study, the observed population reflects a selected yet comprehensive group of patients with hyperprolactinemia referred for pituitary MRI, rather than the general population as would be encountered in an autopsy series. Our study could be limited by the question of clustering of cases within the study region and the effect that might have on our estimates. In addition, the study shares the limitations of all retrospective studies.

In conclusion, the current study shows an increased frequency anterior pituitary hormone deficiency in patients with idiopathic hyperprolactinaemia, not with pitutary microadenoma. A prospective study would be required to assess the underlying cause for these abnormalities, as they suggest a nontumour pan-pituitary process.

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