The epidemiology of pituitary adenomas in a community-based hospital: a retrospective single center study in Saudi Arabia

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BACKGROUND: Data on pituitary adenoma (PA) prevalence in Saudi Arabia are scarce. OBJECTIVE: To estimate the epidemiology of PA in a well-defined population

DESIGN: Retrospective analysis.

SETTING: Departments of Endocrinology and Radiology at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia.

PATIENTS AND METHODS: Radiological and hormonal data of patients with pituitary adenoma by MRI were reviewed for the period January 2008 to December 2015.

MAIN OUTCOME MEASURES: Prevalence of PA and hormonal abnormalities.

RESULTS: Of 537 patients; 249 subjects (46.4%), 70 (28.1%) males and 179 (71.9%) females, were diagnosed to have PA with mean age 36.3 (14.1) years. Microadenoma and macroadenoma were seen in 171 (69%) and 78 (31%) subjects, respectively. Microadenomas were more prevalent than macroadenomas (68.7% vs. 31.3%). Microadenomas were significantly more prevalent in females, 131 (73.2 %) vs. 40 (57.1%) whereas macroadenomas were significantly more prevalent in males, 30 (42.9%) vs. 48 (26.8%) (P<.001 for both comparisons). Patients with microadenomas were significantly younger than patients with macroadenomas (P<.0001). Advanced age was significantly associated with a larger PA size (r=0.39, P<.0002). Three types of hyperfunctioning PA were seen: prolactinoma, somatotroph adenoma, and corticotroph adenoma. Five types of hypofunctioning PA were seen: panhypopituitarism, secondary hypogonadism, growth hormone deficiency, central hypothyroidism and central adrenal insufficiency. Non-functioning PA were within normal laboratory hormonal values in 2% of cases.

CONCLUSION: Our study showed that the prevalence of PA was greater than previously reported. This increased prevalence may have important implications when prioritizing funding for research and treatment of PA.

LIMITATIONS: Clustering of cases within the study region might have affected estimates and limited study sample size.

Pituitary adenomas (PA) are a diverse group of tumors arising from the pituitary gland. Historically, PA have been classified according to size. If the tumor is 10 mm or larger, it is considered a macroadenoma; if less than 10 mm, a microadenoma. Microadenomas are slightly more common than macroadenomas (57.4% vs. 42.6%). The prevalence data are important for the estimation of disease burden in populations and are often used to calculate health care resource distribution within and among clinical specialties. Existing data on the prevalence of PA are discordant. Given the small size of many PA and their propensity to exist without symptoms or with only insidious, nonspecific symptoms, it is a challenge to accurately measure the prevalence of PA in the general population. Histological analysis of autopsy specimens and radiologic (computed tomography [CT] and magnetic resonance imaging [MRI]) data from patients being treated or studied for conditions related and unrelated to pituitary disease are the two principal methods that have been used to estimate the population prevalence of PA.
Many studies have been performed using these two approaches to define the prevalence of PA. However, PAs constitute 10% to 15% of intracranial tumors in surgical specimens and both methods have generated estimates ranging from 1% to 30%.²⁴

PA are also categorized based on primary cell origin and type of hormone secreted. If the PA does not secrete a sufficient level of hormones to be detectable in the blood or to result in clinical manifestations, it is considered non-functioning. Prolactinomas comprise 40% to 57% of all PA, followed by non-functioning adenomas (28% to 37%), growth hormone-secreting adenomas (11% to 13%), and adrenocorticotropic hormone secreting adenomas (1% to 2%). PA that secrete follicle-stimulating hormone, luteinizing hormone, or thyroid-stimulating hormone are rare.¹³

Existing epidemiological data suggest that the incidence of PA is rising, although it is difficult to determine whether this is due to widespread access to CT or MRI and accurate biochemical testing, leading to improved recognition of clinically relevant PA.⁶ The uncertainty regarding the true prevalence of clinically active PA led us to undertake a retrospective epidemiological study of the presence of PA in a defined geographical area in Jeddah, Saudi Arabia.

**PATIENTS AND METHODS**

All MRI pituitary records for the period between January 2008 and December 2015 were collected from the radiology department database at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia. The records of subjects with incomplete clinical records or a repeat MRI were excluded. The MRIs and clinical records of the remaining subjects were analyzed. Information was collected from clinical case records at the endocrinology or other services and from data on hormonal analysis, including neurodynamic tests. MRI pituitary radiological findings reported by our the center radiologists were reviewed.

The PA were divided according to their size on MRI scan into microadenoma (less than 10 mm in diameter) and macroadenoma (more than or equal to 10 mm in diameter). The PA were further subclassified as having lactotroph-secreting adenoma, panhypopituitarism, somatotroph adenoma, non-functioning pituitary, secondary hypogonadism, growth hormone deficiency, corticotroph adenoma, secondary adrenal insufficiency or central hypothyroidism.

Continuous variables were described by means and standard deviations. Univariate analysis of baseline demography between groups were done using unpaired t tests and chi-square tests. The Pearson test was used for correlation of age with PA size. A P value <.05 was chosen to represent statistical significance. The statistical analysis was conducted with SPSS version 22.0 for Windows.

**RESULTS**

From an initial screening of 630 subjects, 93 were excluded from the study as they had either incomplete clinical records or the MRI was a repeat. Over the 7-year period, MRIs of the pituitary were performed on the remaining 537 patients. About half (n=249, 46.4%) were diagnosed with PA. In this sample, 65% of patients were younger than 40 years old. The mean and median ages were 36 and 33 years (range 13 to 90 years), respectively. Females were younger than males (34.6[11.5] vs 40.8 [18.6] years). There were 70 (28.1%) males and 179 (71.9%) females. Of 537 patients, microadenoma and macroadenoma were seen in 171 (31.8%) and 78 (14.5%) subjects, respectively. Microadenomas were more seen than macroadenomas (68.7% vs. 31.3%) (Table 1). Microadenomas were seen significantly more often in females, 131 (73.2%) vs. 40 (57.1%), whereas macroadenomas were seen significantly more often in males 30 (42.9%) vs. 40 (26.8%) (P<.001). Prolactinoma were the most common type (n=183, 73.5%) (73.5%) (P<.001). More females than males had prolactinomas (71.9% vs. 28.1%). Microadenomas were seen significantly more often at younger ages compared with macroadenomas. Most of the subjects presented in the third and fourth decades of life. Age was positively correlated and significantly associated with PA size in 85 subjects (r=0.39, 95% confidence interval 0.19-0.56, P<.0002) (Figure 1), although for PA size less than 10 mm, the correlation was weak and statistically nonsignificant. Three types of hyperfunctioning PA were seen: prolactinoma, somatotroph adenoma, and corticotroph adenoma. Five types of hypofunctioning PA were seen: panhypopituitarism, secondary hypogonadism, growth hormone deficiency, central hypothyroidism and central adrenal insufficiency. Non-functioning PA were within normal laboratory hormonal values in 2% of cases.

**DISCUSSION**

PAs are the most common intracranial neoplasm comprising approximately 5% to 20% of primary central nervous system tumors, which translates into a relatively low prevalence. 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. There are limited data on the prevalence of PAs despite epidemiologic, postmortem, and radiologic studies. 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. There was a wide range in PA prevalence estimates in individual studies, from 1% to nearly 40% in the imaging studies (40% is a lower prevalence than in our report) and from approximately 1% to 35% in the postmortem studies. The overall estimated prevalence of PA across both groups of studies was 16.7%.\textsuperscript{1,10-20}

We found that 68.7% of PA were microadenomas. This is a higher prevalence than previously reported (57.4%). The 31.3% prevalence for macroadenoma was lower than previously reported (42.6%).\textsuperscript{1} Unrecognized macroadenomas and macroadenomas are probably common.\textsuperscript{3,21} It should be taken into account that PAs mostly affect young and economically active individuals in whom diagnostic delay translates into loss of productivity. These data highlight the need for increasing the awareness of these treatable conditions, thereby minimizing the adverse sequelae of late diagnosis.

The 249 patients with clinically relevant PA identified in a population of 300,000 translates to a mean prevalence of 83 per 100,000 population, which is similar to a report from Fernandez et al (77.6 cases per 100,000). Furthermore, data extracted from tertiary referral centres are influenced by selection bias and by wide variations in referral patterns. Davis et al found prevalence figures for prolactinoma, nonfunctioning adenoma, somatotrophinomas and corticotrophinomas of 6–10 cases/ per 100,000, 7–9 cases per 100,000, 4–6 cases per 100,000 and 2–3 cases per 100,000, respectively, which is a higher prevalence than in our report (Table 2).\textsuperscript{22,34,35} Compared with reports from Western countries and nationally, our series revealed the following special features: The percentage of PAs (46%) was relatively high, the percentage of microadenomas (68.7%) was relatively high, prolactinoma was the most common type (73.5%), and there were more females than males with prolactinomas (81.4% vs. 18.6%). The higher prevalence of PA is probably attributable not only to advances in (and easier access to) diagnostic tools (imaging and hormonal assays), but also and importantly, to the increased awareness and higher index of suspicion. Also, underdiagnosis of this condition cannot be excluded. Another factor may be that most of our patients were referred to endocrinology service for evaluation of hyperprolactinemia. Our department protocol is to obtain an MRI for all cases of high serum prolactin if elevation persists on two samples.

MRI imaging is the procedure of choice in the evaluation of sellar masses.\textsuperscript{23} The diagnostic approach to suspected PA depends on presenting symptoms and hormone values. 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.\textsuperscript{24-29} A patient who presents with symptoms of hormone excess likely has a functioning adenoma. Evaluation can be geared toward the specific hypersecretory syndrome. Approximately 65% of PA secrete a hormone causing typical hypersecretory syndromes.\textsuperscript{30} The remaining (35%) do not secrete a hormone and are thus referred to as nonfunctioning (or nonsecreting) adenomas. Due to compression of pituitary tissue, pituitary stalk and its

### Table 1. Prevalence, sex ratio, age and subtypes of pituitary adenomas.

| Parameters | Total n=249 (46.4) | MRI findings | Microadenoma n=171 (68.7) | Macroadenoma n=78 (31.3) |
|------------|-------------------|--------------|--------------------------|-------------------------|
| Age (years) | 36.3 (14.1) | 33.7 (12.0) | 42.1 (16.6)\textsuperscript{a} |
| Gender | | | | |
| Male | 70 (28.1) | 40 (23.4) | 30 (38.5)\textsuperscript{b} |
| Female | 179 (71.9) | 131 (76.6) | 48 (61.5) |
| Tumor diameter (mm) (n=85) | 9.8 (8.9) | 4.7 (2.2) | 19.3 (8.8)\textsuperscript{c} |
| Associated pituitary abnormalities | | | | |
| Lactotroph secreting adenoma | 183 (73.5) | 134 (73.2) | 49 (26.8) |
| Panhypopituitarism | 3 (1.2) | 1 (33.3) | 2 (66.7) |
| Acromegaly | 10 (4) | 3 (30) | 7 (70) |
| Nonfunctioning pituitary adenoma | 5 (2.0) | 3 (60) | 2 (40) |
| Secondary hypogonadism | 18 (7.2) | 8 (44.4) | 10 (55.6) |
| Growth hormone deficiency | 4 (1.6) | 4 (100) | 0 |
| Corticotroph adenoma | 1 (0.4) | 1 (100) | 0 |
| Central hypothyroidism | 10 (4.0) | 7 (70) | 3 (30) |
| Secondary adrenal insufficiency | 15 (6.0) | 10 (66.7) | 5 (33.3) |

Data are number (%) or mean (standard deviation). P-values: \textsuperscript{a}<.0001 \textsuperscript{b}=.01 <.0001; All comparisons are microadenoma vs macroadenoma; males vs females for microadenomas.
vascular supply, partial or total hypopituitarism may occur, resulting in a deficit of production of some or all pituitary hormones. The most common pituitary deficit in these patients is hypogonadism. Hypogonadotropic hormone deficiencies should also be evaluated because hypopituitarism is present in up to 30% of adenomas, and because of the need to address deficiencies in future treatment regimens. Our study showed a high percentage of PA with hormonal secretion (78%); the remaining PA were either nonsecreting adenomas (2%) or hypofunctioning adenomas (20%).

In the current study, prolactinomas comprised 73.5% of the entire series, which is higher than previously reported (66%). The majority were microadenomas (73.2%) that were mostly in female patients in keeping with previous data from surgical series and immunohistochemical studies of autopsy data (76%). Despite the fact that the majority of prolactinomas were small, the attendant use of health care resources appears sizable, given the performance of multiple MRI scans, dynamic pituitary function tests, and the frequent requirement for medical or surgical therapy.

Autopsy and radiology estimates do not include clinical correlates, such as symptoms and hormonal data, whereas the strength of the current study is that it included clinically relevant PA that had already been diagnosed with verifiable hormonal and radiological profiles. A potential limitation is the possibility of clustering of cases within the study region and the effect that might have had on our estimates. In addition, the current study population is limited in size and therefore may underestimate the true prevalence of PA in the general population.

In conclusion, the current study is the first to report a high frequency of PA in Saudi Arabia. In the absence of registry data, larger cooperative studies involving diverse population samples from multiple centers should help to provide further information on the true prevalence of PA nationally.

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Conflict of interests
The authors declare no conflict of interests.

Table 2. Prevalence (% and cases per 100 000) of types and subtypes of pituitary adenomas in different studies.

| Name                        | Studies prevalence (%)* | Current study | Western | Saudi Arabia |
|-----------------------------|-------------------------|---------------|---------|--------------|
|                             | Per 100 000 | %     | %     | %     |
| Microadenoma                | 57          | 68.7  | 57.4  | 12    |
| Macroadenoma                | 26          | 31.3  | 42.6  | 88    |
| Lactotrophs secreting adenoma | 61          | 73.5  | 14.7–57 | 34.9 |
| Panhypopituiturism           | 1           | 1.2   | 30    | NA   |
| Acromegaly                  | 3.3         | 4     | 11.56.6 | 20.5 |
| Nonfunctioning pituitary adenoma | 1.7        | 2.0   | 28–37 | 37.3 |
| Secondary hypogonadism      | 6           | 7.2   | 40    | NA   |
| Growth hormone deficiency   | 1.3         | 1.6   | NA    | NA   |
| Corticotroph adenoma        | 0.3         | 0.4   | NA    | 4.8  |
| Gonadotroph adenomas        | 0           | 0     | 15    | NA   |
| Thyrotroph adenoma          | 0           | 0     | 1-2   | NA   |
| Central hypothyroidism      | 3.3         | 0.4   | NA    | 4.8  |
| Secondary adrenal insufficiency | 5           | 0     | 15    | NA   |

*References: 1, 5, 34, 35
REFERENCES

1. Daly AF, Richardson D, Wilding C. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol (Oxf). 2010;72(3):377–382.

2. Nammour GM, Ybarra J, Naheedy MH, Romeo JH, Aron DC. Occult pituitary macroadenoma: a population-based study. Am J Med Sci. 1997;314:287–291.

3. Verdecchia A, De Angelis G, Capoccia R. Estimation and projections of cancer prevalence from cancer registry data. Stat Med. 2002;21:3511–3526.

4. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol (Oxf). 2010;72(3):377–382.

5. Cherubin CE, Cassin D, Miller FG, Levine PH. Incidental pituitary lesions in 1,000 unselected autopsy specimens. Neurosurgery. 1981;21:155–159.

6. Kepes J, Chen W, Pang L, Kepes M. Pituitary macroadenoma: a population-based study. AJNR Am J Neuroradiol 2008;29:613–15.

7. Cherubin CE, Cassin D, Miller FG, Levine PH. Incidental pituitary lesions in 1,000 unselected autopsy specimens. Neurosurgery. 1981;21:155–159.

8. Siqueira MG, Guembarovski AL. Subclinical pituitary microadenomas. Surg Neurol. 1984;22:149–156.

9. Lovasteng G, Ferrarg, Ross G. Epidemiology of primary intracranial neoplasms. 1981;8:287–305.

10. Cherubin CE, Cassin D, Miller FG, Levine PH. Incidental pituitary lesions in 1,000 unselected autopsy specimens. Neurosurgery. 1981;21:155–159.

11. Satherland G, Fiorell, Louwe, Choi W, Sima A: Epidemiology of primary intracranial neoplasms in Manitoba, Canada. Can J Neurol Sci, 1987;14:586-592.

12. Chambers EF, Turski PA, LaMasters D, Newton TH. Regions of low density in the contrast-enhanced pituitary gland: normal and pathologic processes. Radiology. 1982;144:109–113.

13. Hall WA, Luciano MG, Doppman JL, Patrinos NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. Ann Intern Med. 1994;120:817–820.

14. Chong BW, Kucharzyk W, Singer W, George S. Pituitary gland MR: a comparative study of healthy volunteers and patients with microadenomas. Am J Neuroradiol. 1994;15:675–679.

15. Muh C, Bergstrom K, Grimalius L, Larsson SG. A parallel study of the roentgen anatomy of the sella turica and the histopathology of the pituitary gland in 205 autopsy specimens. Neuroradiology. 1981;21:55–65.

16. Teramoto A, Hirakawa K, Sanno N, Osamura Y. Incidental pituitary lesions in 1,000 unselected autopsy specimens. Radiology. 1994;193:161–164.

17. Burrow GN, Wortzman G, Newcassel NB, Holgate RC, Kavcs K. Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. N Engl J Med. 1981;304:156–158.

18. Costello RT. Subclinical adenoma of the pituitary gland. Am J Pathol. 1936;12:205–206.

19. Yue NC, Longstreth WT Jr, Elster AD, Jungreis CA, O’Leary DH, Potier VC. Clinically serious abnormalities found incidentally at MR imaging of the brain: data from the cardiovascular health study. Radiology. 1997;202:41–46.

20. Davis JR, Farrell WE, Clayton RN. Pituitary tumours: pathophysiology, clinical manifestations and management. Endocr Relat Cancer. 2002;28:287–305.

21. Chambers EF, Turski PA, LaMasters D, Newton TH. Regions of low density in the contrast-enhanced pituitary gland: normal and pathologic processes. Radiology. 1982;144:109–113.

22. Vance ML. Diagnosis, management, and prognosis of pituitary tumors. In: Thapar V, Vadas F, editors: The epidemiology of pituitary adenomas in a major neuroradiological unit in Saudi Arabia. Emirates Medical Journal (1995) 13: 39-44

23. Zargar A, Bashir A, Laway, Sharir R. Masoodi D, Ganie M, Bhat M, Wani A, Bashir M. Clinical and endocrine aspects of pituitary tumors. Saudi Med J 2004; Vol. 25 (10): 1428-1432

24. Mindermann T, Wilson CB 1994 Age-related and gender-related occurrence of pituitary adenomas. Clin Endocrinol (Oxf) 41:359–364