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Clinical and Epidemiological Characteristics of Pituitary Tumours using a Web-based Pituitary Tumour Registry in Oman

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الصفات السريرية والوبائية لأورام الغدة النخامية باستعمال الشبكة العالمية في سلطنة عمان

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الملخص: الهدف: في هذه الدراسة قمنا بتجميع المعلومات عن جميع المرضى المصابين بأورام في الغدة النخامية في مستشفى جامعة السلطان قابوس في خلال الثماني السنوات السابقة وقمنا بتحليلها وإدخالها في السجل العُماني الخاص بأورام الغدة النخامية في الشبكة العالمية. **الطريقة:** تم تسجيل كل المرضى المصابين بأورام الغدة النخامية في مستشفى جامعة السلطان قابوس للفترة من يناير 1998 إلى فبراير 2006 في سجل خاص بأورام الغدة النخامية بالشبكة العالمية. قام طبيبين بتجميع كل المعلومات عن هؤلاء المرضى. يتكون السجل من معلومات تتعلق بحالة المريض الصحية . مستوى الهرمونات في الدم وصور الرنين المغناطيسي التي تُبين الأورام ومختلف طرق العلاج. **النتائج:** تم تسجيل 160 حالة مصابة بتورم الغدة النخامية. بلغ متوسط أعمار المرضى(12±32 سنة) . والمدى من (8 الى73 سنة). معظم المرضى من الإناث (114 - 71%). تم تسجيل 81 مريضا مصابا بورم الغدة النخامية لا يفرز أي هرمون بنسبة (50.6%) . و 59 مريضا مصابا بورم يفرز هرمون البرولاكتين (36.9%) . و 8 مرضى مصابين بورم يفرز هرمون النمو (5%). و 7 مرضى مصابين بوَرَمٍ قِحْفِيٍّ بُلْعومِيٍّ في الغدة النخامية (4.4%). و 4 مرضى مصابين بورم يفرز الهُرْمُونُ المُوَجِّهُ لقِشْرِ الكُظْر ومريض واحد مصاب بساركويدوسيس (0.6%). يتم أيضاً تحليل المجموعات الفرعية وقد تبين انتشار 3 أنواع من الأورام (الأورام التي لا تفرز هرمونات والأورام التي تفرز هرمون البرولاكتين والأورام التي تفرز هرمون النمو). أكثر الحالات كانت تعاني من انقطاع الدورة الشهرية (55 حالة - 37%) و الصداع (31 حالة - 21%) والارهاق (23 حالة - 16%). أكثر طرق العلاج شيوعاً في هذه الدراسة كان العلاج بواسطة الأدوية (58 مريضا - 39%) والملاحظة (56 مريضا - 38%) والتدخل الجراحي (31 حالة - 21%) والتدخل الجراحي مع الأدوية (3 مرضى - 2%). لم يتوفى أي من هؤلاء المرضى خلال فترة الدراسة. **الخلاصة:** يعد هذا السجل العُماني لأورام الغدة النخامية في الشبكة العالمية من أوائل السجلات في الخليج العربي. أن تكوين هذا السجل سوف يساعد الأطباء والباحثين على سهولة تجميع المعلومات عن هؤلاء المرضى. مما يساعد على إجراء البحوث عن هذه الأورام. وهذاسيؤدي إلى تسهيل طرق علاجهم ورفع الكفاءة الصحية في المجتمع العُماني.

مفتاح الكلمات: وَرَمٌ غُدِّيٌّ نُخامِيّ، تسجيل، عُمان، سريري، علم الاوبئة.

ABSTRACT ***Objective:*** From a recently instituted web-based pituitary tumour registry at Sultan Qaboos University Hospital, Oman, this study explores the results of comprehensive clinical evaluation, hormonal levels, radiological evidence of pituitary mass lesion using magnetic resonance (MRI) and the different treatment modalities. ***Methods:*** All patients who were diagnosed with pituitary mass tumours in our tertiary care endocrinology clinic between January 1998 and February 2006 were registered in the Oman pituitary tumour registry. Two physicians performed hospital chart review and data entry. ***Results:*** A total of 160 entries were made into the pituitary tumour registry. The overall mean age of the cohort was 32 ±12 years (age range 8-73 years). The majority of registrations were female (n=114; 71%). There were 81 patients with non-functioning adenomas (50.6%), 59 with prolactinoma (36.9%) eight with acromegaly (5%), seven with craniopharyngioma (4.4%), four with Cushing's disease (2.5%) and one with sarcoidosis (0.6%). Sub-group analyses were done only for the subjects with the 3 most prevalent pituitary tumours (non-functioning adenomas, prolactinomas, and acromegaly). The most prevalent symptoms are amenorrhea-galactorrhea (n=55; 37%), headache (n=31; 21%) and fatigue (n=23; 16%). The most common treatment modality was medical (n=58; 39%), followed by observation (n=56; 38%), surgery (n=31; 21%) and surgery plus medical (n=3; 2%). None of the patients in this registry are recorded to have died. ***Conclusion:*** To our knowledge, this is the first pituitary tumour registry in the Arabian Gulf countries using a web-based programme. This tumour registry will enable us to

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characterize clinical and the epidemiological features of pituitary tumours in the Sultanate of Oman.

Keywords: Pituitary adenomas, Registry, Oman, Clinical, Epidemiology.

Pituitary adenomas are tumours of the anterior pituitary that are relatively common neoplasms representing 10% to 15% of all intracranial tumours.[1, 2] Pituitary adenomas are the most common cause of a mass in the sella constituting over 90% of pituitary lesions.[3, 4] The prevalence of silent pituitary microadenomas detected by high-resolution computer-tomography (HRCT) or magnetic-resonance imaging (MRI) is approximately 20%.[5, 6, 7, 8, 9] At autopsy, careful histological assessment identifies pituitary adenomas in 10% to 20% of unselected series.[10] The incidence peaks in the third and fourth decades of life; children and adolescents account for about 10% of total patients.[10,11]

For clinical purposes, pituitary adenomas are arbitrarily divided by size into microadenomas (<1.0 cm in diameter) or macroadenomas (≥1.0 cm in diameter). When tumours erode the dura or bone, they are considered invasive and may infiltrate surrounding structures, such as the cavernous sinus, cranial nerves, blood vessels, sphenoid bone and sinus or brain. Locally invasive pituitary adenomas are nearly always histologicaly benign.[12] They can also be classified on the basis of excessive hormonal secretion into secreting and non-secreting types.[2] Pituitary tumours with no enhanced biological activity of the anterior pituitary hormones are called non-functioning pituitary adenomas (NFPA). However, approximately 90% of these tumours will produce or secrete low amounts of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and or their α and β subunits [2,13] Using immunoassay and in-situ hybridization, a minority of the NFPAs shows no evidence of hormone production. These tumours are called null cell adenomas.

The true incidence of pituitary tumours is still not known and accurate tumour type-specific epidemiological information is unreliable.[14] This is probably due to the lack of an international pituitary tumour registry, the long natural history of tumours and the low annual incidence of pituitary adenoma diagnosis. In an effort to register these patients in Oman, we created a retrospective and prospective pituitary tumour registry in the year 2004 using an Access 2000 Microsoft web-based programme. This programme was used to collect demographic data, biochemical results, therapeutic options and clinical outcomes from patients with different pituitary mass lesions referred to our endocrinology clinic at Sultan Qaboos University Hospital (SQUH), the main referral hospital for these patients, or submitted by other tertiary institutions since January 1998. The web-address for the registry (http://www.omands.org:2082/frontend/rvblue/files/showfile.html?dir=/home/omands&file=list.htm) is password-protected to prevent any unauthorized access and preserve the privacy and confidentiality of the patients. The purpose of this study is to use this pituitary tumour registry to characterize the clinical and epidemiological features of pituitary tumours in the Sultanate of Oman.

METHODS

All patients who were suspected to have a pituitary mass tumour and were referred to our tertiary care endocrinology clinic at SQUH, between January 1998

Table 1 : ***Demographic and tumour characteristics of the three most prevalent pituitary tumours***

Characteristic	NFPA (n=81)	Prolactinomas (n=59)	Acromegaly (n=8)	Total (n=148)	*p*-value
Age, mean±SD	33±14	32 ±8	42 ±15	33 ±12	0.058
Male gender, n (%)	23 (28%)	14 (24%)	5 (63%)	42 (28%)	0.087
Microadenoma, n (%)	54 (67%)	51 (86%)	2 (25%)	107 (72%)	<0.001
Macroadenoma, n (%)	27 (33%)	8 (14%)	6 (75%)	41 (28%)	
With extension, n (%)	24 (30%)	4 (7%)	4 (50%)	32 (22%)	<0.001
Without extension, n (%)	57 (70%)	55 (93%)	4 (50%)	116 (78%)	

Non-functioning Adenomas; SD=Standard Deviation; Percents are total percents; *p*-values were generated using univariate statistics; The 0.058 represents the p-value for the overall F-statistic, derived from univariate regression analysis. However, group-wise differences for age did exist, especially between the cohorts, acromegaly and NFPA (42 vs. 33 years; p=0.045) and acromegaly and prolactinomas (42 vs. 32 years; p=0.018).

Table 2: ***Clinical features of the three most prevalent pituitary tumours***

Feature	Column percentages		
	Non-functioning Adenomas (n=81)	Prolactinomas (n=59)	Acromegaly (n=8) =148
Amenorrhea-Galactorrhea	4 (4.9%)	50 (84.7%)	1 (12.5%)
Headache	29 (35.8%)	2 (3.4%)	0
Visual Field Defects	4 (4.9%)	0	0
Diabetes Insipidus	3 (3.7%)	0	0
Hypogonadal symptoms	11 (13.6%)	4 (6.8%)	0
Delayed Growth	2 (2.5%)	0	0
Hypopituitary symptoms	7 (8.6%)	1 (1.7%)	1 (12.5%)
Fatigue	21 (25.9%)	2 (3.4%)	0
Acral Enlargement	0	0	6 (75.0%)

and February 2006, were included in the newly developed Oman pituitary tumour registry. Other tertiary hospitals in the country were invited to submit their data. The analysis performed was retrospective and did not in anyway interfere with the management of the patients. Futhermore, those involved in the data analysis did not have access to patient details. Therefore, present study was not deemed to contravene ethical dimensions or patient confidentiality. After confirming the diagnosis for each new patient, his/her data were entered in the software programme, a web-based pituitary tumour registry computer programme, Access 2000 from Microsoft Corporation, 2000. Up to February 2006, the study had enrolled 160 patients. The data include demographic information (age, gender, area of residence), a comprehensive clinical evaluation, hormonal levels, medications and radiological evidence of pituitary mass lesion using MRI. Pituitary tumour type was confirmed by the clinical presentation of patients, hormones levels, radiographic presentations, and immuno-histochemical detection of hormone content whenever available. The standard protocol for the evaluation of pituitary gland with MRI was used to visualize intrasellar pituitary mass lesion. It consists of obtaining T1-weighted images and then repeating the T-1 images after administration of an intravenous contrast agent containing Gadolinium-based media.[12] Not all of the MRI's were done at SQUH. Others were performed elsewhere and brought in by patients themselves. The size of the adenomas was classified by radiographic analysis. Pituitary adenomas were divided by size into microadenomas (<1.0 cm in diameter) or macroadenomas (≥1.0 cm in diameter).[12] The hormonal samples were analyzed using Beckman-Coulter Immunochemistry System Analyzer for Prolactin, FSH, LH, growth hormone (GH), thyroid-stimulatory hormone (TSH), cortisol and insulin-like growth factor (IGF-I). All variables were updated and tracked on each visit. Patient confidentiality was maintained by entering a pre-assigned arbitrary identification number known only to the investigators. Clinical and mortality outcomes were also collected and tracked on flow worksheets.

Statistical analysis

Descriptive statistics were used to describe the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analyzed using Pearson's X^2 tests (or Fisher's exact tests for cells less than 5). For continuous variables, means and standard deviations (±SD) were presented. Mean differences between groups were analyzed using *Student's t*-tests. An *a priori* two-tailed level of significance was set at the 0.05 level.

RESULTS

Demographic and tumour characteristics

Over an 8-year period (1998-2006), a total of 160 entries representing a heterogeneous mixture of the Omani population were made into the pituitary tumour registry. The overall mean age of the cohort was 32±12 years with an age range from 8 to 73 years. The majority of the registrations were females (n=114; 71%). Just over half of the pituitary tumours were non-functioning adenomas (n=81; 50.6%), followed by prolactinomas (n=59; 36.9%), acromegaly (n=8; 5.0%), craniopharyngiomas (n=7; 4.4%), Cushing's disease (n=4; 2.5%), and sarcoids (n=1; 0.6%). Sub-group analyses

Table 3: ***Therapeutic modalities of the three most prevalent pituitary tumours***

	Non-functioning Adenomas (n=81)	Prolactinomas (n=59)	Acromegaly (n=8)
Medical	0	98%	0
Observation	69%	0	0
Surgery	31%	0	75%
Surgery+Medical	0	2%	25%
Total	100%	100%	100%

were performed only for those subjects with the three most prevalent pituitary tumours (non-functioning adenomas, prolactinomas and acromegaly).

There were significant age differences in patients with the three most prevalent pituitary tumours [Table 1]. The subjects with acromegaly were significantly older compared to those with non-functioning adenomas (42 versus 33 years; p=0.045) or prolactinomas (42 versus 32 years; p=0.018). Those with acromegaly were more likely to be males than females (63% versus 37%; p=0.042). Furthermore, subjects with acromegaly were significantly more likely to have macroadenomas than those with either non-functioning adenomas or prolactinomas (75% versus 33% versus 14%; p<0.001). Additionally, those with acromegaly were also more likely to have tumours with extension than those with either non-functioning adenomas or prolactinomas (50% versus 30% versus 7%; p<0.001). Those with extension were significantly more likely to be males than females (38% versus 15%; p=0.002). In addition, males were also significantly more likely to have macroadenomas as compared to females (45% versus 21%; p=0.003).

Tumour-specific presenting clinical features are presented in Table 2. The most prevalent symptoms were amenorrhea-galactohorrhea (n=55; 37.2%), headache (n=31; 21%) and fatigue (n=23; 16%). The symptom, amenorrhea-galactohorrhea, was mostly associated with those patients with prolactinomas rather than those with non-functioning adenomas or acromegaly (84.7% versus 4.9% versus 12.5%; p<0.001). Headache was most associated with those with non-functioning adenomas rather than those with either prolactinomas or acromegaly (35.8% versus 3.4% versus 0%; p<0.001). Furthermore, fatigue was also mostly associated with non-functioning adenomas rather than prolactinomas or acromegaly (25.9% versus 3.4% versus 0%; p=0.001).

therapy and clinical outcome

Several therapeutic modalities were employed for the treatment of the different pituitary tumours including observation, medical, surgery, and medical *plus* surgery [Table 3]. Out of the three most prevalent pituitary tumour types, the most common treatment modality was medical (n=58; 39%) followed by observation (n=56; 38%), surgery (n=31; 21%) and surgery *plus* medical (n=3; 2%). Those with prolactinomas were all medically treated compared with those with either non-functioning adenomas or acromegaly (98% versus 0% versus 0%; p<0.001). Observation was the main treatment modality for those with non-functioning adenomas, compared with those with either prolactinomas or acromegaly (69% versus 0% versus 0%; p<0.001). Surgical intervention was mostly associated with those that have acromegaly than those with either non-functioning adenomas or prolactinomas (75% *ve*rsus 31% versus 0%; p<0.001). Up to February 2006 none of the patients were recorded to have died.

DISCUSSION

During the past 3 decades, the Sultanate of Oman has undergone a remarkable transformation and modernization in all fields, including education and health care. It has progressively established a nationwide network of modern health services that are accessible even at the village level and have ranked Oman with the developed world.[15] World wide, tumour registries have become one of the strongest tools used to help health workers in the clinical and epidemiological studies of cancer. The true incidence of pituitary tumours is still not known and accurate tumour type-specific epidemiological information is lacking, due to the non-existence of any web-based international pituitary tumour registry. In addition, accurate records of outcomes and mortality are not available. For all these reasons, we developed a web-based programme in which all patients in Oman with pituitary tumours are registered and followed. To our knowledge, this is

the first pituitary tumour registry in the Arabian Gulf countries and the Middle East.

Of maximum interest is the unexpectedly large number of new patients (160) registered in a country with a population of a 2.3 million[15] over the past 8-year period, giving one case per 14,375 of the population. The majority of patients were symptomatic and almost half of them had functioning adenomas. In a recent article by Drange et al., who reviewed the hospital charts of patients with pituitary tumours between 1982 to 1999 in California State (with a population of more than 35 million), USA, they found 404 patients,[14] an incidence of 1 per 86,634 of the population. There are many factors that might explain the higher numbers in the Omani population. Genetic, ethnic and environmental differences and the extended use of traditional medicine may contribute. These hypotheses need further studies.

The mean age of acromegalic patients at diagnosis (42 years) did not differ from those reported in previous series.[14,16] There was a significant male predominance 63% versus 37% (p=0.042). Beauregard et al. reported a similar male predominance, however several other studies reported female predominance.[17] The female predominance may be due to the fact that females usually present earlier with amenorrhea.[2, 3, 11, 12, 13, 15] Additionally, those with acromegaly were also more likely to have tumours with extension than those with either non-functioning adenomas or prolactinomas (50% versus 30% versus 7%; p<0.001). Those with extension were significantly more likely to be males than females (38% versus 15%; p=0.002). In addition, males were also significantly more likely to have macroadenomas as compared to females (45% versus 21%; p=0.003). This gender difference could be due to the fact that more men feel shy to complain about their sexual problems (decreased libido and impotence). In our study, these patients appeared to be less symptomatic in comparison to patients with other tumour types. This can be explained by the fact that growth harmone GH secreting tumours grow slowly and result in subtle changes in body features. All of them were treated surgically and 25% of them received medical treatment as well GH receptor antagonist.

Fifty-nine patients in the database were confirmed as having prolactinomas; females (44) constituted 76% of them. They were predominantly microadenomas (86%). These results are consistent with the results of previously published figures.[18] In our patients, the most frequent clinical presentations were amenorrhea and galactorrhea followed by hypogonadal symptoms and headache**.** The tumour showed evidence of extension in 2 males (14.3%) and 2 females (4.6%). Males were more likely to have tumour extensions due to their late presentation**.**

Non-functioning pituitary tumours were the most frequent tumour (n=81) and most commonly affected the females (72%). They were mostly microadenoma with no extension (70%). The most common presenting symptoms were headache (35.8%) followed by fatigue (25.9%), hypogonadal symptoms (13.6%) and amenorrhea (4.9%). In our study we found that 8.7% of patients with non-functioning adenomas had hypopituitary symptoms. Pituitary insufficiency can be encountered in patients with any size or type of intrasellar mass and, thus, serves as an important diagnostic indicator of a pituitary lesion.[19]

CONCLUSION

A tumour registry systematically collects information about the occurrence of cancer, the types of cancer that occur (site, morphology and behaviour), extent of disease at the time of diagnosis (stage), the kinds of treatment received by cancer patients and the outcomes of treatment (survival). The ultimate goal of the analysis of cancer data is to prevent and control cancer. Data is also used to respond to local questions about referral patterns and trends by disease site, by treatment modality and even by clinician. The registry's role of evaluating clinical outcomes and quality of medical care includes assessing treatment patterns, complications, cancer recurrence and survival. The goal of the pituitary tumour registry is improvement in early identification of these patients, tumour management strategies, and long-term outcomes.

In conclusion, we have developed a novel computerized pituitary tumour registry programme in the Sultanate of Oman designed to collect comprehensive demographic, therapeutic, pathologic, and outcome information on patients harbouring these rare tumours and who are referred for tertiary consultation. This registry can be used to improve surveillance protocols and long-term therapeutic outcomes.

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