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OPERATING ON THE MASTER GLAND: 100 CONSECUTIVE HYPOPHYSECTOMIES AT AGA KHAN UNIVERSITY HOSPITAL, KARACHI

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ABSTRACT

Objective: To review the epidemiology and surgical outcomes of patients presenting with pituitary adenomas. **Materials and Methods:** Hospital charts were retrieved using the ICD9-Clinical Modifications system, and data recorded on a structured form. A total of 100 consecutive patients undergoing surgery at our hospital for sellar masses from 1998 to 2004, and with final histopathological diagnosis of pituitary adenoma, were selected. Information was collected on multiple variables and standard statistical analyses were performed. **Results:** Of 100 patients, 65 were male and 35 female. Mean age was 38 ± 16 years (range 1-76 years). Commonest symptoms were headache and visual disturbance (seen in 60%); twenty four patients presented with features of acromegaly. Mean duration of symptoms (excluding apoplexy), was 16 months (range 1 month-18 years). Ten patients had pituitary apoplexy. Hormone studies were available for 90 patients; (46% functioning adenomas, 54% non-functioning; 53% macro-adenomas, 47% micro-adenomas); commonest elevated hormone was growth hormone. Males were more likely to have macro-adenomas and non-functioning adenomas. Mean pituitary adenoma size was 26.74 ± 16 mm (range 3-78 mm). Commonest surgical approach was trans-nasal trans-sphenoidal (88%). Mean follow-up was 17.34 months (clinical) and 8.79 months (radiological). Post-operative radiotherapy was administered to 14 patients, nine of whom were re-operated for residual tumor. **Conclusion:** Surgical management of pituitary tumors in Pakistan is satisfactory and comparable with the international literature. In contrast with Western series, our patients are more likely to present either with a giant pituitary adenoma or with apoplexy.

The pituitary gland is also known as the "master gland" of the body; although minute in size, it has an influence over every major organ-system. The most common tumor of the pituitary (and therefore the most common reason for surgery on this gland) is pituitary adenoma. Pituitary adenomas are the third most common primary intracranial tumor after gliomas and meningiomas, representing approximately 19% of all surgically resected primary brain tumors.¹ Autopsy studies suggest a prevalence of upto 27%. Two types of adenomas have been described; functioning adenomas are hormonally active, representing 70% of all pituitary tumors; non-functioning adenomas are less common and do not secrete hormones. Clinical presentation is either due to endocrine manifestations (functioning adenomas), or mass effect (non-functioning adenomas, which are also generally larger). Up to 2% of pituitary adenomas also present as pituitary apoplexy, although sub-clinical hemorrhage is evident in 10% of all pituitary surgical specimens even without a preceding history of an apoplectic event.²

Hardy et al proposed a classification of pituitary tumors based on radiological size, including micro- (<10 mm) and macro-adenomas (>10mm), that are further sub-divided into five grades depending upon sellar appearance. Tumors more than 40 mm in maximum dimension are generally considered 'giant pituitary tumors', an entity considered unusual in the modern era of better patient awareness, early presentations, and advanced neuro-imaging.³ Surgical resection has established itself as the cornerstone of management, and may be carried out through a number of approaches. Trans-sphenoidal is the commonest, least traumatic, and regarded as the 'gold standard'.^{4,5} Trans-nasal trans-sphenoidal hypophysectomies are amongst the safest procedures in neurosurgical practice, with operative mortality and major morbidity rates of 0.5 to 1% and 2.2 to 3.4% respectively in different series. Lesser morbidity is been reported in 4-5% of patients, most of whom have complete recovery.^{6,7} Radiotherapy is only indicated as an adjunct to surgery, reserved for residual or recurrent tumors.^{8,9}

In this retrospective audit, we have reviewed our surgical experience with 100 consecutive hypophysectomies performed during a 6-year time period at a single institute. To our knowledge, this is the largest series of hypophysectomy cases thus far reported from Pakistan.

MATERIALS AND METHODS

Medical records at our facility from 1998-2004 were searched using the ICD-9 Clinical Modifications code for the term "hypophysectomy." Information was extracted on the following variables: demographics, clinical presentation, biochemical and radiological data, duration of the operative procedure, length of hospital stay, complications, and clinical, biochemical and radiological follow-up.

All patients had MRI scans before and after the surgery, the findings of which were available in the file, although only seventy of the preoperative and sixty four of the postoperative scans were available in the hospital radiological records room for comparison at the time of this study. Post-operative regression in tumor size was estimated either from the clinical record or by imaging studies. All patients underwent complete hormonal work-up before and after surgery (except for the ten cases who presented with pituitary apoplexy, who had post-operative hormonal studies only). Tumors were classified as functioning and non-functioning according to hormonal status. Complications were also recorded although transient diabetes insipidus (lasting <72 hours requiring none or a single dose of intravenous or intranasal desmopressin), mild self-limiting CSF rhinorrhea and temporary hormone replacement after surgery (lasting less than the hospital stay) were not considered as complications and overlooked for this purpose. Data was analyzed using Statistical Package for Social Sciences SPSS (version 13.0) software; results were expressed as mean \pm standard deviation and median (with range) for all continuous variables, and as percentages and proportions for categorical data.

RESULTS

During the six-year study period, a total of 100 patients were operated for histopathologically proven pituitary adenoma. Of these, 65 were male and 35 female. Sixty three patients were permanent residents of Karachi, with the rest coming from other cities of Pakistan and one individual from Afghanistan. Mean age of patients at the time of the diagnosis was 38 ± 16 years (range 1-76 years). The mean age of male patients was 39 ± 17 years

and of females was 33 ± 12 years. A majority (43%) of patients were in their 3rd and 4th decades of life. A relatively high frequency (20%) was noted in the 0-20 year age group.

The most commonly reported symptom was headache or visual disturbance or both, seen in 60% of patients, including the 10 patients with pituitary apoplexy (<10 days duration of symptoms). Twenty four patients presented with features of acromegaly. Mean duration of symptoms (excluding those who presented with apoplexy) was 16 months (range 1 month-18 years).

Of the 90 patients without apoplexy, 46% had functioning and 54% had non-functioning adenomas. The number of patients who had macro-adenomas was 48, with 42 having micro-adenomas. The remaining ten patients had pituitary apoplexy and eight of these patients were male. Of 57 male patients who had pre-operative hormone levels available, 21 (37%) had functioning and 36 (63%) had non-functioning adenomas. Functioning adenomas in females were 20 out of a total of 33 (60%). The remaining 13 (40%) female patients had non-functioning adenomas. Male patients were thus found more likely to present with non-functioning adenomas as compared to female patients, who were more likely to present with functioning adenomas. Male patients were also found more likely to present with macro-adenomas (35 of 55) and female patients with micro-adenomas (22 of 35). The most commonly raised hormone was growth hormone in 25 patients (24 with apparent features of acromegaly), followed by cortisol in 15 patients and prolactin in 12 patients.

Of the seventy pre-operative MRI scans that were available, the mean size of pituitary adenomas was 26.74 ± 16 mm (range 3-78 mm). Sixteen (21%) tumors exceeded 40 mm in size (so-called giant pituitary tumors). Sixteen cases were classified as microadenomas (<10 mm). The main surgical approach was trans-nasal trans-sphenoidal, performed in 88 cases. In 9 cases the approach was trans-labial trans-sphenoidal, and 3 patients underwent craniotomy. Mean operative time was 120 ± 62 minutes (range 45-500 minutes). Mean length of hospital stay was 8 ± 8 days (range 2-73 days). Final histopathology revealed pituitary adenoma in all patients, with suggestion of apoplexy in 10 patients.

Mean clinical follow-up was 17.34 ± 20 months (range 1-96 months). Radiological follow-up of 8.79 ± 11.97 months (range 0-48 months) was available in 64 cases. Mean postoperative size of adenomas in this subgroup was 5.30 ± 6.1 mm (range 0-31 mm), with complete resection (0-5% residual tumor) achieved in 40 (63%) of

the cases. Overall, more than 50% resection was achieved in 55 (86%) of these 64 patients. Post-operative hormonal supplementation was required in 30 of the 100 patients, with only 15 requiring hormone supplementation beyond 3 months. Post-operative radiotherapy was administered to 14 patients, of which 9 were re-operated for residual tumor.

Mortality was limited to 1 individual, a 9-month old child with a macro-adenoma for which craniotomy was underway, and who died of excessive intra-operative blood loss. Other major complications included CSF rhinorrhea in 4 and meningitis in 2 patients. Minor morbidities included diabetes insipidus in 10 and other hospital-acquired infections (such as urinary tract infection) in 6 cases.

DISCUSSION

This is a relatively modest series of hypophysectomies when compared with the published international data. A possible reason may be the small number of pituitary surgeries in Pakistan; to our knowledge this is, nevertheless, the largest series of hypophysectomies reported from Pakistan. On average 14 to 18 hypophysectomies are performed every year at our institution, although the trend shows a consistent annual increase. The current study provides comprehensive information on demographics and tumor behavior in patients with pituitary adenomas in our population. It may be argued that the series is based on the results of a single institute and may not be widely representative, we believe it may reflect to some extent the true spectrum of surgically treated pituitary tumors in Pakistan. In contrast to several other series, in our study female patients were outnumbered by male patients. This pattern has been noticed in reports from this part of the world, where males may be more likely to seek medical care.^{10,11} However, as with other series of pituitary adenomas, the mean age of female patients was less than that of males.

Age distribution in our study is very similar to what has been reported in the literature from other centers.^{12,13} We found a large number of patients presenting in the fourth and fifth decades of life, in accordance with what has been reported in literature. There was also a relatively increased frequency of patients less than 20 years of age. This is in contrast to the fact that pituitary adenomas represent only 2-5% of all primary brain tumors in children^{14,15} as compared to 15-19% in adults.¹

Worldwide, the most common presentation of pituitary adenomas is endocrinological abnormalities and their

manifestations.¹⁰ However, in our series, a larger proportion of patients presented with symptoms of headache, visual disturbances, or both. Another important finding was the strikingly high number of patients who presented with apoplexy. Internationally reported data suggest that only 1-2% of patients with pituitary adenoma present with apoplexy.² Interestingly, 80% of patients presenting with apoplexy were male. Another difference between male and female patients was noted when comparing micro- and macro-adenomas. Male patients were more likely to present with a macro-adenoma when compared with female patients. An observation of relatively less significance is the greater frequency of functional adenomas in females.

Overall, we found more macro-adenomas than microadenomas. Our series also shows that a significant proportion (21%) had giant pituitary adenomas, although the reported frequency of giant pituitary tumors is not more than 6% of all cases of pituitary adenomas.¹⁶ An epidemiologic basis of this high frequency may be suggested on the basis of similar statistics (13.7%) in a series reported from Mumbai recently.⁹

Apart from the possibility that pituitary tumors in this part of the world are biologically distinct, there are other possible explanations. There may be reluctance to seek medical care due to poverty, especially for those symptoms which are not immediately alarming and do not interfere with a daily wagers work (for e.g., headache and fatigue as compared to sudden loss of vision). It may also be due to low population literacy and huge popularity of various forms of alternative medicine and quacks where the patients might just be provided with symptomatic care without a thorough clinical examination and investigations for a more sinister underlying diagnosis. A third reason may be the non-availability of specialized healthcare in remote areas and absence of a proper referral system in areas where healthcare is available. Hence patients in our population may be more likely to present with pituitary apoplexy and giant pituitary tumors than patients in developed countries.

In our center, more patients had functionally inactive tumors than functioning active ones, although the international literature reports that a majority of tumors are functionally active at diagnosis, with a reported proportion of seventy percent.¹⁷ Our finding of a relatively high frequency of non-functioning pituitary adenomas could perhaps be explained by the smaller number of female patients in our study, as females are more likely to present with endocrinopathies. Additionally, patients in our population are less likely to

undergo a thorough hormonal workup because of a lack of laboratories offering this facility. It is also worth noting that in contrast to the published literature prolactinomas in our study were not the most commonly encountered functioning adenomas.¹⁷ The majority of macro-adenomas in our series were non-functioning while most micro-adenomas were functionally active, a pattern that has also been reported in the literature.

Trans-sphenoidal surgery is the major route for hypophysectomy used in our institution, as has been advocated in the literature.^{4,5} In 40 of the 64 patients whose post operative MRI scans were available, the tumor resection was complete, with more than 50% resection of the tumor and remission of symptoms achieved in 55 of these 64 patients. An operative mortality of one percent for transsphenoidal hypophysectomy at our institution is less than what has been reported over the years.^{6,7} The incidence of major and minor morbidities in our study population is comparable to what has been reported from the rest of the world as well. CSF rhinorrhea occurred in four patients (reported incidence 3.9%), meningitis in 2 patients (reported incidence 2-6%), 10 patients had diabetes insipidus (reported incidence 17-18%), and 6 patients had other infections such as urinary tract infections (reported incidence up to 10%). Proportion of patients requiring hormone replacement beyond three months was 15%, which is far more than the reported incidence of 3-5% of iatrogenic hypopituitarism.

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