Arch Iran Med. December 2017;20(12):746-751

http www.aimjournal.ir

ARCHIVES OF IRANIAN MEDICINE

Original Article

Open Access

Iran Pituitary Tumor Registry: Description of the Program and Initial Results

Mohammad Ebrahim Khamseh, MD[1*]; Mohammad Reza Mohajeri Tehrani, MD[2]; Zohreh Mousavi, MD[3]; Mojtaba Malek, MD[4]; Mehrnaz Imani, MD[1]; Nasim Hoshangian Tehrani, MD[1]; Mohammad Ghorbani, MD[5]; Hamideh Akbari, MD[1]; Farzaneh Sarvghadi, MD[6]; Atieh Amouzegar, MD[6]; Fatemeh Esfahanian, MD[7]; Nahid Hashemi Madani, MD[1]; Zahra Emami, PhD[1]

[1]Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences (IUMS), Tehran, Iran,
[2]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences (TUMS), Tehran, Iran
[3]Endocrine Research Center, Imam Reza/Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[4]Research Center for Prevention of Cardiovascular Disease, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences (IUMS), Tehran, Iran
[5]Department of Neurosurgery and Neuro-Intervention, Firoozgar hospital, Iran University of Medical Sciences (IUMS), Tehran, Iran
[6]Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[7]Department of Endocrinology, Imam Khomeini Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Background: This study was designed to present initial results on clinical presentation, therapeutic modalities, and outcome information of patients with pituitary tumors registered in Iran Pituitary Tumor Registry (IPTR).

Methods: We collected data from a web-based electronic medical records of patients with various pituitary tumors referred to four tertiary care centers in the country. Retrospective analysis was performed on demographic, clinical, and therapeutic information of 298 patients including 51 clinically nonfunctioning adenoma (CNFA), 85 acromegaly, 135 prolactinoma, and 27 Cushing's disease (CD).

Results: From October 2014 to July 2016, 298 people with the diagnosis of pituitary tumor were registered. Prolactinoma was the most prevalent tumor (45.3%), followed by Acromegaly (28.6%), CNFPA (17.1%), and CD (9%). Female dominance was seen among patients with prolactinoma and CD, while the majority of patients with CNFPA were male and acromegaly was equally distributed between men and women. Hypogonadal symptoms were almost always seen in all types of pituitary groups. Surgery alone was the most common therapeutic modality used in cases of acromegaly, CNFPA, and CD. However, medical therapy alone was frequently applied for cases of prolactinoma. Finally, biochemical cure was achieved in most cases of prolactinoma and CD, but only in 36.5% of acromegalics. Moreover, 80% of patients suffering from CNFPA showed no residual tumor in their imaging.

Conclusion: In conclusion, this comprehensive tumor registry enables early identification, selection of best therapeutic approaches, and evaluation of long-term treatment outcomes. Furthermore, this registry can be used to improve surveillance protocols.

Keywords: Pituitary adenoma, Pituitary tumor, Registry

Cite this article as: Khamseh ME, Mohajeri Tehrani MR, Mousavi Z, Malek M, Imani M, Hoshangian Tehrani N, et al. Iran pituitary tumor registry: description of the program and initial results. Arch Iran Med. 2017;20(12):746–751.

Received: February 1, 2017, Accepted: December 27, 2017, ePublished: December 31, 2017

Introduction

The prevalence of pituitary tumors has increased over the past decades.[1] This could be due to widespread access to magnetic resonance imaging (MRI) and accurate biochemical tests. Postmortem and imaging series estimated a prevalence of 14.4% and 22.5%, respectively.[2] In a review by Freda et al among the issues which lead to difficulty in management of pituitary tumors, the slowly growing nature of these tumors and the need for long term follow-up were the major concerns.[3] In fact, loss to follow-up leaves a major gap in data collection and management.

In addition, pituitary tumors arise from different clonal origins with diverse pathological, clinical, and prognostic characteristics which necessitate individualized treatment protocols.[4] Adding these to the low incidence of pituitary adenomas and their subtypes further complicates the situation.

Patient registries are organized systems to collect structured information in order to evaluate specific outcomes for a population defined by a particular disease. Pituitary tumor registry could provide a basis for early identification of patients with pituitary tumors, and comparing various management strategies and long-term outcomes. The goal of Iran Pituitary Tumor Registry (IPTR) is to decrease mortality and morbidity of patients with pituitary mass lesions.

The purpose of this study was to briefly introduce the program of IPTR and present the initial results on epidemiological pattern and clinical outcomes of various

***Corresponding Author:** Mohammad Ebrahim Khamseh, MD; Endocrine Research Center, Institute of Endocrinology and Metabolism, No. 10, Firoozeh St., Vali-asr Ave., Vali-asr Sq., Tehran Iran. Tel: +98-21-88945172, Fax: 98-21-88945173, Email: khamseh.m@iums.ac.ir.

pituitary tumors registered in this registry.

Methods

Web-Based Pituitary Tumor Registry Program

IPTR is a patient registry established by the Institute of Endocrinology and Metabolism affiliated to Iran University of Medical Science as a tertiary referral center for endocrine disorders. The program was recognized as a national registry by the ministry of health in 2014 (approval code: 4343). It provides a basis for collaboration with other referral centers namely Endocrinology and Metabolism Research Institute affiliated to Tehran University of Medical Sciences, endocrine research center of Mashhad University of Medical Sciences, and Endocrinology and Metabolism Research Institute affiliated to Shahid Beheshti University of Medical Sciences.

This registry collects data using a web-based electronic medical record system. The system comprises all demographic, clinical, para-clinical, and treatment outcomes from patients with various types of pituitary tumors including, acromegaly, prolactinoma, Cushing's disease (CD), and clinically nonfunctional pituitary adenoma (CNFPA). Active surveillance is performed every three to six months based on clinical and biochemical status of the patients. Relevant data were extracted and reviewed from 2014-2016 using the electronic medical record database.

Patient Population

All types of pituitary lesions are included in the registry program. There are no exclusion criteria. Data regarding clinical, biochemical, histological, and radiological findings as well as therapeutic modalities and clinical outcomes are recorded. The diagnosis of tumor type is based on clinical presentation, biochemical profile, and immunohistochemistry (IHC) results, if available.

To describe the initial results of this registry, electronic medical records were thoroughly reviewed by 2 specialists who are directly involved with data collection at the Institute of Endocrinology and Metabolism affiliated to Iran University of Medical Sciences. In this report, we focused on the most important pituitary tumors, namely, prolactinoma, CD, CNFA, and acromegaly. TSH-secreting tumors, gonadotropin secreting adenomas, and other sellar or suprasellar masses were not included in the analysis due to the small number of these tumors in the registry up to the time of data collection. To that date, 298 patients, including 135 prolactinoma, 85 acromegaly, 27 CD, and 51 CNFA cases were registered.

Definitions

Tumor type was classified as nonfunctional versus clinically functional pituitary adenomas. Nonfunctional pituitary adenomas were defined as tumors with no clinical signs of prolactin, growth hormone, or adrenocorticotropic hormone (ACTH) excess. Functional pituitary tumors were classified as prolactinoma, GH-secreting tumors, and ACTH-secreting tumors.

Tumor size was determined by MRI, reporting the maximum tumor diameter. Micro-adenoma was defined as pituitary adenoma with the greatest dimension less than 10 mm. Pituitary tumors greater than or equal to 10 mm in the greatest dimension were considered as macro-adenomas.

No residual tumor was defined as maximum tumor resection ≥80%. Postoperative hypopituitarism included new pituitary-target organ defect developed after surgery. Hypogonadal symptoms were diagnosed when decreased-libido/erectile dysfunction or oligo-amenorrhea occurred. Prolactinoma was diagnosed when prolactin level was higher than 25 μg/L for women and 20 μg/L for men, depending on the laboratory's normal range, in the presence of evidence of pituitary mass in MRI scans. The potential pitfalls, including the presence of macroprolactin, and hook effect were considered, if necessary. Acromegaly was defined as elevated IGF-1 level (adjusted for age and sex) plus non-suppressible GTT level after glucose tolerance test. CD was diagnosed by standard two-day dexamethasone suppression test in a patient with symptoms and signs of hypercortisolism.

Biochemical remission for prolactinoma was defined as normalized prolactin levels. For acromegaly, biochemical remission was considered by normalized adjusted IGF-1 and suppressed GTT level less than or equal to 2 μg/dL. Biochemical remission for CD was defined as early morning serum cortisol level <5 μg/dL within 7 days of tumor resection or glucocorticoid dependency more than six months after operation.

Permanent diabetes insipidus (PDI) was defined as need for long-term treatment with desmopressin, documented in follow-up records at least 2 weeks after operation.

Visual field defect (VFD) was diagnosed as any degree of visual disturbances detected by standard perimetry testing.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD) or frequency and proportion as indicated. Normality distribution was checked by histogram and Kolmogorov-Smirnov test. We used analysis of variance (ANOVA) and Duncan post hoc test for comparison of continuous variables between more than two groups and chi-square or Fisher exact test for categorical variables as indicated. *P* value <0.05 was considered as significant. All analyses

were performed using IBM® SPSS 19 software.

Results

Tumor Distribution Among Registered Patients

A total of 298 patients with diagnosis of pituitary tumor were registered from October 2014 to July 2016. The most prevalent tumor type was prolactinoma (45.3%, n = 135) followed by acromegaly (28.6%, n = 85), CNFA (17.1%, n = 51), and CD (9%, n = 27). Acromegaly was equally distributed between females and males (44.7% vs. 55.3%; *P*-value: 0.2), while CD and prolactinoma were more frequently seen in females (77.8%; *P* value: 0.03 and 81.5%; *P* value: 0.04, respectively). Moreover, CNFPA was more prevalent in males (31.4%; *P* value: 0.01) (Figure 1). Macroadenoma was seen in 72.9% of acromegalics, followed by 45% of CNFPA, 32% of prolactinoma, and 17.2% of CD patients.

Clinical Characteristics of the Registered Patients at Presentation

Mean age at the time of diagnosis was 43.9 ± 12.1 years for patients with acromegaly, 34.5 ± 8.9 years in patients with prolactinoma, 47.09 ± 12.8 years and 36.5 ± 12.2 years among those with CNFPA and CD, respectively (Figure 2). Patients with acromegaly most frequently presented with acral enlargement (81.2%, n = 69) as a unique feature of GH excess, followed by hypogonadal symptoms (68.2%, n = 58) and headache (63.5%, n = 54). Those with CNFPA generally presented with hypogonadal symptoms (68.6%, n = 35), and headache (66.7%, n = 34). Proximal myopathy (74.1%, n = 20), and fatigue (66.7%, n = 18) were the most prevalent symptoms among patients suffering from CD. Patients with prolactinoma most frequently presented with galactorrhea (75.5%, n = 83), followed by headache (40%, n = 54) and hypogonadal symptoms (35.6%, n = 48). However, only 4% of cases of prolactinoma presenting with galactorrhea were male (Table 1).

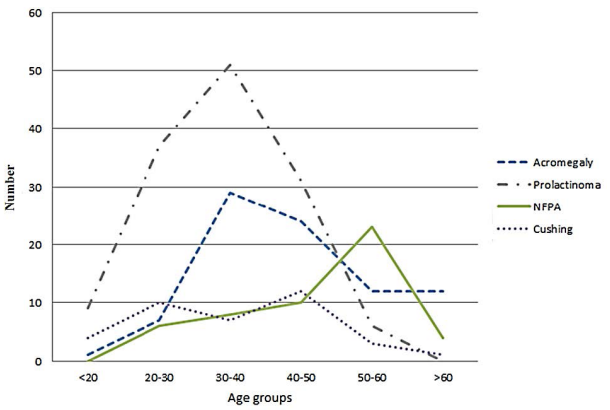

Figure 2. Age at Diagnosis in Patients With Acromegaly, Nonfunctional Pituitary Adenoma, Prolactinoma, And Cushing.

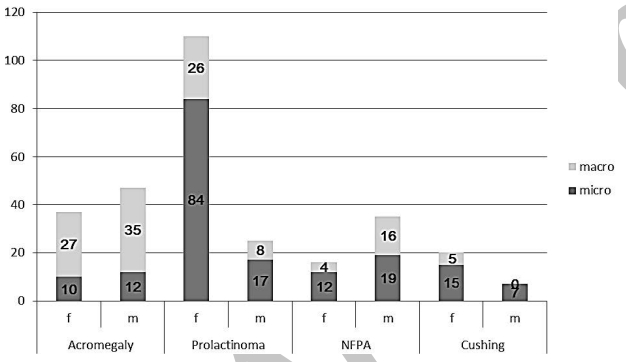

Figure 1. Distribution of Tumor Type by Size and Gender.

Therapeutic Modalities and Clinical Outcomes

There are several therapeutic modalities for management of pituitary tumors including surgery, medical therapy, and irradiation. Therapeutic modalities used for each tumor type in this registry are shown in Table 2. Surgery alone was the most frequent modality in management of CNFPAs (94.1%, n = 48), CD (92.6%, n = 25), and acromegaly (61.2%, n = 52). Medical treatment with dopamine agonists (either Bromocriptine or

Table 1. Clinical Characteristics of the Registered Patients at the Time of Diagnosis

	Acromegaly, 85 (28.6%)	Prolactinoma, 135 (45.3%)	CNFPA, 51 (17.1%)	Cushing, 27 (9%)
Gender (F), No. (%)	38 (44.7)	110 (81.5)	16 (31.4)	21 (77.8)
Age (y) (mean ± SD)	43.93 (12.13)	34.58 (8.98)	47.09 (12.88)	36.5 (12.2)
Body mass index (mean ± SD)	30.4 (8.2)	28.1(5.8)	27.97 (4.82)	30.5 (6.2)
Headache	54 (63.5)	54 (40)	34 (66.7)	10 (37)
Hypogonadal symptoms	58 (68.2)	48 (35.6)	35 (68.6)	16 (59.3)
Visual field deficit, No. (%)	25 (29.4)	17 (12.6)	13 (25.5)	3 (11.1)
Galactorrhea, No. (%)	8 (9.4)	83 (75.5)	4 (7.8)	-
Acral enlargement, No. (%)	69 (81.25)	-	1 (2%)	-
Proximal myopathy, No. (%)	36 (42.45)	-	24 (47.1)	20 (74.1)
Arthralgia, No. (%)	51 (60)	-	2 (3.9)	-
Fatigue, No. (%)	41 (48.2)	9 (6.7-)	27 (52.9)	18 (66.7)
Easy bruising, No. (%)	-	-	-	16 (59.3)

Table 2. Therapeutic Modalities Used for Each Tumor Type

	Acromegaly, 85 (28.6%)	Prolactinoma, 135 (45.3%)	CNFPA, 51 (17.1%)	Cushing, 27 (9%)
Surgery alone	52 (61.2)	0 (0)	48(94.1)	25 (92.6)
Medical alone	0 (0)	122 (90.4)	0 (0)	0 (0)
Irradiation alone	0 (0)	0 (0)	0 (0)	0 (0)
Surgery + medical	23 (27.1)	3 (2.2)	0 (0)	2 (7.4)
Surgery + irradiation	10 (11.7)	0 (0)	3 (5.9)	0 (0)
No treatment	0 (0)	10 (7.4)	0 (0)	0 (0)

The data are presented as No. (%).

Table 3. Clinical Outcomes Following the Treatment Modalities in the Registered Patients

	Acromegaly, 85 (28.6%)	Prolactinoma, 135 (45.3%)	CNFPA, 51 (17.1%)	Cushing, 27 (9%)
No residual tumor	33 (38.8%)	126 (93.3%)	41(80.4)	26 (96.3%)
Biochemical control	31 (36.5%)	133 (98.5%)	NA	24 (88.9%)
Post-surgery PDI	4 (4.7%)	0 (0)	3 (5.8%)	2 (7.4%)
New-onset hypopituitarism	7(8.2%)	0 (0)	5 (9.8%)	3 (11.1%)
Other complications*	6 (7%)	0 (0)	6 (11.8%)	6 (22.2%)
Death (all causes)	1 (1.17%)	0 (0)	0 (0)	2 (7.4%)

The data are presented as No. (%).
[a] Other complications after surgery include CSF leak and meningitis.
Abbreviations: NA = not applicable; PDI, permanent diabetes insipidus.

Caberguline) was used in 90.4% (n = 122) of patients with prolactinoma. Among patients who suffered from prolactinoma, 2.2% (n = 3) received both surgery and medical therapy while 7.4% (n = 10) of them were not offered any treatment because they had asymptomatic microprolactinoma. However, combination of surgery and medical therapy was used for 27.1% (n = 23) of acromegalics, followed by 7.4% (n = 2) of patients with CD. Both surgery and irradiation were applied for 11.7% (n = 10) of acromegalics and 5.9% (n = 3) of patients with CNFPA.

Radiographic cure, defined as more than 80% tumor resection, was observed in 80.4% (n = 41) of patients with CNFPA, 38.8% (n = 33) of acromegalics, 93.3% (n =126) of patients with prolactinoma, and 96.3% (n = 26) of those with CD. Biochemical remission, according to the defined criteria, was achieved in 36.5% (n = 31) of acromegalics, 98.5% (n = 133) of patients with prolactinoma, and 88.9% (n = 24) of those who suffered from CD. Moreover, permanent post-surgery DI was seen in 4.7% (n = 4) of acromegalics, 5.8% (n = 3) of patients with CNFPA, and 7.4% (n = 2) of those with CD. New-onset hypopituitarism, as a complication of surgery, was reported in 8.2% (n = 7) of acromegalics, 9.8% (n = 5) of patients with CNFPA, and 11.1% (n = 3) of those with CD. However, none of the surgically treated cases of prolactinoma were complicated with neither PDI nor new-onset hypopituitarism.

In addition, three deaths occurred in registered patients, one case of acromegaly and two cases of CD, but the exact cause was not discovered due to lack of death certificates.

Discussion

IPTR was developed to collect complete and accurate data on all types of pituitary mass lesions among Iranian population. The goal of this project was to provide information regarding epidemiology, clinical and biochemical presentation, treatment strategies, as well as clinical outcomes of the most prevalent pituitary tumors including CNFPA, GH-secreting tumors, ACTH-secreting tumors, and prolactinomas.

In this registry, female predominance was seen among patients suffering from prolactinoma and CD while CNFPA was more prevalent in men and acromegaly was equally distributed between men and women. Mean age at the time of diagnosis was higher for the cases of CNFPA and acromegaly, and lower for those with prolactinoma and CD. Gender-related distribution of pituitary tumors in this registry is consistent with that of other surveys.[5,6] Different investigators have shown a tendency to gender-related differences not only in the distribution of tumor types but also in the age at presentation, presenting symptoms and signs, tumor size, tumor histology, and even surgical outcomes. These results give new insights into the cellular understanding of the pituitary adenoma.[7]

Considering the clinical presentation at the time of diagnosis, hypogonadal symptoms were common in patients with CNFPA (68.6%), acromegaly (68.2%), CD (59.3%), and prolactinoma (35.6%). Pituitary insufficiency is a common presentation in almost all types and sizes of intrasellar mass lesions.[8] Hypogonadotropic hypogonadism is the most frequent hormone deficiency for all tumor types and presents with hypogonadal symptoms as a pre-therapeutic finding. The possible

causes are hyperprolactinemia, destruction of the normal pituitary gland by the expanding mass, or, maybe, focal necrosis due to compression of the portal circulation.[9]

However, galactorrhea (75.5%) and headache (40%) were the most common presentations in prolactinoma, patients with CNFPA frequently presented with mass related symptoms such as headache (66.7%) and VFD (12.5%), those suffering from CD mostly reported to have proximal myopathy (74.1%), and fatigue (66.7%), and acromegalics often presented with acral enlargement (81.2%), as well as headache (63.5%). These findings are in line with those from previous studies.[6,10,11] Moreover, our study confirmed the results of previous studies that the incidence of headache among patients harboring different types of pituitary adenoma ranges from 37.3% to 68.8%.[11,12] The presence of headache in pituitary tumors is related to a combination of factors some of which are related to tumor location, such as cavernous sinus invasion, chiasm compression, and intrasellar pressure (ISP), and some are due to the functional disturbance within the hypothalamo-pituitary axis.[12] The fact that somatostatine analogues[13] and dopamine-agonists[14] may be highly effective in relieving headache associated with acromegaly and prolactinomas, respectively, suggests the hypothesis of biochemical-neuroendocrine participation in the genesis of headache in pituitary tumors. On the other hand, the genetic predisposition of the patient to primary headache, and family history of headache also determine whether headache occurs with pituitary tumors.[15] Taken together, these results may motivate the investigators to carefully search into the alteration of neuroendocrinological signaling pathways which may contribute to initiation of headache.

Regarding the treatment modalities applied for different types of pituitary adenomas, surgery alone was used for 94.1% of cases of CNFPA, followed by 92.6% of those with CD, and 61.2% of acromegalics. None of the cases of prolactinoma underwent surgery as a single therapeutic modality; the majority of these patients received only medical therapy, as expected. When we further analyzed the patients who underwent surgery due to CNFPA, we found that 45% of these patients were assigned for surgery due to symptomatic macro-adenoma. However, the remaining of those who underwent surgery suffered from "large micro-adenoma" (5-9 mm). Although this is not a well-defined criterion for surgery, the majority of patients in this group had undergone surgery due to patient preference or lack of compliance for long-term surveillance. Obviously, the first-choice treatment for CNFPA is surgery, and VFD due to macro-adenoma is the main indication for surgery.[16] However, asymptomatic large micro-adenoma (>5 mm) is not an acceptable criterion for surgery and active surveillance is recommended in these cases.[16] Based on this result, we should move towards criterion-based surgeries for cases of CNFPA. Moreover, these patients should be informed regarding the possible risks of surgery and assured to keep under close surveillance. Thus, development and implementation of a standard protocol are essential for this registry. The rest of patients in this registry received combination therapy of either surgery with medication or surgery with irradiation. This finding reflects the fact that as tertiary referrals, most registered patients had resistant or complicated disease.

In this registry, 98.5% of cases of prolactinomas achieved biochemical cure, defined as normal prolactin level, within the first year of initiation of treatment and maintained remission during the follow-up period. However, withdrawal trial was examined in none of them because they had not been on maintenance dose of their medication for at least 2 years, the safety time for gradually decreasing dopamine agonists.[17] However, these patients should be kept under surveillance for evaluation of long-term remission rate. In addition, biochemical cure for cases of acromegaly and those with CD, defined by the strict criteria, was achieved in 36.5% and 88.9% of patients, respectively. Cure rate in CD was comparable to the previous studies.[18] However, early postoperative cure does not preclude long-term recurrence; Therefore, patients require long-term biochemical follow-up. In the cases of acromegaly, insufficient data were available to evaluate preoperative medical therapy. However, 27.1% of the patients received medical therapy after surgery. Somatostatin analogues were the most common medication used in these cases. Moreover, 38.3% of the patients showed no residual tumor on imaging. The rate of biochemical cure in acromegaly was somewhat lower than that of the previous studies.[19,20] This can be explained by the difference in the definition of "cure" applied in each study. Moreover, we collected data from a tertiary center in which the number of patients having macro-adenoma was large. Another explanation for the low cure rates is most likely related to a large number of neurosurgeons operating in different centers. This finding highlights the importance of specialist pituitary surgeon and the need for training neurosurgeons interested in working in this field.

Finally, when we assessed post-surgery PDI and new-onset hypopituitarism as complications of surgery, we found that PDI occurred in 7.4% of CD, followed by 5.8% of CNFPA, and 4.7% of acromegalics. This finding is consistent with those of previous studies.[21] The incidence of post-surgery DI varies from 1 to 67% across the literature. This wide range reflects the inconsistency in definition of DI.[21] Tumor size, adherence to surrounding structures, surgical approach, and even histopathology of

the lesion may affect the rate of post-surgery DI.[21]

In conclusion, this pituitary tumor registry program will provide comprehensive demographic, therapeutic, and pathologic information as well as outcomes regarding different types of pituitary lesions among Iranian population. This registry may help early diagnosis of the pituitary tumors, improve follow-up adherence, define the efficacy and safety of different treatment modalities, and assess prognostic factors for recurrence. Moreover, the initial report of this registry highlights the high rate of unnecessary surgery in cases of CNFPA and encourages the endocrinologists and neurosurgeons involved in this registry to develop standard protocols for better management of these patients.

However, this study was only a report of initial results which could not present some important information such as IHC results or exact causes of death due to insufficient data. Moreover, the findings could not be generalized to all Iranian patients with pituitary tumors since these patients probably displayed a group with more advanced disease who needed more vigorous therapeutic interventions.

Authors' Contribution

MEK, MRMT, ZM, MM, FS, AM, and FE contributed to the data acquisition and interpretation. MI, HA, and MG contributed to the data entry and analysis. NHT drafted the manuscript. MEK and NHM critically revised the manuscript. ZE contributed to the research program.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

References

1. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J Clin Endocrinol Metab. 2006;91(12):4769-75. doi: 10.1210/jc.2006-1668.
2. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. The prevalence of pituitary adenomas: a systematic review. Cancer. 2004;101(3):613-9. doi: 10.1002/cncr.20412.
3. Freda PU, Beckers AM, Katznelson L, Molitch ME, Montori VM, Post KD, et al. Pituitary incidentaloma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(4):894-904. doi: 10.1210/jc.2010-1048.
4. Annegers JF, Coulam CB, Laws ER. Pituitary tumors: epidemiology. In: Givens JR, ed. Hormone-Secreting Pituitary Tumors. Chicago: Year Book Medical Publishers; 1982:393-403.
5. Mindermann T, Wilson CB. Age-related and gender-related occurrence of pituitary adenomas. Clin Endocrinol. 1994;41(3):359-64. doi: 10.1111/j.1365-2265.1994.tb02557.x.
6. Drange MR, Fram NR, Herman-Bonert V, Melmed S. Pituitary tumor registry: a novel clinical resource. J Clin Endocrinol Metab. 2000;85(1):168-74. doi: 10.1210/jcem.85.1.6309.
7. Schaller B. Gender-related differences in growth hormone-releasing pituitary adenomas. A clinicopathological study. Pituitary. 2002;5(4):247-53. doi: 10.1023/a:1025329900839.
8. Vance ML. Hypopituitarism. N Engl J Med. 1994;330(23):1651-62.doi:10.1056/nejm199406093302306.
9. Arafah BM. Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. J Clin Endocrinol Metab. 1986;62(6):1173-9. doi: 10.1210/jcem-62-6-1173.
10. Ferrante E, Ferraroni M, Castrignano T, Menicatti L, Anagni M, Reimondo G, et al. Non-functioning pituitary adenoma database: a useful resource to improve the clinical management of pituitary tumors. Eur J Endocrinol. 2006;155(6):823-9. doi: 10.1530/eje.1.02298.
11. Abe T, Matsumoto K, Kuwazawa J, Toyoda I, Sasaki K. Headache associated with pituitary adenomas. Headache. 1998;38(10):782-6. doi: 10.1046/j.1526-4610.1998.3810782.x.
12. Gondim JA, de Almeida JP, de Albuquerque LA, Schops M, Gomes E, Ferraz T. Headache associated with pituitary tumors. J Headache Pain. 2009;10(1):15-20. doi: 10.1007/s10194-008-0084-0.
13. Williams G, Ball JA, Lawson RA, Joplin GF, Bloom SR, Maskill MR. Analgesic effect of somatostatin analogue (octreotide) in headache associated with pituitary tumours. Br Med J (Clin Res Ed). 1987;295(6592):247-8.
14. Levy MJ, Matharu MS, Goadsby PJ. Prolactinomas, dopamine agonists and headache: two case reports. Eur J Neurol. 2003;10(2):169-73. doi: 10.1046/j.1468-1331.2003.00549.x.
15. Levy MJ, Matharu MS, Meeran K, Powell M, Goadsby PJ. The clinical characteristics of headache in patients with pituitary tumours. Brain. 2005;128(Pt 8):1921-30. doi: 10.1093/brain/awh525.
16. Chanson P, Raverot G, Castinetti F, Cortet-Rudelli C, Galland F, Salenave S. Management of clinically non-functioning pituitary adenoma. Ann Endocrinol (Paris). 2015;76(3):239-47. doi: 10.1016/j.ando.2015.04.002.
17. Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf). 2006;65(2):265-73. doi: 10.1111/j.1365-2265.2006.02562.x.
18. Hameed N, Yedinak CG, Brzana J, Gultekin SH, Coppa ND, Dogan A, et al. Remission rate after transsphenoidal surgery in patients with pathologically confirmed Cushing's disease, the role of cortisol, ACTH assessment and immediate reoperation: a large single center experience. Pituitary. 2013;16(4):452-8. doi: 10.1007/s11102-012-0455-z.
19. Taghvaei M, Sadrehosseini SM, Miri SM, Zeinalizadeh M. Endoscopic Transsphenoidal Approach for Surgical Treatment of Growth Hormone Secreting Pituitary Adenoma: Endocrinological Outcome in 49 Patients Based on 2010 Consensus Criteria for Remission - Preliminary Results. Arch Neurosci. 2017;4(3):e14131. doi: 10.5812/archneurosci.14131.
20. Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, et al. Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab. 2000;85(2):526-9. doi: 10.1210/jcem.85.2.6363.
21. Schreckinger M, Szerlip N, Mittal S. Diabetes insipidus following resection of pituitary tumors. Clin Neurol Neurosurg. 2013;115(2):121-6. doi: 10.1016/j.clineuro.2012.08.009.