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RESEARCH ARTICLE

REVISED Spectrum of Pituitary disorders: A retrospective study from Basrah, Iraq [version 2; peer review: 2 approved]

Previously titled: Spectrum of Sellar and Parasellar Region Lesions: A retrospective study from Basrah, Iraq

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Abstract

Background: Pituitary disorders spectrum includes a wide variety of diseases.This study aimed at a comprehensive description of such disorders for patients from Faiha Specialized Diabetes, Endocrine and Metabolism Center (FDEMC) in Basrah (Southern Iraq).
Methods: Retrospective data analysis of FDEMC for the period from January 2012 through June 2017. We included all patients with pituitary disorders who have MRI pituitary.
Results: The pituitary disorders were more common among women. Those with macroadenoma were older than those with microadenoma with nearly equal gender prevalence of macroadenoma. Pituitary adenoma constituted the bulk of pituitary disorders in this registry (67.2%). Growth hormone secreting adenoma were the commonest adenoma seen in 41.0% followed by clinically non-functioning pituitary adenoma(NFPA)in 31.4% and prolactinoma in 26.9%. About 64.8% of pituitary adenoma was macroadenoma. Macroadenoma was seen in 73.4 % of growth hormone secreting adenoma, 61.2% in NFPA and 62.0% of prolactinoma (of them six were giant prolactinoma)
Conclusion: Pituitary adenoma constituted the bulk of pituitary disorders in Basrah, growth hormone secreting adenoma is the commonest adenoma followed by NFPA and prolactinoma due to referral bias. A change in practice of pituitary adenoma treatment is needed.

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 2 (revision) 22 Jun 2018		✓ report
version 1 06 Apr 2018	✓ report	? report

1. **Abdul Al-Toma**, St Antonius Hospital, Nieuwegein, The Netherlands

2. **Khaled Mohammed Al-Dahmani** , Tawam Hospital, Al Ain, United Arab Emirates United Arab Emirates University, Abu Dhabi, United Arab Emirates

Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Sellar and parasellar region lesions, pituitary disease, pituitary adenoma, classification, epidemiology.

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Author roles: Mansour AA: Conceptualization, Data Curation, Investigation, Methodology, Supervision, Validation, Writing – Review & Editing; **Alhamza AHA**: Investigation, Methodology, Project Administration; **Almomin AMSA**: Project Administration, Resources, Visualization, Writing – Original Draft Preparation; **Zaboon IA**: Data Curation, Investigation, Validation, Visualization; **Alibrahim NTY**: Methodology, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Hussein RN**: Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation; **Kadhim MB**: Conceptualization, Formal Analysis, Resources, Software; **Alidrisi HAY**: Investigation, Supervision, Validation, Writing – Review & Editing; **Nwayyir HA**: Investigation, Resources, Software, Supervision, Visualization; **Mohammed AG**: Investigation, Supervision, Visualization, Writing – Original Draft Preparation; **Al-Waeli DK**: Data Curation, Funding Acquisition, Investigation, Validation; **Hussein IH**: Data Curation, Formal Analysis, Funding Acquisition, Software, Validation, Writing – Review & Editing

Introduction

Sellar and parasellar region lesions spectrum includes a wide variety of conditions ranging from adenoma to empty sella syndrome, apoplexy, congenital or acquired condition[1–4]. Other than adenoma, genetic causes of pituitary disease are increasingly recognized[3].

Pituitary adenomas are not rare and account for 20% all intracranial tumors[5,6]. Half of these secrete hormones, and half are microadenoma[2]. Clinically non-functioning adenomas (NFPA) constitute 15–54% of all adenomas. Prolactinomas accounts for 32–66%, growth hormone secreting adenoma (acromegaly) account for 8–16%, adrenocorticotropic hormone (ACTH)-secreting adenoma (Cushing's disease) forms 2–6%, and TSHoma accounts for less than 1%[2,7]. These pituitary adenomas behave as typical or have a more aggressive to malignant behavior[6,8]. They can cause mass effect, in addition to hypersecretion or hypopituitarism[7,9].

Advances in neuroradiology have opened the door for earlier and easier diagnosis of pituitary disease and other sellar and suprasellar lesions[10].

The Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC) in Basrah is a tertiary referral center receiving patients with pituitary diseases from most of Southern Iraq. The FDEMC is trying to adapt the three mission criteria of the pituitary center of excellence, which includes care and support for patients, fellowship training and contribution to pituitary disease research[11]. To our knowledge, there are no studies on sellar and parasellar region lesions in Iraq.

This study aimed at a comprehensive description of pituitary disorders for patients from FDEMC in Basrah (Southern Iraq).

Methods
Study design
Retrospective data analysis of FDEMC database for the period from January 2012 through June 2017.

Inclusion criteria: We included all patients with pituitary disorders who have MRI pituitary regardles the age.

Exclusion criteria: patients with pituitary disorders with missed MRI.

Definition of variables
Sequences of pituitary MRI imaging were classified according to the international standard[12]. Adenomas were classified as macroadenoma if these were 10 mm or more in size, while microadenoma if less than 10 mm and giant prolactinoma if these were 4 cm and above[2].

Pituitary adenoma (NFPA, prolactinoma, growth hormone secreting adenoma [acromegaly], and adrenocorticotropic hormone (ACTH)-secreting adenoma) were defined according to the usual criteria[2,8,12].

Hypopituitarism, whether postoperative or in those with or without adenoma, was considered according to the hormonal assessment with basal and dynamic hormonal tests[13].

Empty sella syndrome, whether primary or secondary to surgery or apoplexy, were considered based on MRI findings[14].

Craniopharyngioma diagnosis was based on clinical behavior with MRI and pathological diagnosis.

Data analysis
Analysis was done in July 2017. All patients with labeling diagnosis of pituitary disease were included. Data were included on an Excel spreadsheet and transferred to SPSS for Windows, Version 23.0 (SPSS Inc., Chicago, USA).

Continuous variables were summarized as number and percentage and dichotomous variables as mean ±SD.

Ethics statement
The ethics committee of the Medical College in Basrah University approved the study design and the Center authorities agreed to review the patients data. At the time of registeration in the Center, all patients included in this study approved the use of their clinical information for research purposes.

Results
A total of 232 patients were included in this study. Pituitary disorders were more common among women (Table 1). Those with macroadenoma were older than those with microadenoma with nearly equal gender prevalence of macroadenoma. Four patients died; two with growth hormone secreting adenoma (acromegaly) and advanced cardiovascular disease, and two with prolactinoma that caused hypopituitarism and adrenal failure.

Table 2 shows that pituitary adenoma constituted the bulk of pituitary disorders in this registry (67.2%). Growth hormone secreting adenoma (acromegaly) were the commonest adenoma seen in 41.0% followed by NFPA in 31.4% than prolactinoma in 26.9%. Hypopituitarism due to various causes was observed in 24.5% in this series. Empty sella syndrome, whether

Table 1. Pituitary disorders patients demography and characteristics.

			N (%); mean ±SD
Gender	All pituitary disorders	Men	84 (36.2)
		Women	148 (63.8)
	Pituitary adenoma*	Men	67 (43)
		Women	89 (57)
Age at registration, years		All	38.2±15.3
		Macroadenoma	42.5±14.9
		Microadenoma	34.8±14.7
Macroadenoma**		Men	51 (50.5)
		Women	50 (49.5)
Died			4

*Of 156 pituitary adenoma

**Of 101 macroadenoma

Table 2. Spectrum of pituitary disorders at the time of registry.

		N (%)
Pituitary adenoma		156 (67.2)
Growth hormone secreting adenoma (acromegaly)		64 (41.0)
Clinically non-functioning pituitary adenoma (NFPA)		49 (31.4)
Prolactinoma*		42 (26.9)
GH-secreting adenoma with hyperprolactinemia*		5
ACTH- secreting pituitary adenoma		2 (1.2)
Hypopituitarism		57 (24.5)
Empty sella syndrome	All	22 (9.4)
	Primary**	9
	Secondary	13
Diabetes insipidus		15
Apoplexy		3
Hyperprolactinemia	All	51
	No adenoma	12
Pituitary enlargement		3
Stalk lesions		1
Miscellaneous		***11
Craniopharyngioma		9 (3.9)
Sheehan syndrome		9 (3.9)
Meningioma		4 (1.7)
Rathke's cleft cyst		3
Total		**232**

*GH-secreting adenoma,2 of them stain on biopsy for lactotroph cell

**Acromegaly in 4

*** Miscellaneous includes galactorrhea, hypogonadotropic hypogonadism, and acromegaloidism

primary or secondary, were seen in 9.4%. Craniopharyngioma and Sheehan syndrome were seen in 3.9% each. Meningioma based on MRI finding was been observed in 4 patients (1.7%).

In this study, 64.8% of pituitary adenoma were macroadenomas (Table 3). Macroadenoma was seen in 73.4% of acromegaly, 61.2% in NFPA and 62.0% of prolactinoma (of them six were giant prolactinoma).

In Table 4 we see hypophysectomy whether transsphenoidal or transcranial or both was performed in 45 patients with pituitary adenoma (28.8%). Stereotactic radiosurgery is done in 5 patients (3.2%) with pituitary adenoma. Growth hormone secreting adenoma (acromegaly) and prolactinomas were treated primarily with medical therapy (71.4% and 76.1% respectively).

> **Dataset 1. Description of patients included in the study**
>
> http://dx.doi.org/10.5256/f1000research.13632.d197439

Table 3. Pituitary adenoma according to the size.

	Microadenoma N (%)	Macroadenoma N (%)	Total
Pituitary adenoma	55 (35.2)	101 (64.8)	156
Growth hormone secreting adenoma (acromegaly)	17 (26.5)	47 (73.4)	64
Clinically non-functioning pituitary adenoma (NFPA)	19 (38.8)	30(61.2)	49
Prolactinoma	16 (38)	26 (62.0)*	42
ACTH- secreting Pituitary adenoma	2 (100.0)	0	2

*Of them six giant Prolactinoma

Table 4. Type of treatment for pituitary adenoma.

		N (%)
Hypophysectomy-transsphenoidal		33 (21.1)
Hypophysectomy-transcranial		8 (5.1)
Hypophysectomy-transsphenoidal followed by transcranial or reverse or repeat same surgery,i.e., twice surgery		4 (2.5)
Stereotactic radiosurgery		5 (3.2)
Radiotherapy		1 (0.6)
Primary medical treatment	Growth hormone secreting adenoma (acromegaly)	46 (71.4)*
	Prolactinoma	32 (76.1)**
Total		156

*Of patients with acromegaly

**Of patients with prolactinoma

Discussion

All pituitary disorders and adenoma were more common among women in this study. The gender predominance among patients with pituitary adenoma is variable in the literature depending on hormone secretion and age of the patients, the size of the tumor and female dominance is not clear[15,16]. However, female dominance has been seen in Saudi Arabia[17] and one series from Argentina[18]. Those with macroadenoma tend to be older in age with no difference in the prevalence between men or women.

Seen in about two-thirds of patients, pituitary adenoma constituted the main bulk of pituitary disease in this study, which is compatible with reports in the literature[16].

The commonest pituitary adenoma was growth hormone secreting adenoma (acromegaly), followed by NFPA and prolactinoma. This is entirely different from the literature on the prevalence of pituitary adenoma[2,16,17,19]. This could be attributed to selection bias because only growth hormone secreting adenoma (acromegaly) patients are being referred, while NFPA and prolactinoma were treated by different specialties, such as neurosurgeons or gynecologists, without referral to a specialized Center like FDEMC. In Basrah, most cases of hyperprolactinemia were seen by a gynecologist because of amenorrhea and infertility, and the neurosurgeon follows patients with NFPA without referring them.

Hypopituitarism is prevalent in a quarter of this pituitary centre, from different causes, ranging from macroadenoma to hypophysectomy. Evaluation for hypopituitarism remains an integral part of the workup for any pituitary lesions because missing such diagnosis could be catastrophic[9,13]. This figure is far higher than that of Saudi Arabia, which was 1.2%[17].

Empty sella syndrome was seen in 9.4% of patients in this study, which can be primary or secondary to surgery or apoplexy. Empty sella syndrome needs an extensive workup to assess pituitary function[20].

Craniopharyngioma and Sheehan syndrome are two diseases with a different spectrum of age distribution, but they were seen at the same frequency in this cohort. Craniopharyngioma is a disease of childhood and adolescence[21]. Sheehan syndrome is supposed to be rare in developed countries, but is still seen in developing countries[22].

Less than two thirds of adenoma in this study were macroadenomas. While in most series macroadenomas constitute 50% of the pituitary adenomas[2]; however in Canada, a similar finding has been seen compared with this study[23]. Again this could be explained by referral bias in this study. In Saudi Arabia, microadenomas were more prevalent[17].

For growth hormone secreting adenoma (acromegaly), more than two thirds were macroadenomas, which is established fact for all acromegaly[2,24,25].

NFPA was a macroadenoma and seen at around 60% in this study. A similar finding was seen in a previous series[2].

Prolactinomas were macroadenoma in around 60% of cases in this study. This differs from the literature, where more than 90% of prolactinomas were microadenomas[2,18].

Hypophysectomy-transsphenoidal as surgical treatment was done in one third of pituitary adenomas, while transcranial approach or stereotactic radiosurgery was contemplated in the minority. This is a typical approach for most of the pituitary adenomas[2,26]. For growth hormone secreting adenoma (acromegaly), the primary treatment in this study was medical treatment in about two thirds of individuals. This is contrary to literature where surgery is the main mode of therapy[26]. The explanation is that we are just building a new neurosurgery unit for pituitary glands over the last few years, and in the future, surgery of pituitary is supposed to improve, and early referral will be the best.

For prolactinoma, primary medical treatment was done in two thirds of patients, while it should be the main treatment of choice in more than 90%, as seen in previous literature[26].

Malignant disease metastasizing to the pituitary is not observed in this study because they are not referred from Oncology Center in Basrah.

Study limitation

This study supposes to involve most of the pituitary disease patients in Basrah because the Center is a tertiary referral center. However, due to referral bias among some neurosurgeons and gynecologologists, we cannot guarantee that the data includes all patients with this condition in Basrah.

Conclusion

Pituitary adenomas constituted the bulk of pituitary disorders in Basrah. Growth hormone secreting adenoma (acromegaly) is the most frequent adenoma followed by NFPA and prolactinoma due to referral bias. A change in the practice of pituitary adenoma treatment is needed.

Data availability

Dataset 1: Description of patients included in the study 10.5256/f1000research.13632.d197439[27]

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    Data Source

Open Peer Review

Current Peer Review Status: ✓ ✓

✓   **Khaled Mohammed Al-Dahmani** (iD)

1 Divison of Endocrinology, Tawam Hospital, Al Ain, United Arab Emirates
2 Department of Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Abu Dhabi, United Arab Emirates

While the authors addressed some of the raised comments, I see a need for the following:

1. Simplify Table 2 into 4 main groups as mentioned before. It is understandable that patients with seller masses may also have hyperprolactinemia and hypopituitarism. These cases should be counted under sellar masses category and not included under hyperprolactinemia and hypopituitarism catergories. This will clarify the spectrum of pituitary disorders seen in this study and will be easy to compare if similar studies from other centers were to be published in the future.

2. Under "miscellaneous" group, galactorrhea and acromegaloidism need not to be included in the study unless there is a pituitary disorder to explain such diagnosis. The other case(s) of hypogonadism should be counted under the category of hypopituitarism (which is already present as a category by itself).

3. For Table 3, the total number of adenomas (156) should exactly equal the sum of all adenoma subtypes. If a patient has a mixed adenoma (GH & PRL secreting adenoma) it should be counted as 1 adenoma under GH category for example and not included both.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pituitary, thyroid

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 14 June 2018

?

Khaled Mohammed Al-Dahmani (iD)
[1] Divison of Endocrinology, Tawam Hospital, Al Ain, United Arab Emirates
[2] Department of Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Abu Dhabi, United Arab Emirates

The study by Mansour AA et al. is an important contribution to the limited pituitary research in the middle East and North Africa (MENA) region.

The following points need further modifications/clarifications;

- Sellar and parasellar region lesions usually refers to structural abnormalities and do not necessarily include other pituitary pathologies like hyperprolactinemia and hypopituitarism. Therefore, I suggest using the term "pituitary disorders" instead; more comprehensive.

- The inclusion of patients needs further clarifications in the "Method" section. what diagnoses where looked for?

- Pituitary adenoma includes all functioning and non-functioning pituitary tumors. In some part of the text, it was used separately from its subtype (see paragraph; Definition of variables). Maybe just typo.

- Table (2) needs to be simplified. The total number of patients should equal clearly equal 232. I suggest using 3-4 categories only; Sellar masses/abnormalities, Hyperprolactinemia, hypopituitarism and others.

- The "miscellaneous" cases need to be mentioned; what diagnoses are here?

- Table 3 the sum of patient with pituitary adenoma subtypes are not equal to the total number of cases.

- In the conclusion, "A change in the practice of adenoma treatment is needed" is very general. Based on the presented data, change in the management of GH secreting adenomas is more specific and relevant.

- Additional language editing will further enhance the manuscript.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pituitary, thyroid

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 19 Jun 2018

Abbas Mansour, Diabetes, Endocrine and Metabolism Division, Department of Medicine, Basrah College of Medicine,Hattin post office. P.O Box: 142, Iraq

The study by Mansour AA et al. is an important contribution to the limited pituitary research in the middle East and North Africa (MENA) region.

The following points need further modifications/clarifications;
- Sellar and parasellar region lesions usually refers to structural abnormalities and do not necessarily include other pituitary pathologies like hyperprolactinemia and hypopituitarism. Therefore, I suggest using the term "pituitary disorders" instead; more comprehensive.

Done

- The inclusion of patients needs further clarifications in the "Method" section. what diagnoses where looked for?

Retrospective data analysis of FDEMC database for the period from January 2012 through June 2017.
Inclusion criteria:We included all patients with pituitary disorders who have MRI pitutiary regardles the age .

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Done

- Table (2) needs to be simplified. The total number of patients should equal clearly equal 232. I suggest using 3-4 categories only; Sellar masses/abnormalities, Hyperprolactinemia, hypopituitarism and others.

Its cant be 232 because some may have more than one diagnosis

- The "miscellaneous" cases need to be mentioned; what diagnoses are here?

Miscellaneous includes galactorrhea, hypogonadotropic hypogonadism, and acromegaloidism

- Table 3 the sum of patient with pituitary adenoma subtypes are not equal to the total number of cases.

GH-secreting adenoma,2 of them stain on biopsy for lactotroph cell
GH-secreting adenoma with hyperprolactinemia in 5 patients

- In the conclusion, "A change in the practice of adenoma treatment is needed" is very general. Based on the presented data, change in the management of GH secreting adenomas is more specific and relevant.

A change in the practice of pituitary adenoma treatment is needed.
All adenomas treatment needed reevaluation .

- Additional language editing will further enhance the manuscript.

Done

Competing Interests: No competing interests were disclosed.

Reviewer Report 30 April 2018

https://doi.org/10.5256/f1000research.14810.r32887

✔ **Abdul Al-Toma**
Department of Internal Medicine, Gastroenterology and Hepatology, St Antonius Hospital, Nieuwegein, The Netherlands

Dr. Mansour and co-authors investigated the Spectrum of pituitary disease (Sellar and Parasellar Region Lesions) in a large cohort of patients from a tertiary referral center in the southern region of Iraq. This center receives patients with pituitary diseases from most of Southern Iraq, a population of 6-8 million.
The authors provided a well written retrospective analysis of the study population. The manuscript is focused on providing an attractive epidemiological description of the studied patients.

Abstract section: concise text and states clearly the objective of the report. In their conclusion

they stated that a change in practice of adenoma treatment is needed. It would be more informative if they provide some data on how they reached to this conclusion. A minor correction: the following 2 sentences need to be separated by full stop mark instead of comma (*Pituitary adenoma constituted the bulk of sellar and parasellar region lesions, growth hormone secreting adenoma is the most common adenoma followed by NFPA and prolactinoma due to referral bias*.)

The following sections are well written and data were clearly presented:

Methods and results. In addition they included an appropriate Statistical analysis. However, minor English language edition is needed.

The discussion section described the study results in comparison with recent literature. Recent literature has been adequately addressed. The authors stated the limitation f their manuscript clearly. It would be interesting to provide some information on the prognosis of their study patients, both for surgically or medically treated patients.

The references are clearly presented and conform the current standards.

The tables are clearly written.

Minor comments: although the manuscript is well written, however some revision of the English text needs to done.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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