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Association of the severity and pattern of pituitary adenoma-related headache with the size and type of adenoma

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Abstract

Introduction: Headache is one of the essential symptoms of pituitary adenoma associated with the tumor and the patient's characteristics. The pattern of adenoma-related headaches varies widely and can significantly impact the patient's quality of life.
Objectives: We aimed to investigate the severity and pattern of headaches in patients with pituitary adenoma in Iran.
Patients and Methods: In this cross-sectional study, we investigated 109 patients with an initial complement of headaches. The diagnosis of pituitary adenoma was confirmed. Patients' demographic characteristics [e.g., gender, body mass index (BMI), and age] and tumor characteristics (e.g., subtype of tumor and size of tumor) were collected by interview, clinical examination, and imaging. We measured the severity of the headache using Headache Impact Test-6 (HIT-6) questionnaire version 1.1.
Results: In our study, the most common subtype of pituitary adenoma was prolactinoma, followed by non-functional growth hormone (GH)-releasing and adrenocorticotropic hormone (ACTH)-releasing adenomas. Functional adenoma was significantly more common in women; however, the incidence of non-functional adenoma was more in men (61%), indicating the correlation between gender and subtype of adenoma ($P=0.008$). Most tumors were functional microadenomas (69%), while macroadenomas were primarily non-functional (50%). The HIT-6 scores demonstrated that functional microadenomas had higher HIT-6 scores and patients with prolactinoma experienced more severe headaches than other subtypes ($P=0.003$).
Conclusion: Our study revealed significant effects of the type of adenoma on the severity of headaches, as patients with functional microadenomas had more muscular headaches. Additionally, the hormone-releasing function of tumors plays a vital part in the advent and severity of adenoma-related headaches.

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Introduction

Pituitary adenomas are benign pituitary tumors arising from adenohypophysis and account for 10% to 15% of intracranial tumors (1). They are heterogeneous tumors mostly confined to the sella turcica and rarely present with overt clinical symptoms; however, some adenomas may express symptoms related to local mass effects or excessive hormone secretion (2). Generally, the clinical manifestation of pituitary adenoma is associated with the structural and functional properties of the tumor. Headache, visual disturbance, weight gain, galactorrhea, and amenorrhea are common symptoms of pituitary adenoma (3). Prolactinoma (prolactin-secreting adenoma) is the most common type of pituitary adenoma, followed by non-functional pituitary adenomas, GH-secreting adenoma, adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) secreting adenomas (4). Based on their size, adenomas are classified as Microadenomas (smaller than 1 cm) and Macroadenomas (at least 1 cm). Macroadenomas can cause headaches due to distortion of surrounding tissue, cavernous sinus invasion, and stretch of local dura matter (5).

Headache is a common symptom worldwide associated with a wide range of diseases and can significantly affect the quality of life of people. Headache represents diagnoses based on location, duration, onset, accompanying symptoms, and patient's condition. Tension headaches, migraine headaches, cluster headaches, and intracranial lesion-related headaches

Key points

- Pituitary adenomas are benign pituitary tumors classified into different subtypes based on size and secreting function. Our study revealed that the gender of patients had an essential role in a subtype of pituitary adenoma.
- Headache is one of the most common symptoms associated with various disorders. Our study showed that headache is an important clinical presentation of pituitary adenoma and can significantly affect patients' quality of life.
- In this study, adenoma size was inversely associated with the severity of adenoma-related headaches. Patients with microadenoma experienced more severe headaches compared to patients with macroadenoma
- Severity of adenoma-related headache was associated with a subtype of adenoma

are common types of headaches (6). Intracranial tumors are one of the crucial causes of headaches. Based on the International Classification of Headache Disorders (ICHD-III), elevated intracranial pressure and the lesion's characteristics play a crucial role in the pathogenesis of intracranial tumor-related headaches (1). Pituitary adenomas are also linked to headaches in some patients. Some studies have revealed that the prevalence rate of headaches in pituitary adenoma varies from 33% to 72% (7). In addition to the mass effect, the secretory function of pituitary adenoma plays an essential role in adenoma-related headaches, e.g., prolactin-secreting microadenomas present with chronic headaches in some patients (4,8). Various phenotypes of headaches (such as classical migraine and cluster-like headaches) have been reported in patients with pituitary adenoma (8,9).

Determining the pattern and severity of headaches in various disorders can provide a better approach to diagnosing underlying conditions.

Objectives

Therefore, this study aims to investigate the severity and pattern of pituitary adenoma-related headaches in Iran.

Patients and Methods

Study design

To investigate the severity and pattern of pituitary adenoma-related headaches, we studied adult patients with an initial complement of headaches referred to the public or private medical centers of Tabriz City in 2020. Patients' pituitary adenoma diagnosis was determined by clinical examination, laboratory tests, and magnetic resonance imaging (MRI). Patients who received analgesics or drugs that induce prolactin secretion, pregnant and breastfeeding women, and patients with a decreased level of consciousness were excluded from the study. Eventually, 109 patients were involved in our study based on inclusion and exclusion criteria. We measured the severity of headaches using Headache Impact Test-6 (HIT-6) version 1.1.

Headache assessment

The HIT-6 is a questionnaire developed to determine the severity of the headache and its effect on the patient by examining some criteria such as pain, social functioning, vitality, cognitive functioning, role functioning, and psychological distress.

The answers are scored as follows: 6 = never, 8=rarely, 10=sometimes, 11=very often, 13 = always. Total score ranges from 36 to 78, and results are classified into four groups; scores ≤49 represent little or no impact; scores between 50 and 55 represent some impact; scores between 56 and 59 represent substantial impact; and scores ≥60 indicate severe impact. (Validation of the HIT-6 in patients with chronic migraine).

Demographic variables

Demographic and clinical characteristics were obtained through the interview and access to the patient's documents, history, and laboratory results and were recorded according to our own-designed checklist. To investigate the function of pituitary adenoma in our subjects, we recorded the level of hormones secreted by adenohypophysis, including ACTH, TSH, prolactin, LH, FSH, and their downstream hormones cortisol, insulin-like growth factor (IGF-1), and free T4. Correspondingly, the tumor size in each patient was obtained by the MRI report.

Statistical analysis

We performed statistical analysis using SPSS software 22.0 (IBM Corp., Armonk, NY, USA). All data were shown as the mean ± standard deviation. The one-way or two-way analysis of variance (ANOVA) was conducted to analyze the difference between groups, and the chi-square test was used to compare the results. Statistical significance was set to $P<0.05$.

Results

In this study, we included 109 subjects among patients with confirmed pituitary adenoma referred to the medical centers of Tabriz in 2020. The mean patients' age was 38 years, and most were female (64%). The frequency of different types of pituitary adenoma was as follows: 69 prolactinomas (63%), 31 non-functional adenomas (28%), 7 ACTH-releasing adenomas (7.5%), 2 GH-releasing adenomas (1.5%) (Table 1). In 69% of patients, the adenoma size was less than 1mm (microadenoma), and most microadenomas were functional tumors secreting prolactin, GH, or ACTH. We found a significant correlation between the size and function of the adenoma, as most functional tumors (prolactinoma, ACTH-releasing adenoma, and GH-releasing adenoma) were micro-adenomas ($P=0.001$). These results are consistent with previous studies and the general incidence of different pituitary adenomas (Table 2). Incidence of different types

Table 1. Frequency of gender in different subtypes of adenoma

		Gender		Total
		Male	Female	
Diagnosis	Prolactinoma	19 (27%)	50 (73%)	69
	Non-functional	19 (61%)	12 (39%)	31
	ACTH-releasing adenoma	0 (0%)	2 (100%)	2
	GH-releasing adenoma	2 (28%)	5 (82%)	7
Total		40 (36%)	69 (64%)	109
P value				0.008

ACTH; Adrenocorticotropic hormone, GH; Growth hormone.

Table 2. Frequency of different subtypes of adenoma based on the size of the tumor

		Size of adenoma		Total
		Micro	Macro	
Diagnosis	Prolactinoma	56 (81%)	13 (19%)	69
	Non-functional	11 (35%)	20 (65%)	31
	ACTH-releasing adenoma	1 (50%)	1 (50%)	2
	Acromegaly	1 (14%)	6 (86%)	7
Total		69 (63%)	40 (37%)	109
P value				0.001

ACTH; Adrenocorticotropic hormone.

of functional adenomas was significantly higher in women, and non-functional tumors were more common in men; this study showed a significant correlation between gender and tumor type ($P=0.008$; Table 1). The result of the HIT-6 questionnaires demonstrated that score of severity of headache was 53±9 in patients with microadenoma and 45±7 in patients with macroadenoma. These results indicate that the tumor size is not the only determining factor for the severity of adenoma-related headaches, as in some subjects, the intensity of the headache was higher in patients with microadenoma. There was no correlation between the adenoma size and the HIT-6 score ($P=0.078$). However, according to Tables 3 and 4, there was a significant correlation between the type of adenoma and the severity of headaches based on HIT-6 scores ($P=0.003$). Among all adenoma subtypes, prolactinoma was associated with more severe headaches with HIT scores of 54±9, defined as some impact. HIT-6 score of ACTH-releasing adenoma, GH-releasing adenoma, and non-functional adenoma was less than 50, categorized as having no effect. Table 3 provides an overview of the association of the severity of adenoma-related headaches with the patient's and tumor's characteristics.

Discussion

The true incidence of pituitary adenoma is usually underestimated due to lack of symptoms or presenting with unspecified symptoms such as headaches. Headache is an introductory presentation of adenoma, although the exact relationship between adenoma and the pattern of headaches is still undefined. In this study, we investigated the severity and pattern of adenoma-related headaches in a different type of pituitary adenoma in Iran to create a better approach for adenoma-related headaches. Our main findings are as follows;

1. There is a significant relevance between the adenoma subtype and the patient's gender.
2. The size of the adenoma is inversely associated with the severity of the headache, as in our study, patients with microadenoma experienced more substantial

Table 3. Overview of correlation of severity of headache based on Headache Impact Test-6 (HIT-6) to tumor and patients characteristic

	Prolactinoma	Non-functional	ACTH-releasing adenoma	GH-releasing adenoma	*P* value
Age (y)	35.04 ± 11	45± 13	30± 1	43 ± 9	0.001
BMI (kg/m^2)	27± 3	27.05 ± 2	33.2 ± 2.34	27.65 ± 3.5	0.003
LH (IU/mL)	24 ± 14.9	4.01 ± 3	7 ± 2	4 ± 2	0.004
FSH (IU/mL)	3 ± 3	4 ± 0.4	9 ± 1	4 ± 1	0.023
Estradiol (pg/mL)	58.06 ± 26	37 ± 3	69 ± 8	53.2 ± 13.5	0.021
Testosterone (ng/dL)	1 ± 1	9 ± 2.1	No data	57 ± 11	0.020
Prolactin (ng/mL)	2121 ± 215.6	730 ± 23	35 ± 13	283 ± 12	0.002
ACTH (pg/mL)	8	32 ± 5	59 ± 12	32 ± 7.5	0.006
GH (ng/mL)	No data	2 ± 0.2	No data	14 ± 2.1	0.012
IGF-1 (ng/mL)	152 ± 53.2	113.8 ± 21	181 ± 62	670 ± 82	0.032
Cortisol (mcg/dL)	10 ± 5	15 ± 3.5	16 ± 1	8 ± 2	0.034
TSH (mIU/L)	3 ± 0.4	2 ± 1	2.05 ± 0.3	2	0.015
Free T4 (ng/dL)	3 ± 0.9	1 ± 0.2	1 ± 0.1	1.02	0.001
HIT-6 score	54 ± 9	46.09 ± 4	41 ± 4	38 ± 1	0.003

ACTH; Adrenocorticotropic hormone, GH; Growth hormone, BMI; Body mass index, LH; Luteinizing hormone, FSH; Follicle stimulating hormone, IGF-1; Insulin-like growth factor, TSH; Thyroid stimulating hormone

Table 4. HIT-6 scores of different subtypes of adenoma

Subtype of adenoma	HIT-6 score
Microadenoma Prolactinoma	56±8
Microadenoma non-functional	45±5
Microadenoma ACTH-releasing adenoma	45± 1
Microadenoma GH-releasing adenoma	38±2
Macroadenoma Prolactinoma	49±9
Macroadenoma nonfunctional	46±4
Macroadenoma ACTH-releasing adenoma	38±2
Macroadenoma GH-releasing adenoma	37±1
P value	0.003

ACTH; Adrenocorticotropic hormone, GH; Growth hormone; HIT-6; Headache Impact Test-6.

headaches than patients with macroadenoma.

3. The type of adenoma affects the severity of headaches in patients.

Pituitary adenoma usually occurs in 30-50-year-olds and is mainly diagnosed with imaging or autopsy (10,11). In previous studies, patients with pituitary adenoma were middle-aged, and prolactinoma was the most common subtype of adenoma. In our study mean age of patients was 38, and consistent with previous studies, prolactinoma was the most common subtype (63%) (12). Different subtypes of pituitary adenomas have distinct clinical and biological characteristics in a gender-related matter (10). In a previous study, Schaller et al showed that GH-releasing pituitary adenoma was larger, more invasive, and led to worse clinical outcomes in men. Schaller claimed that gender-related difference in GH-releasing adenoma is associated with a biological difference in genders (13). In another study, Calle-Rodrigue et al compared clinicopathological features of prolactinoma in men and women, and the results demonstrated that prolactinoma in male and older female patients is more proliferative compared to a young female. Moreover, Calle-Rodrigue et al showed that gender-based differences in prolactinoma might be associated with different expressions of sex steroid hormone receptors and growth factors or different tumor vascularization (14). In the current study, we also found a significant correlation between the subtype of adenoma and the gender of patients, as functional adenomas were more common in women. In contrast, non-functional adenomas were more common in men. We conclude that gender-related differences in the endocrine system and endocrine milieu affect the development of different adenoma subtypes.

Interestingly, the presenting study showed an inverse relationship between the size of the tumor and the severity of the headache, which highlights the effect of the function of adenoma in the development and severity of adenoma-related headaches. Several studies have considered a biochemical-neuroendocrine origin for adenoma-related headaches. Pascual et al showed that endocrine treatment could improve adenoma-related headaches significantly in small GH-releasing adenomas (15). The same relieving effect has been observed in headaches related to prolactinoma-releasing microadenoma after treatment with dopamine agonists (16,17). Furthermore, Gondim et al have revealed that in addition to anatomical features of tumor- such as size, optic chiasm compression, sellar destruction, and cavernous sinus invasion- the hormone-secreting function of adenoma, especially in prolactinoma, plays a vital role in the severity of adenoma-related headache (18). Consistent with these studies, our study demonstrated that based on HIT-6 scores, the severity of headache in patients with microadenoma was more than in patients with macroadenoma, and patients with prolactinoma had the most vital headache compared to other adenoma subtypes. These results confirm the critical role of the biochemical-neuroendocrine function of adenoma in the development and severity of subsequent headaches.

Conclusion

Our study revealed that headache is an essential symptom of pituitary adenoma and is associated with the patient's adenoma characteristics. In addition to the size and invasion of adenoma, a hormone-secreting function of adenoma plays an essential role in adenoma-related headaches. Prolactin-releasing adenoma and GH-releasing adenoma are associated with more severe headaches than other adenoma subtypes. For further investigations, we suggest studying the effects of various treatments on reducing the severity of adenoma-related headaches.

Limitations of the study

One of our limitations was the small number of study patients. It is suggested that more patients on this subject be investigated in future studies.

Authors' contribution

Conceptualization: Farzad Najafipour.
Formal analysis: Newsha Hedayati.
Investigation: Newsha Hedayati.
Methodology: Farzad Najafipour.
Project administration: Farzad Najafipour, Newsha Hedayati.
Resources: Newsha Hedayati.
Supervision: Farzad Najafipour, Newsha Hedayati.
Validation: Farzad Najafipour.
Visualization: Neda Hedayati.
Writing–original draft: Neda Hedayati.
Writing–review and editing: Farzad Najafipour, Newsha Hedayati, Mehdi Farhoudi.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Tabriz University of Medical Sciences approved this study (Ethical code#IR.TBZMED.REC.1399.1126). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from M.D., thesis of Dr. Newsha Hedayati at this university (Thesis#66464). Besides, ethical issues

(including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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References

1. Melmed S, Kaiser UB, Lopes MB, Bertherat J, Syro LV, Raverot G, et al. Clinical Biology of the Pituitary Adenoma. Endocr Rev. 2022 Nov 25;43:1003-1037. doi: 10.1210/endrev/bnac010.
2. Srirangam Nadhamuni V, Korbonits M. Novel Insights into Pituitary Tumorigenesis: Genetic and Epigenetic Mechanisms. Endocr Rev. 2020;41:821–46. doi: 10.1210/endrev/bnaa006.
3. Brue T, Castinetti F. The risks of overlooking the diagnosis of secreting pituitary adenomas. Orphanet J Rare Dis. 2016 Oct 6;11:135. doi: 10.1186/s13023-016-0516-x.
4. Gruppetta M, Mercieca C, Vassallo J. Prevalence and incidence of pituitary adenomas: a population based study in Malta. Pituitary. 2013;16:545-53. doi: 10.1007/s11102-012-0454-0.
5. Lv X, Wu Z, Li Y. Innervation of the cerebral dura mater. Neuroradiol J. 2014;27:293-8. doi: 10.15274/NRJ-2014-10052.
6. Zis P, Mitsikostas DD. Nocebo Responses in Brain Diseases: A Systematic Review of the Current Literature. Int Rev Neurobiol. 2018;139:443-62. doi: 10.1016/bs.irn.2018.07.025.
7. Abe T, Matsumoto K, Kuwazawa J, Toyoda I, Sasaki K. Headache associated with pituitary adenomas. Headache. 1998;38:782-6. doi: 10.1046/j.1526-4610.1998.3810782.x.
8. Pineyro MM, Sosa G, Finozzi MR, Stecker N, Pisabarro R, Belzarena MC. Chronic cluster-like headache in a patient with a macroprolactinoma presenting with falsely low prolactin levels: bromocriptine versus cabergoline? Clin Case Rep. 2017;5:1868-1873. doi: 10.1002/ccr3.1208.
9. Lee AH. Pituitary adenoma causing classical migraine. Br J Neurosurg. 1990;4:347-8. doi: 10.3109/02688699008992746.
10. Mindermann T, Wilson CB. Age-related and gender-related occurrence of pituitary adenomas. Clin Endocrinol (Oxf). 1994;41:359-64. doi: 10.1111/j.1365-2265.1994.tb02557.x. Erratum in: Clin Endocrinol (Oxf) 1994;41:700.
11. Burrow GN, Wortzman G, Rewcastle NB, Holgate RC, Kovacs K. Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. N Engl J Med. 1981;304:156-8. doi: 10.1056/NEJM198101153040306.
12. van der Klaauw AA, Kars M, Biermasz NR, Roelfsema F, Dekkers OM, Corssmit EP, et al. Disease-specific impairments in quality of life during long-term follow-up of patients with different pituitary adenomas. Clin Endocrinol (Oxf). 2008;69:775-84. doi: 10.1111/j.1365-2265.2008.03288.x.
13. Schaller B. Gender-related differences in growth hormone-releasing pituitary adenomas. A clinicopathological study. Pituitary. 2002;5:247-53. doi: 10.1023/a:1025329900839.
14. Calle-Rodrigue RD, Giannini C, Scheithauer BW, Lloyd RV, Wollan PC, Kovacs KT, et al. Prolactinomas in male and female patients: a comparative clinicopathologic study. Mayo Clin Proc. 1998;73:1046-52. doi: 10.4065/73.11.1046.
15. Pascual J, Freijanes J, Berciano J, Pesquera C. Analgesic effect of octreotide in headache associated with acromegaly is not mediated by opioid mechanisms. Case report. Pain. 1991;47:341-344. doi: 10.1016/0304-3959(91)90226-N.
16. Hartman N, Voron SC, Hershman JM. Resolution of migraine following bromocriptine treatment of a prolactinoma (pituitary microadenoma). Headache. 1995;35:430-1. doi: 10.1111/j.1526-4610.1995.hed3507430.x.
17. Gabrielli M, Gasbarrini A, Fiore G, Santarelli L, Padalino C, De Martini D, et al. Resolution of migraine with aura after successful treatment of a pituitary microadenoma. Cephalalgia. 2002;22:149-50. doi: 10.1046/j.1468-2982.2002.00314.x.
18. Gondim JA, de Almeida JP, de Albuquerque LA, Schops M, Gomes E, Ferraz T. Headache associated with pituitary tumors. J Headache Pain. 2009;10:15-20. doi: 10.1007/s10194-008-0084-0.