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Management of Hyperprolactinemia in Clinical Practice

Bayar Ahmed Qasim *
Kajeen Rashid Hussein**
Mazyar Jabbar Ahmed***
Sherwan Ferman Salih****
Mohammed Aziz Sulaiman*****

Abstract

Background & objectives: Hyperprolactinemia is defined as an increased prolactin level above the normal reference range, in women more than 25 ng/dl; with a prevalence rate of 10% in the general population. Hyperprolactinemia is associated with different clinical presentations various from oligomenorrhea, amenorrhea, galactorrhea, and infertility. This study aims to be to assess the current practice regarding the management of hyperprolactinemia in non-pregnant women in the Kurdistan region, Iraq.

Subjects and Methods: An electronic questionnaire on current practice concerning diagnosis and treatment of hyperprolactinemia in non-pregnant women was sent through e-mail to 167 clinicians, 166 of them completed the survey and they were from different cities (Duhok, Sulaymaniyah, Erbil and Halabja) of the Kurdistan region, Iraq.

Results: A total of 166 valid questionnaires were collected. The response received from 166 clinicians. Almost 97 % of the responders were asking about the presence of symptoms of prolactinoma in patients with hyperprolactinemia and the majority of responders were made an exclusion of physiological causes related to hyperprolactinemia. When hyperprolactinemia occurred, only 81.3% of the respondents would test for thyroid-stimulating hormone routinely. Majority of the responders (79.5%) did not confirm the biochemical diagnosis of hyperprolactinemia before starting treatment and only two-thirds of them do pituitary imaging. Also, our results show an important role of clinician's characteristics like age group on the management outcome, as the age group 25-35 was better when compared to age group 46-55 (p-value =0.044) and the internist specialty and family medicine specialty have better impact on management outcome in comparison to endocrinologist with (p-value =0.046 and 0.043 respectively).

Conclusions: We found that the current clinical practice for the management of hyperprolactinemia is not uniform with some scientific defects. Therefore, it is necessary to develop the national guidelines for management and treatment of hyperprolactinemia.

Key words: Clinical Practice; Hyperprolactinemia; Prolactinoma.

Introduction

Prolactin is a pituitary hormone synthesis and secreted from lactotrophs cells of the anterior pituitary gland, which is affected by both inhibitory and stimulatory factors, predominantly inhibitory by dopamine.[1-2] Prolactin is a protein of 199 amino acids and it has more than 300 separate actions.[3] It has an important role in lactation; it stimulates differentiation and proliferation of mammary cells.[4-5] During lactation, it enhances proliferation and hypertrophy of lactotrophs cells, which allow further increase in prolactin level in subsequent lactation.[6- 7] Hyperprolactinemia is defined

* M.B.Ch.B., FRCP (Edinburgh), MRCP (London), FKBMS, Endo Diploma (UK), Assistant professor of endocrinology and diabetes, College of Medicine, University of Duhok
** BVMS, MS, Lecturer in clinical biochemistry, College of medicine, University of Duhok
*** MBChB, FIBMS, HDE, Endocrinologist, Kurdistan board of medical specialties, Hawler
**** MBChB, FIBMS, Assistant professor, College of Medicine, University of Duhok
***** MBChB, FIBMS Assistant professor, College of Medicine, University of Duhok
Corresponding author: Bayar Ahmed Qasim. Email: bayarsabc@gmail.com

as an increased prolactin level above the normal reference range, in females more than25 ng/dl; with a prevalence rate of 10% in the general population.[8-9] Prolactinoma is associated with different clinical presentations varies from oligomenorrhea, amenorrhea (29%), galactorrhea (30-80%) and infertility. Moreover, 9% of females with amenorrhea have hyperprolactinemia, and 25% of females with galactorrhea have hyperprolactinemia, whereas 70% of females with both of them have hyperprolactinemia.[10-12] In addition to many physiological conditions that are associated with Hyperprolactinemia such as pregnancy, lactation, there are many pathological causes such as prolactinoma, hypothyroidism, renal failure and parasellar tumors. Drug-induced hyperprolactinemia is a common occurrence in clinical practice, and it should be considered as a very important differential diagnosis in all patients who present with hyperprolactinemia. That is why it is necessary to rule out medication use and other secondary causes of hyperprolactinemia before requesting MRI of the pituitary gland.[13] Prolactinoma is the most frequent type of pituitary adenoma; It is divided into microprolactinoma (tumor size less than 10 mm) and macroprolactinoma (tumor size more than 10 mm).[14-16] In addition to the presence of a high number of unrecognized prolactinoma, its prevalence range variesfrom 25/100000 to 63/100000 in different populations.[17] Furthermore, and in contrast to other types of pituitary adenoma, majority of prolactinoma has an excellent response to medical treatment especially dopamine agonist.[18] To compare the approach of our clinicians with that of the Endocrine Society Clinical Practice Guidelines regarding the management of hyperprolactinemia and microprolactinoma, we performed an electronic survey among our clinicians in the Kurdistan region, Iraq, to assess diagnostic and therapeutic preferences for management of hyperprolactinemia and microprolactinoma in non-pregnant females. This is the first survey to investigate the management of hyperprolactinemia in the Kurdistan region, Iraq.

Subjects and methods

In 2021 and within one month (1st of July to 30th of July), an electronic questionnaire survey on current practice concerning diagnosis and treatment of hyperprolactinemia in non-pregnant females was sent through e-mail to 167 clinicians. One of them apologized to complete the survey. Of the remaining clinicians, 166 completed the survey and were of different specialties (endocrinologist, general internist, obstetricians, Family medicine, general practitioners), from different cities (Duhok, Sulaymaniyah, Erbil and Halabja) and they worked in different hospital in Kurdistan region, Iraq. The consent was taken from participants by asking them a direct question do you agree to participate in this survey? The study approved by ethical committee of Kurdistan Board of Medical Specialties. The survey was based on 9 questions, 4 of the questions concerning clinician characteristics and include: gender, specialty, age, and residence of clinicians, the remaining 5 questions related to the screening and treatment of hyperprolactinemia in nonpregnant women provided by Endocrine Society Clinical Practice Guidelines which include: Do you ask about symptoms of prolactinoma like amenorrhea and galactorrhoea? Would you exclude physiological causes like pregnancy, lactation...etc or drug-induced high prolactin? If you find incidentally high prolactin level, do you check TSH routinely? If you find incidentally high prolactin level, do you treat patients before confirming the diagnosis with dopamine agonists like cabergoline? If you find

incidentally high prolactin level, at which level you will think of pituitary microadenoma and you may order MRI of pituitary? For statistical analyses regarding the categorical data, frequencies and percentages are used, whereas for continuous data, mean and standard deviation are used. The Chi square test is used to examine the relationships between the variables, the appropriate and inappropriate answers, with p-values of less than or equal to 0.05 considered significant. The Statistical Package for Social Sciences is used to examine the data (SPSS 25 IBM: USA).

Results

We received a response by email from 166 clinicians of our locality; they were from different governorates in Kurdistan region, Iraq, including Duhok 58 (34.9%), Sulaymaniyah 28 (16.9%), and Erbil 79 (47.6%) and Halabja 1 (0.6%). Majority of them were female 94 (56.6%) and more than three quarters were obstetricians 67 (40.4%) and internists 63 (38.0%) as shown in Table (1).

Table (1): Showing the general characteristics of the involved physicians

Main categories	Subcategories	Frequency	Percentages
Specialty	Endocrinologist	11	6.6%
	Family medicine	20	12.0%
	General practitioner	5	3.0%
	Internist	63	38.0%
	Obstetrician	67	40.4%
Sex	Male	72	43.4%
	Female	94	56.6%
Age(years)	25-35	35	21.1%
	36-45	88	53.0%
	46-55	30	18.1%
	56-65	12	7.2%
	>65	1	0.6%
City of practice	Duhok	58	34.9%
	Erbil	79	47.6%
	Sulaymaniyah	28	16.9%
	Halabja	1	0.6%
Total		166	100%

The answers of the responders regarding question related to the presence of the symptoms of prolactinoma, 162 (97.6%) were asked about the symptoms, comparing to 4 (2.4%) were not asking about the presence of symptoms of prolactinoma among in nonpregnant females with hyperprolactinemia Table (2). With exception of 3 (1.8%) of the responders, all the remaining, 163 (98.2%) were made an exclusion of physiological causes related to hyperprolactinemia in nonpregnant females Table (2). To exclude the primary hypothyroidism as a cause of hyperprolactinemia in nonpregnant females, majority of responders 135 (81.3%) did the measurement of TSH level, comparing to 31 (18.7%) that were not measured the TSH level Table (4). Majority of the responders 132 (79.5%) did not confirm the diagnosis of hyperprolactinemia in nonpregnant females by measuring of the prolactin level for the next time before staring treatment, whereas, 34 (20.5%) did a confirmation of hyperprolactinemia before staring treatment Table (2). Regarding the last question that is relation of level of prolactin with diagnosis of prolactinoma, two third of the responders 105 (63.3%) had an appropriate answer and the remaining 61 (36.7%) had an inappropriate answer Table (2).

Table (2): Showing the clinicians' responses to different questions

Question	Response	Frequency	Percent
Do you ask about symptoms of prolactinoma like amenorrhoea and galactorrhoea?	Appropriate answer (Yes) In appropriate answer (No)	162 4	97.6% 2.4%
Would you exclude physiological causes like pregnancy, lactation...etc or drug-induced high prolactin?	Appropriate answer In appropriate answer	163 3	98.2% 1.8%
If you find incidentally high prolactin level, do you check TSH routinely?	Appropriate answer In appropriate answer	135 31	81.3% 18.7%
If you find incidentally high prolactin level, do you treat patients before confirming the diagnosis with dopamine agonists like cabergoline?	Appropriate answer In appropriate answer	34 132	20.5% 79.5%
If you find incidentally high prolactin level, at which level you will think of pituitary microadenoma and you may order MRI of pituitary?	Appropriate answer In appropriate answer	105 61	63.3% 36.7%

Collectively, the percentage of inappropriate answers among endocrinologists and obstetricians was 9.70 % and 43.7% consequently with p value = 0.046 Figure (1). Meanwhile the percentage of inappropriate answers among endocrinologist and family medicine was 9.7% with p value =1.0 Figure (1).

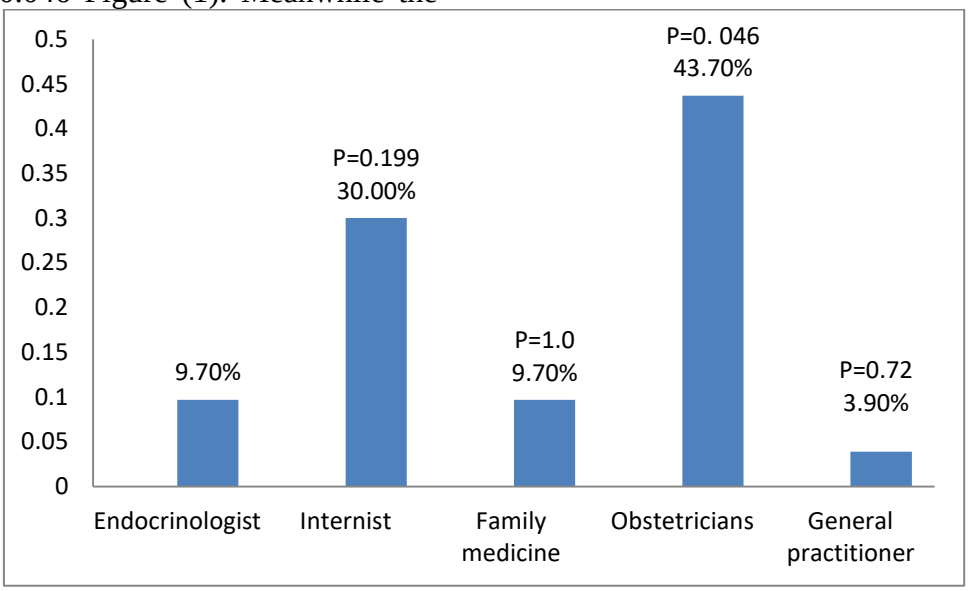

Figure (1): A simple bar chart showing the percentage of inappropriate answers among different specialities based on the questions asked.

Also, our results show an important role of clinician's characteristics like age group on the management outcome, as the age group 25-35 was better when compared to age group 46-55 (p value =0.044, Table (3) and the internist specialty and family medicine specialty have better impact on management outcome in comparison to endocrinologist with (p value =0.046 and 0.043 respectively, Table (3).

Table (3): Showing the correlation between the management outcome and different clinician's charecteristics and management steps.

Category	Subcategories	Outcome of management		p-value
		Appropriate 63(38.0%)	Inappropriate 103(62.0%)	
Sex	Male	27(37.5%)	45(62.5%)	
	Female	36(38.3%)	58(61.7%)	0.916
Age(years)	25-35	14(40.0%)	21(60.0%)	
	36-45	40(45.5%)	48(54.5%)	0.582
	46-55	5(16.7%)	25(83.3%)	0.044
	56-65	3(25.0%)	9(75.0%)	0.355
	>65	1(100%)	0(0.0%)	0.370
Specialty	Endocrinologist	1(9.1%)	10(90.9%)	
	Internist	29(46.0%)	34(54.0%)	0.046
	Family medicine	10(50%)	10(50%)	0.043
	Obstetricians	22(32.8%)	45(67.2%)	0.141
	General practitioner	1 (20.0%)	4(80.0%)	0.550
City of practice	Duhok	17(29.3%)	41(70.7%)	
	Hawler	32(40.5%)	47(59.5%)	0.178
	Sulaymaniyah	13(46.6%)	15(53.6%)	0.121
	Halabja	1 (100%)	0(0.0%)	0.236

Appropriate management: when all steps were correct.
Inappropriate management: when one step or more than one step was incorrect.

Discussion

This survey is the first that reports clinical practice relating to the diagnosis and treatment of hyperprolactinemia in nonpregnant females in Kurdistan region, Iraq. The result of our survey demonstrates some of agreement between our responders' clinical practice and Endocrine Society Clinical Practice Guidelines such as confirming the diagnosis of hyperprolactinemia before starting treatment and some area of in agreement such as level of prolactin in suspecting microprolactinoma as a cause of hyperprolactinemia A number of physiological conditions are associated with mild to moderate increased level of prolactin among nonpregnant females such as breast feeding, stress and exercise.[19] It's remarkable that nearly all the responders recommend the exclusion of these conditions as a cause of hyperprolactinemia that is consistent with the Endocrine Society Clinical Practice Guidelines. The most important cause of hyperprolactinemia is prolactinoma, whereas; hyperprolactinemia was found in 40% of primary hypothyroidism patients.[20, 21] Therefore; all patients with hyperprolactinemia must exclude hypothyroidism. Hypothyroidism in hyperprolactinemia is due compensatory increase in thyrotrophin releasing hormone from hypothalamus which results in stimulatory increase in prolactin release.[22] In our survey, and in contrary to the Endocrine Society Clinical Practice Guidelines and other study done in Brazil by their endocrinologist and gynecologist, [23, 24] approximately one quarter of our responders did not exclude primary hypothyroidism as to confirm the TSH level is within the normal references range. The Endocrine Society Clinical Practice Guidelines mentioned that a single measurement of prolactin above the reference limit to confirm the diagnosis of hyperprolactinemia as long as the stressful conditions has been excluded. However,

it's necessary to confirm the diagnosis whenever it's clinically indicated by requesting MRI of pituitary gland before starting the treatment.[23] It's worthy to remember that, in our survey, three quarter of our responders used single high level of prolactin to confirm the diagnosis of hyperprolactinemia and unfortunately, they started the treatment with cabergoline before confirming the diagnosis by MRI of pituitary gland. In nonpregnant female, the normal level of fasting serum prolactin varies between 5 and 25 ng/ml, with higher level in the afternoon than in the morning. Prolactinoma represent 40% of functioning pituitary tumor and it is the most frequent cause of chronic hyperprolactinemia (non-fluctuating hyperprolactinemia).[25] Prolactinoma are commonly encountered in females, and mostly are sporadic.[26] Although, MRI remains the method of choice for diagnosis of prolactinoma, the fasting serum prolactin level remains very important in suspected cases of prolactinoma.[27] The Endocrine Society Clinical Practice Guidelines recommended that fasting serum prolactin level above 200 ng/ml is highly suggestive for the presence of macroprolactinoma, however prolactin level above 100 ng/ml is suspicious for microprolactinoma and despite of that, one third of the responders suggested that level of prolactin as a non-suspicious for prolactinoma. We are hoping that this study will improve the management of hyperprolactinemia and stimulate further research and studies in our region. There is a clear need for national guidelines for management of hyperprolactinemia in nonpregnant women.

Conclusions

We found that the current clinical practice for the management of hyperprolactinemia is not uniform with some scientific defects. Therefore, it is necessary to develop the national guidelines for management and treatment of hyperprolactinemia.

Conflicts of interest

The author reports no conflicts of interest.

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