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Presenting Pattern and Etiologies of Hyperprolactinemia in North West of Iran

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Abstract: Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis. We have not any documented data about frequency of various etiologies of hyperprolactinemia in our region. For determination of the pattern of presentation and distribution of causes of hyperprolactinemia the presenting study were designed and conducted. In a descriptive study, we extract medical records of patient presented to our clinic with diagnosis of hyperprolactinemia between first day of 2001 until last day of 2006. At this time interval we found 127 patients with diagnosis of hyperprolactinemia, of which 14 excluded due to absence of sufficient data for determination of etiology. The remaining 113 subjects' data were collected and analyzed. In our study, 27 (23%) of patients were male and 86 (76%) were female. Grater than 63% of subjects had 20-40 years old. The presenting sings and symptoms of patients were in order of frequency: Menstrual abnormalities, galactorrhea, infertility, headache, visual disturbances and sexual dysfunction. Pituitary adenoma was the most frequent etiology of hyperprolactinemia in our subjects. Other causes of hyperprolactinemia were: Idiopathic hyperprolactinemia, hypothyroidism, medications and polycystic ovary syndrome.

Key words: Prolactin, hyperprolactinemia, presentation, etiology, north west, Iran

INTRODUCTION

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis. Pathological hyperprolactinemia is defined as a consistently elevated serum prolactin level when physiological causes of prolactin hypersecretion have been excluded. Hyperprolactinemia occurs more commonly in women. The prevalence of hyperprolactinemia ranges from 0.4% in an unselected normal adult population to as high as 9-17% in women with reproductive disorders (Biller, 1999; Casanueva *et al*., 2006). The diagnosis of hyperprolactinemia is made when serum prolactin levels are found on 2 separate occasions to be above the normal established for the laboratory used (usually 20-25 ng mL^{-1} or 400-500 mU L^{-1}) (Luciano, 1999). Its etiology, may be physiological, pharmacological, or pathological. Any drug that affects the hypothalamic dopamine system and/or pituitary dopamine receptors can result in an elevated prolactin level (Luciano, 1999; Molitch, 2008). Prolactinomas account for 25-30% of functioning pituitary tumors and are the most frequent cause of chronic hyperprolactinemia (Webster *et al*., 1997). Lesions affecting the hypothalamus and pituitary stalk rarely result in prolactin elevation of greater than 250 ng mL^{-1} (5000 mU L^{-1}) (Bevan *et al*., 1992). Pathological hyperprolactinemia can be caused by nonhypothalamic-pituitary disease. Forty percent of patients with primary hypothyroidism have mild elevation of prolactin levels that can be normalized by thyroid hormone replacement (Luciano, 1999). About 30% of patients with chronic renal failure and up to 80% of patients on hemodialysis have elevated prolactin levels (Ayub and Fletcher, 2000).

We have not any documented data about frequency of various etiologies of hyperprolactinemia in our region. For determination of the pattern of presentation and distribution of causes of hyperprolactinemia the presenting study were designed and conducted.

MATERIALS AND METHODS

The outpatient endocrine and diabetes clinic of Sina Medical Center in Tabriz is a referral center for patients with various endocrinologic problems in North West of Iran. Each patient has a written medical record. Also, there is a computerized patient registry system that presenting subjects data were recorded in that system based on clinical diagnosis. In order to perform, our descriptive study, we extract medical records of patient presented to

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our clinic with diagnosis of hyperprolactinemia between first day of 2001 until last day of 2006. At this time interval we found 127 patients with diagnosis of hyperprolactinemia, of which 14 excluded due to absence of sufficient data for determination of etiology. The remaining 113 subjects' data were collected and analyzed with SPSS version 14. Chi-square test used for comparison of proportions. $p<0.005$ considered significant.

RESULTS

In the time interval that subjects enrolled in study 113 patients had sufficient data for interpretation, of which 27 (23%) were male and 86 (76%) were female. Grater than 63% of subjects had 20-40 years old. In these series, of patents the serum level of prolactin was between 700-10000 mIu L^{-1} (normal range 66-414). About 60% of subjects had prolactin level of 1000-1500 mIu L^{-1}. Although, the number of males were a third of female but very high level of prolactin (>3000 mIu L^{-1}) were seen only in males.

The presenting sings and symptoms of patients were in order of frequency: Menstrual abnormalities, galactorrhea, infertility, headache, visual disturbances and sexual dysfunction. Table 1 represents, frequency and percentage of symptoms and signs in study subjects.

Table 1: Frequency and percentage of symptoms and signs in study subjects

	Frequency				
	Female		Male		
Symptom and signs	Rate	Percentage	Rate	Percentage	p-value*
Menstrual abnormalities	35	46	-	-	-
Galactorrhea	30	39	-	-	-
Infertility	15	19	-	-	-
Headache	4	5	9	39	0.01
Visual disturbances	2	2	6	26	0.003
Sexual dysfunction	-	-	12	52	-

*Comparison of differences of frequencies between male and female

Table 2: Frequency of multiple etiologies and mean±SD of prolactin level in each etiologic subgroup

Etiology	Frequency	Percentage	Prolactin level mean±SD
Prolactin producing pituitary adenoma	67	59	2860±110. 7
Idiopathic hyperprolactinemia*	36	31	2816±100.4
Primary Hypothyroidism	5	4	1028±63.1
Drug induced hyperprolactinemia**	2	1	2455±47.5
Polycystic Ovary Syndrome***	3	2	911±92.7

*Absence of any evidence of other etiologies, **Absence of any evidence of other etiologies and use of medication that known as prolactin elevating agent, ***Diagnosed based on clinical or biochemical signs of hyperandrogenism (Hirsutism, acre or alopecia) and abnormal menstrual periods and/or presence of PCO pattern on a ultrasound study and male out of other causes of hyperandrogenism

Pituitary adenoma was the most frequent etiology of hyperprolactinemia in our subjects. Other causes of hyperprolactinemia were: Idiopathic, hypothyroidism, medications and polycystic ovary syndrome. Table 2 shows the frequency of multiple etiologies and mean±SD of prolactin level in each etiologic subgroups.

DISCUSSION

The present study, reveal that the most common cause of presentation of patients with hyperprolactinemia to their physician is abnormalities of menstrual cycles and abnormal sexual function. The clinical presentation of hyperprolactinemia is related to hypogonadism, galactorrhea and symptoms caused by mass effects of the tumor. Women may present with oligomenorrhea, amenorrhea, infertility, decreased libido and habitual abortion (Molitch, 2001). Galactorrhea, which requires the presence of both estrogen and prolactin, is frequently present in premenopausal women (Crosignani, 2006). Prolonged hypoestrogenism induced by hyperprolactinemia may result in osteopenia (Klibanski *et al*., 1980). Hyperprolactinemic women may present with signs of chronic hyperandrogenism such as hirsutism and acne, possibly due to increased dehydroepiandrosterone sulfate secretion from the adrenals (Biller, 1999). Men with hyperprolactinemia may present with infertility associated with decreased sperm production, galactorrhea, gynecomastia and decreased libido or potency. They may also, have reduced muscle mass and, like women, are at increased risk of osteopenia (Luciano, 1999). Both women and men with macroprolactinomas can present with neurological symptoms caused by mass effects of the pituitary tumor. There are other studies that shown the main presenting cause of patients were infertility (Azima and Jalali, 2003; Morris and Sauer, 1993).

When a patient present with hyperprolactinemia we must obtain a careful history, especially a drug history, perform a complete physical examination; take blood chemistry, thyroid function tests and a pregnancy test. If the results fail to identify a cause of the hyperprolactinemia, the patient most likely has hypothalamic-pituitary disease. Any patient, who has hyperprolactinemia without an identified cause requires imaging of the hypothalamic-pituitary area. In cases, where other causes of hyperprolactinemia have been excluded and no adenoma can be visualized with MRI, the hyperprolactinemia is referred to as idiopathic.

In our series, the most frequent etiology of hyperprolactinemia was pituitary adenoma followed by

idiopathic hyperprolactinemia. The relative higher frequency of the last condition my be interpreted by lower precision of imaging apparatuses that are usually available. In most cases, the imaging procedure were commercial CT Scan. However, the recommended choice of imaging procedure is MRI with contrast agent injection (Cortet-Rudelli *et al*., 2007).

Other causes of hyperprolactinemia seen in our subjects were hypothyroidism, medications and polycystic ovary syndrome. We had not patients with other etiologies such as hypothalamic disorders, other sellar masses, renal failure, etc. This is related to a selection bias, because the clinic, in which the study performed is an outpatient basically endocrine center that patients referred for specific treatment options and others who have not need medical treatment, or need surgical treatment were not included. Also, we search and entered medical records with diagnosis of hyperprolactinemia in our survey, the probable existence of hyperprolactinemia beside other endocrinologic conditions such as acromegaly were ignored.

CONCLUSION

We found that in our series the most frequent presenting problem of patients with hyperprolactinemia was menstrual disturbances in females and sexual dysfunction males. The most frequent cause of hyperprolactinemia was pituitary prolactin secreting adenomas.

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