SPECTRUM OF DISORDERS LEADING TO HYPERPROLACTINEMIA

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ABSTRACT

Objective: To determine the frequency of disorders leading to hyperprolactinemia (HP) in patients who reported to AFIP Rawalpindi.

Study Design: Cross- sectional study.

Place and duration of study: Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology Rawalpindi, from January to June 2011.

Patients and Methods: Patients with serum prolactin levels > 530 ml U/l in females and 360 ml U/l in males were included. Patients with hyperprolactinemia(HP) due to physiological causes (pregnancy and lactation etc), drug induced, irradiation and hypothyroid patients on thyroxin treatment were excluded. Seventy six samples were collected from the patients for the workup of pathological conditions. Serum prolactin, FSH, LH, estradiol, testosterone, GH, cortisol, TSH and free T_4 were analysed on Immulite 2000, while LFTs and RFTs on Hitachi. Pituitary adenomas were confirmed by MRI.

Results: Seventy six patients had HP due to pathological causes, 13(17%) males and 63(83%) females had mean age of 30±11 years. Pituitary microadenoma was the cause of hyperprolactinemia in 30 (39.5%) cases, pituitary macroadenoma in 12 (15.8%), subclinical hypothyroidism in 14 (18.4%), primary hypothyroidism in 10 (13.2%), PCOS in 4 (5.3%), cirrhosis in 2 (2.6%), idiopathic in 2 (2.6%), CKD in 1 (1.3%) and acromegaly in 1 (1.3%) patient. HP was significantly correlated with size of prolactinoma and serum TSH levels (primary and subclinical hypothyroidism)(p value < 0.05).

Conclusion: It is concluded that prolactinoma is the commonest pathology causing hyperprolactinemia, followed by hypothyroidism and PCOS in patients who reported to AFIP Rawalpindi. This will help in early diagnosis along with further management of the patient.

Key words: Prolactinoma, Serum prolactin, Hypothyroidism, Serum TSH.

INTRODUCTION

Prolactin (PRL) is a polypeptide hormone, secreted by lactotroph cells of anterior pituitary. PRL secretion is mainly under tonic inhibitory control of dopamine. It could be stimulated by hypothalamic PRL releasing peptides, thyrotropin releasing hormone and estrogens[1,2]. It is secreted in pulsatile fashion, high during sleep, early morning and low in the afternoon. It is metabolized by liver and kidney. PRL acts primarily on the breast, it enhances its development and induces lactation[1].

Hyperprolactinemia (HP) is the most frequent endocrine disorder in hypothalamic-pituitary axis[2,3]. HP is caused by physiological conditions (pregnancy, lactation, stress, sleep, coitus, exercise), prolactinomas (56%), drugs (dopamine receptor blocker, dopamine synthesis inhibitors, labetalol, verapamil, H_2 antihistamines, oral contraceptives / their withdrawal and estrogen), primary hypothyroidism, polycystic ovarian syndrome (PCOS), chronic kidney disease (CKD), liver cirrhosis, acromegaly, chest trauma, head injury and irradiations[1,4].

Prolactinoma is the most common pituitary tumour, with an estimated prevalence of 100 per million populations in the adults[5]. In 1928 prolactinoma was first described by Sticker. It accounts for 40% of all pituitary tumors[6], female to male ratio is 10 to 1 with peak age of 20-40 years[7,8,9]. The macro adenomas (30%) usually come to clinical attention because of local mass effects. In women, most prolactinomas are micro adenomas (70%). Other tumors arising in or near the pituitary can block the flow of dopamine from the brain to the PRL-secreting

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cells. Such tumors include growth hormone (GH) producing tumors (acromegaly), and Cushing's disease.

Careful history, investigations like LFT's, RFT's, serum PRL, FSH, LH, estradiol, testosterone, GH, cortisol, TSH, free T_4 and magnetic resonance imaging (MRI) brain, help in establishing the diagnosis[3]. Visual field defects like bitemporal hemianopia are elucidated by perimetry. As the prevalence of pathological conditions leading to HP differ in various regions, and management depends on the cause. So knowing well the frequency of common causes of HP in our setup and establishing correlation of serum PRL with serum TSH levels and size of prolactinoma could be helpful in early diagnosis of disease and further management of the patient. The objective of this study was to determine the frequency of disorders leading to HP in patients reporting to Armed Forces Institute of Pathology (AFIP) Rawalpindi.

PATIENTS AND METHODS

This cross-sectional study was conducted at Department of Chemical Pathology and Endocrinology, AFIP Rawalpindi, Pakistan from Jan to Jun 2011 after approval of the institutional review committee. Patients with serum PRL levels > 530 mIU/l in females and 360 mIU/l in males were included. Three thousand two hundred and eight patients reported to AFIP Rawalpindi for the analysis of serum PRL during six months. Three thousand results were within reference range and 208 patients had HP. Out of these, 132 patients with HP due to physiological causes (pregnancy and lactation etc), drugs, irradiations and hypothyroid patients on thyroxin treatment, were excluded.

Seventy six samples were consecutively collected from the patients after their informed consent for the workup of pathological causes of HP. All samples were collected in vacutainer tubes (BD, NJ USA). Blood samples were allowed to clot and then centrifuged for 10 min at 1,000g. The serum was separated and stored at 80^0C until assayed. History of illness, findings of physical examination, demographic data and baseline routine investigations were carried out at the start of the study.

Serum PRL, FSH, LH, estradiol, testosterone, GH, cortisol, TSH and free T_4 were analysed by chemiluminescent enzyme immunoassay on random access immunochemistry analyzer (Immulite 2000), while LFTs and RFTs by Roche assay on Hitachi chemistry auto-analyzer. MRI pituitary fossa and ultra sonography (USG) abdomen was carried out at Radiology department Military Hospital, Rawalpindi.

Diagnostic criteria for prolactinoma were based on Magnetic Resonance Imaging evaluation of pituitary fossa. For macroadenoma size was >1 cm and microadenoma <1 cm.

- In primary hypothyroidism serum TSH >4.5 mIU/l and serum free T_4 <8 pmol/l10.
- In subclinical hypothyroidism serum TSH >4.5 mIU/l, and serum free T_4 between8-21 pmol/l[10].
- In PCOS serum LH / FSH ratio >2.5 times, serum estradiol > upper limit of reference (ULR) {for female- follicular phase 420, luteal 1002, ovulatory 1960, post-menopausal 110 pmol/l}[1,3], serum testosterone >ULR (for female 2.5 nmol/l) and multiple ovarian cysts on USG.
- In acromegaly basal serum GH > 14 mIU/l, no suppression on OGTT and GH secreting tumor detection on MRI pituitary fossa.
- In Cushing's disease morning serum cortisol >690 nmol/l, plasma ACTH >79 pg/ml and ACTH secreting tumor detection on MRI pituitary fossa.
- In CKD serum creatinine >2 times ULR (for females 97 umol/l and for males 115 umol/l)[11].
- In cirrhosis bilirubin > 17 umol/l, ALT > 40 U/L, ALP >130 U/L , albumin <35 g/l, prolonged prothrombin time and cirrhotic changes of liver on USG, biopsy[12].

Table-1: Serum prolactin levels in different types of disorders leading to hyperprolactinemia (n=76).

Disorders	Serum Prolactin (mIU/l)	
	Median	IQR
Macroadenoma	3911	(2335 - 5237)
Microadenoma	1096	(812 - 1573)
Primary hypothyroidism	949	(706 - 3431)
Subclinical hypothyroidism	765	(596 - 942)
PCOS	620	(565 - 1052)
Idiopathic	700	(476 - 735)

Note: IQR: Inter quartile range

Data was analyzed using statistical package for social sciences (SPSS) version 17 (SPSS Inc, Chicago, IL, USA). Mean and SD were calculated for quantitative variables like age.

Frequencies and percentages were calculated for qualitative variables like gender and disorders leading to HP. Spearman correlation was applied between serum PRL and pathological parameters leading to HP. A *p*-value of < 0.05 was considered significant.

RESULTS

Seventy six patients with HP due to pathological causes comprised of 13 (17%) males and 63 (83%) females with mean age of 30, ranged from 19 to 65 years.

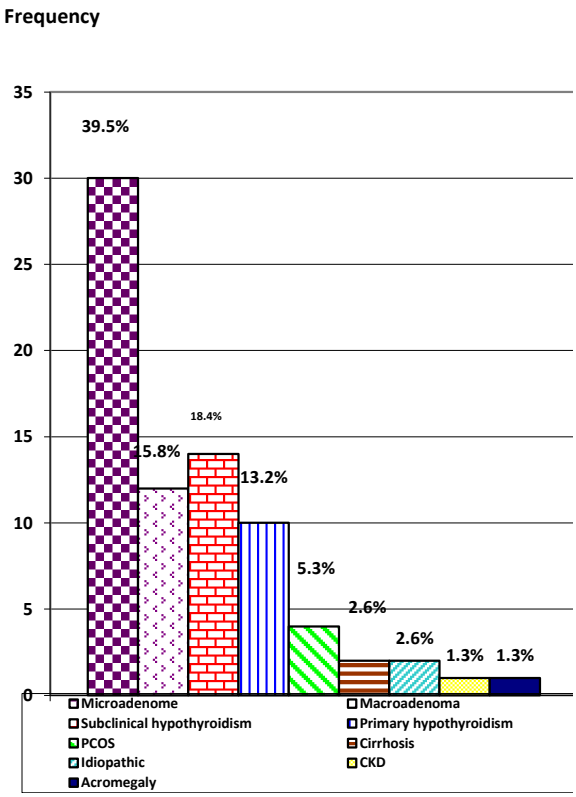

Figure-1: Different types of disorders leading to hyperprolactinemia (n=76)

Pituitary microadenoma was the cause of HP in 30 (39.5%) cases, Pituitary macro adenoma in 12 (15.8%), subclinical hypothyroidism in 14 (18.4%), primary hypothyroidism in 10 (13.2%), PCOS in 4 (5.3%),

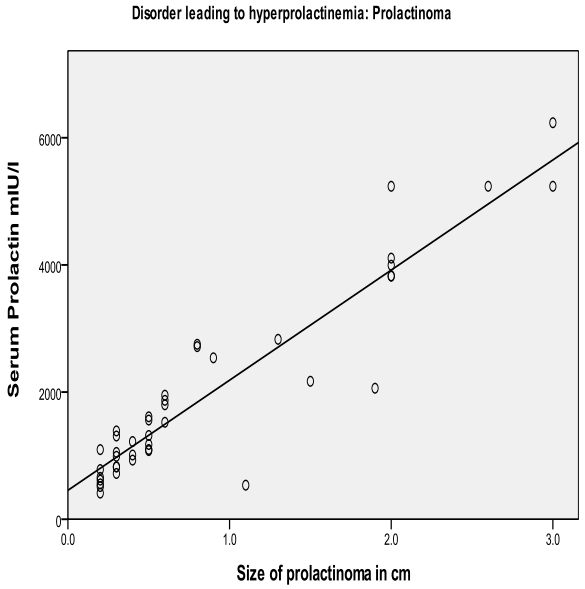

Fig2: Correlation between serum prolactin

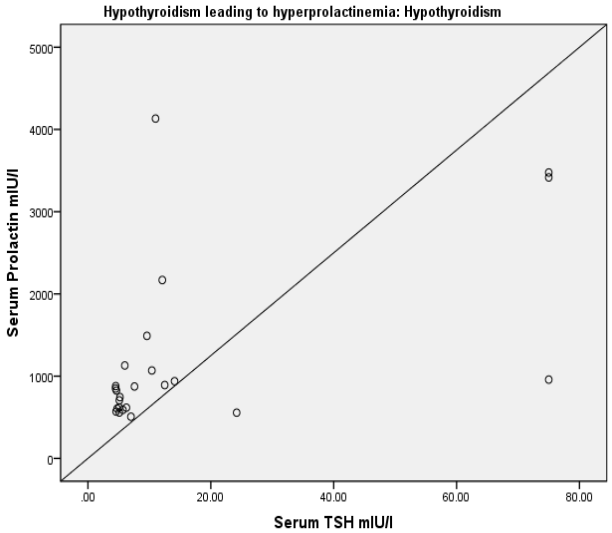

Fig3: Correlation between serum TSH and serum.

cirrhosis in 2 (2.6%), idiopathic in 2 (2.6%), CKD in 1 (1.3%) and acromegaly 1 (1.3%)patient. (Fig-1)

Median levels of serum PRL (mIU/l) were 3911 in macroadenoma, 1096 in microadenoma, 949 in primary hypothyroidism, 765 in subclinical hypothyroidism, 753 in acromegaly, 700 in idiopathic causes, 620 in PCOS, 449 in cirrhosis and 425 in CKD (Table-1).

Spearman correlation showed significant correlation of HP with size of prolactinoma (r=0.88, *p*=0.001) and serum TSH levels (primary and subclinical hypothyroidism), (r=0.51, *p*=0.01)(Fig-2,3). But correlation was insignificant with other causes of HP.

DISCUSSION

Among the pathological causes of HP, increased release of thyrotropin releasing hormone, tumors like craniopharyngioma and infiltrations leading to hypothalamic pituitary stalk damage are the hypothalamic causes[1]. Prolactinoma and acromegaly are the main pituitary causes while primary hypothyroidism, PCOS, CKD and cirrhosis are the main systemic causes of HP. As PRL levels are affected by a large number of drugs, hence a proper drug history plays an important role in determining the cause of elevated serum PRL.[1,4]

In this study male to female ratio of the patients with HP was 1.7 to 8.3 as compared to studies in literature of 1 to 10[7,8,9]. Maximum age group was 20 to 40 years, similar to other studies[7,8,9]. This study showed higher rates of prolactinoma as the commonest pathological cause of HP, followed by subclinical hypothyroidism, primary hypothyroidism and PCOS as compared to other studies in literature. Vilar et al. in 2008 showed that 56.2% patients had prolactinomas, 14.5% drug-induced HP, 9.3% macroprolactinemia, 6.6% non functioning pituitary adenomas, 6.3% primary hypothyroidism, 3.6% idiopathic HP, and 3.2% acromegaly.[13] Zargar et al. in India showed microprolactinoma in 35.8% cases of HP, 27.8% idiopathic HP, 16 % non-functioning pituitary macroadenoma, 12.8% PCOS, 5.3% drugs and 2.1% hypothyroidism. The reported prevalance of microadenomas varies from 23 to 27%[3].

Kumkum, et al in India showed incidence of hypothyroidism to be 25.5% in HP[14]. Tasneem et al in Lahore (Pakistan) observed 22.7% of hypothyroidism in HP subjects[15]. Tolino, et al showed that the prevalence of subclinical hypothyroidism was 28 % in HP patients[16]. Few studies showed hypothyroidism in 8% of HP patients[17,18]. In comparison with other studies in Brazil, India and Pakistan, this study showed almost similar results for adenomas, lower for PCOS and acromegaly but higher for hypothyroidism as literature[14,15,16] showed that in subcontinent hypothyroidism was more common cause for elevated serum prolactin levels.

In this study serum PRL levels were elevated to 4000 mIU/l in macroadenomas, similar findings were reported in literature where pituitary macroadenomas had serum PRL levels around 5000 mIU/L, while in other common causes of HP, serum PRL levels were found to be less than that[1]. Spearman correlation showed significant correlation of HP with size of prolactinima and serum TSH levels (primary and subclinical hypothyroidism). In few studies, correlation was not found between serum PRL and TSH concentrations[18-20]. Although serum TSH levels were significantly correlated with PRL levels in other studies.[10,14,21]

Limitation of the study was to find out the adverse effects of HP. Further studies are required to find and compare the frequency of all causes of HP in different areas of Pakistan aiming to find the adverse effects of HP.

CONCLUSION

Prolactinoma was the commonest pathological cause of HP, followed by hypothyroidism and PCOS in patients who reported to AFIP, Rawalpindi. Estimation of pituitary hormonal profile provides the basis for early diagnosis and better management of affected patients.

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