

ORIGINAL ARTICLE

The incidence of hyperprolactinaemia and associated hypothyroidism: local experience from Lahore

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Abstract

Aims The aim of the study was to determine the incidence of hyperprolactinaemia, document the underlying causes and consequences of hyperprolactinaemia, and to investigate the correlation between hyperprolactinaemia and hypothyroidism in a group of patients referred for hormonal profile assessment from local hospitals and clinics.

Methods This study includes 1365 subjects (46 males, 1319 females) referred to the Centre for Nuclear Medicine in Lahore, for hormonal estimation to investigate the possibility of an underlying hormonal disorder based on clinical grounds. Serum Prolactin and thyroid stimulating hormone levels were measured using IRMA kits.

Results In our study population, the incidence of hyperprolactinaemia was estimated at 4.90 percent. Menstrual irregularity appeared to be the major consequence in females. In male subjects, the major complaints observed were infertility and azoospermia. The incidence rate

was the highest in the age range of 22-27 years. Hypothyroidism in hyperprolactinaemic subjects was observed to be 22.7%.

Conclusion The incidence of hypothyroidism in hyperprolactinaemic subjects in our study population was found to be significantly high. Based on the results of our study, we would recommend thyroid hormone estimation in all patients with abnormal serum prolactin.

Key words: Hyperprolactinaemia, hypothyroidism, infertility, menstrual disorders.

Introduction

Prolactin (PL) is a peptide hormone produced by the anterior pituitary gland, primarily associated with lactation and plays a vital role in breast development. The anterior pituitary gland also controls the secretion of the thyroid stimulating hormone (TSH), luteinising hormone (LH), follicle stimulating hormone (FSH) and growth hormone (GH) [1].

Hyperprolactinaemia, the presence of abnormally high levels of PL in the blood is the most common endocrine disorder of the hypothalamic-pituitary axis [2]. Clinical and experimental studies have suggested a close relationship between the hypothalamic-pituitary-thyroid axis and the hypothalamic-pituitary-ovarian axis [3, 4].

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Hypothyroidism and hyperprolactinaemia are found to be closely interrelated. Hypothyroidism may cause failure to ovulate or failure to ovulate regularly in women of reproductive age. Some of the women with high prolactin levels have been diagnosed with hypothyroidism characterized by high levels of serum TSH and low T3 and T4.

Subclinical hypothyroidism associated with hyperprolactinemia is also quite frequently reported. Menstrual problems, including oligomenorrhea, amenorrhoea, polymenorrhea and galactorrhea are commonly observed in hypothyroidism [5-7]. Further, the incidence of infertility in hypothyroid females is frequently higher than in euthyroid females with a higher risk of an abnormal pregnancy outcome.

Serum PL and TSH levels were measured in 1365 patients referred to the Centre for Nuclear Medicine in Lahore, for hormonal estimation to investigate the possibility of an underlying hormonal disorder based on clinical grounds including infertility or subfertility, hirsutism, azoospermia, galactorrhea, gynaecomastia, acne vulgaris and menstrual problems.

The present study was conducted to determine the incidence of hyperprolactinaemia in the local population sent for hormonal evaluation with an aim to elucidate the underlying causes and also to determine a possible correlation between hyperprolactinaemia and thyroid dysfunction.

Patients and Methods

Patients

The study comprised of a total of 1365 patients (46 males, 1319 females) referred to the Centre for Nuclear Medicine, Mayo Hospital Lahore, over a period of seven months (January to July 2010). The patients from Lahore and the surrounding areas, were sent for hormonal evaluation for a variety of clinical problems, including subfertility and infertility

(primary or secondary), hirsutism, azoospermia, galactorrhea, gynaecomastia, acne vulgaris or menstrual disorder. The age range of the female patients was 16-45 years with the majority of these (50.7%) aged from 22-27 years. The male patients ranged in age from 13 to 90 years. Relevant clinical history was taken from all the patients and the details recorded in writing. Patients with a history of thyroid disease, previous thyroid surgery or current thyroid medication were excluded from this study.

Methods

Patient's blood samples were transferred to sample tubes with no additives. Serum was then separated by centrifugation and aliquots stored at 2-8°C if the assay was scheduled to be performed within 24 hours but for longer storage the serum was kept frozen at <-18°C. Serum prolactin levels were measured using immunoradiometric assay (IRMA) kit (Immunotech, France), which is a sandwich assay method using two non-competing mouse monoclonal antibodies directed against two different epitopes of prolactin. The assay has no detectable cross reactivity with LH, FSH, CG, GH and TSH.

The measurement range of the assay is 0.5-180 ng/ml (21.74-7826.04 pmol/L). Performance of the assay was monitored using two quality sera (Immunotech, France). The concentration ranges of PL in control sera for QC1 and QC2 were 3.75-6.81 ng/ml (163.04-296.08 pmol/L) and 20.9-34.9 ng/ml (908.69-1517.38 pmol/L) respectively. The normal range for PL in healthy males is 1.0-18.0 ng/mL (43.48-782.604 pmol/L). For cyclic or menopausal females, the range was 1.0-27.0 ng/ml (43.478-1173.90 pmol/L) and the range for post-menopausal females was 2.0-13.0 ng/ml (86.956-565.214 pmol/L).

The assay procedure involves the addition of serum or calibrators and controls (50 µL) in the anti-prolactin monoclonal antibody coated tubes followed by addition of 500 µL of the radiotracer (¹²⁵I labeled monoclonal antibody).

Table 1 Incidence of hyperprolactinemia in different age groups of female subjects and major consequences of hormonal disturbances

Age Groups	Menstrual Irregularity n=26 (40.6%)	Primary Infertility n=17 (26.5%)	Secondary Infertility n=6 (9.5%)	Hirsutism n=5 (7.8%)	PCOS n=5 (7.8%)	Others n=8 (12.5%)
16-21	6 (23.0%)	—	—	4 (80%)	—	2 (25.0%)
22-27	10 (38.5%)	12 (70.6%)	3 (50.0%)	—	3 (66.6%)	2 (25.0%)
28-33	4 (15.4%)	4 (23.5%)	2 (33.3%)	—	—	1 (12.5%)
34-39	4 (15.4%)	1 (5.9%)	1 (16.7%)	—	23 (3.3%)	—
40-45	2 (7.7%)	—	—	1 (20%)	—	—

radiotracer (^{125}I -labelled monoclonal anti body). The tubes are incubated for one hour at 18-25°C whilst being shaken (>350 rpm). Contents of the tubes are then aspirated, washed twice with wash buffer (2 mL) and then counted for one minute for bound radioactivity, which is directly proportional to the concentration of prolactin in the sample. Standard curve is plotted using cubic spline method. Prolactin concentration in the samples is calculated by interpolation from the standard curve.

Serum TSH levels were also measured using IRMA methodology with a supersensitive sandwich type TSH assay kits (Immunotech, France) using mouse monoclonal antibodies directed against two different epitopes of TSH. The assay has no detectable cross reactivity with LH, FSH, CG, GH and PL. The lowest and the highest limits of measurable concentration of TSH in serum using this kit were 0.025 mIU/L and 50mIU/L respectively. Normal range of the assay for euthyroid subjects is 0.17 - 4.05 mIU/L. The performance of the assay was

monitored using two quality sera (Immunotech, France). The concentration range of TSH in control sera was QC1: 1.21-1.89 mIU/L and QC2: 11.4-17.0 mIU/L, respectively. Assay procedure involved the incubation of the samples for one hour with shaking followed by two subsequent washings with wash buffer. Standard curve was plotted using four parameter Logit-log method. Bound activity was measured using a 20-well gamma counter (GENESYS™ 5000 Series Multi-well gamma counter, Laboratory Technologies Inc., USA). Bound radioactivity is directly proportional to the TSH concentration in the sample.

Results

In the females with hyperprolactinaemia, the clinical presentation in decreasing order of frequency was oligomenorrhoea in 41%, primary infertility in 26.5%, secondary infertility in 9.5%, hirsutism or polycystic ovarian syndrome (PCOS) in 8% (Table 1).

Table 2 Age-related hormone levels in different age groups

Age (years)	Frequency	Prolactin (ng/mL)			TSH (mIU/L)		
		Range	Mean	S.D.	Range	mean	S.D.
16-21	8 (11.9%)	30-158	115.1	7.7	1.3-6.7	3.16	2.41
22-27	34 (50.7%)	33->173	99.6	54.9	0.58-4.4	2.64	1.59
28-33	11 (16.4%)	29-59	47.8	29.7	2.5-9.2	5.88	4.7
34-39	8 (11.9%)	30-75	65.4	40.4	2.0-3.3	2.81	0.66
40-45	6 (8.95%)	46-98	72	36.8	-	-	-

Table 3 Symptom-related hormone levels in females patients

Age (years)	Frequency	Prolactin (ng/mL)			TSH (mIU/L)		
		Range	Mean	S.D.	Range	Mean	S.D.
Menstrual Irregularity	26 (40.6%)	34->173	86.2	51.55	1.3-6.7	3.39	2.90
Primary Infertility	17 (26.5%)	29->173	80.9	48.6	2.4-9.2	5.37	3.47
Secondary Infertility	6 (9.37%)	30-71	46.6	21.5	3.32	3.32	0
Hirsutism	5 (7.81%)	32-89	48.2	23.4	0.58-3.09	2.05	1.06
PCO Syndrome	5 (7.81%)	28-156	66.8	60.2	-	-	-
Others	8 (12.5%)	29-104	58.8	2.82	3.06	3.06	0

The serum PL and TSH levels in the female patients in different age groups are shown in Table 2. The hormone levels in female patients with different clinical disorders are detailed in Table 3. Mean Prolactin levels were highest (86.2 ng/ml) in the patients with menstrual irregularities compared with a mean PL level of

80.9 ng/ml in patients with primary infertility.

The clinical problems on presentation in the males are detailed in Table 4. The major presentation in males were azpospermia, primary or secondary infertility, gynaecomastia, bilateral atrophied or undescended testis and micropenis.

Table 4 Major complaints in male patients referred for hormonal screening

Complaints	Number	Ages (years)	Percentile
Azospemia	11	19-40	23.9
Primary Infertility	9	19-40	19.5
Secondary infertility	2	25-31	4.32
Gynaecomastia	3	16-25	6.52
Bilateral atrophied testes	1	24	2.17
Undescended testes	2	21-22	4.32
Micropenis	1	13	2.17
Unknown	17	17-90	36.9

Thyroid hormonal evaluation was performed in 22 of the 67 patients (46%) of the hyperprolactinaemic patients. Biochemical hypothyroidism was documented in five (33%) patients with the remainder of the 17 patients (77%) being euthyroid. All of the five hyperprolactinaemic patients with hypothyroidism were females but all the males in this study were found to be euthyroid.

The overall incidence of hyperprolactinaemia in our study population was 4.90% (67/1365 patients) including 6.5% (3/46) males and 4.85% (64/1319) females. The highest incidence of the hyperprolactinaemia (50.74%) was observed in the age group 22-27 years (Figure 1).

Discussion

One of the major causes of hyperprolactinemia is a prolactinoma or lactotrophic adenoma (functioning pituitary adenomas), which produces excessive PL. Hyperprolactinaemia can cause amenorrhoea, oligomenorrhoea, galactorrhoea, hypogonadism, infertility, sexual dysfunction, and loss of bone mineral density resulting in osteoporosis and the associated risk of fractures [3]. Infertile

women with a normal menstrual cycle may also be hyperprolactinaemic.

Some of the women with high prolactin levels have been observed with hypothyroidism characterized by high levels of serum TSH and low T3 and T4. Subclinical hypothyroidism associated with hyperprolactinaemia is also reported in some cases. Clinical and experimental studies have suggested a close relationship of hypothalamic-pituitary-thyroid axis (HPT) and the hypothalamic-pituitary-ovarian axis (HPO) [4]. The specific thyroid hormone receptors at the ovarian level might regulate the reproductive function, as well as the influence of oestrogens at the higher levels of the HPT axis, seems to integrate the reciprocal relationship of these two major endocrine axes.

In our study, the highest incidence (51%) of hyperprolactinemia was observed in the age group 22-27 years. A similar study carried out in the Netherlands to determine the age and sex specific incidence and prevalence of hyperprolactinemia, found that 84% of the patients were females and only 16% males. The overall incidence rate was observed to be

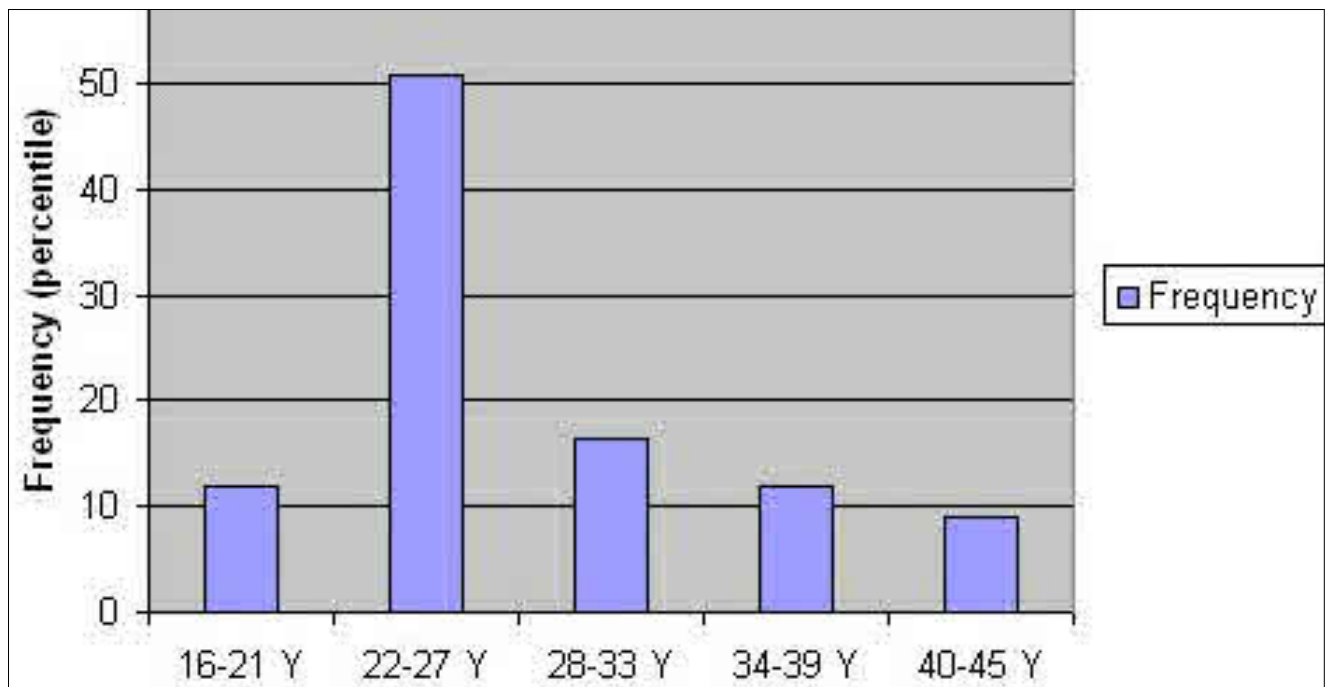


Figure 1 Frequency of hyperprolactinaemia in different age groups of female subjects

be 5.1 per 100,000 person-years. In women, the calculated incidence rate was 8.7 per 100,000 person-years, and in men 1.4 per 100,000 person-years. The highest incidence rate in women was found between 25 and 34 years (23.9 per 100,000 person-years) [8].

A study from Iraq, reported a 60% prevalence of hyperprolactinaemia [9], with another study reporting a 41% incidence of hyperprolactinaemia in infertile patients in India [10]. Coala et al. studied gender differences in hyperprolactinaemia and found that non-tumoral hyperprolactinaemia was more frequent in women [11].

Regarding the correlation of TSH with prolactin, a study carried out in USA questioned the need of TSH along with Prolactin levels in infertile women. The results obtained by them were not promising to carry the both analyses simultaneously, 2.48% of patients (21 out of 846 patients) had abnormal levels of TSH, and 1.77% (15 out of 844 patients) had elevated levels of PRL [12]. In

contrast, the reports from the subcontinental regions have reported a significantly higher incidence of hypothyroidism in hyperprolactinaemic patients, including a study from India, which reported a 25.5% incidence of hypothyroidism [13], with another study from Bangladesh, reporting a 8.64% incidence of hypothyroidism in hyperprolactinaemic patients [14].

The results of our study also emphasize the importance of evaluating thyroid hormone levels in hyperprolactinaemic females due to the high incidence of hypothyroidism documented in hyperprolactinaemic subjects in our patient population.

Women with hypothyroidism may not only be infertile but may also have a higher risk of birth defects in their offsprings including abnormalities of the heart, kidney or brain, as well as other defects such as cleft lip or cleft palate.

There is relatively limited data on males, which may be attributable to the fact that the signs

and symptoms appear later in men than in women. One of the limitations of our study was the fact that the data collected from the males in our study, did not allow any statistical deductions because all the hyperprolactinaemic males in our study were shown to euthyroid. However, we hope to investigate the possibility of a correlation between hyperprolactinaemia and thyroid hormone levels in men in our local population.

Conclusions

This study has indicated a higher prevalence of hyperprolactinemia together with a greater propensity for thyroid disorders in infertile subjects compared to those with normal fertility. Based on our findings, we suggest that all hyperprolactinaemic females must be further investigated to rule out the presence of concurrent hypothyroidism through the determination of serum TSH levels. In conclusion, this report underscores the importance of establishing the thyroid functional status in all hyperprolactinaemic women in our local population

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