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Original Article

Prevalence and predictors of hyperprolactinemia in subclinical hypothyroidism

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ABSTRACT

Background and aims: Hyperprolactinemia has been reported in 0–57% of primary hypothyroidism. Data on hyperprolactinemia in subclinical hypothyroidism (ScH) is scant and inconsistent. This study aimed to determine the prevalence and predictors of hyperprolactinemia in ScH.
Methods: Consecutive patients diagnosed to have normal thyroid function, ScH or overt primary hypothyroidism underwent serum prolactin, gonadotropins, testosterone and estradiol estimation. Patients with pregnancy, pituitary adenomas, secondary hypothyroidism, hyperthyroidism, comorbid states and drug-induced hyperprolactinemia were excluded.
Results: From initially screened 4950 patients, hormonal data from 2848 individuals who fulfilled all criteria were analyzed. The occurrence of hyperprolactinemia (females:males) was highest in primary hypothyroidism (42.95%:39.53%) (n = 192), followed by ScH (35.65%:31.61%) (n = 770) and euthyroid individuals (2.32%:2.02%) (n = 1886) ($P < 0.001$). Hyperprolactinemia in ScH with TSH 5–7.5, 7.5–10 and >10 mIU/L (females: males) was 25.56%:20.73%, 49.07%:50% and 61.43%:35.71% respectively ($P < 0.001$). Significant positive correlation between TSH and prolactin was noted in ScH and primary hypothyroidism. In females, testosterone was lowest in patients with primary hypothyroidism. In males, serum estradiol was significantly higher, and testosterone significantly lower in men with ScH and primary hypothyroidism. Regression analysis revealed serum TSH followed by free T_4, to be best predictors of serum prolactin in both sexes.
Conclusion: Hyperprolactinemia is common in ScH, especially in those with TSH > 7.5 mIU/L. ROC analysis confirmed that TSH ≥ 7.51 mIU/L in females and ≥8.33 mIU/L in males had a sensitivity of ≈50% with a very high specificity of >90% in detecting hyperprolactinemia. Prolactin screening may be warranted in ScH with TSH > 7.5mIU/L, and may form an indication for treating ScH.

1. Introduction

Hyperprolactinemia is a relatively common endocrinopathy seen in clinical practice, with prevalence ranging from 0.4% in healthy population to 5% in family planning clinics [1,2]. Pregnancy and lactation are the most common causes of physiologic hyperprolactinemia with levels up to 207 ng/mL being reported [3]. Perhaps the most common cause of pathologic hyperprolactinemia is iatrogenic (drug induced) [4]. Neuroleptics, tricyclic anti-depressants, certain selective serotonin receptor antagonists, chlorpromazine, phenytoin, estrogen containing medications, H_2 anti-histamines and prokinetics are commonly associated with hyperprolactinemia [4,5]. Prolactinomas, the most common pituitary adenomas, in contrast are much rarer having an annual incidence of 30 per 100,000 persons [6]. Consequences of long standing hyperprolactinemia include secondary hypogonadism and associated menstrual irregularities, galactorrhea (inconsistently, primarily in females), sexual dysfunction, infertility and impaired bone health [4,7,8].

Though primary hypothyroidism is a well-known cause of hyperprolactinemia, it is not observed in all patients. Hyperprolactinemia has been reported in 0–40% of males and 39–57% of females with overt primary hypothyroidism [9–11]. In contrast, data on hyperprolactinemia in subclinical hypothyroidism (ScH) is scant, coming from case reports and small studies, being inconsistent, with some but not all studies reporting a mild increase in occurrence of hyperprolactinemia [11–13]. Hence the aim of this study was to determine the prevalence and predictors of hyperprolactinemia in patients with ScH from northern India.

2. Methods

Consecutive patients undergoing thyroid function evaluation at the department of biochemistry were considered. Pregnant women were

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not considered for this study. Patients diagnosed to have pituitary adenomas, secondary hypothyroidism, multiple pituitary hormone deficiency, and subclinical or overt hyperthyroidism, were excluded. Patients with associated severe comorbid states like chronic liver disease, renal disease, and those taking medications like neuroleptics, antipsychotics and oral contraceptives were excluded. The study protocol was explained and only those who gave informed written consent were included in the study. Serum prolactin was assayed from samples of patients undergoing thyroid function evaluation who fulfilled the above criteria and were diagnosed to have either ScH, overt primary hypothyroidism or had normal thyroid function. The reference range of free tri-iodothyronine (FT_3), free tetra-iodothyronine (FT_4) and thyroid stimulating hormone (TSH) in our laboratory is 2–4.4 pg/mL, 0.6–2.2 ng/dL and 0.5–5 mIU/L respectively. ScH was defined as patients having normal FT_4 levels with TSH levels above the normal range [9]. Overt primary hypothyroidism was defined as patients having TSH levels above the normal range accompanied by low FT_4 levels [9]. Serum was separated from samples collected, and stored at −80 °C. Patients with drug-induced hyperprolactinemia were excluded. Serum luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol and testosterone were also evaluated from the stored samples. The study duration was from August 2014 to March 2016. The institutional ethics committee approved the study.

Serum prolactin was measured using chemiluminescence microparticle immunoassay (CLIA) (VITROS® ECiQ Immunodiagnostic System, Johnson & Johnson, USA) having an analytical range of 0–150 ng/mL, intra and inter-assay coefficient of variation (CV) of 3.4% and 5.5% respectively. The normal ranges of serum prolactin were 2.8–27 ng/mL in females and 2.1–17 ng/mL in males. Hyperprolactinemia was defined as serum prolactin >27 ng/mL in females and >17 ng/mL in males. VITROS® ECiQ Immunodiagnostic System, Johnson & Johnson, USA was also used for estimation of free tri-iodothyronine (FT_3), free tetra-iodothyronine (FT_4), thyroid stimulation hormone (TSH), LH, FSH, estradiol and testosterone. FT_3 assay had an analytical sensitivity of 0.50 pg/mL, an analytical range of 0.50–22.8 pg/mL, and intra and inter-assay coefficient of variation (CV) of 2.2% and 6.3% respectively. FT_4 assay had an analytical sensitivity of 0.07 ng/dL and an analytical range of 0.07–6.99 ng/dL with intra and inter-assay coefficient of variation (CV) of 2.4% and 5.8% respectively. TSH assay had an analytical sensitivity of 0.015 mIU/L, an analytical range of 0.015–100 mIU/L with intra and inter-assay coefficient of variation (CV) of 3.3% and 7.2% respectively. LH assay has an analytical sensitivity of 0.216 mIU/mL, an analytical range of 0.216–200 mIU/mL with intra and inter-assay coefficient of variation (CV) of 8.8% and 11.3% respectively. FSH assay has an analytical sensitivity of 0.66 mIU/mL, an analytical range of 0.66–200 mIU/mL with intra and inter-assay coefficient of variation (CV) of 2.8% and 10.1% respectively. Testosterone assay has an analytical sensitivity of 0.16 μg/dL, an analytical range of 4.90–2163 ng/dL with intra and inter-assay coefficient of variation (CV) of 3.8% and 7.4% respectively.

Serum samples from patients having elevated serum prolactin levels with normal thyroid function were evaluated for macroprolactinemia using the polyethylene glycol (PEG) precipitation test (treatment of equal parts of serum with PEG followed by centrifugation), to remove macroprolactin. Macoprolactinemia was diagnosed if post-PEG prolactin was <40% of pre-PEG levels [14].

3. Statistical analysis

Normality of the distribution of variables was assessed using the Kolmogorov–Smirnov test. Chi-square tests were used for categorical variables. Pearson's (r) or Spearman's (σ) correlation coefficient was calculated for normally distributed and skewed variables, respectively. Stepwise linear regression analyses were done to determine variables that independently influenced the serum prolactin levels. The receiver-operating-characteristics (ROC) curves were plotted, and areas under the curves (AUROC) with 95% CI were calculated to explore the diagnostic efficacy and determine cut-offs of serum TSH in predicting hyperprolactinemia in females and males. The Youden index, defined as (sensitivity + specificity) − 1 was used to determine the optimal cut off points. A P-value <0.05 was considered statistically significant. SPSS version 20 was used for analyses.

4. Results

A total of 4590 patients undergoing thyroid function evaluation at the department of biochemistry were screened of which serum prolactin was evaluated in 3063 patients who fulfilled the inclusion and exclusion criteria (Fig. 1). Two-hundred and fifteen patients were subsequently diagnosed to have drug induced hyperprolactinemia, hence excluded. Serum LH, FSH, estradiol and testosterone were estimated from the stored samples of the remaining 2848 individuals who fulfilled all criteria. Data from these 2848 individuals who were either euthyroid or had subclinical or overt hypothyroidism were analyzed.

Of these 2848 individuals, 85% were females (n = 2422) and 15% were males (n = 426). Of these 2422 females, 46 were ≤10 years of age (1.90%) (pre-pubertal), 404 were 10–20 years of age (16.68%) (peri-pubertal), 1859 were 20–50 years of age (76.75%) (reproductive age group), and 113 were >50 years of age (4.67%) (Supplementary Table 1). Of the 1859 females in the reproductive age group, 1303 (70.10%) had normal thyroid function, of which 596 (45.74%) had TSH > 2.5 mIU/L.

Serum prolactin was significantly higher in patients with ScH and primary hypothyroidism as compared to euthyroid individuals in both the sexes (Table 1). Median serum prolactin levels were comparable in ScH when compared to those with overt primary hypothyroidism (Table 1). The occurrence of hyperprolactinemia (females:males) was significantly higher in patients with overt primary hypothyroidism (42.95%:39.53%), followed by ScH (35.65%:31.61%) and lowest in euthyroid individuals (2.32%:2.02%) (P < 0.001) (Table 1). Serum samples from 43 euthyroid individuals (38 females and 5 males) with normal thyroid function and elevated serum prolactin were tested for macroprolactinemia. The post-PEG prolactin levels were >60% of pre-PEG precipitation levels in all the tested samples thus ruling out macroprolactinemia.

Sub-group analysis was done in patients with ScH by dividing them into 3 groups, Group-1: TSH 5–7.5 mIU/L; Group-2: TSH 7.5–10 mIU/L; Group-3: TSH > 10 mIU/L. The occurrence of hyperprolactinemia in females and males in Group-1 ScH was 25.56% (103/403 females) and 20.73% (17/82 males) respectively, which was significantly lower when compared to females and males in Group-2 and Group-3 ScH [Group-2: 49.07% (79/161 females) and 50% (20/40 males) and Group-3: 61.43% (43/70 females) and 35.71% (5/14 males) respectively] (P < 0.001).

A significant positive correlation was noted between TSH and prolactin across the spectrum of thyroid function in females (Table 2). A similar significant positive relation between TSH and prolactin was noted in males with ScH and primary hypothyroidism (Table 2). A significant positive correlation was observed between serum testosterone and prolactin levels in euthyroid males (Table 2). Similar correlations between sex steroid levels (testosterone and estradiol) and prolactin were not observed in males and females with ScH or primary hypothyroidism (Table 2). In females, significant correlation was observed between testosterone (but not estrogen) and thyroid function parameters (testosterone and TSH: σ: −0.129; P < 0.001; testosterone and FT4: σ = 0.054; P = 0.082; estrogen and TSH: σ = 0.073; P = 0.249; estrogen and FT4: σ = 0.031; P = 0.430). In males, significant correlation was observed between estrogen (but not testosterone) and thyroid function parameters (estrogen and TSH: σ = 0.189; P = 0.066; estrogen and FT4: σ = −0.288; P = 0.005; testosterone and TSH: σ: −0.058; P = 0.256; testosterone and FT4: σ = 0.023; P = 0.649). (See Table 3.)

Serum gonadotropins were mildly elevated in patients with ScH and primary hypothyroidism in both the sexes when compared to euthyroid individuals (Table 1). The age-group specific serum LH and FSH levels

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