Original Article

Estimation of serum prolactin levels and determination of prevalence of hyperprolactinemia in newly diagnosed cases of subclinical hypothyroidism

Tanvi Sirohi[1], Harkaran Singh[2]

[1]DNB Family Medicine, SBAMI, [2]Department of Medicine, SBAMI, New Delhi, India

Abstract

Background: Hyperprolactinemia is a common endocrine disorder involving hypothalamic–pituitary axis. Prolactin (PRL) secretion is stimulated by dopamine antagonism and thyroid-releasing hormone. Hyperprolactinemia has been reported in subclinical hypothyroidism (SCH) but results are markedly variable and studies on SCH are very few. The objective of this study was to find out prevalence of hyperprolactinema in newly diagnosed subclinical hypothyroid patients. **Materials and Methods:** In this cross-sectional study, serum PRL levels of 150 newly diagnosed subclinical hypothyroid patients were determined using electrochemiluminescence method. **Results:** Raised PRL levels were found in 18 (%) patients with SCH. There was positive correlation between serum thyroid-stimulating hormone and PRL levels. Prevalence of infertility was significantly higher with presence of hyperprolactinemia than normoprolactinemia in subclinical hypothyroid patients. **Conclusion:** Routine prolactin estimation and subsequent treatment is required in patients with subclinical hypothroidism.

Keywords: Hyperprolactinemia, infertility, subclinical hypothyroidism

Introduction

Hyperprolactinemia is an endocrine disorder involving hypothalamic–pituitary axis that results from multiple causes, including medications, hypothyroidism, and pituitary disorders. Prolactin (PRL) secretion is inhibited by PRL inhibitor factor that is secreted from hypothalamus, enhanced by dopamine antagonism and thyroid-releasing hormone (TRH).[1] Hypothyroidism and hyperprolactinemia are found to be closely interrelated. Prevalence of hyperprolactinemia in subclinical hypothyroidism (SCH) has been reported in a wide range of 0%–40% of hypothyroid patients.[2] TRH stimulates both PRL and thyroid-stimulating hormone (TSH) release, therefore causing raised PRL levels;[3] however, a higher prevalence of hyperprolactinemia in hypothyroid is found in females than males because estrogen is required for this effect.[4,5] The elimination of PRL is decreased in hypothyroid patients.[6] The inhibitory action of dopamine and dopamine agonists is reduced due to decrease in sensitivity to dopamine.[7] Thyroid hormone itself is a cause of hyperprolactinemia. It has been revealed in rodent pituitary cells that 3,5,3'-triiodothyronine reduces PRL messenger RNA levels;[8] therefore, it can be concluded that decreased circulating thyroid hormone levels will result in increased PRL synthesis. Hyperprolactinemia in premenopausal age group (marked PRL excess >100 ng/mL) is associated with hypogonadism, galactorrhea, and amenorrhea; oligomenorrhea is associated with moderately elevated PRL levels (51–75 ng/mL); short luteal phase, decreased libido, and infertility are seen in mild hyperprolactinemia (31–50 ng/mL). Osteopenia is associated with duration and severity of hypogonadism.[9] Hyperprolactinemia in men is responsible for impotence, decreased sperm production, infertility, decreased libido, gynecomastia, and rarely galactorrhea. Impotence is unresponsive to testosterone treatment and is associated with decreased muscle mass, body

Address for correspondence: Dr. Tanvi Sirohi, A-2/311, Sunrise Apartments, Rohini (Sec-13), Delhi - 110 085, India.
E-mail: sirohitanvi@gmail.com

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hair, and osteoporosis.[10] SCH is defined as high serum TSH concentration with normal serum thyroxine (free T4) and (free T3) concentrations, associated with few or no sign and symptoms of hypothyroidism.[11] The prevalence is 3%–15%.[12] Incidence of SCH increases with age and is more common in women.[13-16] SCH is also called mild thyroid failure.[17] According to a previous study, 2.6% of patients with SCH progress to clinically overt hypothyroidism [if thyroperoxidase (TPO) antibodies are absent] and 4.3% if they are present.[16] Symptoms of hypothyroidism include dry skin, cold sensitivity, fatigue, muscle cramps, voice changes, puffy eyes, menstrual irregularity, and constipation. Low thyroid hormone level associated with raised PRL levels has been implicated in ovulatory dysfunction leading to infertility. Infertility is defined as the failure to achieve conception (regardless of cause) after 1 year of unprotected intercourse.[18] It has been estimated by World Health Organization that 8%–12% of couples around the world experience problems in conception. About 40% of all cases of infertility are due to problems with the female partner and another 30% are due to problems in the male partner. The remaining 30% of cases are due to a cause which cannot be identified which may affect both the partners.[19] Infertility associated with hyperprolactinemia is reversible with treatment, irrespective of the type of treatment. For ovulation, it is important to decrease serum PRL levels with the help of drugs,[20] and it is seen in various studies that hyperprolactinemia associated with SCH reverses on supplementation of thyroxine. Therefore, assessment of serum PRL and TSH is considered important for evaluation for the cause of infertility. The importance of studying SCH is that it is more common than overt hypothyroidism, hence early diagnosis and treatment may prevent the onset of overt hypothyroidism and its associated effects.[13]

Our current understanding of the effect of thyroid dysfunction and associated hyperprolactinemia on fertility is based largely on retrospective studies. The studies on hyperprolactenemia in SCH are very few and have varied results. This study therefore has been carried out to understand with an intent to estimate serum PRL levels and determine its prevalence in newly diagnosed cases of SCH.

Aims and objectives

1. To estimate and correlate serum PRL levels in subjects with SCH
2. To determine the prevalence of hyperprolactinemia in SCH.

Materials and Methods

The present cross-sectional study was conducted at Sri Balaji Action Medical Institute, Paschim Vihar, New Delhi, from 1st January 2017 to 31st December. All the patients from the outpatient department of medicine and gynecology were enrolled, and the number required for the study to be statistically significant was 150, using Daniel sample size formula (1999); prevalence of hyperprolactinemia in SCH is reported to be 0%–40% in the literature.[2]

Inclusion criteria

1. Subjects between 18 and 45 years of age
2. Subjects with TSH levels between 5 and 10 mIU/L with normal free T3 and free T4 levels.

Exclusion criteria

Pregnant and breastfeeding females; patients using antidepressants and drugs, OCP pills, antilipidemic drugs, and thyroid medications; patients after thyroid surgery, irradiation, and suprasellar surgery; patients who are known case of diabetes mellitus, congestive heart failure, chronic renal failure, post myocardial infarction, prolactinoma, acromegaly, and thyroid disorder.

Thyroid functions and serum PRL levels were evaluated by electrochemiluminescence assay. The reference range of free tri-iodothyronine (free T3), free tetra-iodothyronine (free T4), TSH, and serum PRL in our laboratory is 0.9–1.7 ng/dl, 2.0–4.4 ng/dL, 0.27–4.2 uIU/mL, and 1.9–25 ng/mL, respectively. IBM SPSS version 17.0 software was used for statistical analysis. Ethical clearance was obtained by the institutional ethics committee and a written informed consent was obtained from the patient.

Results and Discussion

The clinical profile of the patients is summarized in Table 1.

The mean age of the patients was 31.82 ± 6.18 years, 90% being females and 10% being male. Of 150 patients with SCH, 27 (18%) had hyperprolactinemia. About 0%–40% are reported in the literature.[2] Meir *et al.* in their study on 66 hypothyroid patients showed prevalence of hyperprolactinemia to be 19%.[21] About 18.5% females and 13.3% males had hypoprolactinemia. Similar results were obtained in a study by Bahar *et al.* (2011).[22] The majority of patients in our study group were asymptomatic, which was expected as patients with SCH lack frank symptoms of hypothyroidism.[23] Ovulatory dysfunction or corpus luteum dysfunction occurs in hypothyroidism as thyroid hormones affect granulosa cells, corpus luteum, and oocytes directly and also hypothyroidism causes decreased binding activity of sex-hormone-binding globulin, increased PRL levels, and delayed luteinizing hormone response to gonadotropin-releasing hormone.[24,25] Overall, the most common complaints in the study group were found to be menstrual irregularities (16.7%) followed by infertility (16.7%). Hair loss was found in 12.7%, and same was the frequency of bowel disturbance (constipation). A similar association was observed by Binita Goswami in her study between hyperprolactinemia and menstrual disturbances in the background of subclinical hypothyroid,[26] thereby explaining the causative role of hyperprolactinemia in infertility. A similar report of increase in the serum PRL levels in infertile women when compared with those in the fertile by Turankar *et al.* corroborates the aforesaid association.[27] In our study, positive correlation was found between low TSH and elevated serum PRL ($r = 0.219$, $P = 0.007$). A similar finding was observed in the study by Hekimsoy *et al.*[28] On comparison, patients with

TSH in higher range (7.5–10 mIU/L) had significantly higher prevalence of hyperprolactinemia (33%) than in patients with TSH (5–7.4 mIU/L) who had prevalence of 13.7%, which is explained as higher TRH levels in patients with more severe hypothyroidism (higher TSH levels) leads to a greater TRH mediated PRL release from lactotrophs.[29] Shenenberger and Klachko reported that production of PRL is stimulated by thyrotropin-releasing hormone, epidermal growth factor, dopamine receptor antagonists, and vasoactive intestinal peptide wherein they concluded that primary hypothyroidism with high levels of thyrotropin-releasing hormone can lead to hyperprolactinemia.[30]

The clinical profile of the patients is summarized in Table 1. On comparison of clinical symptoms in subjects with SCH in two groups with TSH (5.1–7.49) and TSH (7.5–10.0), we found that fatigue and hair loss were significantly more in patients with TSH in higher range (7.5–10 mIU/L). Carlé A *et al.* (2014) similarly reported fatigue and hair loss in 81% and 4.15% of hypothyroid patients, respectively.[31] Hypothyroidism and hyperprolactinemia have effective roles in stimulating androgenic alopecia, Therefore, coexistence of these two disorders can cause intensive alopecia.[22] Sharma LK *et al.* (2016) in their study reported that

Table 1: Clinical profile of hypothyroid patients with and without hyperprolactinemia

PARAMETER	OBSERVED VALUE
Mean Age ± SD	31.82 ± 6.18
Male : female	15/ (10%):135/(90%)
Mean free T3: Mean free T4: Mean TSH	2.63 ± 0.58: 1.14 ± 0.22: 6.54 ± 1.32
Mean serum Prolactin	15.76 ± 7.62
Prevalence of hyperprolactinemia	27 (18%)
Mean age with hyperprolactinemia : without hyperprolactinemia	29.30 ± 3.69 : 32.37 ± 6.48 (P=0.001)
Hyperprolactinemia (male : female)	2(13.5%) : 25 (18.5%)
Bowel disturbances : Menstrual irregularities : Infertility: Hairloss	18 (12%): 25 (16.7%) : 21 (14%):19 (12.7%)
Infertility with hyperprolactnemia : infertility without hyperprolactinemia	47.6% : 13 .2 % (P=0.001)
MeanBMI in kg/cm with hyperprolactnemia : without hyperprolactinemia	25.88 ± 2.26 : 25.56 ± 1.59
Mean Respiratory rate with hyperprolactnemia : without hyperprolactinemia	13.19 ± 1.76 : 12.72 ± 1.44
Alopecia with hyperprolactnemia : without hyperprolactinemia	20.0% : 80%
Pedal edema with hyperprolactnemia : without hyperprolactinemia	50.0% :50%
Puffiness around eyes with hyperprolactnemia : without hyperprolactinemia	33.3% : 66.7%
Mean free T3 with hyperprolactnemia : without hyperprolactinemia	2.77 ± 0.45 : 2.60 ± 0.61
Mean free T4 with hyperprolactnemia : without hyperprolactinemia	1.12 ± 0.25 : 1.14 ± 0.22
Mean tsh with hyperprolactnemia : without hyperprolactinemia	6.75 ± 1.39 : 6.52 ± 1.29 (P=0.025)
Hyperprolactnemia in TSH (5.1 - 7.49) : TSH (7.5 - 10.0)	33.3% : 13.7 % (P=0.009)

hyperprolactinemia and SCH coexist commonly and a TSH level higher than 8 mIU/L has a very high specificity of approximately 90% in detecting hyperprolactinemia, a landmark observation. They were of the opinion that further studies like this study were required to exude confidence in the statistically significant association of hyperprolactinemia and SCH.[32]

Conclusion

Routine PRL evaluation is required in patients with SCH, especially in those with TSH 7.5 mIU/L, and elevated PRL levels may be one of the indications for treatment of asymptomatic SCH. Being a cross-sectional study, the impact of levothyroxine supplementation on PRL levels in SCH could not be evaluated. More studies are required to validate the routine treatment of SCH in patients with hyperprolactinemia without elevated levels of anti-TPO antibodies, a parameter the authors were unable to exclude.

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Conflicts of interest

There are no conflicts of interest.

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