Original Article

Macro-Thyrotropin Syndrome: Prevalence and Clinical Profile of an Under-Recognised Rare Entity in Thyroidology

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Abstract

Introduction: Macro-thyrotropin syndrome (macro-TSH) is a rare condition characterised by the formation of a complex between thyroid-stimulating hormone (TSH) and an unknown component, resulting in elevated TSH levels that do not accurately reflect thyroid status. This study aimed to investigate the prevalence and clinical profile of macro-TSH among patients with subclinical hypothyroidism (SCH). **Methods:** A total of 1500 patients were evaluated, with 135 exhibiting elevated TSH levels (>10 IU/mL) and normal free-thyroxine levels. Macro-TSH was diagnosed based on persistent elevated TSH levels despite serial dilutions and confirmed by less than 60% TSH recovery following polyethylene glycol (PEG) precipitation. **Results:** Finally, 115 were diagnosed with SCH, 15 with macro-TSH, and 1245 were categorised into non-thyroid groups. The prevalence of macro-TSH, SCH, and heterophilic antibodies interfering with immunoassay was 1.09%, 8.36%, and 0.36%, respectively. Among macro-TSH patients, 13.33% exhibited classical hypothyroid features, contrasting with the 52.0% observed in SCH patients. Female gender and a family history of hypothyroidism were associated with higher odds of having macro-TSH. Diabetes mellitus, clinical symptoms of hypothyroidism (except lethargy), higher TSH level, and post-PEG TSH recovery were significantly associated with SCH compared to macro-TSH. The mean TSH level was five times higher in macro-TSH compared to SCH. **Conclusion:** Macro-TSH syndrome represents a distinct clinical entity within the spectrum of SCH, characterised by disproportionately high TSH levels. Recognising macro-TSH is crucial for accurate diagnosis and appropriate management of SCH.

Keywords: Electrochemiluminescence immunoassay, free-T4, Free-T3, immunoassay interference, macro-thyrotropin, subclinical hypothyroidism, thyroid stimulating hormone

Introduction

Subclinical hypothyroidism (SCH) is characterised by elevated thyrotropin (TSH) levels while maintaining normal free-T3 and free-T4 levels.[1-3] As per the latest recommendations, SCH with TSH of more than 10 IU/mL is suggested treatment with levothyroxine (LT4) to prevent overt hypothyroidism and cardiovascular and neuropsychiatric complications.[4] However, TSH levels between 4.5 and 10 IU/mL SCH require treatment on an individual basis as per demographic details, race, associated comorbidities, and pregnancy.[5,6] Differential diagnoses for SCH include macro-TSH, TSH resistance syndromes, biologically inactive TSH, the recovery phase of thyroiditis, and laboratory interferences.[7,8] Macro-TSH, a macromolecule formed by the autoimmune complex of TSH and immunoglobulins (Ig), is biologically inactive.[9,10] Due to its large size, macro-TSH has a delayed clearance and can accumulate in the bloodstream, resulting in elevated serum TSH levels, which may lead to the wrong diagnosis of SCH.[10,11] Detecting macro-TSH in SCH patients is crucial to avoid unnecessary treatment.[10,11]

Macro-TSH should be suspected in SCH patients exhibiting high TSH levels without clinical hypothyroidism symptoms,

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normal anti-thyroid antibody levels, and normal thyroid ultrasound findings.[9,11,12] Typically, macro-TSH presents with very high TSH levels, often exceeding 100 mIU/L, prompting clinicians to initiate LT4 therapy.[9,13,14] TSH measurement techniques have advanced from immunoradiometric assays (IRMA) to chemiluminescence immunoassays, enhancing precision, accuracy, and measurement range.[15-17] However, current immunoassays techniques cannot distinguish macro-TSH from bioactive TSH, posing challenges in SCH diagnosis.[9,18]

Despite improvements, thyroid test immunoassays may still encounter interferences, including heterophilic antibodies, anti-mouse antibodies, and macromolecules such as macro-TSH.[9,17,19,20] Macro-molecules are biologically inactive but can affect circulating hormone measurements.[9,20] In endocrinology, macro-prolactin (macro-PRL) is a well-defined condition.[9] Polyethylene glycol (PEG)-mediated precipitation is a cost-effective and reliable method for detecting macro-PRL and is widely used in clinical practice.[21] The gold standard for detecting macro-TSH is chromatography.[9,22] However, due to its high costs, chromatography is limited in clinical practice. Alternatively, PEG precipitation tests have been reported as reliable for detecting macro-TSH when chromatography is unavailable.[9,21]

This prospective observational study aims to determine the prevalence and clinical profile of macro-TSH in patients diagnosed with SCH.

Material and Methods

Study population

Since January 2022, 1500 patients aged 18 years and above attending the outpatient department were tested for free-T3 (FT3), free-T4 (FT4), and thyrotropin (TSH) levels by using the electrochemiluminescence immunoassay (ECLIA) method. Patients were excluded if they were receiving drugs interfering with thyroid metabolism, had overt hypothyroidism or hyperthyroidism, or had experienced a recent severe illness or major surgery. A total of 125 patients were excluded: 54 with overt hypothyroidism, 15 with overt hyperthyroidism, 22 with consuming drugs interfering with thyroid metabolism, 10 having anti-TPO positive, five with recent major surgery, and 19 with severe medical illness. This left 1375 patients for further evaluation.

Subclinical hypothyroidism and Macro-TSH evaluation

Out of the 1375 patients, 135 had SCH (TSH > 10 IU/mL with normal FT4 levels) and were further evaluated for macro-TSH. Data collection included demographic information (age, gender, BMI, and medical history) and clinical assessments of hypothyroidism symptoms (fatigue, weight gain, constipation, cold intolerance, skin changes, muscle cramps, mood changes, and anxiety).

Patients with high TSH (>10 IU/mL) were further evaluated using additional ECLIA serial assays, thyroid antibody tests, and basic metabolic profiles. Serial dilutions of patient plasma (1:2, 1:5, and 1:10) were analysed for TSH measurement to rule out interference from heterophilic antibodies such as human anti-mouse and other animal antibodies. Linear and identical dilution patterns suggested the possibility of TSH complex formation with an unknown component (macro-TSH). Macro-TSH testing was conducted using the PEG precipitation method. Briefly, 100 µL of PEG 8000 solution (250 g/L) was mixed with 200 µL of pooled patient plasma, and control was prepared with 200 µL of plasma mixed with deionised water. Both samples were incubated at 37°C for 30 minutes, precipitated by centrifugation at 13,000 rpm for 3 minutes, and the supernatants were analysed for TSH levels. The recovery of TSH [(post-PEG TSH/non-PEG TSH) ×100] after PEG treatment is normally more than 75%, while results of 65%–75% are equivocal.[23,24] Therefore, post-PEG TSH recovery of less than 60% was set as the cut-off for macro-TSH diagnosis in our study. ACTH stimulation tests and imaging studies, including thyroid ultrasound and MRI of the pituitary gland, were performed when indicated. Finally, the patients were classified into 'macro-TSH,' 'SCH', and 'non-thyroid' groups.

Statistics

The sample size was calculated based on an expected prevalence of macro-TSH in SCH of 0.7%–1.4% and prevalence of SCH with a margin of error of 5% and a confidence level of 95%. Descriptive statistics were used to express the prevalence of macro-TSH as a percentage and to summarise demographic and clinical characteristics by using means, medians, and standard deviations for continuous variables and frequencies for categorical variables. Comparative analyses included student *t*-tests for continuous variables and Chi-square tests for categorical variables to compare clinical and biochemical parameters between macro-TSH positive and negative groups by using the IBM SPSS statistics version 20 software. Logistic regression was employed to identify independent predictors of macro-TSH presence in patients with SCH.

Ethical aspects

Ethical approval for this study was obtained from the Sangini Hospital Ethics Committee. Written informed consent was obtained from all participants, and patient confidentiality was strictly maintained throughout the study under the Helsinki guidelines 1964.

The study protocol was approved on 10th January 2021 with Ref: ABL_02033_1023124.

Results

In total, 135 patients with TSH levels greater than 10 IU/L were tested for repeat TSH measurements using different ECLIA kits with serial dilutions. Further testing for post-PEG recovery of TSH greater than 75% confirmed the diagnosis of SCH in 115 patients. Among the remaining 20 cases, two had TSH levels measured by different ECLIA kits that were less than 4.5 IU/L. Additionally, three of the remaining 18 patients had TSH levels greater than 10 IU/L by the second method.

These five patients with serial dilutions demonstrating a non-linear graph and post-PEG recovery of TSH exceeding 75% were diagnosed as pseudo-macro-TSH due to heterophilic antibodies [Figure 1] and reclassified into the non-thyroid subgroup, resulting in a total of 1245 non-thyroid participants. Fifteen patients exhibited linear and identical graphs with serial dilutions of TSH measurements. These patients underwent further testing with PEG precipitation, and a post-PEG TSH recovery of less than 60% confirmed the diagnosis of macro-TSH [Figure 2].

The demographic and clinical characteristics of the study population are summarised in Table 1. The mean age distribution was similar across all groups. However, the proportion of female participants was significantly higher in the SCH group compared to the macro-TSH and non-thyroid groups, Notably, individuals with SCH had a higher prevalence of diabetes and a family history of hypothyroidism compared to those with macro-TSH, with a significant *P* value. Clinical features of hypothyroidism except lethargy were significantly more prevalent in the SCH group compared to the macro-TSH group. The mean TSH levels were five times higher in the macro-TSH compared to SCH groups, but substantially higher in both the groups than in the non-thyroid group. A key difference was observed in the post-PEG TSH percentage, which was significantly lower in the macro-TSH group compared to the SCH group. Table 2 details the clinical features of patients with macro-TSH. The female-to-male ratio was 3:2. Out of the 15 patients, only two exhibited hypothyroid features.

Table 3 presents the logistic regression analysis identifying significant predictors of macro-TSH. Female gender and family history of hypothyroidism were associated with higher odds of having macro-TSH. Diabetes mellitus, clinical symptoms of hypothyroidism except lethargy, higher TSH level, and post-PEG TSH recovery were significantly associated with SCH when compared to macro-TSH.

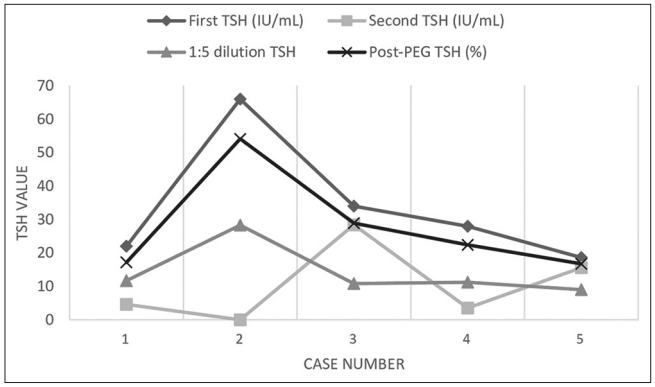

Figure 1: Graphical presentation of TSH measurement by different ECLIA methods, 1:5 serial dilution, and post-PEG precipitation of pseudo-macro-TSH (heterophilic antibodies) against TSH

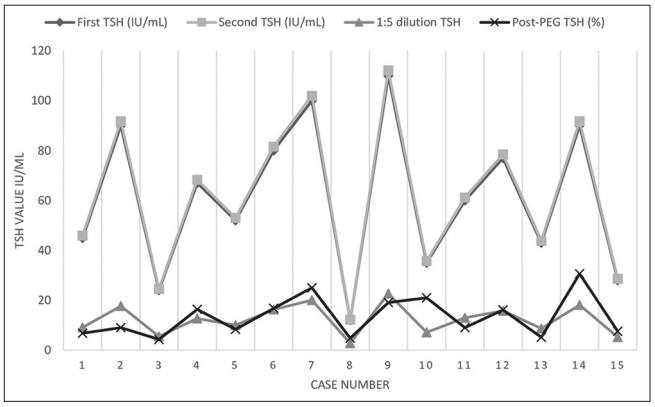

Figure 2: Graphical presentation of TSH measurement by different ECLIA methods, 1:5 serial dilution, and post-PEG precipitation of Macro-TSH

Table 1: Demographic and clinical characteristics of the study population

Character	Macro-TSH (*n*=15)	SCH (*n*=115)	Non-thyroid (*n*=1245)	*P* (Macro-TSH vs SCH)	*P* (SCH vs non-thyroid)
Age (Years, Mean±SD)	50.1±11.3	50.2±11.8	49.8±13.1	0.732	0.762
Female gender (%)	9 (60.0%)	92 (80.0%)	656 (52.7%)	0.045	<0.001
Smoking/Tobacco (%)	2 (13.3%)	20 (17.4%)	230 (18.5%)	0.759	0.827
Family history of Hypothyroidism (%)	4 (30.0%)	60 (52.0%)	380 (30.5%)	0.049	0.988
Hypertension (%)	4 (26.7%)	30 (26.1%)	320 (25.7%)	0.951	0.963
Diabetes mellitus (%)	3 (20.0%)	69 (60.0%)	270 (21.7%)	0.039	0.983
Weight gain (%)	1 (6.7%)	45 (39.1%)	90 (7.2%)	0.031	0.952
Oedema (%)	1 (6.7%)	17 (15.0%)	75 (6.0%)	0.002	0.989
Dry skin (%)	2 (13.3%)	25 (21.7%)	175 (14.0%)	0.012	0.983
Lethargy (%)	2 (13.3%)	16 (13.9%)	22 (1.7%)	0.954	0.046
Menstrual irregularities (%)	1 (6.7%)	26 (23.0%)	71 (5.7%)	0.008	0.992
Anxiety (%)	1 (6.7%)	35 (30.4%)	108 (8.7%)	0.002	0.974
Mood swings (%)	2 (13.3%)	41 (36.1%)	143 (11.5%)	0.004	0.976
Constipation (%)	1 (6.7%)	50 (43.5%)	102 (8.2%)	0.040	0.974
Overall hypothyroid features	2 (13.33%)	60 (52.0%)	175 (14.0%)	<0.001	<0.001
Haemoglobin (Mean±SD, g%)	10.5±1.2	8.4±1.3	10.3±1.4	0.812	0.923
TSH (Mean±SD, IU/mL)	61.5±5.7	12.4±2.5	2.3±1.1	<0.001	<0.001

Table 2: Clinical profile of macro-TSH

Case	Age	Gender	Habits	Hypothyroid Features	Comorbidity
1	45	F		Yes	-
2	50	M	Smoking	No	Hypertension
3	52	F		Yes	-
4	47	F		No	Diabetes
5	49	M		No	Hypertension
6	53	F		No	-
7	44	M	Tobacco	No	Diabetes
8	48	F		No	-
9	51	F		No	-
10	46	M		No	-
11	54	F		No	Hypertension
12	55	F		No	Hypertension
13	48	M		No	-
14	47	F		No	Diabetes
15	52	M		No	

Table 3: Logistic regression analysis between macro-TSH and SCH groups

Variable	Odds Ratio	95% confidence Interval	*P*
Age	1.01	0.99-1.03	0.732
Female gender	2.67	1.02-7.00	0.045
Smoking/Tobacco	0.73	0.15-3.61	0.759
Family history of Hypothyroidism	2.36	1.00-5.60	0.049
Hypertension	1.02	0.27-3.78	0.951
Diabetes mellitus	0.20	0.04-0.96	0.039
Weight gain	0.12	0.01-1.06	0.031
Oedema	0.39	0.03-4.81	0.002
Dry skin	0.55	0.14-2.09	0.012
Lethargy	0.94	0.16-5.47	0.954
Menstrual irregularities	0.23	0.04-1.21	0.008
Anxiety	0.15	0.02-1.20	0.002
Mood swings	0.21	0.05-0.85	0.004
Constipation	0.37	0.05-2.93	0.040
Haemoglobin	1.09	0.71-1.67	0.812
TSH	0.97	0.79-1.18	<0.001
Post-PEG TSH	0.72	0.58-0.89	<0.001

Discussion

As per our knowledge, this is the first study of macro-TSH prevalence and clinical profile in India. In our study, the prevalence of SCH was 8.36% (115 out of 1375 patients). Additionally, we identified 15 cases of macro-TSH among the 1375 patients, resulting in a prevalence rate of 1.09%. These findings align with previous studies, which have reported SCH prevalence rates ranging from 8% to 10% and macro-TSH prevalence rates between 0.7% and 1.4% in the general population.[9,25] The prevalence of macro-TSH among individuals with SCH in our study was 13.04%, which aligns with the 9%–14% range reported in previous studies.[9,25] It is important to note that the prevalence of these conditions can vary based on factors such as the age and race of the population studied and the diagnostic methods employed.[9,24] Additionally, in our study, 3.70% (5 out of 135) of patients with pseudo-macro-TSH had raised TSH due to laboratory interference, potentially caused by heterophilic antibodies such as anti-mouse antibodies against the TSH monomer. G Ward *et al*. reported a 3.4% prevalence of heterophilic antibodies against TSH,[26] whereas our study found a much lower prevalence of 0.36% (5 out of 1375). These findings highlight the importance of considering potential laboratory interferences when diagnosing and managing thyroid function abnormalities.

Demographic analysis revealed that macro-TSH and SCH predominantly affected females, with 60.0% and 90% female cases, respectively. This gender distribution is consistent with previous research, demonstrating a female preponderance in macro-TSH and SCH instances.[27,28] However, our study showed a lower prevalence of hypothyroid features in the macro-TSH group, with only 13.33% of patients exhibiting clinical manifestations typically associated with hypothyroidism. This contrasts with the higher prevalence (52.0%) of such features observed in SCH patients.

Despite the lower prevalence of hypothyroid features, biochemical markers of SCH, such as elevated TSH levels with normal free-thyroxine (FT4) concentrations, were characteristic of macro-TSH. Additionally, macro-TSH patients exhibited five times higher mean TSH levels compared to the SCH group (61.5 vs 12.4), a characteristic feature consistent with existing literature.[15,29] Hence, clinicians should consider macro-TSH syndrome in cases where biochemical features of SCH with disproportionate high TSH are present without accompanying hypothyroid symptoms. Furthermore, several clinical features associated with hypothyroidism, including weight gain, dry skin, menstrual irregularities, anxiety, mood swings, and constipation, overlapped between the macro-TSH and SCH groups. These findings underscore the importance of recognising the clinical manifestations of macro-TSH to differentiate it accurately from other thyroid disorders.

A logistic regression analysis identified significant associations between macro-TSH and female gender and family history of hypothyroidism, while diabetes mellitus features of hypothyroidism except lethargy, TSH level, and post-PEG TSH showed inverse association. These findings corroborate previous studies highlighting the role of genetic predisposition and metabolic factors in the pathogenesis of macro-TSH.[19,29]

Limitations

Our study has several strengths, including a relatively large sample size, prospective study design, and comprehensive clinical evaluation of patients with macro-TSH. However, it is not without limitations. The single-centre study may limit the generalisability of our findings. Additionally, the diagnosis of macro-TSH relied on PEG precipitation tests, which, although widely used, may have limitations in certain cases. Gel filtration chromatography is the state-of-the-art method

for detecting macro-TSH.[9,22] However, it is costly and not available everywhere.[9,22]

What is known about this topic?

- Macro-TSH is a rare condition caused by the binding of TSH to other plasma proteins, most often immunoglobulins. This results in falsely elevated TSH measurement.
- The biochemical profile mimics SCH and may lead to inappropriate levothyroxine replacement.

What does this research add?

- This report highlights the importance of screening for macro-TSH in patients with SCH, especially in the absence of hypothyroid features with disproportionately high TSH.
- None of the existing immunoassays can identify the presence of macro-TSH.

Conclusion

Our study provides valuable insights into the prevalence and clinical profile of macro-TSH, emphasising the need for increased awareness and accurate diagnosis of this rare syndrome in clinical thyroidology. Further research, including prospective multicentre studies and molecular investigations, is warranted to elucidate macro-TSH's pathophysiology and optimise its management strategies fully.

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Authors contribution

The first author Dr Dhruvkumar Patel drafted an idea for the topic and did an extensive literature review and critical improvement in drafting. Dr Dhara Patel, Dr Chetan Dharaiya, and Dr Maitri Patel reviewed laboratory records and statistical studies. Maitri Patel, Lalit Patel, Ravi Vasani, Mukundkumar Patel, and Dhara Patel collected data from case reports, drafted the article, did the literature search, and drafted the manuscript. Dr. Mukundkumar Patel, Dr. Maitri Patel, Dr Ravi Vasani, and Dr Chetan Dharaiya reviewed clinical records.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability statement

Necessary data are included in the main manuscripts. However, readers are requested to contact the corresponding author's email ID for additional data.

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