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# The outcome of TSHoma from a tertiary care institute in India

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## ABSTRACT

**Background:** Thyroid-stimulating hormone (TSH)-secreting pituitary adenoma (TSHoma) is the rarest functioning pituitary adenoma.

**Methods:** A retrospective analysis of eight patients of TSHomas to highlight the presentations, diagnostic challenges, and treatment outcomes.

**Results:** Median age at diagnosis was 42 years, median latency to diagnosis was 2.5 years, and thyrotoxic and compressive symptoms were the most common presenting symptoms. At presentation, three cases were pluri-hormonal, six cases were on medical treatment including thyroxine, and two cases were incidentally discovered. Imaging revealed macroadenoma in all cases. Seven cases underwent pituitary surgery, after which three achieved remission. Another case entered remission after adjunctive radiotherapy. Thyrotropin (TSH) immunostaining was demonstrated in six out of seven adenomas.

**Conclusion:** TSHoma is a rare functioning pituitary tumor with both silent and symptomatic presentations. Diagnosis can be established with biochemical and imaging features, even without dynamic tests.

**Keywords:** Non-suppressed thyroid-stimulating hormone, Secondary hyperthyroidism, Thyroid-stimulating hormone-secreting pituitary adenoma

## INTRODUCTION

Thyroid-stimulating hormone (TSH)-secreting pituitary adenoma (TSHoma) is the rarest functioning pituitary adenoma. Despite being functional, late diagnosis, or misdiagnosis is the rule. The patient usually presents with compressive symptoms of headache, visual field defects, and multiple pituitary hormone deficiencies (MPHD).[5,12] Even though TSHoma causes secondary hyperthyroidism, it is inadvertently managed as primary hyperthyroidism. TSHomas are characterized by a non-suppressed TSH with elevated free thyroid hormones. Since the advent of ultrasensitive TSH assays, many cases have been reported, which has led to increased recognition of the entity.[1,6,7,11,14,15,17,25,29] In this report, we outline the clinical and biochemical

profiles, management strategies, and long-term outcomes of eight cases of TSHoma and briefly review this rare disease.

## MATERIALS AND METHODS

This is a retrospective, record-based study of eight cases with biochemically, radiologically, and histologically (all but one) verified TSHoma that presented at Post Graduate Institute of Medical Education and Research, Chandigarh, from the year 2012 to 2019. During this period, approximately 1500 pituitary surgeries were performed. The study was approved by the Institute Ethics Committee and informed written consent was obtained from all the study participants. Baseline characteristics are summarized in [Table 1], while treatment and outcomes are reviewed in [Table 2]. Preoperative pituitary imaging was done by contrast-enhanced magnetic resonance imaging (CEMRI; Siemens Magnetom). Each case was analyzed for TSH, T4, free T4 (fT4), T3 and free T3 (fT3), and anti-TPO by electro-chemiluminescence immunoassay (Roche ELECSYS System, Cobas 6000, Mannheim, Germany). The reference range for the above hormones is as follows: TSH 0.27–4.2 mIU/ml, T4 4.8–12.7 μg/dL, fT4 0.7–1.8 ng/ml, T3 0.8–2 ng/mL, fT3 1.7–4.2 pg/mL, and anti-TPO <34 IU/mL. Immunohistochemistry (IHC) for TSH was performed and quantified in all tumor specimens. Data were analyzed using Microsoft Excel (version 16) and continuous variables are depicted as median with range.

## CASES

### Case 1

A 48-year-old male presented with history of total thyroidectomy for diffuse toxic goiter 10-years ago [Figure 1a] when the patient had weight loss, palpitations, heat intolerance, hypertension, tremors, hyper defecation, and thyroid function tests (TFT) as follows: TSH 12.78 mIU/mL, fT4 9.5 ng/dL, and fT3 13 pg/mL. Previously, a CEMRI had revealed a pituitary mass (size unavailable); however, the patient refused pituitary surgery and radiotherapy. Post thyroidectomy patient developed iatrogenic hypoparathyroidism and was lost to follow-up. There was poor compliance to thyroxine (100 μg) and calcium replacement. Ten years later (2012) patient presented with abrupt onset stridor and tetany. After receiving an emergency tracheostomy, the patient was evaluated and treated for hypocalcemia. The patient had coarse facial features as well. Biochemistry at presentation was: calcium 6.22 mg/dL (8.6–10.2), parathyroid hormone 3.59 pg/mL (12–70), TSH 674.7 mIU/mL (in 1:10 dilution), T4 6.31 μg/dL, T3 0.64 ng/mL, anti-TPO 15 IU/mL, and nadir growth hormone (GH) 2.20 ng/mL after 75-g glucose tolerance test (GTT). CEMRI sella showed a 3.7*3.8*3.7 cm lobulated sellar mass with supra-sellar, para-sellar, and infra-sellar extensions. Visual field charting (VFC) showed bi-temporal

**Table 1:** Baseline characteristics.

| Case number | Age/Sex | TSH (mIU/mL) | T4 (μg/dL) | T3 (ng/mL) | fT4 (ng/dL) | fT3 (pg/mL) | 8 AM Cortisol (nmol/L) | GH-GTT (ng/mL) | Prolactin (ng/mL) | MRI size (cm) | Thyroid scan (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 48/M | 674.7* | 6.31 | 0.64 | - | - | 103.2 | 2.2 | 6.04 | 3.8 | - |
| 2 | 50/F | 10.61 | 18.51 | 2.36 | 3.31 | 6.36 | 231.8 | 0.28 | 7.75 | 2.5 | 7.2 |
| 3 | 40/F | 1.33 | 17.53 | 2.05 | 2.49 | 5.11 | 244 | 56.48 | 0.93 | 4.4 | 4.5 |
| 4 | 19/F | 6.52 | 24.88 | 4.36 | 10.36 | 20 | 557.3 | 2.36 | 9.49 | 1.3 | 28.2 |
| 5 | 44/M | 3.03 | 15.2 | 1.91 | 2.04 | 5.19 | 449.4 | 0.03 | 5.92 | 1.9 | 3.3 |
| 6 | 47/M | 14 | 13 | 1.68 | 1.68 | 9.01 | 436 | - | 17.54 | 2.1 | 9.9 |
| 7 | 40/M | 12.84 | 11.91 | 2.41 | - | - | 60.96 | 0.03 | 0.302 | 5 | 5.8 |
| 8 | 20/M | 2.04 | 17.50 | 2.33 | 2.29 | 6.14 | 63.7 | 0.14 | 19.21 | 2 | 2.1 |

*Post total thyroidectomy. Normal range: TSH (0.27–4.2 mIU/ml), T4 (4.8–12.7 μg/dL), T3 (0.8–2 ng/mL), fT4 (0.7–1.8 ng/ml), fT3 (1.7–4.2 pg/mL), cortisol (171–536 nmol/L), GH-GTT (<1 ng/mL), Prolactin (4.8–23.3 ng/mL), Thyroid scan uptake (0.5–3.5%).
GH-GTT: Growth hormone-glucose tolerance test, ft3: Free T3, ft4: Free T4, MRI: Magnetic resonance imaging, TSH: Thyroid-stimulating hormone

**Table 2:** Treatment, histopathology, and clinical outcomes.

| Case number | Preoperative medical treatment | Surgery | Outcome | IHC for TSH (%) | Complications | Postoperative TSH | Postoperative T4 |
|---|---|---|---|---|---|---|---|
| 1 | Thyroxine | TSS | Death | 70 | IVH, Death | NA | NA |
| 2 | Octreotide, ATD | TSS, GKRS | Residual | 80 | Nil | 13.2 | 5.25 |
| 3 | Octreotide, ATD | TSS | Remission | 0 | MPHD, DI | 0.013 | 5.6 |
| 4 | Octreotide, ATD | - | Residual | - | Nil | NA | NA |
| 5 | ATD | TSS | Remission | 30 | Meningitis, MPHD, Death | 0.005 | 6.76 |
| 6 | ATD | TSS | Residual | 30 | Nil | 1.6 | 9.35 |
| 7 | ATD | TSS | Residual | 30 | MPHD, meningitis | 6.4 | 7.9 |
| 8 | ATD | TSS | Remission | 30 | DI | 0.037 | 7.98 |

ATD: Anti-thyroid drugs, DI: Diabetes insipidus, IHC: Immunohistochemistry, IVH: Intraventricular hemorrhage, GKRS: Gamma-knife radio-surgery, MPHD: Multiple pituitary hormone deficiencies, TSH: Thyroid-stimulating hormone, TSS: Transsphenoidal surgery

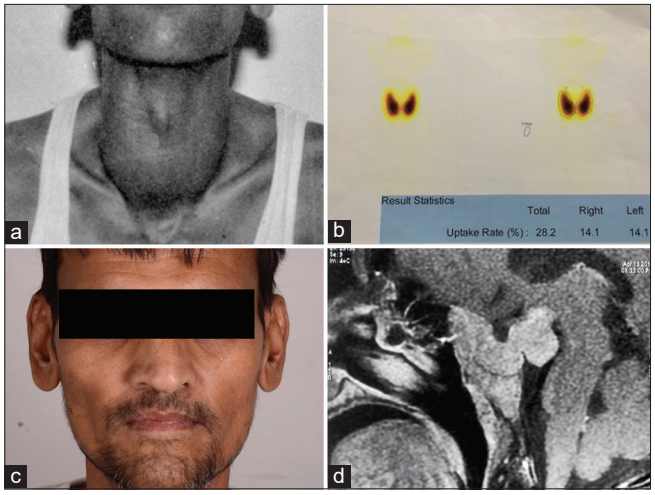


**Figure 1:** (a) Goiter in Case 1 (picture from 2002); (b) thyroid scan showing increased thyroid uptake in Case 4; (c) regression of secondary sexual characteristics in Case 7; (d) giant pituitary adenoma in Case 7.

hemianopia. Thyroid scintigraphy did not reveal any residual thyroid tissue. The patient underwent pituitary transsphenoidal surgery (TSS) after stabilization. The postoperative course was stormy with the development of hypocalcemia, hypocortisolism, diabetes insipidus (DI), and intra-ventricular hemorrhage resulting in his death. IHC showed diffuse positivity for TSH and scattered positivity for GH.

### Case 2

A 48-year-old female presented with secondary amenorrhea, decreased vision, and headache. A TFT done 2-years earlier showed TSH 25.4 mIU/mL, T4 4.02 µg/dL, and T3 0.66 ng/mL. Even after initiating thyroxine (100 µg), her TSH never normalized. Palpitations, tremor, hair loss, heat intolerance, sweating, systolic hypertension, and Grade II goiter were present, and TFT (on thyroxine 250 µg) was as follows: TSH 10.61 mIU/mL, T4 18.51 µg/dL, fT4 3.31 ng/dL, T3 2.36 ng/mL, fT3 6.36 pg/mL, and anti-TPO 356.6 IU/mL (<60). The patient remained thyrotoxic despite stopping thyroxine. CEMRI sella revealed a 2.2*1.8*2.5 cm sellar-suprasellar mass with para-sellar extension. VFC showed bi-temporal hemianopia. Ultrasound neck revealed thyromegaly and thyroid scintigraphy revealed increased trapping function in both lobes of the thyroid (7.2%). The patient was started on carbimazole 30 mg daily, octreotide LAR 30 mg once a month, and underwent TSS 3 months later. Postoperatively her TSH remained elevated. There were no complications of the surgery. Histopathology confirmed pituitary adenoma and IHC was positive for TSH in 80% cells. For residual adenoma (size: 1.4*1.4*0.9 cm), the patient underwent gamma-knife radio-surgery (GKRS) and achieved remission 1 year later.

### Case 3

A 40-year-old female presented with secondary amenorrhea, headache, enlargement of hands and feet, and decreased vision. Although clinically diagnosed as acromegaly, thyrotoxic symptoms (heat intolerance, tremor, and palpitations) and Grade Ib goiter were present. Hormone analysis was as follows: TSH 1.33 mIU/mL, T4 17.53 µg/dL, fT4 2.49 ng/dL, T3 2.05 ng/mL, fT3 5.11 pg/mL, and nadir GH 56.48 ng/mL on GTT. CEMRI sella revealed 4.4*3.8*3.4 cm sellar mass with supra-sellar and para-sellar extensions. VFC showed bi-temporal hemianopia. Thyroid scan revealed increased trapping function in both lobes of the thyroid (4.5%). The patient was started on carbimazole 30 mg daily and octreotide LAR 30 mg once a month, and underwent TSS with near-total resection 3 months later. Surgical complications included CSF rhinorrhea and DI. Although GH remained elevated postoperatively, TSH became undetectable, and T4 normalized. Histopathology showed adenoma; however, IHC showed 90% positivity for GH and scattered positivity for TSH. Further IHC analysis revealed ubiquitous PIT1 expression. IHC for GATA-2 could not be done due to its unavailability.

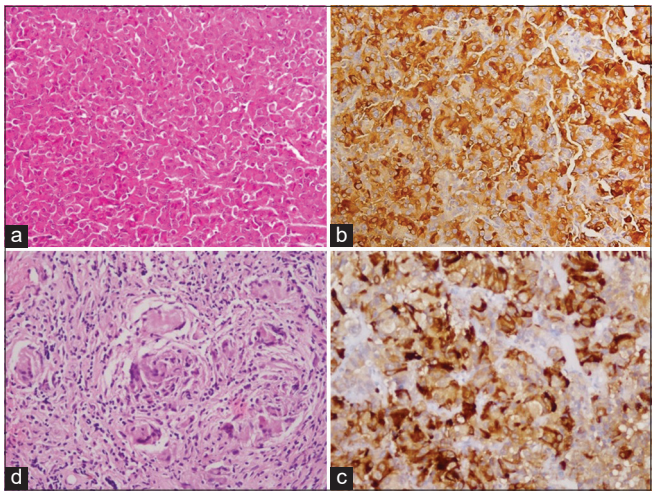


**Figure 2:** (a and b) Histopathology (20×) depicting monomorphic adenoma cells with abundant cytoplasm, arranged in sheet and nest such as pattern and diffuse (80%) thyroid-stimulating hormone (TSH) stain positivity in TSH-secreting pituitary adenoma of case 7; (c and d) 30% TSH stain positivity in adenoma cells and meningeal biopsy (20×) showing multiple granuloma (fungal) in Case 8.

### Case 4

A 19-year-old female presented with thyrotoxicosis (weight loss, sweating, palpitations, increased appetite, tremor, hair loss, anxiety, and heat intolerance) and Grade II goiter. Baseline TFT was: TSH 8.79 mIU/mL, T4 26.99 μg/dL, fT4 10.36 ng/dL, T3 5.20 ng/mL, and fT3 20 pg/mL. Despite being on carbimazole 40 mg for >1 year, there was no improvement in symptoms. At presentation TFT was: TSH 6.52 mIU/mL, T4 24.88 μg/dL, and T3 of 4.36 ng/mL. Although clinical features of acromegaly were lacking, the patient had nadir GH of 2.36 ng/mL on GTT and elevated Insulin-like growth factor-1 (IGF-1) levels (909 ng/mL). CEMRI brain showed a 1.3*1.0 cm sellar-suprasellar mass. Thyroid scan revealed increased trapping function in both lobes of the thyroid (28.2%) [Figure 1b]. Carbimazole was continued and octreotide LAR 30 mg once a month was started; however, the patient refused surgery and has been in irregular follow-up since.

### Case 5

A 44-year-old male presented with headache. A local physician advised a CEMRI brain which revealed a 1.6*1.9*1.4 cm pituitary macroadenoma. Hormone analysis was normal except for deranged TFT: TSH 3.03 mIU/mL, T4 15.2 μg/dL, fT4 2.04 ng/dL, T3 1.91 ng/mL, and fT3 5.19 pg/mL. There were no clinical features of thyrotoxicosis or goiter. Thyroid scan revealed borderline increased trapping function in both lobes of the thyroid (3.3%). The patient underwent TSS and had surgical complications of secondary hypocortisolism, CSF rhinorrhea, and transient DI. Postoperatively, the patient achieved remission. Histopathology was consistent with adenoma and IHC revealed 30% positivity for TSH. The patient presented 1-month later with sudden-onset high-grade fever, generalized tonic-clonic seizure, and altered sensorium. The patient was diagnosed to have acute bacterial meningitis and succumbed to the illness.

### Case 6

A 47-year-old male presented with headache, weight loss, palpitations, sweating, increased appetite, tremors, fatigue, and hypertension. On basis of TSH of 10.9 mIU/mL and fT4 of 2.07 ng/dL, carbimazole was initiated, however, both symptoms and TSH never normalized. At presentation TFT was: TSH 6.80 mIU/mL, fT4 5.3 ng/dL, and fT3 16.6 pg/mL. CEMRI sella revealed a 2.1*1.9*1.8 cm macroadenoma with para-sellar extension. Grade II goiter was present. VFC was normal. Thyroid scan showed increased trapping function in both lobes of the thyroid (9.9%). The patient underwent TSS without any surgical complications. Histopathology was consistent with adenoma with IHC showing positivity for TSH in 30% cells. The patient entered clinical remission, however, TSH remains detectable.

### Case 7

A 40-year-old male presented with symptoms of headache and weight loss (40 kg). There was a history of uncontrolled Type 2 diabetes with palpitations, sweating, increased frequency of stools, fatigue, tremors, heat intolerance, loss of libido, and regression of secondary sexual characteristics [Figure 1c]. Three years before the presentation TFT was: TSH 7.08 mIU/mL and fT4 1.54 ng/dL, based on which thyroxine was prescribed. During follow-up, both symptoms and TSH failed to normalize. At presentation to us, TFT was: TSH 12.84 mIU/mL, T4 11.91 μg/dL, and T3 2.41 ng/mL. CEMRI sella revealed a 4*2.8*5 cm mass with supra-sellar and para-sellar extension along with bone erosion [Figure 1d]. VFC showed bi-temporal hemianopia. Goiter Grade II was present and thyroid scintigraphy revealed increased uptake in both the thyroid lobes (5.8%). Carbimazole 20 mg was initiated along with replacements for untreated MPHD. The patient underwent TSS and developed DI postoperatively. Within 1-month patient developed CSF rhinorrhea and meningitis which was managed conservatively. Histopathology was consistent with adenoma with IHC showing positivity for TSH in 80% cells [Figure 2a and 2b]. Postoperatively, intensity-modulated radiation therapy (IMRT) (5.4 Gray, 34 cycles) was administered. The patient continues to be on carbimazole due to persistent thyrotoxicosis.

### Case 8

A 20-year-old male presented with headache and recurrent loss of consciousness. A CEMRI done elsewhere revealed

a sellar mass 1.7*2.0*1.3 cm along with diffuse meningeal enhancement for which a CSF analysis was performed suggesting chronic meningitis. The patient was referred with a diagnosis of non-functioning pituitary adenoma and tubercular meningitis. Clinically, features of hypogonadism (poor virilization, testicular volume 3 mL) were present. Hormone analysis was as follows: TSH 2.04 mIU/mL, T4 17.5 μg/dL, fT4 2.29 ng/dL, T3 2.33 ng/mL, fT3 6.14 pg/mL, and elevated gonadotrophins (FSH > LH). Both ultrasound neck and thyroid scan were normal. In view of long leggedness, small testes, and elevated gonadotrophins, karyotyping was done which revealed 46, XXY. Repeat CSF analysis revealed 40 cells (all lymphocytes) and elevated proteins (114 mg/dL). With a diagnosis of TSHoma and chronic meningitis of unknown etiology, the patient underwent TSS and meningeal biopsy. Postoperatively, patient developed transient DI. Histopathology was consistent with adenoma; IHC showed positivity for TSH in 30% cells [Figure 2c and 2d] and the meningeal biopsy showed fungal granulomas (*Aspergillus flavum*). The patient is currently in biochemical remission and on voriconazole and testosterone for fungal meningitis and hypogonadism, respectively.

## RESULTS

### Patient characteristics

Patients were middle-aged (median: 42 years; range 19–50) with a slight male preponderance (5:3). Median latency to diagnosis was 2.5 years (range 0.17–11). Symptomatic thyrotoxicosis (5/8) and headache (6/8) were the most common modes of presentation. Other symptoms included visual field defects (4/8), hypogonadism (5/8), and acromegaly (1/8). The diagnosis was incidental in two cases. On examination, goiter was present in 5/8 cases. Six patients received prior treatment in the form of thyroxine (3/6), anti-thyroid drugs (4/6), and total thyroidectomy (1/6). No patient received thyroid ablation with radio-iodine.

### Biochemical findings

Irrespective of the prior treatment modality, 7/8 cases were biochemically thyrotoxic at presentation. Median TSH (Case 1 excluded due to post thyroidectomy status) was 6.52 mIU/mL (range 0.69–12.84). In individual cases, TSH was inappropriately high for the corresponding thyroid hormone levels. Median T4 and T3 were 14.96 μg/dL (range 6.31–24.88) and 2.2 ng/mL (range 0.64–4.36), respectively [Table 1]. Three cases had pluri-hormonal adenoma as their nadir GH was elevated on GTT. None of the cases had hyper-prolactinemia, rather two had hypo-prolactinemia [Table 2]. Five cases (1, 2, 3, 7, and 8) had MPHD preoperatively. Anti-TPO was elevated in Case 2. TRH (thyrotropin-releasing hormone) stimulation test and T3 suppression test were not done as both are not available at our center. Other tests including serum glycoprotein hormone alpha-subunit (α-GSU), α-GSU/TSH molar ratio, sex-hormone binding globulin (SHBG), and carboxy-terminal cross-linked telopeptide of Type I collagen (ICTP) were not done.

### Radiological findings

CEMRI sella revealed a macroadenoma in all eight cases. The median largest diameter was 2.3 cm (range 1.3–5). KNOSP grade was 3–4 in all cases. Ultrasonography neck confirmed thyromegaly in all cases where goiter was clinically detected. $^{99m}$Tc pertechnatate thyroid scintigraphy revealed increased trapping function in both lobes of the thyroid in all cases (and no residual thyroid tissue in Case 1).

### Preoperative medical preparation

Three cases received octreotide LAR before surgery. All cases received anti-thyroid drugs, Lugol's iodine, and propranolol a few days before surgery to prevent thyroid storm.

### Treatment and complications

Excluding Case 4 (declined surgery), all patients underwent TSS as the primary modality of treatment. Cases 2 and 7 received radiation therapy within a year of surgery. Postoperative complications included CSF leak, MPHD (new and persistent), acute meningitis, and transient or permanent DI. Case 1 developed intraventricular hemorrhage which resulted in his death. Case 5 developed meningitis after 1 month of discharge and later succumbed to the illness.

### Outcomes

TFT was obtained within 1–2 weeks of surgery. Median postoperative TSH was 0.82 mIU/mL (range 0.005–13.2) and T4 was 7.14 μg/dL (range 5.25–9.35) [Table 2]. Remission was defined as undetectable TSH 1 week after surgery. Remission was seen in three cases (3, 5, and 8). Residual disease was confirmed biochemically and radiologically in cases 2 and 7. Among the latter, Case 2 underwent GKRS and 1 year later achieved remission and Case 7 underwent IMRT and continues to be on carbimazole. Case 6 had clinical and radiological remission, however, his TSH remains detectable. Case 3 was lost to long-term follow-up. Case 4 remains in irregular follow-up on treatment with octreotide LAR and carbimazole. Two cases (1 and 5) died postoperatively.

### Histology

Among the seven operated cases, pituitary adenoma was confirmed in all. Positive immunostaining for TSH was seen in 6/7 resected specimens (range 30–80%). Case 3 had diffuse positivity for GH and scattered positivity for TSH. Although

three cases had plurihormonal presentation, IHC positivity for both GH and TSH could not be demonstrated. Ki-67 was <1% in both Cases 2 and 7, despite their large and invasive nature on imaging and dural invasion on histology.

## DISCUSSION

The results of our study suggest that combined assessment of clinical features (thyrotoxicosis, goiter, and compressive symptoms), biochemical tests (non-suppressed TSH with elevated free thyroid hormones), and appropriate imaging is necessary for the diagnosis of TSHoma. The results also show that mismanagement with thyroxine or ATDs is a rule rather than an exception and that TSHoma can be pluri-hormonal.

Graves' disease is the most common cause of hyperthyroidism overall. Secondary hyperthyroidism was first recognized in 1960 when a case of Graves' disease had remission following radiotherapy for a pituitary neoplasm. It was only after the advent of the radioimmunoassay for TSH that the syndrome of inappropriate secretion of TSH was recognized. TSHoma is characterized by non-suppressed TSH levels with high levels of free thyroid hormones (fT4 and fT3). Despite their functioning nature, late diagnosis, incidental diagnosis, and misdiagnosis are common.

TSHoma is rare pituitary adenomas with a prevalence of 0.5–2%.[1,5,7] The Swedish Pituitary Registry demonstrated an increased incidence of TSHoma over time (0.05/1 million/year in 1990–1994 to 0.26/1 million/year in 2005–2009), the national prevalence in 2010 being 2.8/1 million inhabitants.[22] This is likely because of greater reporting, cranial imaging, and improved methods of estimation of TSH. Our series showed a prevalence of 0.53% in approximately 1500 cases operated at our institute over the past 8 years.

The age of presentation of TSHoma is variable; most cases are diagnosed in the fifth or sixth decades.[5] The occurrence is equal in men and women, in contrast to the female predilection seen in primary thyroid disorders. In our series, most cases (6/8) were diagnosed in the fifth decade with a slight male predilection.

Except for Cases 5 and 8, all other patients underwent a long diagnostic process and/or treatment before presenting to us. Lack of recognition of the characteristic biochemical abnormality, failure to disclose compressive symptoms, incomplete TFT (TSH only), and poor awareness among general practitioners were the factors contributing to delayed diagnosis. Six patients received prior treatment in the form of thyroxine ($n$ = 3), anti-thyroid drugs ($n$ = 4), and total thyroidectomy ($n$ = 1). The median latency from the beginning of the first symptom to diagnosis was 2.5 years. In four of our cases, the diagnosis was made within 2 years of presentation which could be attributed to referral bias and a lower threshold for cranial imaging.

Presentation of TSHoma can be variable, from asymptomatic to life-threatening apoplexy. Clinical features (in descending order of frequency) include goiter, symptoms of thyrotoxicosis, defects in vision, headache, MPHD, and galactorrhea.[5,9] We report a similar frequency of presenting complaints, but galactorrhea was conspicuous by its absence. Despite TSHoma being functional, it is often the compressive symptoms (headache, visual defects, ad MPHD) that result in cranial imaging and bring the patient to the specialist. MPHD was present in five cases preoperatively in this study. Except Case 1 (post thyroidectomy status), all cases were hyperthyroid with a non-suppressed TSH at presentation. Hyperthyroid features were dwarfed by features of acromegaly in Case 3, a pattern well described previously.[4] Hyperthyroidism can be due to acromegaly itself, wherein elevated GH and IGF-1 can both stimulate growth and functioning of thyroid follicular epithelium.[18] Cases 5 and 8 were clinically euthyroid at the time of diagnosis, and this clinical picture has also been described earlier.[6,24] In our study, Case 2 had concurrent autoimmune thyroiditis. Even concomitant Graves' disease has been described previously.[13] TSHomas can be pluri-hormonal in up to 30% cases, with GH (18%) and prolactin (10%) co-secretion being most common.[5] This is due to the shared pituitary transcription factors Prop-1 and Pit-1 between thyrotrophs, somatotrophs, and lactotrophs.

Pituitary imaging became important in the diagnosis of TSHoma, due to lack of dynamic tests, in the current study. CEMRI sella revealed macroadenoma in all eight cases. In larger series of TSHoma, 15–30% microadenomas have been reported.[10,11] This finding is of great significance as the incidence of pituitary incidentaloma is also similar, thereby reducing the specificity of pituitary imaging in the diagnosis of TSHoma. However, in the current study, macroadenomas on imaging in conjunction with biochemical and clinical profiles, aided in the diagnosis of TSHoma. Newer modalities of molecular imaging need to be studied.[27]

The European thyroid association has advocated surgical resection as the definitive therapy for TSHoma.[3] TSHomas are challenging to resect completely due to substantial fibrosis, large size, and extensive local invasion. They have been referred to as "pituitary stones" due to increased levels of basic fibroblast growth factor.[28] Re-surgery in these tumors is even more complex with attendant morbidity.[21] Preoperative preparation with somatostatin analogs (SSA) and ATDs along with beta-blockers has been used to make the patient euthyroid and reduces the adenoma size.[10] Both octreotide LAR ($n$ = 3) and anti-thyroid drugs ($n$ = 6) were used in our cases preoperatively and 7/8 cases underwent TSS.

Pituitary radiotherapy and SSAs are two adjunctive treatment modalities for TSHoma, particularly residual disease.[3] Our own experience with both of them is limited due to the

financial constraints of the patients, especially with SSAs. Treatment with SSAs leads to a reduction of TSH and α-GSU secretion in almost all cases, with the restoration of the euthyroid state in the majority of patients.[24] Shrinkage in adenoma size and visual improvement has been described in >50% cases.[17,29] Dopamine agonists have also been used with positive effects being mainly observed in patients with mixed PRL/TSH adenoma.[20] Only in Case 4, octreotide LAR was used as a primary treatment. Two cases received postoperative radiotherapy, wherein Case 2 achieved remission 1 year after GKRS and Case 7 has persistent hyperthyroidism.

On tissue examination, TSHoma cells are chromophobic, polymorphic (angular or irregular) and have long cytoplasmic processes with stippled chromatin and prominent nucleoli.[5,19] Cells are arranged in cords and nests. The ultrastructure is like ordinary pituitary cells, and there is usually no exocytosis. IHC for β-TSH subunit is used to confirm the identity of TSHoma; however, this does not correlate with hormone over-secretion as silent TSHomas have been reported.[2,6] Except Case 3, other six operated tumors showed significant positivity (>30%) for TSH immunostain. In the event of negative or poor β-TSH immunoreactivity, use of transcription factors Pit-1 and GATA-2 is of value.[19]

There are multiple prespecified criteria for remission of TSHoma.[16] Some of them have poor predictive value (clinical and biochemical remission from hyperthyroid features, normalization of fT4, TSH, and α-GSU) while the others have good prognostic value (undetectable TSH 1 week postsurgery, positive T3-suppression test with undetectable TSH, and no response to TRH).[5] All of these criteria suffer from lack of clarity due to heterogeneity in available literature in terms of primary treatment modality (surgery vs. radiotherapy) and prior medication administered (SSA, thyroid ablation). We used undetectable TSH 1 week postsurgery as our criterion for remission. Based on this criterion, three cases achieved remission postsurgery.

Our study has certain lacunae. First, various dynamic tests and biological effects that have been described for TSHoma (TRH stimulation, T3 suppression, α-GSU, SHBG, and ICTP) were not performed. Second, postoctreotide and anti-thyroid drug administration normalization of T4, fT4, GH, and shrinkage in adenoma size were not documented. The impact of various intra-operative findings and post-operative care has not been evaluated.[8,23,26] IHC for GATA-2 could not be performed in Case 3. Postoperative fT4 and fT3 were not documented in all cases.

## CONCLUSION

This is the first study of TSHoma from India. The presence of eight cases of TSHoma among 1500 pituitary surgeries performed over 8 years at a single center, confirms its rarity. In conclusion, this study of TSHoma outlines the heterogeneous clinical presentation (clinically asymptomatic to frank thyrotoxicosis, goiter, and compressive symptoms), biochemical idiosyncrasies (non-suppressed TSH in the presence of elevated free thyroid hormones), treatment dilemmas (TFT not normalized despite erroneous treatment with thyroxine, anti-thyroid drugs or post thyroidectomy), diagnosis in the absence of dynamic tests (biochemical tests and imaging concomitantly), and the frequent requirement of multimodality treatment.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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### Conflicts of interest

There are no conflicts of interest.

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