ENDOCRINE TUMOURS

Thyrotropin-secreting pituitary adenoma: a structured review of 535 adult cases

Carlien De Herdt¹, Eva Philipse^{1,2} and Christophe De Block^{1,3}¹Department of Endocrinology-Diabetology-Metabolism, Antwerp University Hospital, Antwerp, Belgium,²Department of Endocrinology-Diabetology, Heilig Hart Hospital Lier, Antwerp, Belgium, and ³University of Antwerp, Faculty of Medicine and Health Sciences, Antwerp, BelgiumCorrespondence
should be addressed
to C De Block**Email**
christophe.deblock@uza.be

Abstract

Background and aims: Thyrotropin-secreting pituitary adenomas (TSHomas) are a rare entity, occurring in one per million people. We performed a systematic review of 535 adult cases summarizing the clinical, biochemical, hormonal and radiological characteristics of TSHoma. Furthermore, we discussed the current guidelines for diagnosis and treatment.

Methods: A structured research was conducted using Pubmed and Web of Science with the following MeSH terms: 'thyrotropin secreting pituitary adenoma' OR 'TSHoma' OR 'thyrotropinoma.'

Results: Our analysis included 535 cases originating from 18 case series, 5 cohort studies and 91 case reports. The mean age at diagnosis was 46 years. At presentation, 75% had symptoms of hyperthyroidism, 55.5% presented with a goitre and 24.9% had visual field defects. The median TSH at diagnosis was 5.16 (3.20–7.43) mU/L with a mean FT4 of 41.5 ± 15.3 pmol/L. The majority (76.9%) of the TSHomas were macroadenoma. Plurihormonality was seen in 37.4% of the adenoma with a higher incidence in macroadenoma. Surgical resection of the adenoma was performed in 87.7% of patients of which 33.5% had residual pituitary adenoma. Post-operative treatment with a somatostatin analogue (SSA) led to a stable disease in 81.3% of the cases with residual tumour. We noticed a significant correlation between the diameter of the adenoma and residual pituitary adenoma ($r = 0.490$, $P < 0.001$). However, in patients preoperatively treated with an SSA, this correlation was absent.

Conclusion: TSHomas are a rare cause of hyperthyroidism and are frequently misdiagnosed. Based on our structured analysis of case series, cohort studies and case reports, we conclude that the majority of TSHomas are macroadenoma being diagnosed in the fifth to sixth decade of life and presenting with symptoms of hyperthyroidism. Plurihormonality is observed in one-third of TSHomas. Treatment consists of neurosurgical resection and SSA in case of surgical failure.

*European Journal of
Endocrinology*
(2021) **185**, R65–R74

Introduction

Hyperthyroidism is mainly due to autoimmune thyroid disorders, a toxic thyroid nodule or goitre and is rarely caused by a thyrotropin-secreting pituitary adenoma (TSHoma), a pituitary tumour characterized by an autonomous secretion of thyroid-stimulating hormone (TSH) (1). TSHomas are the

rarest form of pituitary adenoma accounting for 3% of all pituitary tumours and are frequently misdiagnosed, leading to an inappropriate treatment such as thyroidectomy (1, 2, 3, 4). In 2013, the first European guidelines concerning the diagnosis and treatment of TSHomas were issued by

the European Thyroid Association and updated in 2019 (1, 3). Here, we provide a structured analysis of the clinical, biochemical, hormonal and radiological presentation of previously published cohort studies, case series and case reports. Because we assessed individual data of case reports, we were able to describe the patients in detail, analysing clinical and hormonal characteristics not described in the previous reviews. We also describe rare cases of TSHoma with concomitant Graves' disease or thyroid carcinoma and TSHoma complicated by a thyroid storm.

Methods

Search strategy

A structured search was conducted using Pubmed and Web of Science with the following MeSH terms: 'thyrotropin secreting pituitary adenoma' OR 'TSHoma' OR 'thyrotropinoma.' All case reports, case series and cohort studies published in English between 1991 and October 2020 were considered. Articles published before 1991 frequently missed important information, as listed subsequently, and were, therefore, not included. The results of the search process are summarized in a flowchart (Fig. 1). Exclusion criteria were as follows:

- (1) diagnosis other than TSHoma,
- (2) missing more than six of the following eight characteristics: age at diagnosis, clinical presentation, presence/absence of goitre, visual field assessment, level of TSH and free T4 (FT4), the diameter of the adenoma, or treatment modalities,
- (3) age under 16 years as their reference ranges of thyroid hormones and TSH differ from those of adults.

Diagnosis of TSHoma had to be confirmed by dynamic testing or TSH had to be unsuppressed in a hyperthyroid patient with a pituitary adenoma with positive immunohistochemistry to be included in the systematic review. We included 107 articles in this review consisting of 91 case reports, 18 case series (including ≥ 5 cases) and 5 cohort studies resulting in a total of 535 cases. The case series and cohort studies included in the review are summarized in the supplemental table (see section on [Supplementary materials](#) at the end of the article).

Statistical analysis

Statistical analysis was performed using the statistical package SPSS (version 26; Armonk, NY, IBM Corp).

Figure 1 Flowchart of the literature study.

Descriptive statistics were used to analyse population characteristics. Distributions of continuous data were tested for normality by the Kolmogorov-Smirnov test and Q-Q plot. To investigate a correlation between two variables, Spearman's correlation was used. Study population characteristics and laboratory measurements were presented as mean values $\pm$ s.d. if normally distributed and as median with lower and upper quartile when not normally distributed.

Results

General characteristics

The female to male ratio for TSHoma was 1.07. The mean age at diagnosis was 46 ± 6 years in the case series and 45 ± 14 years in the case reports (Table 1). Symptoms and signs of hyperthyroidism were present in 75% of patients

Review	C De Herdt and others	Thyrotropin-stimulating pituitary adenoma	185:2	R67
---------------	-----------------------	---	--------------	------------

Table 1 Characteristics of the patients at the time of diagnosis and treatment. The mean values of the study population characteristics and laboratory measurements of the case series and cohort studies are presented as mean values $\pm$ s.d. or as n (%) if normally distributed and as median with lower and upper quartile when not normally distributed.

	Case series and cohort studies	Not reported	Case reports	Not reported	All data
Reported cases, n	444		91		535
(A) Demographics					
Males	219 (49.3)		40 (44.0)		259 (48.4)
Age (years)	46 $\pm$ 6		45 $\pm$ 14		
(B) Clinical presentation					
Hyperthyroidism	302 (75.3)	43 (9.7)	64 (73.6)	4 (4.4)	366 (75.0)
AF and/or cardiac failure	25 (9.5)	181 (40.8)	14 (15.9)	3 (3.3)	39 (11.1)
Goitre	109 (52.7)	237 (53.4)	46 (63.9)	19 (20.9)	155 (55.5)
Visual field defect	86 (25.2)	103 (23.2)	14 (23.3)	31 (34.1)	100 (24.9)
(C) Biochemical presentation					
TSH [†] (mU/L)	6.75 (4.02–11.90)		5.16 (3.20–7.43)*		
FT4 (pmol/L)	35.7 $\pm$ 8.5		41.5 $\pm$ 15.3*		
TRAbs			4 (4.4)		
(D) Adenoma					
Macroadenoma	334 (77.9)	15 (3.4)	62 (78.5)	7 (7.7)	396 (76.9)
Diameter (mm)	21.5 $\pm$ 7.9		19.8 $\pm$ 13.6		
Ectopic tumour			5 (5.5)		
(E) Co-secretion					
Plurihormonal	140 (35.9)	54 (12.2)	34 (49.3)	22 (24.2)	174 (37.9)
Co-secretion of GH	78 (55.7)		22 (64.7)		100 (57.5)
Co-secretion of prolactin	56 (40.0)		16 (47.1)		72 (41.4)
Co-secretion of ACTH			0		
Co-secretion of FSH			9 (26.5)		
Co-secretion of LH			3 (8.8)		
(F) Treatment					
Transsphenoidal resection	396 (89.2)		80 (87.9)		469 (89.0)
SSA preoperatively	143 (36.1)		26 (32.5)		169 (36.0)
SSA post-operatively	62 (15.7)		23 (28.8)		85 (18.1)
Radiotherapy	74 (16.7)		7 (7.7)		81 (15.1)
SSA monotherapy			8 (8.8)		

[†]Values presented as median (lower and upper quartile); *exclusion of (10) cases who underwent a thyroidectomy before diagnosis of TSHoma.

ACTH, adrenocorticotropic hormone; AF, atrial fibrillation; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TRAbs, thyroid-stimulating hormone receptor antibodies.

and 55.5% had a goitre. In half of the cases, the presence of a goitre was not assessed/reported. Atrial fibrillation or heart failure were seen in 11.1% of the cases. Visual field defects were noticed in 100 patients (24.9%).

The median TSH at diagnosis was 6.75 (4.02–11.90) mU/L in the case series and 5.16 (3.20–7.43) mU/L in the case reports whereas FT4 averaged 35.7 $\pm$ 8.5 and 41.5 $\pm$ 15.3 pmol/L, respectively. Ten cases underwent total thyroidectomy before the diagnosis of TSHoma and had a median TSH of 3.75 (2.16–25.3) mU/L.

The majority (76.9%) of TSHomas were macroadenoma with a mean diameter of 21.5 $\pm$ 7.9 mm and 19.8 $\pm$ 13.6 mm in the case series and reports, respectively. Five out of 91 case reports had an ectopic TSHoma, localized in the nasopharynx in 4 cases and in the sinus sphenoidalis in 1 case. Immunohistostaining revealed that the majority of

adenomas (62.1%) were pure TSHomas. Co-secretion with growth hormone (GH) was seen in 57.5% and co-secretion with prolactin was seen in 41.4% of the plurihormonal adenoma. In the case reports, co-secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were reported in 26.5 and 8.8% of the plurihormonal adenoma, respectively. No case had co-secretion with adrenocorticotropic hormone (ACTH). Plurihormonality was more frequent in macroadenoma (51.1%) than in microadenoma (27.3%). Table 2 illustrates which mixed pituitary adenoma resulted in overproduction of the co-secreted pituitary hormone(s). Eleven out of 23 adenomas with positive immunohistostaining for GH had acromegaly. Three out of 16 adenomas with positive immunohistostaining for prolactin had elevated prolactin levels. Overproduction of FSH and LH were

Review	C De Herdt and others	Thyrotropin-stimulating pituitary adenoma	185:2	R68
---------------	-----------------------	---	--------------	------------

Table 2 Overview of the results of immunohistochemical examination of the adenoma vs biochemical overproduction. Analysis of the case reports.

Hormone	Immunohistostaining	Biochemical overproduction	Not reported
Growth hormone	22	11	6
Prolactin	16	3	4
ACTH	0	0	0
FSH	9	1	4
LH	3	1	0

ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

seen in respectively one out of nine and one out of three adenomas with positive immunostaining for the gonadotrophins.

Transsphenoidal resection was performed in 89% of cases of which 36% were preoperatively treated with a somatostatin analogue (SSA) to normalize the thyroid function. Residual pituitary tumour was present in 33.5% of the operated cases. The treatment modalities of the case reports were evaluated in detail. Of the 91 case reports, 80 cases were operated of which 20 had residual disease. Of these 20 cases, 16 were post-operatively treated with SSA of which 13 had a stable disease with a median follow-up time of 12 (4–16) months. Five out of 80 operated case reports had a relapse. The median follow-up time was 11 (5–24) months. Relapse occurred within the first year after surgery in two out of five cases (median time to relapse was 12 months).

Treatment with pituitary radiation therapy including stereotactic gamma knife radiosurgery was performed in 15.1% of cases.

We found no correlation between the level of FT4 or TSH and the diameter of the adenoma or the presence of a goitre or atrial fibrillation/heart failure. We did observe a significant correlation between the diameter of the adenoma and residual pituitary adenoma ($r=0.490$, $P < 0.001$). However, in patients preoperatively treated with SSA, this correlation was absent. There were no differences in age or sex between those with vs without residual pituitary adenoma.

Concomitant Graves' disease

Four patients with TSHoma had concomitant Graves' disease (5, 6, 7, 8). The first case was a 55-year-old man who presented with atrial fibrillation, heat intolerance, tremor and a goitre (5). Laboratory tests revealed an unmeasurable high FT4 with a TSH of 0.75 mU/L. Thyroid-stimulating hormone receptor antibodies (TRAbs) were positive (15.28 IU/L, normal value < 2). Graves' disease was diagnosed, and methimazole was started. Due to visual field defects, an MRI

of the pituitary was performed revealing a macroadenoma. The adenoma was resected and immunohistochemical staining was positive for TSH and prolactin. One year post-operatively, an elevated FT4 (36.36 pmol/L) with a mildly suppressed TSH (0.22 mU/L) was seen. The MRI showed no residual tumour. TRAbs were still elevated (5.62 IU/L), and methimazole was restarted. The second patient was a 55-year-old woman presenting with classical symptoms of hyperthyroidism and a goitre (6). Laboratory tests showed an elevated FT4 (51.07 pmol/L) with an inappropriately normal TSH (0.337 mU/L). TRAbs were positive (5.63 IU/L). The pituitary MRI revealed a macroadenoma. The adenoma was resected and was immunohistochemically positive for TSH. Post-operatively, the symptoms of hyperthyroidism did not improve, and FT4 remained elevated (30.72 pmol/L) with an inappropriately normal TSH of 0.765 mU/L. TRAbs remained mildly elevated (6.11 IU/L), and methimazole was started. The third patient was a 40-year-old woman who underwent an MRI because of a headache which revealed a microadenoma (7). The patient had no symptoms of hyperthyroidism. Laboratory tests revealed an elevated FT4 (29.6 pmol/L) with only a mildly suppressed TSH of 0.27 mU/L. TRAbs were positive (5.0 IU/L). Graves' disease was diagnosed, and methimazole was started. The headache relapsed and an MRI was repeated showing enlargement of the adenoma. Thyroid-releasing hormone (TRH) stimulation test showed an impaired response of TSH. The adenoma was resected and immunohistostaining was positive for TSH. The fourth patient was a 36-year-old woman with symptoms of hyperthyroidism and a goitre (8). Laboratory tests revealed an elevated FT4 (37.6 pmol/L) with a normal TSH (1.8 mU/L) and positive TRAbs (14 IU/L). Radionuclide scan showed a diffusely increased uptake. Graves' disease was diagnosed, and a partial thyroidectomy was performed. Hyperthyroidism recurred with an elevated FT4 (48.3 pmol/L) and a non-suppressed TSH of 5.4 mU/L. TRH stimulation test showed an impaired response of TSH. An MRI of the pituitary revealed a macroadenoma. The patient was pre-treated with an SSA after which the adenoma was

resected. Immunohistochemistry showed positive staining for TSH. Post-operative thyroid function test remained normal throughout 18 years of follow-up.

Thyroid cancer

Nine out of 91 case reports had a thyroid carcinoma (9, 10, 11, 12, 13, 14). In all patients, the carcinoma was found on ultrasound performed in the context of hyperthyroidism or a goitre, except for one case where the finding of thyroid carcinoma was years before the diagnosis of TSHoma (15). Eight patients had a papillary thyroid carcinoma with a diameter ranging between 12 and 40 mm and the presence of lymph metastases in two cases (12, 15). One patient had a follicular thyroid carcinoma of 15 mm (15).

Thyroid storm

Two cases of TSHoma complicated with a thyroid storm peri- or post-operatively have been published (16, 17). The first patient was an 18-year-old man presenting with a headache without signs of hyperthyroidism (16). The MRI of the brain revealed a large mass. Craniopharyngioma was suspected, and the tumour was immediately resected. The day before the operation, the patient's TSH level was 6.4 mU/L. FT4 was not measured. The patient underwent right frontal craniotomy with debulking of the tumour. During the surgical procedure, the patient developed tachycardia and hypertension. Immediately post-operatively, the patient had a fever and became lethargic and confused without arguments of infection. Thyroid function test revealed a highly elevated FT4 of 87.5 pmol/L. The patient was treated with propylthiouracil, β -adrenergic blockade and dexamethasone. Histopathological examination of the tumour revealed a pituitary adenoma with positive immunohistostaining for TSH and GH. The level of IGF-1 was not measured. Post-operative thyroid levels normalized. Twelve weeks post-operatively thyroid hormone levels rose again and a residual tumour was shown on the MRI for which SSAs were started.

The second case was a 54-year-old woman presenting with longstanding symptoms of hyperthyroidism (17). Laboratory tests showed an FT4 of 89.8 pmol/L and a TSH of 9.19 mU/L. An MRI of the pituitary revealed a macroadenoma. Transsphenoidal resection of the adenoma was performed. Immediately thereafter the patient developed a fever, hypertension and tachycardia while still being intubated. She was treated with hydrocortisone and potassium iodide. Immunohistochemically the adenoma

was positive for TSH and GH. IGF-1 was normal. Thyroid hormones remained elevated and SSAs were started one year post-operatively which normalized the thyroid hormone levels.

Discussion

TSHomas are rare, occurring in one in a million people and representing 0.5–3% of all pituitary adenoma (1, 2, 3, 4). In the last three decades, an increased incidence has been described, which is probably due to an increased practitioner awareness, the introduction of ultrasensitive immunometric TSH assays and routine measurement of thyroid function. TSHomas are equally distributed between men and women (female to male ratio of 1.07 in our analysis) (2). Age of diagnosis is variable but is mostly in the fifth and sixth decade of life (1, 2). In our analysis of the case series, mean age at diagnosis was 46 ± 6 years. Because of the often delayed diagnosis of TSHoma, age at diagnosis probably differs from the age of onset of disease. In the past, many patients had a long history of hyperthyroidism or were misdiagnosed with another thyroid disease that led to inappropriate treatment as was seen in 11% of the studied cases.

Pathogenesis and plurihormonality

The molecular mechanisms involved in thyrotrope adenomatous transformation are still unknown. TSHomas are monoclonal in origin. No mutations in oncogenes commonly activated in human cancer have been identified. TSHoma might arise after a transforming event providing a gain of proliferative function followed by a secondary mutation favouring tumour progression. Overexpression of the pituitary-specific positive transcription factor 1 (Pit-1) gene has been demonstrated, but its exact role in the pathogenesis is not clear (1, 2).

In our analysis, 62.1% of the adenomas were pure TSHomas and 37.9% co-secreted another anterior pituitary hormone (9, 10), most frequently GH (57.5%) and prolactin (41.4%), possibly leading to acromegaly and amenorrhoea or galactorrhoea, respectively (1, 3).

These mixed pituitary adenomas can be explained by the expression of common transcription factors by thyrotrophic and lactotrophic cells, such as Pit-1. Plurihormonality does not always translate into hormonal overproduction, called biological silent adenoma, as

Review	C De Herdt and others	Thyrotropin-stimulating pituitary adenoma	185:2	R70
--------	-----------------------	---	-------	-----

also shown in our analysis (3). Until now no case of a mixed pituitary TSHoma with hypercortisolism has been reported.

Clinical features

Symptoms and signs of hyperthyroidism, present in 75% of cases, are often mild in comparison to primary hyperthyroidism. A goitre was present in 55.5%. Thyrotoxic heart failure and atrial fibrillation were found to be present in 11.1% of cases (2, 3).

The majority of TSHomas are large and invasive at the time of diagnosis which explains why 30–40% of patients are present with symptoms of local compression including temporal visual field defects (2, 3, 4). In our analysis, visual field defects were noticed in 24.9% of cases. Unilateral exophthalmos is reported in a few cases due to orbital invasion by the TSHoma and has to be distinguished from unilateral and bilateral exophthalmos secondary to Graves' disease (2). A controversial subject is the concomitant finding of thyroid cancer in patients with TSHoma. In our literature search, 9 out of 91 case reports had a diagnosis of thyroid carcinoma, as compared to an incidence of 17.6 per 100 000 persons per year in the general population (18). The higher prevalence of thyroid cancer in patients with TSHoma may be attributed to the frequent use of ultrasound in this particular population.

Diagnosis

A TSHoma is considered when the TSH level is inappropriately normal or elevated in a hyperthyroid patient. The first step in diagnosing central hyperthyroidism is to repeat laboratory testing to exclude assay interference and transitory changes in thyroid hormone levels which may be seen in a variety of conditions such as interference from medication (e.g. oestrogens), pregnancy, non-thyroidal illness and subacute autoimmune thyroiditis (2). A TSHoma must be considered in patients who underwent a thyroidectomy or received radioactive iodine and are unable to normalize their TSH level despite increasing the dose of L-thyroxine (4). The coexistence of Graves' disease and TSHoma has been reported in four case reports (5, 6, 7, 8).

Diagnosing a TSHoma is challenging. In 2013, the European Thyroid Association proposed a diagnostic approach (1). A diagnostic flowchart is shown in Fig. 2. The first step in a patient with central hyperthyroidism is the measurement of glycoprotein hormone alpha-subunit

(α -GSU), which is elevated in about 70% of the TSHoma, in particular, in macroadenoma (1). A normal level makes the diagnosis less likely but does not exclude it. In the past, the α -GSU to TSH ratio was determined. However, using the ratio cut-off to suggest a TSHoma must take the circulating levels of LH and FSH into account. This leads to a much higher ratio in postmenopausal women in contrast to men. Therefore, the use of a single ratio cut-off of more than one as indicative for a TSHoma is no longer recommended (3, 4).

In patients with resistance to thyroid hormone (RTH), thyroid function tests are indistinguishable from those in TSHoma. RTH is an autosomal dominant inherited mutation in the β -isoform of the thyroid hormone receptor leading to reduced responsiveness of target tissues to thyroid hormones. Because of the autosomal dominant character, the first clue is a similar thyroid biochemical phenotype in first-degree relatives (3). The serum α -GSU is normal in patients with RTH. A mutation in the thyroid- β gene is present in 85%. A comparison between TSHoma and RTH is summarized in Table 3.

To diagnose TSHoma, dynamic testing is advised. Dynamic testing includes a TRH stimulation test and a liothyronine (T3) suppression test. In healthy controls and in patients with RTH, TSH level increases after i.v. administration of 200 μ g TRH but not in up to 85% of subjects with TSHoma (3). With the T3 suppression test, the patient is given a dose of 80 to 100 μ g liothyronine a day during 8–10 days. TSH is not suppressed in response to the T3 administration in all subjects with TSHoma. This dynamic test is considered the most sensitive (100%) and specific but is contraindicated in elderly patients and in those with cardiovascular disease because it can induce tachycardia and in some heart failure (1, 4). The T3 suppression test is, therefore, only used if there is uncertainty about the diagnosis (4).

An MRI of the pituitary is only recommended in the presence of dynamic testing suggestive for TSHoma. The majority of TSHomas are macroadenoma invading the surrounding structures (3, 4). Our analysis showed 76.9% of TSHoma to be macroadenoma with a mean diameter of 21.5 ± 7.9 mm in the case series. The presence of a macroadenoma in a patient with hyperthyroidism is highly suggestive for a TSHoma, particularly if associated with an elevated serum α -GSU. We found no correlation between the diameter of the adenoma and the level of FT4 or TSH. The finding of a microadenoma is not specific for a TSHoma and can be seen as an incidental finding in 10% of the normal population, including patients with RTH (3). So far, only five cases of an ectopic TSHoma in adults have been reported (19, 20, 21, 22, 23).

Figure 2
Diagnostic flowchart.

Treatment

Treatment guidelines published by the European Thyroid Association in 2013 and updated in 2019 are based on case series and clinical experience (1, 2, 3). The treatment of choice is transsphenoidal resection of the adenoma as was performed in 89% of the analysed cases. According to the largest published series, surgery can effectively restore thyroid function in up to 80% of patients with TSHoma (3). In comparison to other pituitary adenomas, TSHoma tends to have a higher degree of microscopic invasion and intra- and peritumoural fibrosis. Tumour invasion has been reported to be associated with a worse surgical outcome (2, 4). We also describe a worse clinical outcome in relation to the diameter of the adenoma, but not in relation to TSH or FT4 levels, age or sex.

SSAs have inhibitory effects on the secretion of TSH, ACTH and GH. Most thyrotrophic cells express a variable number of somatostatin receptor (SSTR), particularly SSTR 2 and SSTR 5 (4). In case of surgical failure, SSAs

have been found to normalize TSH secretion in 90% of patients and reduce tumour size in 30 to 50% of adenoma within the first 3 months of treatment. Side effects of SSA are hyperglycaemia, diarrhoea and cholelithiasis, all with a prevalence between 10 and 30%. Administration of SSA preoperatively could improve surgical outcome by reducing tumour size, but until now there is no consensus since some studies did not observe improved outcomes and because preoperative euthyroid status was not associated with a higher rate of remission (2, 24). Importantly, in subjects preoperatively treated with SSA, we could not observe a link between outcome and the diameter of the adenoma. Another reason suggested to give SSA preoperatively is to prevent a thyroid storm but this is not evidence-based. We found two cases who suffered from a thyroid storm post-operatively (16, 17). Pre-treatment with SSA does not always lead to a euthyroid stage before surgery (25). In our analysis, 6 out of 26 case reports pre-treated with SSA did not become euthyroid before operation. Some authors have recently suggested that SSA may play a role

Review	C De Herdt and others	Thyrotropin-stimulating pituitary adenoma	185:2	R72
--------	-----------------------	---	-------	-----

Table 3 Comparison between the characteristics of thyrotropin-secreting pituitary adenoma (TSHoma) and resistance to thyroid hormones (RTH).

	TSHoma	RTH
Anamnesis/clinical examination		
Positive familial history	No	Yes
Visual field defect	30–40%	No
Atrial fibrillation	Mostly not*	Mostly not*
Goitre	Mostly yes (70%)	Mostly yes (80%)
Epidemiology		
Incidence	1–2/million	1/40 000
Sex	M = F	M = F
Age at diagnosis	Mostly 40–50 years	Mostly at childhood
Biochemical		
TSH	↑	↑
α-GSU	↑	=
Dynamic testing		
TRH stimulation test	TSH mostly stable (85%)	TSH ↑**
T3 suppression test	TSH unsuppressed	TSH ↓***
DNA mutation analysis	Negative	positive in 85%****
MRI pituitary	Macro- (80%)/micro-adenoma	Microadenoma is possible
Treatment	Surgery	L-thyroxine if necessary

*Less vs primary hyperthyroidism; **rise of TSH to 5–30 mU/L after 20 min; ***TSH < 1 mU/L; ****mutation in the thyroid-β gene. M, males; F, females; α-GSU, glycoprotein hormone alpha-subunit; ↑, increase; ↓, decrease; =, within the reference range.

in the treatment of TSHoma as primary therapy reducing the risk of post-operative hypopituitarism (24). In 4 case series including 131 patients, 21 subjects (16%) developed hypopituitarism between 4 months and 15 years after surgery (26, 27, 28, 29). During a mean follow-up time of 12 (7–15) months, seven out of the eight analysed case reports treated with SSA in monotherapy had normalization of TSH secretion. Studies are needed to objectify the role of SSA as primary therapy and to determine the duration of administration.

Before the introduction of SSA, pituitary radiation therapy was used when surgery was contraindicated or in patients with residual or recurrent TSHoma (2). As a result of the availability of effective SSA and the risk of panhypopituitarism, radiation therapy is currently much less used.

Total thyroidectomy or thyroid ablation with radioiodine are only indicated when pituitary surgery is not curative and the patient suffers from life-threatening hyperthyroidism which is very rare in TSHoma (3). In our analysis, one case underwent total thyroidectomy because of refusal of pituitary surgery (30).

Follow-up

After complete tumour resection, TSH is undetectable in the immediate post-operative phase (with a lowest level the first and second week post-operatively) and gradually increases back to normal levels after several months or may

occasionally remain permanently low (2). An undetectable TSH level one week after surgery is indicative of complete resection (1). Transient levothyroxine replacement is required. Until now, there is no definition for biochemical remission. Some authors focus on TSH and thyroid hormone levels while others evaluate remission by a normal response to TRH stimulation or T3 suppression test (2). The most sensitive and specific test to document complete removal of the adenoma is a T3 suppression test (1). Recurrence has been reported in up to 30% of the case series of Kirkman *et al.* and van Varsseveld *et al.* with a median follow-up of 7 years (range 1–21) (31, 32). In our analysis, only 5 out of 80 operated case reports relapsed but no follow-up was available for 36 cases. Larger studies are needed to obtain accurate data. Recurrence seems to be infrequent in the first year after successful surgery (1). The current guidelines suggest to clinically and biochemically evaluate the patient three times in the first post-operative year and once yearly thereafter. Pituitary imaging is recommended every 2–3 years regardless of thyroid function test and earlier if thyroid hormone levels increase or visual field defects occur (1).

Conclusion

TSHoma is a very rare cause of hyperthyroidism. In our review of 535 cases, TSHoma occurred equally in men and women, mostly at their fifth and sixth decade. Three-

quarters are present with signs of hyperthyroidism, 55.5% have a goitre and visual field defects are present in one-quarter of patients. Most TSHomas were macroadenoma. Plurihormonality is more frequently seen in macroadenoma. However, only one-quarter of these patients also have hormonal overproduction, mostly of GH and prolactin. In rare cases, there is a concomitant diagnosis of thyroid carcinoma. Diagnosing a TSHoma is challenging. Misdiagnosis can lead to inappropriate therapy as was seen in one-tenth of patients. The diagnosis of a TSHoma includes either a TRH stimulation test or a T3 suppression test, followed by an MRI of the pituitary. The treatment of choice for TSHoma is transsphenoidal resection with or without adjunctive SSA therapy. Tumour invasion has been reported to lead to poor surgical outcomes (2). We are the first to report a link between the diameter of the TSHoma and the residual pituitary tumour.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-21-0162>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Author contribution statement

C D H and E P performed the literature search and analyzed the data. C D H, E P and C D B discussed the process of literature search and content of the manuscript. C D H wrote the first draft of the manuscript and made figures/tables. All authors discussed the data and edited the manuscript. C D H and C D B are guarantors of this work and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

- Beck-Peccoz P, Lania A, Beckers A, Chatterjee K & Wemeau JL. 2013 European Thyroid Association guidelines for the diagnosis and treatment of thyrotropin-secreting pituitary tumors. *European Thyroid Journal* 2013 **2** 76–82. (<https://doi.org/10.1159/000351007>)
- Amlashi FG & Tritos NA. Thyrotropin-secreting pituitary adenomas: epidemiology, diagnosis, and management. *Endocrine* 2016 **52** 427–440. (<https://doi.org/10.1007/s12020-016-0863-3>)
- Beck-Peccoz P, Giavoli C & Lania A. A 2019 update on TSH-secreting pituitary adenomas. *Journal of Endocrinological Investigation* 2019 **42** 1401–1406. (<https://doi.org/10.1007/s40618-019-01066-x>)
- Tjornstrand A & Nystrom HF. Diagnosis of endocrine disease: diagnostic approach to TSH-producing pituitary adenoma. *European Journal of Endocrinology* 2017 **177** R183–R197. (<https://doi.org/10.1530/EJE-16-1029>)
- Li J, Tan H, Huang J, Luo D, Tang Y, Yu R & Huang H. Case report of recurrent atrial fibrillation induced by thyrotropin-secreting pituitary adenoma with Graves' disease. *Medicine* 2018 **97** e11047. (<https://doi.org/10.1097/MD.00000000000011047>)
- Fu J, Wu A, Wang X & Guan H. Concurrent Graves' disease and TSH secreting pituitary adenoma presenting suppressed thyrotropin levels: a case report and review of the literature. *Frontiers in Endocrinology* 2020 **11** 523. (<https://doi.org/10.3389/fendo.2020.00523>)
- Arai N, Inaba M, Ichijyo T, Kagami H & Mine Y. Thyrotropin-producing pituitary adenoma simultaneously existing with Graves' disease: a case report. *Journal of Medical Case Reports* 2017 **11** 9. (<https://doi.org/10.1186/s13256-016-1172-4>)
- Kamoun M, d'Herbomez M, Lemaire C, Fayard A, Desailly R, Huglo D & Wemeau JL. Coexistence of thyroid-stimulating hormone-secreting pituitary adenoma and graves' hyperthyroidism. *European Thyroid Journal* 2014 **3** 60–64. (<https://doi.org/10.1159/000355386>)
- Unluturk U, Sriprapradang C, Erdogan ME, Emral R, Guldiken S, Refetoff S & Gullu S. Management of differentiated thyroid cancer in the presence of resistance to thyroid hormone and TSH-secreting adenomas: a report of four cases and review of the literature. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 2210–2217. (<https://doi.org/10.1210/jc.2012-4142>)
- Poggi M, Monti S, Pascucci C & Toscano V. A rare case of follicular thyroid carcinoma in a patient with thyrotropin-secreting pituitary adenoma. *American Journal of the Medical Sciences* 2009 **337** 462–465. (<https://doi.org/10.1097/MAJ.0b013e3181949948>)
- Kiatpanabhikul P, Shuangshoti S, Chantra K, Navicharern P, Kingpetch K, Hounngam N & Snaboon T. A case of coexistence of TSH/GH-secreting pituitary tumor and papillary thyroid carcinoma: challenges in pathogenesis and management. *Journal of Clinical Neuroscience* 2017 **41** 78–80. (<https://doi.org/10.1016/j.jocn.2017.02.050>)
- Kishida M, Otsuka F, Kataoka H, Yokota K, Oishi T, Yamauchi T, Doihara H, Tamiya T, Mimura Y, Ogura T *et al.* Hyperthyroidism in a patient with TSH-producing pituitary adenoma coexisting with thyroid papillary adenocarcinoma. *Endocrine Journal* 2000 **47** 731–738. (<https://doi.org/10.1507/endocrj.47.731>)
- Gasparoni P, Rubello D, Persani L & Beck-Peccoz P. Unusual association between a thyrotropin-secreting pituitary adenoma and a papillary thyroid carcinoma. *Thyroid* 1998 **8** 181–183. (<https://doi.org/10.1089/thy.1998.8.181>)
- Inoue H, Shinojima N, Ueda R, Yamamoto K, Ishii N, Igata M, Kawashima J, Araki E, Iwase H, Mikami Y *et al.* A rare case of thyrotropin-secreting pituitary adenoma coexisting with papillary thyroid carcinoma presenting with visual disturbance without hyperthyroidism. *World Neurosurgery* 2018 **119** 394–399. (<https://doi.org/10.1016/j.wneu.2018.07.274>)
- Perticone F, Pigliaru F, Mariotti S, Deiana L, Furlani L, Mortini P & Losa M. Is the incidence of differentiated thyroid cancer increased in patients with thyrotropin-secreting adenomas? Report of three cases from a large consecutive series. *Thyroid* 2015 **25** 417–424. (<https://doi.org/10.1089/thy.2014.0222>)
- Page KA, Roehmholdt BF, Jablonski M & Mayerson AB. Development of thyroid storm after surgical resection of a thyrotropin-secreting pituitary adenoma. *Endocrine Practice* 2008 **14** 732–737. (<https://doi.org/10.4158/EP.14.6.732>)
- Fujio S, Ashari, Habu M, Yamahata H, Moinuddin FM, Bohara M, Arimura H, Nishijima Y & Arita K. Thyroid storm induced by TSH-secreting pituitary adenoma: a case report. *Endocrine Journal* 2014 **61** 1131–1136. (<https://doi.org/10.1507/endocrj.14-0278>)
- Olson E, Wintheiser G, Wolfe KM, Droessler J & Silberstein PT. Epidemiology of thyroid cancer: a review of the National Cancer

Review	C De Herdt and others	Thyrotropin-stimulating pituitary adenoma	185:2	R74
--------	-----------------------	---	-------	-----

- Database, 2000–2013. *Cureus* 2019 **11** e4127. (<https://doi.org/10.7759/cureus.4127>)
- 19 Foppiani L, Del Monte P, Ruelle A, Bandelloni R, Quilici P & Bernasconi D. TSH-secreting adenomas: rare pituitary tumors with multifaceted clinical and biological features. *Journal of Endocrinological Investigation* 2007 **30** 603–609. (<https://doi.org/10.1007/BF03346356>)
 - 20 Cooper DS & Wenig BM. Hyperthyroidism caused by an ectopic TSH-secreting pituitary tumor. *Thyroid* 1996 **6** 337–343. (<https://doi.org/10.1089/thy.1996.6.337>)
 - 21 Nagai K, Sakata S, Wu CC, Wada H, Yokoyama K, Takada M, Kashiwai T & Tokimitsu N. Thyrotropin-secreting pituitary adenoma: a case report. *Endocrinologia Japonica* 1992 **39** 413–419. (<https://doi.org/10.1507/endocrj1954.39.413>)
 - 22 Koriyama N, Nakazaki M & Hashiguchi H, Aso K, Ikeda Y, Kimura T, Eto H, Hirano H, Nakano S, Tei C. Thyrotropin-producing pituitary adenoma associated with Graves' disease. *European Journal of Endocrinology* 2004 **151** 587–594. (<https://doi.org/10.1530/eje.0.1510587>)
 - 23 Usui T, Izawa S, Sano T, Tagami T, Nagata D, Shimatsu A, Takahashi JA & Naruse M. Clinical and molecular features of a TSH-secreting pituitary microadenoma. *Pituitary* 2005 **8** 127–134. (<https://doi.org/10.1007/s11102-005-3759-4>)
 - 24 Cossu G, Daniel RT, Pierzchala K, Berhouma M, Pitteloud N, Lamine F, Colao A & Messerer M. Thyrotropin-secreting pituitary adenomas: a systematic review and meta-analysis of postoperative outcomes and management. *Pituitary* 2019 **22** 79–88. (<https://doi.org/10.1007/s11102-018-0921-3>)
 - 25 Macchia E, Gasperi M, Lombardi M, Morselli L, Pinchera A, Acerbi G, Rossi G & Martino E. Clinical aspects and therapeutic outcome in thyrotropin-secreting pituitary adenomas: a single center experience. *Journal of Endocrinological Investigation* 2009 **32** 773–779. (<https://doi.org/10.1007/BF03346535>)
 - 26 Rotermund R, Riedel N, Burkhardt T, Matschke J, Schmidt NO, Aberle J & Flitsch J. Surgical treatment and outcome of TSH-producing pituitary adenomas. *Acta Neurochirurgica* 2017 **159** 1219–1226. (<https://doi.org/10.1007/s00701-017-3105-4>)
 - 27 Yamada S, Fukuhara N, Horiguchi K, Yamaguchi-Okada M, Nishioka H, Takeshita A, Takeuchi Y, Ito J & Inoshita N. Clinicopathological characteristics and therapeutic outcomes in thyrotropin-secreting pituitary adenomas: a single-center study of 90 cases. *Journal of Neurosurgery* 2014 **121** 1462–1473. (<https://doi.org/10.3171/2014.7.JNS1471>)
 - 28 Gatto F, Grasso LF, Nazzari E, Cuny T, Anania P, Di Somma C, Colao A, Zona G, Weryha G, Pivonello R *et al.* Clinical outcome and evidence of high rate post-surgical anterior hypopituitarism in a cohort of TSH-secreting adenoma patients: might somatostatin analogs have a role as first-line therapy? *Pituitary* 2015 **18** 583–591. (<https://doi.org/10.1007/s11102-014-0611-8>)
 - 29 Sanno N, Teramoto A & Osamura RY. Long-term surgical outcome in 16 patients with thyrotropin pituitary adenoma. *Journal of Neurosurgery* 2000 **93** 194–200. (<https://doi.org/10.3171/jns.2000.93.2.0194>)
 - 30 Daousi C, Foy PM & MacFarlane IA. Ablative thyroid treatment for thyrotoxicosis due to thyrotropin-producing pituitary tumours. *Journal of Neurology, Neurosurgery, and Psychiatry* 2007 **78** 93–95. (<https://doi.org/10.1136/jnnp.2006.095661>)
 - 31 Kirkman MA, Jaunmuktane Z, Brandner S, Khan AA, Powell M & Baldeweg SE. Active and silent thyroid-stimulating hormone-expressing pituitary adenomas: presenting symptoms, treatment, outcomes, and recurrence. *World Neurosurgery* 2014 **82** 1224–1231. (<https://doi.org/10.1016/j.wneu.2014.03.031>)
 - 32 van Varsseveld NC, Bisschop PH, Biermasz NR, Pereira AM, Fliers E & Drent ML. A long-term follow-up study of eighteen patients with thyrotrophin-secreting pituitary adenomas. *Clinical Endocrinology* 2014 **80** 395–402. (<https://doi.org/10.1111/cen.12290>)

Received 16 March 2021

Revised version received 4 June 2021

Accepted 15 June 2021