DIAGNOSIS OF ENDOCRINE DISEASE

Diagnostic approach to TSH-producing pituitary adenoma

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Abstract

Thyrotropin (TSH)-secreting adenomas (TSHomas) are the rarest form of pituitary adenomas, and most endocrinologists will see few cases in a lifetime, if any. In most cases, the diagnostic approach is complicated and cases may be referred after being presented as a syndrome of inappropriate TSH secretion or as a pituitary mass. This review aims to cover the past, present and possible future diagnostic approaches to TSHomas, including different clinical presentations, laboratory assessment and imaging advances. The differential diagnoses will be discussed, as well as possible coexisting disorders. By evaluating the existing reports and reviews describing this rare condition, this review aims to present a clinically practical suggestion on the diagnostic workup for TSHomas, Major advances and scientific breakthroughs in the imaging area in recent years, facilitating diagnosis of TSHomas, support the belief that future progress within the imaging field will play an important role in providing methods for a more efficient diagnosis of this rare condition.

Introduction

In 1960, Jailer and Holub proposed that the pituitary could be responsible for excessive production of thyrotropin (TSH) and secondary hyperthyroidism (1). It was later confirmed (2) that the underlying cause was a TSH-secreting pituitary adenoma (TSHoma). After that, TSHoma reports were scarce in the literature. It was not until the 1980s that a few limited reports on the diagnosis of TSHomas were published (3, 4, 5, 6, 7, 8). Subsequently, the diagnostic and therapeutic management of these rare pituitary adenomas has evolved substantially. This is due to the following reasons: use of ultrasensitive TSH methods since the late 1980s (9, 10); the introduction of the concept ‘syndrome of inappropriate TSH secretion’ (11); advances in imaging procedures, moving from computed tomography (CT) to magnetic resonance imaging (MRI) with superior visualization of the pituitary area (12); and the use of somatostatin analogs in the therapeutic management of these patients (13, 14).

Invited Author’s profile

Helena Filipsson Nyström is a senior consultant within thyroidology at Sahlgrenska University Hospital in Göteborg, Sweden, and the leader of the largest thyroid unit in the country. Her research currently focuses on mental consequences in two groups of patients: women with Graves’ disease and children whose mothers have had mild iodine deficiency during pregnancy. She is the national representative for the Iodine Global Network and is part of the EUthyroid collaboration.
Table 1  Case series with >5 TSHoma cases is presented with demographic and radiologic data including the plurihormonal activity from biochemical and immunohistochemical evaluation.

<table>
<thead>
<tr>
<th>Study (reference no)</th>
<th>Study period</th>
<th>Cases (n)</th>
<th>Men, n (%)</th>
<th>Macroadenoma (≥10 mm), n (%)</th>
<th>Invasiveb (%)</th>
<th>Mean age, years (range)</th>
<th>Cohort</th>
<th>Plurihormonal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertholon-Gregoire et al. (6)</td>
<td>1971–1996</td>
<td>12</td>
<td>4 (33)</td>
<td>11 (92)</td>
<td>58</td>
<td>38 (20–62)</td>
<td>Endocrine</td>
<td>42d</td>
</tr>
<tr>
<td>Beckers et al. (5)</td>
<td>1976–1989</td>
<td>7</td>
<td>3 (43)</td>
<td>6 (86)</td>
<td>N/A</td>
<td>50 (18–84)</td>
<td>Endocrine</td>
<td>60c</td>
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<tr>
<td>Socin et al. (17)</td>
<td>1976–2001</td>
<td>43</td>
<td>23 (53)</td>
<td>34 (83)</td>
<td>72</td>
<td>44 (N/A)</td>
<td>Endocrine</td>
<td>40c</td>
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<tr>
<td>Mindermann et al. (8)</td>
<td>1978–1991</td>
<td>19</td>
<td>7 (37)</td>
<td>19 (100)</td>
<td>63</td>
<td>35 (N/A)</td>
<td>Neurosurgery</td>
<td>50d</td>
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<td>Gesundheit et al. (7)</td>
<td>1982–1986</td>
<td>9</td>
<td>2 (22)</td>
<td>7 (78)</td>
<td>67</td>
<td>37 (24–51)</td>
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<td>100c</td>
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<tr>
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<td>25</td>
<td>8 (32)</td>
<td>25 (92)</td>
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<td>44 (15–80)</td>
<td>Neurosurgery</td>
<td>20c</td>
</tr>
<tr>
<td>Losa et al.a (123)</td>
<td>1982–1996</td>
<td>17</td>
<td>10 (59)</td>
<td>14 (82)</td>
<td>N/A</td>
<td>42 (22–63)</td>
<td>Endocrine</td>
<td>29b</td>
</tr>
<tr>
<td>Malchiodi et al.a (16)</td>
<td>1982–2012</td>
<td>70</td>
<td>34 (49)</td>
<td>49 (70)</td>
<td>54</td>
<td>44 (N/A)</td>
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<td>24c</td>
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<tr>
<td>Sanno et al. (124)</td>
<td>1983–1999</td>
<td>16</td>
<td>4 (25)</td>
<td>14 (88)</td>
<td>38</td>
<td>41 (23–60)</td>
<td>Neurosurgery</td>
<td>38c</td>
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<tr>
<td>Elton-Conaglen (125)</td>
<td>1983–2003</td>
<td>6</td>
<td>3 (50)</td>
<td>5 (83)</td>
<td>50</td>
<td>43 (20–58)</td>
<td>Endocrine</td>
<td>50c</td>
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<tr>
<td>Clarke et al. (126)</td>
<td>1987–2003</td>
<td>21</td>
<td>15 (71)</td>
<td>16 (89)</td>
<td>28</td>
<td>46 (26–73)</td>
<td>Neurosurgery</td>
<td>5c</td>
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<tr>
<td>Ness-Abramof et al. (127)</td>
<td>1989–2007</td>
<td>11</td>
<td>6 (55)</td>
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<td>36c</td>
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<td>Varseveld et al. (128)</td>
<td>1989–2011</td>
<td>18</td>
<td>12 (67)</td>
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<td>1990–2010</td>
<td>28</td>
<td>11 (39)</td>
<td>16 (59)</td>
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<td>56 (16–81)</td>
<td>Endocrine</td>
<td>46c</td>
</tr>
<tr>
<td>Perticone et al.a (98)</td>
<td>1990–2013</td>
<td>62</td>
<td>30 (48)</td>
<td>45 (73)</td>
<td>29</td>
<td>43 (14–76)</td>
<td>Neurosurgery</td>
<td>N/A</td>
</tr>
<tr>
<td>Yamada et al. (15)</td>
<td>1991–2013</td>
<td>90</td>
<td>43 (48)</td>
<td>74 (82)</td>
<td>23</td>
<td>42 (11–74)</td>
<td>Neurosurgery</td>
<td>28c</td>
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<tr>
<td>Marucci et al. (119)</td>
<td>1992–2006</td>
<td>10</td>
<td>5 (50)</td>
<td>10 (100)</td>
<td>60</td>
<td>47 (19–71)</td>
<td>Neurosurgery/pathology</td>
<td>20d</td>
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<tr>
<td>Gatto et al. (129)</td>
<td>1993–2011</td>
<td>13</td>
<td>9 (69)</td>
<td>10 (77)</td>
<td>38</td>
<td>42 (27–61)</td>
<td>Endocrine</td>
<td>0c</td>
</tr>
<tr>
<td>Azzalin et al. (silent) (130)</td>
<td>1993–2013</td>
<td>14</td>
<td>7 (50)</td>
<td>14 (100)</td>
<td>N/A</td>
<td>47 (28–75)</td>
<td>Neurosurgery</td>
<td>33c</td>
</tr>
<tr>
<td>Azzalin et al. (over) (130)</td>
<td>1993–2013</td>
<td>6</td>
<td>5 (83)</td>
<td>5 (83)</td>
<td>N/A</td>
<td>41 (24–57)</td>
<td>Neurosurgery</td>
<td>79c</td>
</tr>
<tr>
<td>Kirkman et al. (18)</td>
<td>2002–2012</td>
<td>32</td>
<td>16 (50)</td>
<td>28 (87)</td>
<td>56</td>
<td>53 (20–75)</td>
<td>Neurosurgery</td>
<td>84d</td>
</tr>
<tr>
<td>Total</td>
<td>1970–2013</td>
<td>535</td>
<td>261 (49)</td>
<td>435 (81)</td>
<td>58</td>
<td>44 (11–84)</td>
<td>–</td>
<td>50 (mean)</td>
</tr>
</tbody>
</table>

aCases have to some extent been previously reported; bInvasive includes extrasellar extension and/or invasion to the cavernous sinus; cPlurihormonal activity is reported from clinical manifestation and biochemistry; dPlurihormonal activity is reported from immunohistochemical analysis.

N/A, not available.
Although a rare disease, noteworthy cohorts have been published. The six largest patient cohorts reported are from Japan (\(N=90\)) (15), Italy (\(N=70\)) (16), Belgium and France (\(N=43\)) (17), England (\(N=32\)) (18), Sweden (\(N=28\)) (19) and the United States (\(N=25\)) (20) (Table 1). These series and other reports have contributed to the collation of substantial knowledge on TSHomas over 50 years.

In 2013, a comprehensive guideline from the European Thyroid Association (ETA) on diagnosis and treatment of TSHomas was published (21). The aims of this review are to put TSHoma diagnosing into a practical perspective and present up-to-date information on the differential diagnoses, concurrent diseases, and highlight on recent advances and indicate future areas of research in the imaging area. In this review, the reader will approach the diagnosis step by step. In the majority of cases, TSHomas are located in the pituitary, but a few cases of ectopic TSH production have been described with suprasellar localization (22) or in the nasopharynx (23, 24, 25, 26, 27). This review will also cover the possibility of these rare cases.

**Epidemiology**

Pituitary adenomas are the most common type of abnormal cell growth in the pituitary (28) with a high prevalence in the normal population. In a meta-analysis from 2004, the authors found an overall prevalence of 16.7% (29) (14.4% in autopsy studies and 22.5% in radiologic studies). Clinical manifestations of pituitary adenomas imply a much lower prevalence. A series of studies on well-defined populations report a prevalence of 75.7–94/100000 inhabitants of clinically overt cases (30, 31, 32), and the reported incidence is 3.9–4.1 cases/100000 inhabitants per year (31, 33, 34). Pituitary adenomas are one of the most frequently occurring intracranial tumors, and the occurrence of pituitary adenomas seems to be similar despite geographic or ethnic differences (29, 35, 36).

TSHomas are the rarest among the pituitary adenomas, only representing 0.7–0.94% of all pituitary adenomas (31, 33, 34). A comprehensive study of the Swedish national Pituitary Registry found a national prevalence of 2.8 clinically overt cases per million inhabitants and an incidence rate of 0.15 cases per million inhabitants per year (19). Moreover, during the study period 1991–2011, the detection rate increased fivefold (Fig. 1). This follows a general trend of higher detection rate for all pituitary adenomas, which may be attributed to more sensitive diagnostic methods and the more widespread use of MRI scanners.

Before the 1990s, when the diagnosis of secondary hyperthyroidism was facilitated by modern ultrasensitive TSH methods (9, 10, 37), tumor size was often large at time of diagnosis (17, 20). Since the introduction of the ultrasensitive TSH methods, TSH-producing adenomas are more frequently found at the stage of microadenomas (17, 19, 38, 39, 40). However, macroadenomas (>10 mm in any dimension) still represent approximately 80–85% of all newly discovered TSHomas (Table 1). An inappropriate thyroid ablation seems also to promote the development of macroadenomas (17), suggesting a similar mechanism to the Nelson syndrome in ACTH-producing tumors when cortisol (or T4/T3) feedback is removed. Therefore, a prompt and proper diagnosis is highly warranted.

TSHomas are predominantly diagnosed in middle age, but there are cases reported in the range of 11–84 years of age (Table 1).

**Histopathology of TSHomas**

TSH-secreting pituitary tumors are presumed to represent a clonal expansion of abnormal cells.
The TSH-producing cells represent <5% of all pituitary cells (41). This may explain why TSHomas are so rare (19, 33, 34). Chromophobic polygonal or short-spindled tumor cells are often seen in a diffuse pattern. Also globoid or whorl-like appearance with intertwined cytoplasmic processes, stromal fibrosis, and calcification are often noted (42). This has been attributed to an expression of the basic fibroblast growth factor (bFGF) (43) and corresponds well with clinical findings of fibrotic characteristics (41), seen in approximately 40% of TSHomas (17).

In TSHomas, co-secretion of PIT-1 factor-dependent hormones (growth hormone (GH) and prolactin (PRL)) is common (Table 1). The frequency seems to vary considerably depending on clinical or histopathological classification. In the largest case series of TSHoma patients (15), clinical manifestations of acromegaly and hyperprolactinemia were observed in 14 (16%) and 11 cases (12%), respectively. Microscopically, however, positive immunostaining for GH was found in 36%, GH and PRL in 27% and PRL in 10% of cases (15). In this study, KI-67 was low; in only two patients, KI-67 was >3%.

Pituitary cells express several regulatory receptors. Somatostatin analogs (SSA) have inhibitory effect on the hormone production in TSH-, ACTH- and GH-secreting pituitary tumors (44), which is mediated by somatostatin receptors (SSTR), of which six subtypes have been characterized. TSHomas express SSTR 1, 2, 3, and 5, where SSTR 2 (with subtype 2A and 2B) is most frequent (45). Endogenous somatostatin binds with high affinity to all its receptors, SSTR 1–5, and the activation of SSTR 1, 2, 4 and 5 appears to induce cell-cycle arrest (44, 46).

First-generation SSAs, such as octreotide and lanreotide, show preferential affinity for SSTR2 and moderate affinity for SSTR5. The newly available SSA, pasireotide, shows a preferential binding affinity for SSTR5 > SSTR2 > SSTR1 > SSTR3. Recent clinical studies have shown the efficacy of pasireotide in acromegaly and Cushing’s disease, respectively (47, 48).

**Clinical presentation**

Although TSHomas are rare, they are an important entity with a spectrum of clinical manifestations. Pituitary adenomas can be discovered accidentally in the workup with CT/MRI that is done for other reasons, such as in the diagnostic procedure for a headache, through symptoms connected to hormonal hyperproduction, or on suspicion of visual symptoms. Clinically silent TSHomas or TSHomas that present with active hormone production have similar prognosis and outcome (18). Only a quarter of surgically treated patients with a positive histopathological TSH-immunostaining present clinically (18). In clinically active
TSHomas, often mild-to-moderate classic hyperthyreotic symptoms are common (17, 19, 20), although the time to diagnosis may be long (17, 19, 20). As symptoms may be discrete and the diagnostic procedures are complicated, a referral to tertiary referral centers is often needed.

Also, patients may present by symptoms from local compression, which is the reason for detection in 29–38% of cases (19, 20). The clinical presentation of a TSHoma can also be blurred by the co-production of other hormones from the tumor, predominantly PRL and/or GH (6, 17, 19, 20, 38) (Table 1). Clinically detectable co-production of any of these PIT-1 factor-dependent hormones increases with tumor size, even if many tumors histopathologically express all three hormones regardless of size (17, 49).

In TSHomas, TSH is characteristically unsuppressed, and thyroid hormones are elevated above the upper reference (19). A subgroup represents cases where an initial diagnosis has been missed and the patients have been improperly treated with thyroidectomy or radioactive iodine (RAI). In these cases, TSH increases to supranormal levels when l-thyroxin is administered (19, 20, 27) (Fig. 2A and B). The patient may be referred due to an inability to normalize TSH with increasing l-thyroxin doses without causing supranormal FT4 levels. In these cases, an undiagnosed TSHoma must be considered.

**Diagnostic approach**

TSH secretion in the pituitary is regulated by thyrotropin-releasing hormone (TRH), somatostatin, dopamine and thyroid hormones and is characterized by a diurnal pattern with small bursts (50). In the abnormal cells in a TSHoma, TSH secretion is disorganized, which may be explained by altered functional properties within the tumor. An increased pulse frequency is seen with enhanced non-pulsatile release (51). In TSHomas, the TSH level varies from normal to elevated that can be explained by a change in glycosylation of TSH molecules with higher bioactivity (52): TSHomas also secrete a mixture of isoforms, where the alpha subunit of the glycoprotein is the major component (53).

As mentioned earlier, guidelines for the diagnosis of TSHoma were published in 2013 by the ETA (21). Clinicians are used to work in an evidence-based manner. However, predictive values are not available for different diagnostic tests as TSHomas are rare and there is a lack of power. The frequency of abnormal tests in TSHoma patients is described below.

**Laboratory assessment**

**First step**

Before conducting further investigations for central hyperthyroidism in the presentation as syndrome of inappropriate TSH secretion (SITSH) with suppressed TSH and elevated thyroid hormone levels, interference from medications, like estrogens, pregnancy state, non-thyroidal illness and subacute/silent autoimmune thyroiditis, need to be excluded (54). The timing of the sampling should not be underestimated, and repeated sampling at months’ interval is needed to exclude transitory changes. To exclude thyroid disease, thyroid autoantibodies (thyreoperoxidase (TPO) and TSH receptor-antibodies) are of value. Also, the euthyroid, hypothyroid and hyperthyroid states of the patient need to be assessed. Laboratory interference and genetic causes are more common than TSHomas (see differential diagnoses below). Therefore, when a patient is referred with SITSH, the first diagnostic procedures include a blood test to evaluate pituitary function, thyroid hormone evaluation through testing with several laboratory methods and to take thyroid hormone function tests in first-degree relatives (Fig. 3). Although patients with TSHomas and resistance to thyroid hormones (RTH) have increased production of thyroid hormones in common, the peripheral response differs because of the insensitive TRβ in RTH. To distinguish hyperthyroidism from RTH, carboxy-terminal cross-linked telopeptide of type-I collagen (ITCP) may be used (55). Patients with hyperthyroidism have significantly higher ITCP levels than RTH patients, illustrating the hypermetabolic state in the bone in hyperthyroidism, whereas in RTH, the resistance in the TRβ influences bone resorption markers (56). Furthermore, sex hormone-binding globulin (SHBG) is usually elevated in thyrotoxicosis and is reported to be normal in RTH (57, 58). Therefore, SHBG and ITCP may be used in the first diagnostic workup.

**Second step**

If there are no indications of laboratory error and if first-degree relatives do not demonstrate a similar laboratory picture, then a TRH test is done regardless if pituitary function tests do indicate a pituitary origin or not. This may also be the step of choice for heredity indications in parallel with mutation tests for RTH and/or familial dysalbuminemic hyperthyroxinemia. The normal response in TSH from TRH stimulation is defined as an
increase of >50% and/or an increase of >4 IU/L (17). According to this definition of a normal response, 81% of TSHomas have an abnormal response to the TRH test (17), whereas in the ETA guidelines Beck-Peccoz et al. reported 90% with an abnormal TRH test (21, 59).

Third step

Alpha subunit (αSU) may also be used as a diagnostic tool and is elevated in 30% of cases with a TSHoma (17). Stimulated αSU, defined as a 100% increase after TRH administration, is positive in 44% of cases (17). The molar ratio between αSU and TSH is no longer recommended (21) (Table 2). To possibly confirm or discard the hypothesis of TSHoma requires a thorough detective work.

A somatostatin test may also be used in order to distinguish between a TSHoma and RTH. The patient is given somatostatin subcutaneously and thyroid hormones are checked after 6 h. If this is well tolerated, 20 mg of the somatostatin analog octreotide long-acting release (LAR) may be given intramuscularly every fourth week. After 8 weeks, thyroid hormones are measured. In RTH, there is no reduction in thyroid hormones, whereas in 6 out of 8 cases, TSHomas normalize thyroid hormone levels despite minor changes in immunoreactive TSH levels (13). The thyrotropic cells and TRH-producing hypothalamic cells are regulated through the negative feedback mechanism from the thyroid hormones and react on small changes. The thyroid hormone regulatory feedback mechanism is superior to that of somatostatin regulation. In TSHomas, the TSH production is autonomous, and the negative feedback is redundant.

Table 2  Comparison of the clinical presentation and laboratory findings in TSH-secreting adenomas (TSHomas) and resistance to thyroid hormones (RTH).

<table>
<thead>
<tr>
<th></th>
<th>TSHoma</th>
<th>RTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goiter (%)</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td>Pituitary over/under production of other hormones</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Increased α subunit</td>
<td>+</td>
<td>Negative</td>
</tr>
<tr>
<td>Increase in TSH after a TRH test</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Increase in α subunit after TRH test</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>MRI pituitary</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Visual field disturbances</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>T3 suppression test</td>
<td>Maybe + No TSH suppression</td>
<td>Suppression of TSH</td>
</tr>
<tr>
<td>DNA mutation analysis</td>
<td>−</td>
<td>+ FT4 ↓ &gt;30%</td>
</tr>
<tr>
<td>Somatostatin test</td>
<td>−</td>
<td>FT4 is not affected</td>
</tr>
<tr>
<td>Sinus petrosus catheterization</td>
<td>+</td>
<td>−</td>
</tr>
</tbody>
</table>

MR, magnetic resonance imaging; RTH, resistance to thyroid hormone; TRH, thyrotropin releasing hormone; TSH, thyroid-stimulating hormone.
Hence, in most cases of TSHomas, thyroid hormone levels will be lower.

Fourth step

A difficulty in the diagnosis of TSHomas is that incidentalomas (non-functioning pituitary adenomas (NFPA)) are more common and occur in 10–20% of the normal population (29). There is also a special diagnostic dilemma in differentiating a TSHoma from RTH in combination with a pituitary incidentaloma (60). If the suspicion of a TSHoma arises from a pituitary tumor during MRI and the classical laboratory test results are in accordance with SITSH, the occurrences of a NFPA are more frequent than a TSHoma and autonomous TSH production needs to be established (38).

The T3 suppression test, the liothyronine test, is only used if doubts are raised during diagnosis or a NFPA needs to be excluded. When a MRI scan is performed due to symptoms of an expansive process in the pituitary gland and an adenoma is found in combination with high FT4 and normal TSH and the TRH test is abnormal, the patient could be referred directly for surgery without a T3 suppression test. However, there are situations when results are contradictory, such as in cases of an abnormal TRH test when the MRI does not reveal a pituitary adenoma, or if there is a normal response to TRH in the presence of a pituitary adenoma, or if the patient is thyroidectomized. Also, it has been reported that the frequency of hyperplasia/adenomas in the pituitary from RTH is approximately 20% (61). In cases with long-term primary hypothyreosis, there is hyperplasia of the pituitary (62, 63), and sporadic reports on TSHomas in RTH (64, 65, 66).

The T3 suppression test should not be done in cases of severe pulmonary or cardiovascular disease or any disease that may decompensate from a short period of hyperthyroidism, such as heart disease or psychiatric disease. An example of the T3 test used at our institution, at Sahlgrenska University Hospital Gothenburg, is presented in Fig. 4; this version is modified from Dare et al. (67) and from personal communication with the last author of that publication. The autonomous TSH production is proven by an inability of T3 to suppress TSH.

If MRI does not reveal an adenoma despite laboratory findings indicative of a TSHoma, there are some reports on sinus petrosus catheterization with TRH stimulation used in order to evaluate the presence of a TSHoma (17, 68), but its performance and validity are not described. Perhaps functional imaging may play a future role in these cases. Although less common, an ectopic TSHoma may also be considered (17).

Imaging assessment

Imaging of the pituitary has developed rapidly. Earlier, evaluation with plain skull radiographs was the modality of choice; however, this technique was poor in delineating the soft tissue. The technique focused mainly on secondary findings of pathology in the sella, i.e. calcifications and enlargement. These findings are not considered sensitive
indicators of pituitary gland abnormalities. Thus, plain radiographs were replaced by cross-sectional imaging techniques such as the CT scan and MRI.

**Structural imaging**

**MRI**

MRI techniques for diagnosing pituitary lesions have witnessed a rapid evolution since it first came to use in the early 1980s. The resolution and sensitivity of these techniques were until the early 1990s comparable to those of CT-scans, but presented a superior soft-tissue resolution and a greater delineation to adjacent structures. With the introduction of dynamic contrast-enhanced MRI in the early 1990s (69), the sensitivity for diagnosing pituitary microadenomas increased vastly (70).

MRI is usually the only method needed for the morphological investigation of endocrine active pituitary adenomas. Radiologic evaluations differ in regard to the size of the lesion, i.e. macroadenomas (>10mm) and microadenomas (<10mm). Pituitary macroadenomas are usually located in the center of the sella turcica with extra sellar extension, growing upward toward the third ventricle and sometimes the foramen of Monro (71, 72).

Studies on TSH-producing adenomas using MRI, describe macroadenomas in the majority of cases and usually hypoechoic appearance in respect to normal pituitary tissue after gadolinium administration (73). In comparison to other similar, and more common, pituitary adenomas (such as GH- and PRL-producing adenomas), TSH-producing adenomas tend to have a higher degree of microscopic invasion and intra- and peritumoral fibrosis, which correlate with the findings in surgical material (15). In this regard, a protocol with several sequences (such as dynamic, contrast enhanced, spin echo T1 and T2) is preferable to not just detect elusive lesions but also to delineate tumor tissue to adjacent structures and normal pituitary tissue. Such signs of microscopic invasion can contribute with important prognostic information before surgical treatment (73).

Microadenomas are more difficult to detect, but have often a hypoechoic signal on contrast-enhanced T1 sequences. Microadenomas are now reported with an increased frequency in TSHomas, accounting for about 20% of all recorded cases (Table 1). Smaller lesions require more complex methods and high-field scanners. Different methods and approaches have been assessed in regard to optimize the detection rate of microadenomas. Pinker et al. demonstrated that the use of high-field MRI scanners, i.e. 3.0T, was superior to low-field scanners of 1.0T or 1.5T in predicting local invasion of adjacent structures. They also showed that the use of a 3.0T scanner improved surgical planning of sellar lesions (74). Lee et al. evaluated the technique of simultaneous acquisition of contrast-enhanced coronal and sagittal images on a 3.0T MRI and found a detection rate of more than 92% for microadenomas in the pituitary region (75). In comparison, the detection rate was only 82% for uniplanar coronal and 75% for uniplanar sagittal projections (75). The multiplanar combination of sagittal and coronal projections in gadolinium-enhanced MRI are now the preferred tools for visualization and is considered the modality of choice for pituitary imaging (71, 72). There are however some disadvantages that comes with the use of MRI at 3.0T. Prolonged T1 relaxation time, radiofrequency magnetic field inhomogeneity and increased susceptibility artifacts have been proposed (76). The spoiled gradient recalled acquisition in the steady-state (SPGR) sequence and fast SPGR (fSPGR) are relatively new sequencing techniques that challenge these disadvantages. Kakite et al. demonstrated that vascular pulsation artifacts and partial volume effect were significantly reduced on the SPGR sequence (77). SPGR and fSPGR also demonstrate superior soft-tissue contrast compared with the spin echo technique and can be performed in notably thin-slice sections (78). As SPGR can be performed in sections of 1 mm, the risk of missing small lesions in the pituitary is far less. SPGR has primarily been used in the evaluation of suspected adenomas in Cushing's disease, since they often manifest as microadenomas (usually <2mm) and are notoriously difficult to detect with the standard T1 spin echo MRI sequence. Currently, modern pituitary MRI sequences fail to detect approximately 40% of Cushing's disease cases (79). In these patients, SPGR has increased the detection rate by 10–15%. Masopust et al. achieved a remarkable sensitivity of 100% in 41 Cushing's disease patients by combining three MR sequences: spin echo, SPGR and fSPGR (80).

To our knowledge, SPGR sequences have not been studied on TSH-producing adenomas. SPGR seems to provide higher sensitivity in the MRI evaluations in ACTH-producing adenomas, but these results cannot be generalized to TSHomas. TSHomas usually manifest as macroadenomas and with a fibrous consistency, and thus the sensitivity of the spin echo sequence is, in most cases, sufficient. A diagnostic imaging with higher specificity would be a better contribution in the current diagnostic workup. In this regard, functional imaging seems to have the potential to provide a better detection rate with...
higher specificity in pituitary adenomas in general and in TSHomas in particular.

**Functional imaging**

**Scintigraphy**

As pituitary gland and pituitary adenomas express somatostatin receptors, sSTR, as oppose to adjacent structures and brain tissue, these receptors provide excellent conditions for functional imaging. TSHomas have a high expression density of somatostatin receptors compared to normal pituitary tissue, in particular SSTR 2 and 5, which makes it a good candidate for scintigraphic evaluation. Scintigraphy with radio-labeled octreotide can successfully localize most hormone-producing adenomas due to high expression rate of somatostatin receptors (81). TSHomas are detectable with this technique (82); however, the specificity of this technique is low, as positive scans can occur in the case of a pituitary mass of different types, either secreting or non-secreting, and even in normal pituitary tissue.

**Position emission tomography (PET)**

PET/CT has superior resolution and imaging quality over scintigraphy, and there have been promising results in identifying pituitary adenomas. In a case series with seven TSHoma patients examined with 111In-pentetreotide-SPECT (single-photon emission CT) and two patients with 11C-i-methionine PET/CT, both SPECT and PET/CT imaging revealed positive uptake in patients with microadenomas that was not detected by MRI (17). The PET/CT evaluation even detected 2 microadenomas in cases where the 111In-pentetreotide scan did not detect any pathology (17). However, the study was unable to predict the response to somatostatin analog treatment.

PET/CT technique has the advantages of better resolution and the ability to quantify, compared to SPECT. The use of somatostatin receptor PET/CT for the detection of TSHomas has not yet been widely evaluated. A new line of gallium-labeled somatostatin receptor analogs (68Ga-DOTANOC, DOTATATE, DOTATOC) has been increasingly used in the evaluation of neuroendocrine tumors, NETs. This technique has only been evaluated in a small number of case series with successful results in diagnosing an ectopic TSH-producing adenoma (83) and pituitary carcinoma (84), thus implying a promising prospect for better functional imaging in future diagnostic workup of TSHomas. A study evaluating the uptake of 68Ga-DOTATOC in pituitary adenomas is ongoing and will hopefully bring more clarity to the matter (clinicaltrials.gov identifier: NCT02419664).

**Differential diagnoses**

In the workup of a patient’s syndrome of inappropriate TSH secretion, diagnoses other than TSHomas must first be considered, given the low incidence of TSHomas (19). The most important differential diagnoses are laboratory interference and mutations resulting in a changed affinity for the thyroid hormone receptor or to carrier molecules. Also, rarely, thyroxin binding globulin (TBG) deficiency can result in decreased levels of total thyroid hormone and thereby increased free T4 (85), from lower binding capacity, even if TBG deficiency is most commonly presented as central hypothyroidism. Another rare cause of SITSH is inadequate hydrocortisone replacement after surgery in Cushing’s syndrome (86).

Laboratory interference is not a true increase in thyroid hormone production, but results from interfering substances in the laboratory method used, such as thyroid hormone antibodies (87), heterophilic antibodies (88) or other method specific interferences (89, 90), result in falsely increased thyroid hormone levels (54). In clinical practice, different forms of laboratory interference are rarely diagnosed, as the important issue is to find a TSHoma. Laboratory interference can be suspected when thyroid hormone levels vary among different laboratory methods: this can be detected through comparing the results from one sample with several analytical platforms. The TRH- and α-subunit-tests are normal in laboratory interference.

When disturbances due to the laboratory method are excluded, the main differential diagnosis to TSHomas is mutation in the thyroid hormone receptor with the syndrome of RTH (91) (Table 2) or mutations in thyroid hormone transport proteins, familiar FDH (92). These conditions have a variety of mutations. In RTH, both TRH in the hypothalamus and TSH from the anterior pituitary is inappropriately increased in relation to thyroid hormone levels. In RTH, both T4 and T3 are elevated, whereas in the typical scenario, in FDH, only T4 levels are disturbed. However, practically, not only total T4 but also total T3 or free T3 and free T4 are disturbed (elevated) in many patients with FDH. Individuals with genetic variations in thyroid hormone transport proteins are clinically euthyroid, but present with altered thyroid function.
tests, and do not require treatment. In FDH, laboratory interference may occur as the change of binding affinity to prealbumin interacts differently in different methods.

Unlike in TSHomas, in RTH and FDH, familial cases are common. RTH is an autosomal dominant inherited mutation in the β-isof orm of the T3 receptor (93), and FDH is a familiar autosomal dominant disease caused by a mutation in the albumin gene that results in a 10-fold higher affinity of T4 in homozygotic cases; in heterozygote people T4 affinity is doubled (94). FDH is the most common inherited cause of increased T4 (94). In cases of SITSH where the TRH- and α-subunit-tests are normal, FDH may be suspected, especially if the results vary depending on the methods used.

Mutation analyses are costly compared to FT4 and TSH blood samples, thus, a first step may be to analyze thyroid hormones in first-degree relatives, in order to strengthen the suspicion of a heredity cause for the syndrome of inappropriate TSH secretion.

As many patients approach health care with a laboratory constellation of unsuppressed TSH and increased thyroid hormone levels, all differential diagnoses need to be considered in parallel for an effective clinical workup.

In Italy, 99 patients were referred for SITSH, of these, 68 were determined as RTH and 31 as TSHomas (95). In 24% of the RTH cases, no mutation was found, and there were no familial cases; eventually three TSHomas were detected, illustrating the difficulties of distinguishing between the etiologies. To support the investigation, clinical presentation can be useful (Table 2). Goiter is common in patients with TSHomas and RTH, but the response to stimulatory tests differs due to the pituitary involvement (Table 2). Diagnosing a patient with a syndrome of inappropriate TSH secretion is complicated and requires special competences, especially in situations where patients have received treatment for an assumed primary hyperthyroidism (17, 19, 27) or in the rare cases where RTH is coexisting with a TSHoma (64). RTH is considered to predispose to both pituitary hyperplasia and to the development of adenomas and, even in some rare cases, ectopic TSHomas (22, 23, 24, 25, 26, 27), making regular monitoring of these patients a necessity.

Thus, a plausible relationship between TSH stimulation from the pituitary on the thyroid gland was established. A trophic hormone may cause autonomous secretion in the thyroid gland, which resembles what happens in other target glands. Patients exposed to unregulated and inappropriate TSH levels may have an increased risk for well-differentiated thyroid cancer (97). In 62 patients with TSHomas, three cases with this thyroid cancer were found (97), and it is also reported in other case reports (98, 99, 100, 101). A common disease can inevitably co-exist with a more rare disorder without any causal relationship, but there may be a rationale for excluding neoplastic lesions in the thyroid gland, e.g. with an ultrasound.

There may also be an etiologic link between Graves’ disease and TSHomas. Autoimmunity may be induced when TSH levels rapidly decrease after surgical and/or SSA treatment (102). Graves’ disease may also be triggered through affected intrathyroidal lymphocytes harboring the same SSTR 2A as the TSHoma cells. The development of Graves’ disease after treatment for a TSHoma is reported (103, 104, 105), as is Graves’ disease before the detection of a TSHoma (106, 107, 108, 109, 110). The combination of TSHoma and Graves’ disease may be further complicated by the coexistence of exopthalmia. Exophthalmos is reported in TSHoma because of tumor invasion in the orbit (111).

Autoimmune hypothyroidism may co-exist with TSHoma, but any causality is yet unclear (112, 113, 114). Pituitary hyperplasia from increased TSH production in hypothyroidism may in some rare cases mimic a macroadenoma (115). In the same way as TSHoma is reported, in RTH, where longstanding stimulation may promote tertiary tumor evolvement (66, 116), a secondary hyperplasia may mimic a pituitary tumor (117). However, primary hypothyroidism in parallel may complicate the diagnosis of TSHoma and cause delay (118).

Even if most TSHomas are sporadic, there are reports that TSHomas may be the pituitary component in multiple endocrine neoplasia type 1 (MEN-1). In a report from six Belgian and French centers where 43 patients with TSHoma were described, 2 patients were diagnosed with clinical MEN-1, but no MEN-1 mutation was found (17). In another cohort of 166 patients with pituitary tumors, including one TSHoma (119), patients with hyperparathyroidism (n=8, 4.8%) were selected and screened for other manifestations of MEN-1: the TSHoma case was not found among the group of eight pituitary adenomas selected, and prolactinomas appeared dominate in MEN-1. However, TSHoma cases are described in MEN-1 (120).
Pituitary adenomas rarely turn into pituitary carcinomas. The majority of pituitary carcinomas secrete ACTH or prolactin and only two known cases of TSH-producing carcinomas are described in the literature (121, 122). One of these was a NFPA that transformed into a PRL- and TSH-secreting carcinoma (121). A transforming adenoma should be evaluated for the risk of developing into a carcinoma.

**Conclusion**

TSHomas are rare tumors that in most cases demand special competence and involve a complicated routine of investigations. There has been much progress in the ability to separate TSHoma from differential diagnoses with a proper laboratory procedure. As TSHomas are rare and incidentalomas in the pituitary gland are common, an autonomous TSH production needs to be established. The ideal diagnostic approach would be to simultaneously receive both hormonal and morphologic information, as with functional imaging. Major advances in the imaging area in recent years contribute to the conviction that next important steps in the TSHomas’ diagnostic approach will be within the imaging field.

**Declaration of interest**

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

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