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Review article

Thyrotropin-secreting tumor "TSH-PitNET": From diagnosis to treatment

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ABSTRACT

Thyrotropic adenomas (TSH-PitNET) are the rarest pituitary tumours. Most TSH-PitNETs are secreting adenoma, with a biological picture of inappropriate TSH secretion (moderately elevated TSH, elevated FT3 and FT4). Patients present most often clinical hyperthyroidism, but with more moderate symptoms than in peripheral hyperthyroidism. Biological diagnosis is not always easy. The main differential diagnoses are interfering antibody assay interactions, dysalbuminemia and thyroid hormone resistance syndrome. Misdiagnosis is common. However, the diagnosis is easier when macroadenomas are involved (80% of cases), with symptoms of optic chiasm compression, headache and signs of hypopituitarism. Treatment is initially based on surgery. In case of failure, somatostatin analogues are very effective in controlling tumor volume and secretion, although there is a risk of thyroid insufficiency, which is usually transient.

TSH-secreting Pituitary Neuroendocrine Tumor (TSH-PitNET) are the rarest functioning pituitary tumor. Most of them are secreting tumor with mild hyperthyroidism symptoms. TSH-PitNET are characterized by high levels of circulating free thyroid hormones (FT4 and FT3) in the presence of non-suppressed serum TSH-concentration. Failure to correctly diagnose TSH-PitNET is frequent. Differential diagnoses are mainly dosage interaction, dysalbuminemic and resistance to thyroid hormon syndrome (RTH). The diagnosis is easier when macroadenoma is concern (80% of cases) with tumoral syndrome, visual field defect, and a pituitary tumor at MRI. The treatment of choice is surgery. In case of remnant tumor with secretion, somatostatin analogs are very effective for tumoral volume reduction and TSH-normalisation. However thyrotropin deficiency should be screen with this treatment.

Thyrotropic pituitary adenomas (TSH-PitNET) are characterized by a fall in TSH secretion, which cannot be controlled by peripheral hormones. This leads to a so-called central hyperthyroidism [1,2].

1. Epidemiology

The first reported case of TSH-PitNET was in 1960 by Jailer JW et al, with symptoms of hyperthyroidism and an enlarged sella turcica [3]. TSH-PitNETs represent the rarest subcategory of pituitary adenomas 0.5–2%. The prevalence is in the order of 0.5 to 2.8/million population with an incidence in the general population of 0.15 to 1 million population/year [1]. This incidence is increasing over time, notably due to the improvement in imagery (MRI) and assays: the use of ultrasensitive TSH since the 1980s, and the possibility of direct measurement of circulating FT3 and FT4. In a Swedish cohort, it was estimated at 0.05/million/year between 1990 and 1994 and 0.26/million/year between 2005 and 2009 [4].

TSH-PitNET is most common in adults, in the fifth or sixth decade, but cases have been diagnosed between 8 and 85 years of age [2].

2. Clinical appearance

In contrast to peripheral thyroid disease, TSH-PitNET affects both women and men [5]. Most TSH-PitNETs are biologically secretory, around 90% in studies [5,6]. Two thirds of patients present clinical hyperthyroidism [5,7]. The symptomatology is that of moderate hyperthyroidism associating tachycardia, weight loss, heat intolerance, sweating, irritability, sleep disturbance without orbitopathy [2]. Interestingly, patients with equal FT4

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Table 1
Different subtypes of TSH-PitNET and their prevalence. From Beck Peccoz et al., 2019 [1].

	Number of patients	%
TSH-PitNET	461	100
Pure TSH	324	70.3
Mixte	137	29.7
– TSH/GH	84	18.3
– TSH/Prolactin	45	9.7
– TSH/gonadotropin	8	1.7

and FT3 levels are often less symptomatic than in peripheral hyperthyroidism [6,8]. Cases of atrial fibrillation or heart failure are rarer than in peripheral hyperthyroidism: present in 11% of cases versus 16–60% in peripheral hyperthyroidism [9,10].

Very often the hyperthyroidism is long-standing (from 4 months to a few years) with diagnostic errors in 34% of cases in the meta-analysis of Cossu et al. (Graves' disease; toxic multi-nodular goiter) which lead to therapeutic errors: anti-thyroid drug, total thyroidectomy or iratherapy [5]. These errors are less frequent today with the precision of biological assays and imaging (6 misdiagnosis/9 published in 1989; 11/25 in 1999 1/43 in 2013; and 11/536 in a meta-analysis in 2021) [7,9,11,12].

In addition to these symptoms of hyperthyroidism, a tumor syndrome is frequently associated (headache, visual field impairment or decreased visual acuity) in cases of macroadenoma. In addition, hypopituitarism symptoms are also common: depilation, pale skin, decreased libido, etc. However, some patients are asymptomatic [5,9].

3. Biological aspects

3.1. Standard work-up

Biologically, the diagnosis is based on elevated peripheral hormones: FT4 and FT3 in relation to an unrestrained TSH (which is normal in 30% of cases). In the TSH-PitNET series, the median TSH was 6.75 (4.02–11.9) mIU/l; and the mean FT4 was 36 ± 8 pmol/l [9]. Exceptionally TSH secretion can be cyclic: there is one case in the literature of TSH-PitNET with cyclic TSH secretion. The patient presents with inappropriate TSH secretion on admission with normalization the following days, the hypersecretion is repeated one month later and one year later for a period of a few days [13].

Co-secretion is found in about 40% of cases, most frequently with GH or prolactin, rarely associated with gonadotropins (Table 1) [1,5,9].

Associations of TSH-PitNET with basedow disease (4 cases reported) or Hashimoto's thyroiditis have been noted and may confound the diagnosis [14–17]. However, it is important to note that the prevalence of thyroid autoantibodies in TSH-PitNET is identical to that of the general population [14,15,18]. The work-up for TSH-PitNET associated with basedow disease shows elevated FT4 with non-suppressed TSH and positive TSH receptor antibodies [15]. For example, a patient with the following biology: FT4 51 pmol/l, TSH 0.337 mIU/l, anti TSH receptor antibody 5.9 IU/l, was initially diagnosed as basedow disease. The partial efficacy of synthetic antithyroid drugs, the occurrence of headache associated with visual field impairment, and retrospectively, the absence of TSH collapse at diagnosis, led to the diagnosis [14].

3.2. Eliminating biological interference

The first step in the diagnosis of inappropriate TSH secretion is to rule out interferences with either peripheral hormones or TSH measurement [19]. Falsely elevated FT3 or FT4 values may be found in the presence of heparin, biotin, anti-FT3 or anti-FT4 antibodies, anti-animal or heterophilic antibodies, or albumin/transthyretin abnormalities [20,21]. For example, in familial dysalbuminemia, there is a change in thyroid hormone carrier proteins leading most often to a slightly elevated FT4, normal FT3 and normal TSH [22]. Familial dysalbuminemia is found in 10% of cases with this thyroid hormonal profile. In addition, fractionated or unfractionated heparin will lead to an increase in FT3 and FT4. Indeed, under the effect of heparin, the activation of endothelial lipoprotein lipase will lead to an increase in non-esterified free fatty acids which will compete with FT3 and FT4 for their binding capacity to TBG [23]. To avoid these assay errors, a two-step assay with a washing step between the two assays eliminates these errors. However, the reference technique to overcome these assay errors is an equilibrium dialysis RIA assay or a chromatography before measurement, which are not available in all centres [24]. Mass spectrometry may also address these interferences but is not yet routinely available for this assay [25]. For TSH assays, interference is rarer, often related to anti-animal (anti-mouse) antibodies [21,26]. In practice, to remove these interferences, it is advisable to repeat the assays with a different technique, to perform dilutions (non-linear curve due to weak binding of interfering antibodies), or to use agents that precipitate interfering antibodies such as polyethylene glycol [20,26]. The diagnostic strategy for TSH-PitNET was proposed in a European consensus in 2013 (Fig. 1) [19].

4. Differential diagnosis

In specific settings, the differential diagnosis is straightforward. For example, in patients on levothyroxine, a detectable TSH with an elevated F4 and/or FT3 is most often related to compliance failures: a patient who has not taken his treatment for several weeks and who resumes it a few days at a double dose before the bioassay will have a normal or high TSH in relation to an elevated peripheral hormone, because of the inertia of TSH balance related to its half-life [26]. Similarly, in an acute psychiatric context (shizophrenia, psychotics, patients on amphetamines), elevation of peripheral thyroid hormones with normal TSH is relatively frequent (30% of cases). The context and the normalization of the hormone level within 15 days make the diagnosis [27].

The main differential diagnosis of TSH-PitNET is resistance to thyroid hormone (RTH). It is a combination of arguments that will distinguish between the two etiologies and genetic analysis that will confirm the diagnosis (negative in 15% of cases) (Table 2).

Thus, age, sex, and thyroid hormone levels (TSH, FT3, FT4) are identical between the two conditions [28]. In RTH, first degree relatives should be tested because similar hormone profile is found in 50% of cases.

The clinical picture is sometimes similar as thyrotropic adenomas are sometimes clinically unremarkable, with frequent goiter, and in TRβ-mutated RTH, tachycardia and goiter will be found.

In TSH-PitNET, the α-subunit is often elevated, as in gonadotropic or somatotropic adenomas. If the α-subunit is normal, the ratio of α-subunit to TSH > 1 may also help to make the diagnosis, except in postmenopausal women [11].

A number of peripheral thyroid hormone markers have been proposed to help distinguish thyroid hormone resistance from thyroid adenoma, however, with the amelioration of hormone dosage access in relatives, MRI, and genetic, these markers are less useful and lack specificity (Table 2). For example, SHBG can be a discriminating marker, found elevated in TSH-PitNET, provided that interference with oestrogen treatment, liver failure, insulin resistance, obesity, or elevated GH is ruled out [11]. Other markers such as cholesterol, angiotensin convertase, soluble IL2R, bone markers such as osteocalcin, carboxyterminal telopeptide are elevated in TSH-PitNET but not in resistance [29].

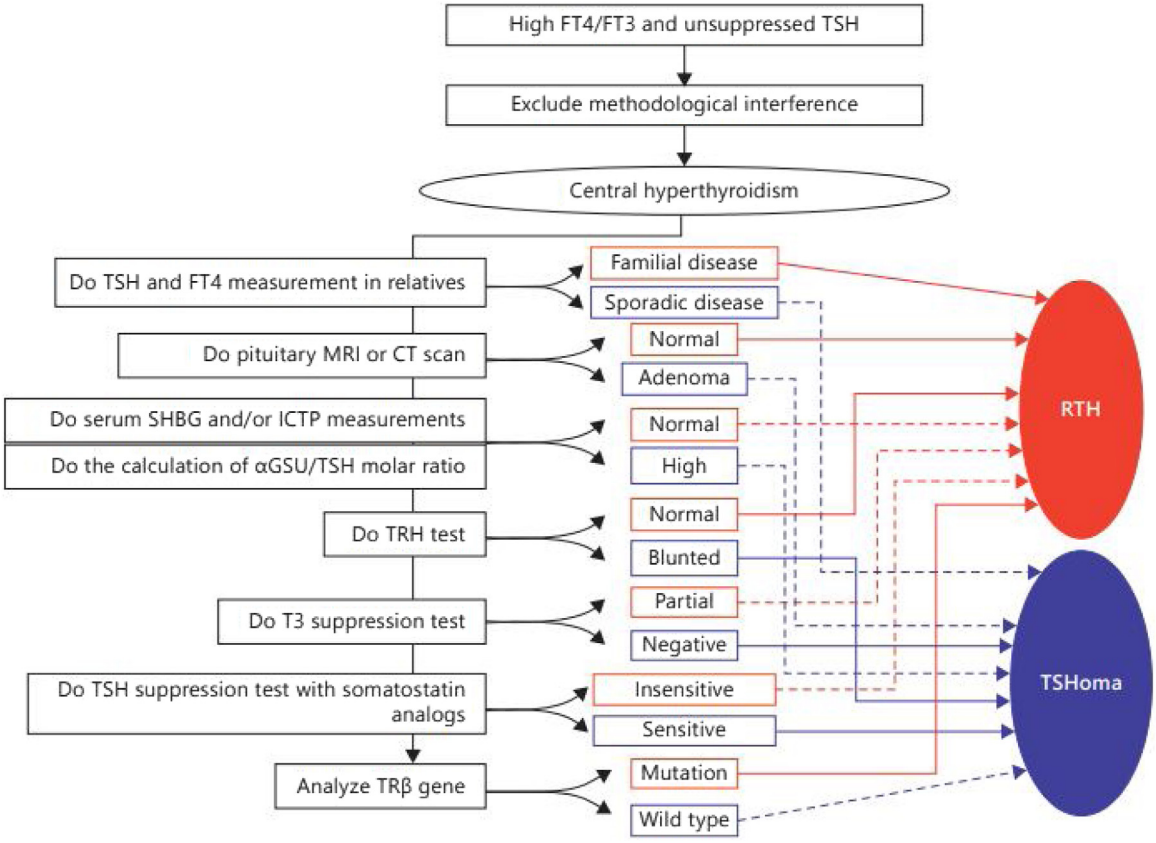

Fig. 1. Strategy of complementary investigations for the differential diagnosis of TSH-PitNET, according to the 2013 European recommendations. Solid lines indicate strong arguments for the diagnosis [19].

Table 2
Comparison of the characteristics of TSH-PitNET in comparison to resistance to thyroid hormone. Adapted from De Herdt et al., 2019 [9].

	TSH-PitNET	RHT
Clinical history		
Similar Familial Context	No	No
Visual field abnormality	30–40%	No
Atrial Fibrillation	Mostly no	Mostly no
Goiter	Mostly yes	Mostly yes
Epidemiology		
Incidence	1/2/million	1/40,000
Sex ratio	1	1
Age at diagnosis	40–50 years old	Mostly < 30 years old
Biology		
TSH	→ or ↑	→ or ↑
FT3-FT4	↑	↑
A sub-unit	↑	normal
Dynamic testing		
TRH stimulation test	TSH →	TSH > ×5
T3 suppression test	TSH →	TSH < 1 mUI/l
Genetic of thyroid hormone receptor (TRβ)	Negative	Positive in 85% of cases
Pituitary MRI	Macro 80%/micro adenoma	Possible microadenoma 20% (incidentaloma)
Treatment	Surgery	levothyroxin if necessary

Dynamic testing have also been proposed to distinguish TSH-PitNET from RTH and can help if MRI is doubtful with no relatives and a negative genetic testing. However, this test can be dangerous, should be performed in a hospital setting under supervision, and is particularly contraindicated in the elderly or coronary patients [19]. Thus, the T3 suppression test is the most sensitive and specific test and can be used for patients who have had a total thyroidectomy. In the context of TSH-PitNET, administration of 80–100 μg/d T3 for 8–10 days does not result in TSH suppression [11]. Another parameter that can be assessed in this test is total cholesterol, which does not decrease in RTH, unlike in healthy patients, due to hepatic resistance to thyroid hormones in TRβ mutation [30]. This test can also be used postoperatively to assess any residual secretion.

A TRH stimulation test (200–400 μg IV) was also widely used, with no response in 85% of TSH-PitNETs and an explosive TSH response in RTH [26]. An elevation of less than 2 times baseline is considered a no response, between 2 and 5 times baseline a normal response and more than 5 times baseline an explosive response [31]. There is also a difference between no TSH elevation and elevation of the α-subunit (present in 44% of cases) in TSH-PitNET [6,7]. However, this test is not very sensitive in cases of thyroidectomy.

A somatostatin analogue suppression test is also proposed. Long acting somatostatin analogues can be used, with a slowing down of secretion in 90% of cases after two months of treatment [32]. In this paper, it was described that RTH slowed their TSH after a subcutaneous injection of 0.1 mg of somatostatin (acute test). More recently, a short test has been proposed with 100 mg of sandostatin administered every 8 hours for 24 hours, demonstrating a TSH braking in TSH-PitNET that is not found in RTH. The sensitivity and specificity of this test for a 44% decrease in TSH are 95% and 94% respectively. In addition, this type of test is predictive of response to long acting somatostatin analogues [33].

However, nowadays, with the quality of MRI, of hormonal measurement, and with the genetic testing, these biological markers and dynamic testing are usually not needed. We proposed a new diagnostic approach to distinguish TSH-PitNETs from RTH (Fig. 2).

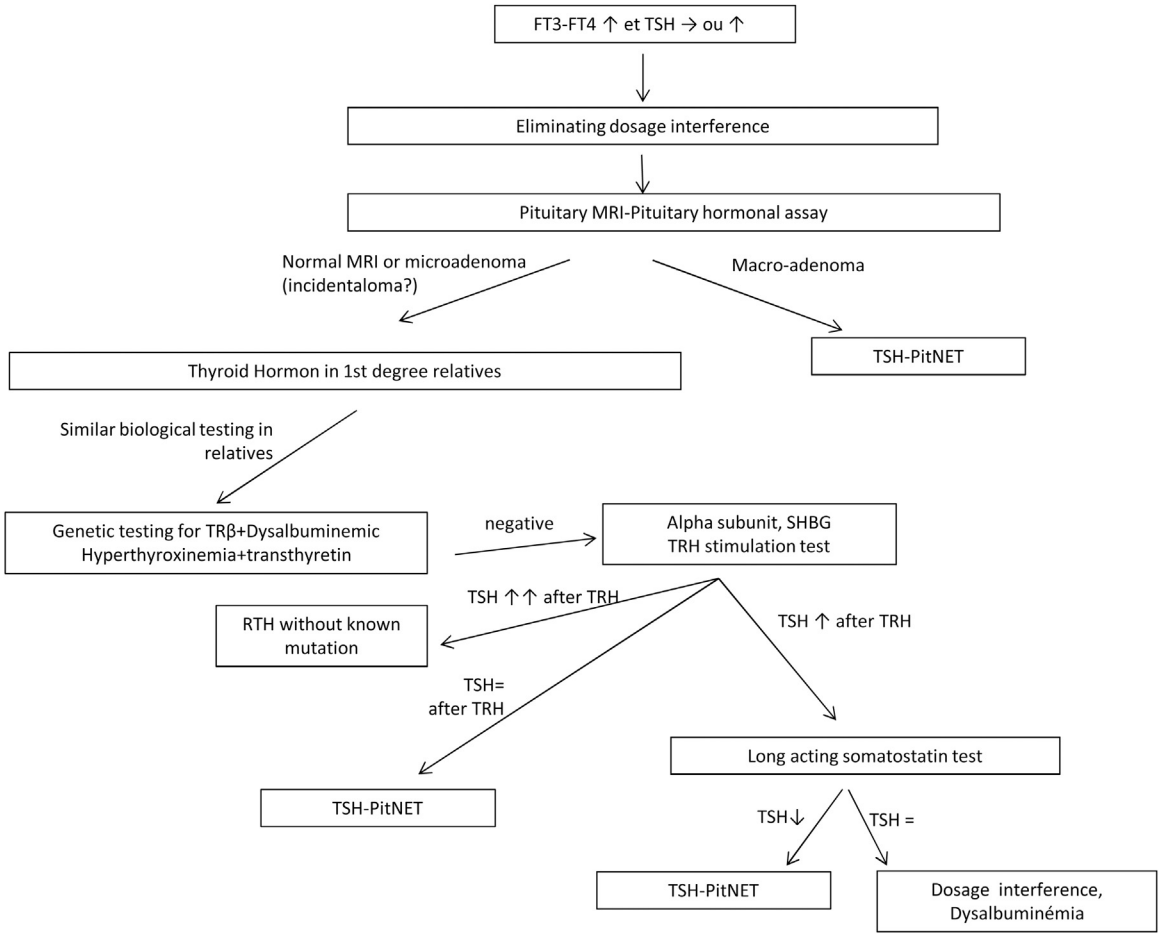

Fig. 2. New strategy of complementary investigations to distinguish TSH-PitNET from thyroid hormone resistance.

5. Genetics

Most TSH-PitNETs are sporadic but a few cases have been documented in MEN 1 families and in one family mutated for Aryl-Hydrocarbon Receptor Interacting Protein (AIP) [34–36].

Genetic analysis for thyroid hormone receptor mutations will lead to a diagnosis of RTH: TRβ (more common) or TRα [34–37]. The mutation is absent in 15% of cases, and an analysis of the thyroid work-up of relatives in cases of suspected RTH may also help for the diagnosis, as these mutations are inherited in over 80% of cases [38]. Other rarer genetic abnormalities may give a pattern of elevated thyroid hormones in relation to normal TSH: mutations in MCT8 associating psychomotor retardation, spastic tetraplegia, and biologically high FT3, low FT4 and normal TSH. Similarly, a deiodase abnormality results in a pattern of elevated thyroid hormones (high FT4, low FT3) in relation to a normal TSH [26]. In familial dysalbuminemia, some variants result in increased binding affinity for FT4 such as the R218H variant in exon 7 of the albumin gene. Other rarer variants increase the affinity for FT3 [39].

6. Imaging

Imaging is really helpful for the diagnosis of TSH-PitNET. On MRI, 65–80% of macroadenomas are found with an average diameter of about 20 mm, 45–60% of which extend into the sphenoidal or suprasellar sinus [7,9,13]. However, there has been an increase in the prevalence of microadenomas due to more reliable bioassays and more accurate imaging techniques. Thus, the prevalence was estimated at 11% before 2000 versus 22% after. The appearance is often that of a rounded, ovoid or lobulated adenoma, sometimes irregular. The signal may be mixed if there is cystic, haemorrhagic, necrotic or calcified degeneration. The pituitary stalk is very often deviated in macroadenoma. Finally, the sella turcica is often enlarged, with a sometimes sellar floor erosion. A CT scan of the skull base bones may then be indicated to assess the risk of CSF leakage postoperatively [2].

Ectopic localizations are rare but possible: a dozen cases have been reported in the literature: notably in the nasopharynx or in the supra-sellar area [40–47]. In this case, scintigraphic images such as DOTANOC PET-Galium, which is more informative than 18F-DOPA PET [45], can be used.

However, the presence of a pituitary adenoma and inappropriate TSH secretion does not indicate a diagnosis of TSH-PitNET since a pituitary incidentaloma is found on MRI in 20% of RTH [48].

On thyroid ultrasound, goiter is very frequent (55% of cases), and even recurrent after partial thyroidectomy [6,8,9].

The prevalence of nodules is higher than in the general population [49]. Cases of autonomous secretion of nodules have been reported,sometimes leading to misdiagnosis [50].

7. Anatomopathology

The β-subunit of TSH is found in adenomatous thyrotropic cells, alone or in heterodimer with the α-subunit. Most TSH-PitNETs secrete only TSH but 20-30% are mixed tumours, co-secreting by frequency GH > PRL > gonadotropin (Table 1) [5].

TSH-PitNETs express somatostatin and dopamine receptors at a level equivalent to non-functioning adenomas. Of the 5

somatostatin receptor subtypes, the most intensely expressed are SST2, 3 and 5 receptors [6,7]. In addition, SST receptors are more frequently expressed during GH- TSH co-secretion [8].

Malignant TSH-PitNET is rare; three cases have been reported in the literature [10–12].

Thyroid cancer associated with a thyroid adenoma is rare. About ten cases are reported in the literature, including 3 cases in a series of 68 TSH-PitNET. These are mainly papillary cancers [47,51–55].

8. Treatment

The first-line treatment is surgery, by transphenoidal approach, more rarely by subfrontal approach which allows immunohistological confirmation of the diagnosis [19,56]. In the meta-analysis by De Herdt et al, this treatment was chosen in 89% of cases, with 36% of preoperative treatment with somatostatin analogue to control thyroid hypersecretion [9]. Most TSH-PitNETs are macroadenomas, which are cured by surgery in 50% of cases versus 87% of cases if microadenomas [5]. Surgical failure is related to supra-sellar, intra-cavernous extension and the often very fibrous consistence of these adenomas [49,57]. Imaging 3 to 6 months after surgery and the thyroid work-up will confirm a possible cure. Anteropituitary insufficiency after surgery is variable: from 9 to 40% of cases [49,58].

Adjuvant radiotherapy was used in 15% of cases in the meta-analysis by De Herdt et al. [9]. Stereotactic or conventional fractionated radiotherapy can be used, with doses of 15 to 25 Gy versus 46 to 54 Gy respectively. This treatment allows control of hormone secretion in 65% of patients, with a risk of ante-pituitary insufficiency in about 30% of cases [5,49].

The pharmacological approach of TSH-PitNET is mainly based on the use of long acting somatostatin analogues (octreotide or lanreotide) which allow normalization of the thyroid balance in more than 80% of cases [5]. The rationale for the use of these analogues comes from the expression of SST receptors on the surface of these adenomas, and in vitro functional studies on primary culture from TSH-PitNET showing a 90% reduction in TSH secretion under octreotide, with an additional anti-proliferative effect [59]. There is no report for second generation of long acting somatostatin analogues (pasireotide) efficacy.

Medical treatment has sometimes been proposed as a first line treatment, in the event of foreseeable failure of surgery, invisible adenoma or refusal of the patient allowing secretory control in almost all cases [6,7,58].

Medical treatment also allows a reduction in tumor volume in more than half of cases, and visual improvement in 70% of cases [7].

In mixed TSH and prolactin adenomas, treatment with a dopaminergic agonist may be proposed, often allowing partial control of TSH secretion [7,19].

The dose of somatostatin analogue and the frequency of administration will depend on the response to treatment and should be individually adapted. Recently, we conducted a retrospective study alerting to cases of thyroid insufficiency under somatostatin analogue in the treatment of TSH-PitNET, occurring within the first 4 weeks of treatment, for a mean duration of three months in 15% of cases [60]. Thyroid function should therefore be monitored early after the introduction of a somatostatin analogue and the frequency of injections may be adapted to the secretory response.

In the meta-analysis by Cossu et al, there was no significant difference between the control of hypersecretion obtained by irradiation or by somatostatin analogue [5]. On the other hand, other studies are less optimistic, thus in 70 thyrotropic adenomas, radiotherapy controls 37% of patients at two years, with new pituitary deficits in 32% of cases, compared with control obtained in 85% of cases with somatostatin analogues [49]. In the event of failure of either adjuvant therapy, the combination of the two can control the majority of patients [5].

In conclusion, TSH-PitNETs are rare pituitary tumours which are not always easy to diagnose (interference of dosage, differential diagnosis of dysalbuminemia or thyroid hormone resistance much more frequent). Treatment is surgical, followed by somatostatin analogue if surgery fails.

Disclosure of interest

Pr Rodien: Honorary consultant Pfizer and Novartis, IPSEN. The other authors declare that they have no conflict of interest.

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