Clinical case

TSH-secreting adenoma improved with cabergoline

À propos d’un cas d’adénome thyroïdote pur, sensible à la cabergoline

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Abstract

TSH-secreting adenomas are rare tumors, representing only 0.5 to 2.5% of pituitary adenomas. Their main clinical characteristics include signs of thyrotoxicosis, diffuse goiter and a compressive syndrome. Biologically, free T4 and T3 serum levels are elevated, contrasting with inadequate serum TSH levels and increased alpha chains. Magnetic resonance (MR) imaging shows a pituitary tumor, the main differential diagnosis being resistance to thyroid hormones. Treatment is based on surgery, possibly associated with somatostatin analogs and radiotherapy. Though the long-term evolution of this rare pathology seems to have improved, some clinical situations are still a challenge to treat. We report one such case that was resistant to both stereotactic radiotherapy and somatostatin analogs, but surprisingly improved with cabergoline. We suggest that cabergoline should be considered as an alternative treatment in cases of pituitary adenomas that resist traditional treatments.

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Résumé

Les adénomes thyroïdotes constituent une pathologie rare, puisqu’ils représentent 0,5 à 2,5 % des adénomes hypophysaires. Ils se manifestent essentiellement par une thyrotoxicose, parfois associée à un goitre diffus et un syndrome tumoral. Il existe une ascension des fractions libres des hormones thyroïdiennes T3 et T4 contrastant avec une concentration inadaptée de TSH associée à une augmentation de la chaîne alpha. L’imagerie par résonance magnétique met en évidence un tumeur hypophysaire. Le traitement se fonde sur la chirurgie, éventuellement associée au traitement médical par analogue de la somatostatine et à la radiothérapie. L’évolution à long terme de cette pathologie rare semble s’être améliorée. Néanmoins, certaines situations cliniques restent de traitement difficile. Nous en rapportons un cas particulier de par sa résistance à la radiothérapie multi-faisceaux et l’amélioration constatée sous cabergoline alors que les analogues de la somatostatine étaient peu efficaces. Cette possibilité thérapeutique doit rester présente à l’esprit dans les adénomes thyroïdotes de traitement difficile.

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Keywords: TSH-secreting adenoma; Cabergoline; Stereotactic radiotherapy; Visual impairment

Mots clés : Adénome thyroïdote ; Cabergoline ; Radiothérapie multi-faisceaux ; Altération visuelle

1. Introduction

TSH-secreting adenomas are rare tumors, representing only 0.5 to 2.5% of pituitary adenomas. Their treatment relies mainly on surgery, which may be coupled with somatostatin analogs and radiotherapy. Though the long term, outcome of this pathology...
seems to have improved, some cases still prove difficult to treat. We report a particular such case that resisted both stereotactic radiotherapy and, to a certain degree, somatostatin, but improved when treated with cabergoline.

2. Case report

2.1. Case history

M. J, age 26, with no particular medical history other than repeated sinus infections, was addressed to us for hyperthyroidism in October 1991. He presented with signs of thyrotoxicosis and a simple goiter, but no compressive syndrome. Also noteworthy were a *pectus excavatum*, rib hyperostosis, and a “café au lait” spot under the left breast. The patient’s father demonstrated similar bone malformations and hip dysplasia. Thyroid hormone levels were elevated, while the other pituitary hormones were negatives. Thyroid uptake was found on the pituitary gland at the same place the sonogram found a hyperechogeneous simple goiter of 36 ml. Levels of TSH (0.59 mUI/ml), but no other disorder. A thyroid sonogram found a hyperechogeneous simple goiter of 36 ml. The visual field defect had become more severe with bitemporal hemianopsia, though its compressive origin was difficult to prove. MR imaging showed residual tumor in the left cavernous sinus, at a distance from the optic chiasm. Because of the persisting clinical and biological thyrotoxicosis, a treatment with cabergoline (Dostinex®, a dopaminergic agonist, was implemented alongside octreotide in October 2002, its weekly doses were progressively increased to maintain T4 levels at the higher levels of the normal range.

In March 1999, treatment was switched to an extended release form of octreotide (octreotide LAR) with doses of 20 mg/28 days, increased to 30 mg/28 days in June 1999. This treatment was pursued until 2002.

In August 2002, pituitary investigations found above-normal levels of thyroid hormones (T4: 26.8 pmol/l) and non-adapted levels of TSH (0.59 mU/ml), but no other disorder. A thyroid sonogram found a hyperechogeneous simple goiter of 36 ml. The visual field defect had become more severe with bitemporal hemianopsia, though its compressive origin was difficult to prove. MR imaging showed residual tumor in the left cavernous sinus, at a distance from the optic chiasm. Because of the persisting clinical and biological thyrotoxicosis, a treatment with cabergoline (Dostinex®, a dopaminergic agonist, was implemented alongside octreotide in October 2002, its weekly doses were progressively increased to maintain T4 levels at the higher levels of the normal range.

In September 1992, after surgery, the patient demonstrated persisting clinical and biological signs of thyrotoxicosis, though there was apparently no residual adenoma. Octreotide (Sandostatin®) treatment was resumed subcutaneously with daily dosages of 150 μg and successfully, though temporarily, lowered thyroid hormone levels. Indeed they soon increased again, though not reaching their anterior levels. Bromocriptine was tentatively associated for a six-week period but was discontinued because of intolerance.

In December 1992, MR images showed residual tumor in the left laterosellar area, causing us to interrupt octreotide and attempt stereotactic radiotherapy using a linear particle accelerator (saturne 18 Mev, intended central dose: 30 grays, reference isodose 70%) in October 1993. Octreotide treatment was resumed with 150 μg daily subcutaneous infusions, stabilizing thyroid hormone levels though not normalizing them.

In August 1995, MR images showed a rounded mass measuring 4 mm that presumably corresponded to residual fibrous tumoral tissue, along with a 1 cm liquid-filled cavity resembling an arachnoidcele. The patient’s visual field was slightly impaired with superior temporal quadrantanopsia. In August 1995, a treatment with lanreotide (Somatuline® LP, IPSEN) was attempted, but soon discontinued on account of severe digestive intolerance and bruises at the injection site. Octreotide was resumed using a subcutaneous implanted pump with daily initial doses of 150 μg that were progressively increased to maintain T4 levels at the higher levels of the normal range.

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2.2. Treatment

Treatment with propranolol and octreotide (Sandostatin®, Novartis, Lyon) 200 μg three times a day subcutaneously soon normalized levels of thyroid hormone. Doses were therefore lowered to 300 μg daily but the MR images remained unchanged, and it was decided to proceed with transsphenoidal surgery in June 1992. Pathologists concluded to a TSH-secreting pituitary adenoma marked with total anti-TSH antibodies, alpha TSH and beta TSH by immunohistochemistry.

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ber 2005. In April 2006, persisting clinical and biological signs of thyrotoxicosis led us to increase cabergoline doses to 2 mg per week and then to 0.5 mg daily. A systematic abdominal sonogram found asymptomatic biliary microcalculi leading to preventive cholecystectomy. In January 2007, over 15 years after the initial diagnosis, our patient was leading a professionally active life and doing well. There were persisting visual field defects that were not attributable to any type of compression: the residual left intracavernal adenoma was distant from the visual pathways. It was not surgically accessible, and renewed radiotherapy was decided against, regardless of its modalities, since no single etiology for visual defects had been pinpointed. Figs. 1 and 2 depict the improvement of thyroid hormones under cabergoline. When cabergoline was temporarily discontinued to detect any late effect of radiotherapy, thyroid hormones reascended (Table 2).

### 3. Discussion

We present the case of a TSH-secreting pituitary microadenoma that recurred after combined surgical and stereotactic radiotherapy and responded only partially to currently available somatostatin analogs, but was successfully treated with cabergoline. This case illustrates the long term evolution of TSH-secreting pituitary adenomas, highlighting [1] their fluctuating responsiveness to somatostatin, both functionally and morphologically speaking; [2] the relevance of cabergoline as an alternative treatment in certain situations; and [3] the apparent radio-resistance of some cases, in which unfortunately, secondary effects on visual functions do occur and require long-term follow-up. Over the past few years, several series of 8–43 patients with TSH-secreting pituitary adenomas have been published [1–7], most of them emphasizing the satisfactory outcome of the tumor.

The management of TSH-secreting pituitary adenomas is multidisciplinary, involving surgery, radiotherapy and medical treatment.

Our patient underwent transsphenoidal tumor resection once hyperthyroidism had been reduced with somatostatin analogs. Despite apparently total tumor resection, hyperthyroidism recurred after surgery.

The objective of surgery, which is usually transsphenoidal, is to retrieve the adenoma without affecting the healthy pituitary tissues and to relieve adjacent structures from compression [2]. This type of surgery is complex due to the usually fibrous nature of TSH-secreting pituitary adenomas (40%) [2,8,9]. The rate of post-operative remission ranges from 22 to 86%, confirming that recurrences are not exceptional findings after surgery. The main risk factors for recurrence include tumor volume, the presence of visual defects, cavernous sinus invasion, late diagnosis, elevated TSH and T4 levels at the onset of management, and initial thyroid treatment [2,5,8]. Morbidity and mortality levels are not negligible in series 3, 4, and 7, while they appear lower in the larger series (mortality < 1%).

Most frequently observed post-surgery complications include transient diabetes insipidus (23%) and hypopituitarism (22%), though these did not occur in our patient [10]. Undetectable TSH levels seven days after surgery might be an indicator of successful outcome [5]; they were measured at 1.85 μUI/ml in our case.

Pathology of the resected tumor often finds invasive cells, possibly providing an explanation for frequent recurrences. In our case, the tumor was not invasive [11].

### Table 2

Levels of TSH and free fraction of thyroid hormones during cabergoline treatment

<table>
<thead>
<tr>
<th></th>
<th>Before cabergoline</th>
<th>During cabergoline treatment (February 2007)</th>
<th>Three months after cabergoline was discontinued (December 2007)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (0.4–3.6 μUI/ml)</td>
<td>1.970</td>
<td>0.495</td>
<td>0.500</td>
</tr>
<tr>
<td>Free T3 (3.3–6.1 pmol/l)</td>
<td>10.8</td>
<td>6</td>
<td>6.2</td>
</tr>
<tr>
<td>Free T4 (10.5–25.5 pmol/l)</td>
<td>29.5</td>
<td>25</td>
<td>29.8</td>
</tr>
</tbody>
</table>
Radiotherapy is often a second line treatment, to reduce residual tumor or recurrences located at a distance from the optic chiasm. Two techniques are used: conventional fractionated radiotherapy for macroadenomas and stereotactic radiotherapy for microadenomas [12,13]. Their comparative efficiency has never been specifically tested on TSH-secreting adenomas. Stereotactic radiotherapy used on our patient did not affect TSH production over ten years after the procedure. This might be due to the fact that the cavernous sinus containing the residual tumor might have been outside the radiation range. The overall efficiency of radiotherapy on adenomas ranges between 50 and 98%, while hormonal treatment is successful in 48 to 100% of cases. The main risk is to develop secondary hypopituitarism (3 to 56% of cases). Regardless of the type of adenoma, visual complications due to optic neuropathy have been reported in about 2% of adenomas [14–16]. Careful dose planning to keep radiation under 8 Gy on the optic tracts should help prevent this complication. In the case we report, there was no initial compression of the optic tracts; the mechanism causing the visual field defects, though they fluctuated over time, have yet to be elucidated.

Medical treatment is based on somatostatin analogs. Somatostatin is a peptide with a short-half-life that is secreted by the hypothalamus. It inhibits the production and secretion of TSH. There are five different types of receptors for somatostatin (SSTR1 to SSTR5), all of which are composed of seven transmembrane domains coupled to a G protein. SSTR2 and 5 have been found on TSH-secreting adenomas, but the density of SSTR2 receptors does not seem to affect the response to somatostatin analog treatment. The first somatostatin analogs were developed in 1982 (octreotide or Sandostatine®, SMS 201 995, with a high affinity for SSTR2 receptor, subcutaneous injection). Then came extended release octreotide analogs LAR in 1995, and lanreotide in 2001. All of these drugs normalize thyroid hormone levels, usually without affecting the size of the tumor, though a few spectacular tumor regressions have been reported [17–21] (we have witnessed one such case). Somatostatin analogs also have a decompressing effect on the optic tracts, independently from tumor size reduction. A few adverse effects such as a case of pituitary apoplexy have been reported [22]. In a minority of patients, treatment is unsuccessful, regardless of the presence of somatostatin receptors on the adenoma [2,23]. In our patient, despite the presence of SMS receptors as attested by scintigraphy and by in vitro studies on the tumor [1], TSH levels were little affected by somatostatin analogs in the long-term, regardless of the type of drug used or its route of administration. Adverse reactions (diarrhea and abdominal cramping) were present initially after lanreotide injection, but subsided shortly [19]. Asymptomatic gallstones were found, as classically described [24]. Adenomas can escape treatment, [25], possibly due to reduced numbers of SSTR2 receptors. That is what we observed in our patient after eight days of treatment. New molecules that associate ligands to different receptors (SOM 230: SSTR1, 2, 3 et 5 ligand; BIM 23A758 SSTR2 and 5 ligand and receptor of DR2 dopamine; BIM 23244: SSTR2 and SSTR5 ligand) are currently being developed, but their efficiency in TSH-secreting adenomas has yet to be tested.

The pharmacopeia available to treat TSH-secreting adenomas also includes dopamine agonists. Five cases in which they were used have been reported in literature: one case where an adenoma secreting only TSH was sensitive to bromocriptine, which was effective both on hormone levels and tumor size; another of a mixed TSH-and prolactin-secreting adenoma where cabergoline lowered hormone levels but did not affect tumor size; and 3 TSH-secreting adenomas in a serie of five patients, one of which was treated with cabergoline (two by bromocriptine, two by octreotide), that reached stable hormone levels and tumor size [26–28]. The mechanism of dopamine agonists might be linked to the presence of D2 receptors on pituitary tumoral cells. Thus it seems the patient we report might be one of the first cases of TSH single-secreting adenoma in which cabergoline lowered hormone levels. This result was disputable on account of the associated treatments, e.g., radiotherapy and somatostatin analogs, therefore we interrupted cabergoline for a 3-month period and measured TSH levels. They increased, confirming that cabergoline was specifically active on the tumor and that it should be continued (Table 2).

Medical treatment is usually the first line treatment of pituitary adenomas, acting both on hormone serum levels and tumor size [9]. Given its resistance to radiosurgery and to somatostatin analogs, we might be facing a new kind of pituitary adenoma, all the more so that there was a “café au lait” spot and bone anomalies. Arguments for Mac Cune Albright syndrome were too brittle and the genetic confirmation too difficult to obtain on account of frequent mosaicism.

In conclusion, though the outcome of TSH-secreting adenomas is usually considered good, we report a case of TSH-secreting adenoma that resisted somatostatin analogs and stereotactic radiotherapy, yet suffered the secondary effects of radiotherapy, namely visual field defects. High dose cabergoline brought TSH-levels back into the normal range and effectively treated thyrotoxicosis signs. Though its efficiency has only been reported in two other cases – one of which was a TSH-prolactin-secreting adenoma – we suggest that cabergoline is a viable alternative treatment for treatment-resistant TSH-secreting adenomas.

References


