Treatment of a thyrotropin-secreting pituitary adenoma (TSH-oma) with pasireotide LAR

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Dear Editor,

Thyrotropin (TSH)-secreting pituitary adenomas (TSH-oma) are rare and account for about 0.5%-3% of all pituitary adenomas. Patients with TSH-oma present themselves mostly with central hyperthyroidism expressing increased circulating levels of TSH, free T4 and T3.[1] TSH-omas are usually benign tumours and express somatostatin receptors subtypes 2 and 5.[2] This has led to the use of somatostatin analogues as medical therapy, although neurosurgery still is the first choice therapy for TSH-omas. As far as we know, pasireotide LAR, a multireceptor-targeted somatostatin analogue with high binding affinity for somatostatin receptor subtypes 1, 2, 3 and 5 is not yet prescribed for TSH-omas.[3] We report a case of a patient with a TSH-oma treated with pasireotide LAR as preoperative medical therapy to restore euthyroidism.

A 57-year-old man was referred to our department with complaints of tremors and weight loss. His family doctor diagnosed hyperthyroidism with an elevated free T4 of 32.6 pmol/L in combination with an elevated TSH of 5.1 mU/L. On physical examination, the patient was clearly thyrotoxic without a palpable goitre. There were no symptoms of acromegaly. Laboratory investigation confirmed hyperthyroidism with free T4 33.0 pmol/L (reference, 11-19.5 pmol/L), free T3 7.9 pmol/L (reference, 4.4-6.7 pmol/L) and inappropriate TSH of 3.8 mU/L (reference, 0.5-4.0 mU/L) (Figure 1). Thyroid autoimmunity was not present (TBII <1 U/L). Heterophilic antibodies could not be detected. In view of the possible central hyperthyroidism, additional tests were performed as follows: prolactin 188 mU/L (reference, <300 mU/L), alpha subunit 0.4 U/L (αSU, reference, 0.0-0.8 U/L) with αSU/TSH ratio of 1.07, GH 0.95 mcg/L (reference, <3 mcg/L) with IGF-1 32.4 nmol/L (SD-score 2.00), SHBG 53 nmol/L (reference, 12-30 nmol/L) with LH 2.5 U/L (reference, 1.7-8.6 U/L), FSH 6.5 U/L (reference, 1.8-7.2 U/L) and testosterone 9.1 nmol/L (reference, 10.9-30.8 nmol/L). GH was suppressed during glucose tolerance test (GTT, from 0.26 to 0.16; normal suppression <1 mcg/L). A TRH stimulation test (200 μg TRH iv) showed no TSH response to TRH (basal, 5.7 mU/L; max, 5.8 mU/L) and a marginal alpha subunit response (basal, 0.6 U/L, max, 0.9 U/L). Thyroid scintigraphy with iodine^{123} showed a slightly increased homogeneous uptake (4 hours 14%; 24 hours 30%). Pituitary MRI showed a microadenoma partly extending downwards (size of 7 × 8 × 12 mm) (Figure 2). A diagnosis of a TSH-secreting microadenoma was made. Before starting preoperative medical treatment to restore euthyroidism, an octreotide suppression test was performed (50 mcg octreotide iv) showing only a minor TSH response to octreotide (basal, 5.5 mU/L; after 120 minutes, 4.6 mU/L). Because in vitro and in vivo data showing expression of somatostatin receptor subtype 2 and 5 in TSH-oma, we interpreted the test results of the octreotide suppression test that there was possibly an excess of somatostatin receptor subtype 5 in the TSH-oma. Therefore, and also because we were interested in the therapeutic effect of pasireotide LAR on TSH-oma aiming for its higher affinity for somatostatin receptor subtype 5, we started preoperative medical therapy with pasireotide LAR 40 mg/4 weeks. Officially, pasireotide LAR is used 'off-label' because it is not registered for the treatment of TSH-oma. Persisting euthyroidism was already present shortly after the second injection of pasireotide LAR (free T4 13.6 pmol/L, free T3 3.2 pmol/L, TSH 0.9 mU/L) (Figure 1). Pituitary MRI after 4 months of treatment showed a stable size of the TSH-oma with possible central degeneration (Figure 2). During treatment, diabetes mellitus developed (HbA1c, 8.0%; glucose, 13.0 mmol/L) that was treated with a DDP-4 inhibitor. Radical endoscopic transsphenoidal surgery was attempted, also because of the favourable MRI characteristics. Pathological examination showed a lesion with mechanical damage, extensive fibrosis and calcium deposits. The cells have only a small amount of cytoplasm and the nuclei are pyknotic. A single cell was positive for Ki67. Immunohistochemistry confirmed the presence of somatostatin receptor subtypes 2 and 5 in the lesion, as well as βTSH. Six months after surgery euthyroidism is still present without the need for any medical therapy (Figure 1). A repeated TRH

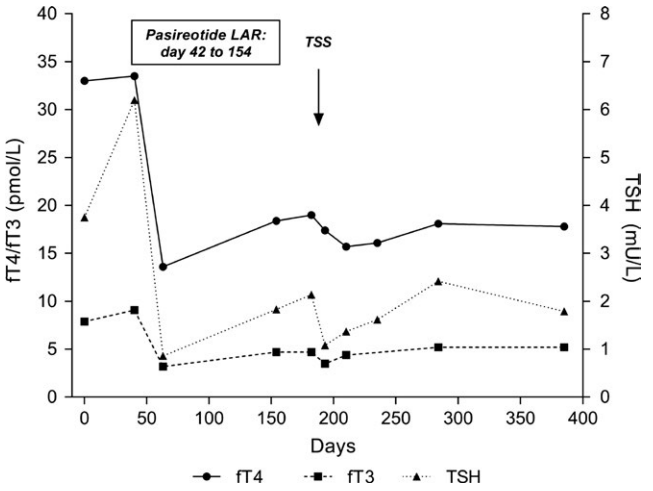

FIGURE 1 Results for free T4, free T3 and thyrotropin (TSH) at presentation, after starting pasireotide LAR and after transsphenoidal surgery (TSS) in a patient with a thyrotropin-secreting pituitary adenoma

stimulation test (200 μg TRH iv) 4 months after surgery showed a normal TSH response to TRH (basal, 1.5 mU/L; max, 6.9 mU/L). Also, 5 months after surgery, a repeated MRI pituitary showed no visible residue of the microadenoma. After discontinuation of the pasireotide LAR, diabetes mellitus disappeared.

As far as we know, this is the first reported case of a patient with a TSH-oma treated preoperatively with pasireotide LAR. The first choice therapy for TSH-oma is surgical resection of the pituitary adenoma.[1] However, it is preferred to restore euthyroidism before surgery takes place. Somatostatin analogues are being used for this purpose, mostly successfully. Unfortunately, surgery may fail due to different factors. First, the operation can be difficult by the firm consistency of the TSH-oma, which is often fibrous possibly due to the expression of basic fibroblast growth factor. Second, TSH-omas are usually large and locally invasive precluding radical surgery.[1] Therefore, continuation of the treatment with somatostatin analogues is not uncommon. One may even speculate about a role as primary medical therapy, partly illustrated by a rare case report describing cure after prolonged medical therapy with octreotide LAR.[4]

The most prescribed somatostatin analogues for TSH-omas are octreotide LAR and Lanreotide Autogel.[1] Both somatostatin analogues have a high affinity for somatostatin receptor subtype 2. However, the octreotide suppression test in our case, which was performed before starting preoperative medical therapy, showed only a minor TSH response to octreotide. This is remarkable as immunohistochemistry confirmed the presence of somatostatin receptor subtypes 2 and 5 in the TSH-oma in our case. A possible explanation for this result is that the dose of octreotide (50 mcg iv) in our suppression test was not high enough resulting in a minor TSH response. However, Varsseveld et al[5] described in their study that in all three cases of TSH-oma, the response of TSH to 50 mcg iv octreotide resulted in a significant decrease in TSH concentration. Moreover, we know that octreotide 50 mcg iv elicited an effect on the pituitary of the patient, as it showed a normal response of GH (basal, 0.2 mcg/L; after 120 minutes, <0.06 mcg/L). A speculative defect in the postreceptor pathway could be an alternative explanation. Furthermore, another explanation for the minor TSH response to octreotide might be the duration of octreotide suppression test. However, there is no consensus about the duration of this test that differs from 5 days to 2 hours in several studies.[2,5-7] We proceeded with pasireotide LAR as medical therapy based on the negative response after an octreotide dose test, although this is not an absolute proof of the ineffectiveness of this compound. The choice for pasireotide LAR was also based on firm experimental evidence that pasireotide LAR could be of great added value in TSH-oma.[2] Moreover, extensive experience has already been obtained with the use of pasireotide LAR in other patient groups. In our case, euthyroidism was already present shortly after the second injection of pasireotide LAR without any loss of effect for 4 months thereafter. Therefore, pasireotide LAR is probably a good alternative somatostatin analogue in the medical treatment of TSH-oma, especially for short-term preoperative therapy. The compound seems less suitable for long-term use because of its tendency for provoking diabetes mellitus like in our case. However, additional studies with larger numbers of cases with TSH-oma are necessary to establish the role of somatostatin receptor subtypes in the choice of medical therapy for TSH-omas.

In conclusion, pasireotide LAR, a somatostatin analogue with high affinity for somatostatin receptor subtypes 2 and 5, can be successfully applied as short-term alternative preoperative medical therapy in thyrotropin-secreting pituitary adenomas.

DISCLOSURE

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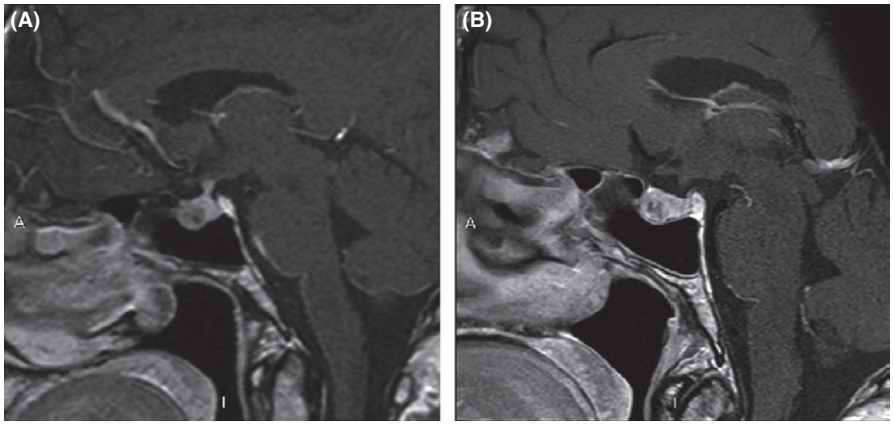

FIGURE 2 Contrast enhanced T1-weighted MR images of the pituitary gland in a patient with thyrotropin-secreting pituitary adenoma. (A) Before starting treatment with Pasireotide LAR, an area with inhomogeneous diminished enhancement is seen, ventrally in the pituitary gland, consistent with a microadenoma (size of 7 × 8 × 12 mm). (B) After 4 months of treatment with pasireotide LAR. Although scanned at a slightly different angle, the plane through the pituitary is similar and suggests a stable size of the TSH-oma with increase in peripheral enhancement and a more hypointense centre, possibly representing degeneration

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Assessment of time to glucose peak during an oral glucose tolerance test

Dear Editor,

We read with interest the article from Chung et al.[1] on the association between time to glucose peak and prediabetes. We agree with the authors in that the morphology of the glucose curve is worth investigating as an additional indicator of prediabetes and diabetes risk. This is a rather well-studied topic in the literature, and most authors agree that adding an intermediate glucose measurement (at 30 or 60 minutes) improves the ability to identify subgroups with forms of dysglycaemia not picked up by the traditional guidelines based on fasting and 2-hour values. However, a more detailed understanding of the most important features of the glucose curve requires analysis of frequently sampled oral glucose tolerance tests (OGTTs). Few large-scale clinical studies have measured glucose at five or more time points during the OGTT, and most previous studies that did have this unique opportunity, including the study from Chung et al., have not exploited the data optimally in our opinion. Instead of aiming to describe and understand individual glucose curves in their totality, studies tend to look at the five time points independently and select the time point with the highest value as the peak. We have previously studied the heterogeneity of glucose curves based on an individual-level pooled data set with up to 11 measurements per person during the OGTT in 1267 individuals, and observed that time to glucose peak varied markedly between individuals, but usually did not happen before 30 minutes.[2] Therefore, the categorization used by the authors (peak at 30 minutes vs later) is a bit unfortunate, and the generalization of their conclusion suggesting an association between a glucose peak after 30 minutes and prediabetes seems to be of limited clinical relevance.

We suggest a relatively simple solution to assess time to glucose peak as a continuous variable and illustrate the advantages compared to the commonly used approach using a real data set. First, we fit a multilevel model for change, a special case of mixed-effects models, often used in longitudinal studies.[3] The main difference between a simple linear regression (a fixed-effects model) and a mixed-effects model lies in the inclusion of random effects which, in our case, facilitate the estimation of differences between the population mean and each individual.