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Long-Term Follow-Up in a Male Patient with Micro-TSH-Oma Diagnosed at 8-Yr-Old

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Abstract

Background: TSH-secreting pituitary adenomas (TSH-omas) are very rare and an infrequent cause of thyrotoxicosis.

Case Report: A 7.9-yr-old boy was referred to our Pediatric Endocrinology Unit due to a goiter. On admission, patient was thyrotoxic with diffuse goiter. Laboratory evaluation suggested inappropriate TSH secretion as the cause of hyperthyroidism: high serum TSH in presence of elevated levels of TT_4, TT_3 and fT_4, and TSH unresponsive to TRH stimulation and to T_3 suppression. Initially, α-subunit (aSU) was in the upper limit of normalcy and pituitary MRI was normal. One year after, patient was still hyperthyroid, despite regular use of methimazole; TSH was 12.6 mU/mL, αSU was elevated and MRI detected a pituitary 8 mm width adenoma, establishing the diagnosis of TSH-oma. Peak GH (ng/dL) on ITT and TSH after TRH were 5.9 and 4.2, respectively. Cortisol and prolactin (PRL) responded normally to ITT and TRH tests. Transsphenoidal surgery was done and, postoperatively, transient diabetes insipidus and adrenal insufficiency ensued. Two and five months after surgery fT_4, TT_4 and TT_3 were normal, albeit peak TSH after TRH was 1.54. PRL and GH were unresponsive to adequate stimuli. Fourteen months after surgery, TT_4, TT_3 and fT_4 were low normal. He presented with low IGF-1, low GH peak on dinanic tests and hypogonadism and was treated with recombinant human growth hormone (rhGH) and testostenone. At 16 yr-old, we reached final height, above target height.

Conclusion: TSH-oma may be an etiology of thyrotoxicosis in children. To our knowledge, this is one of the youngest patients with TSH-oma yet reported.

Keywords: Pituitary tumor; TSH-oma; Hyperthyroidism; Thyrotoxicosis; Transsphenoidal surgery; Final height

Introduction

In most children with thyrotoxicosis the main cause is Graves' disease. Other causes include toxic adenoma, thyroiditis, iodine-induced hyperthyroidism, McCune-Albright syndrome, syndrome of resistance to thyroid hormone (RTH) and thytroid-stimulating hormone (TSH) secreting pituitary adenoma (TSH-oma). TSH-oma comprises 0.5 to 3% of all pituitary tumors. Patients present with signs and symptoms related to thyroid hormone (TH) excess and/or to tumor size (headache, visual field disturbances, cranial nerve palsies). The presence of goiter is frequent [1,2]. Elevated TH levels in presence of non-suppressed TSH should occur in TSH-omas, as well as in other conditions such as early phase of destructive thyroiditis, irregular replacement of l-thyroxine, assay interference of heterophilic antibodies and RTH. The combination of high serum free TH, inappropriately normal or elevated TSH, high serum α-subunit (αSU) or increased αSU/TSH molar ratio and a pituitary tumor strongly suggests the diagnosis of a TSH-oma.

Triiodothyronine (T3) suppression test is generally reserved for patients with inconclusive results in above tests, because genetic tests for detection of mutations in thyroid receptor (TR)α and TRβ genes are expensive. Administering long-acting somatostatin analogs has been proposed for distinguishing between thyrotropinomas and RTH, since patients with thyrotropinomas would be likely to show a significant reduction in free thyroxine (fT_4) and T_3 levels. Approximately one third of patients with TSH-oma were misdiagnosed as having primary hyperthyroidism and mistakenly treated with thyroidectomy or radioiodine [2]. The majority of TSH-omas is monoclonal in origin, like other types of pituitary adenomas. Pituitary-specific transcription factor-1 (Pit-1) may play a role in adenomatous

cell proliferation and its overexpression was detected in growth hormone- (GH), prolactin- (PRL) and TSH-secreting adenomas more frequently than in normal pituitary. Reduced expression of TR was demonstrated, and it could explain the abnormal negative feedback of TH on TSH production by tumor cells [2,3].

TSH-omas are more fibrotic than other pituitary tumors and it can worsen surgical outcome and somatostatin analog treatment should be considered as the first-line treatment in adults with macroinvasive TSH-omas [2,4,5]. Such an adenoma is infrequent in adults and has rarely been report in children, we describe an 8-yr-old boy with TSH-oma, and his follow-up until final height. The patient and his mother assigned consentient term.

Case Presentation

A 7.9-yr-old white pre-pubertal boy was referred to Pediatric Endocrinology Unit due to goiter. His mother noticed he was more irritable, and lost weight albeit an increased appetite. History was negative for insomnia, headache or visual disturbance. Physical examination disclosed a lean and hyperactive child with stare opened eyes, warm and moist hands, with fine tremors. Height was 138cm (1.78SDS; target height -0.96SDS), weight 27.2kg (0.40SDS), and BMI 14.28 (-1.14SDS). Pulse rate was regular (108bpm) and blood pressure 100/60mmHg. Thyroid was tender, diffusely enlarged (app.30g). Deep tendon reflexes were exacerbated. Laboratory work-up revealed a bone age (BA, Greulich & Pyle) of 9-yr, and the following thyroid function profile (normal values in brackets) was found: TT_3 181.9 (45-137ng/dL), TT_4 24 (6-12µg/dL), fT_4 3.68 (0.71-1.85ng/dL), TSH 4.77 (0.49-4.67µU/mL); basal and peak TSH on TRH test 4.6 and 6.2, respectively; pre and post T_3 suppression test RAIU (24h) values were 42.1 and 30% respectively, while TSH did not change significantly (4.15) whereas fT_4 exhibited some reduction (2.64). Anti-thyroid receptor (TRAb), anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibodies were negative. Calcium and PTH levels were normal. αSU was 0.86 (≤0.8ng/mL), αSU/TSH molar ratio 2 (<1) and magnetic resonance imaging (MRI) of pituitary was normal.

Patient was managed with propranolol (1 mg/kg/day) and methimazole (MTZ, 0.5 mg/kg/day) and thereafter, with MTZ exclusively. Table 1 summarizes main preoperative clinical and laboratory events. While on MTZ, T_4 and T_3 did not normalize, TSH values ranged between 5.81 and 12.59 and goiter was slightly enlarged. MTZ was withdrawn and thyroid and pituitary functions were evaluated three weeks later. On combined insulin hypoglycemia (ITT)/TRH tests, prolactin (PRL) and cortisol rose properly, peak GH (ng/mL) was 5.9 and TSH was unresponsive (Table 2). Basal LH and FSH were normal and IGF-I was 434 (30-289 ng/mL). RAIU was elevated (75.8%) and rose paradoxically (87%) after T_3 suppression test. Sex hormone-binding globulin (SHBG) was 233 (13-71 nmol/L), and T_4-binding globulin (TBG) was 16 (10-29 mg/dL). Repeated TRAb, anti-TG and anti-TPO were negative. At this time αSU was high to 0.949 (αSU/TSH 4.7) and pituitary MRI revealed the presence of an 8 mm width microadenoma (Figure 1).

Table 1: Preoperative clinical and laboratory events.

CA (yr)	Symptons and signs	TT3 (ng/dL)	TT4 (mg/dL)	fT4 (ng/dL)	TSH (mU/mL)	Treatment
6.8	Goiter	201.8	16.8		4.66	
7.9	Goiter, tachycardia, tremors, emaciation	181.9	24	3.68	4.77	Propranolol
8.1		205.5		2.64	4.15	Methimazole started
8.6			12.7	1.76	8.93	Methimazole
9.3				2.74	12.59	Methimazole withdrawn
9.4		432	19.9	4.7	3.22	TSS
Normal range		45-137	4.5-12	0.71-1.85	0.49-4.67	

CA = Chronological age

Table 2: Pre and post-TSS surgery hormonal profile on TRH and ITT tests.

	Time(min)	TSH (mU/mL)	PRL (ng/mL)	GH (ng/dL)	Cortisol (mg/dL)	Glycaemia (mg/dL)
Preoperative	0	3.22	7.7	0.7	15.2	85
	20			0.8		28
	30	4.2	32.6	5.2	16.6	53
	40			5.5		72
	60	3.54	26.6	5.9	24.6	84
Postoperative	0	0.78	0.7	0.1	8.1	77
	20			0.1		14
	30	1.54	1.1	0.1	12.3	36
	40			0.2		50
	60	1.3	1	0.2	26.9	50

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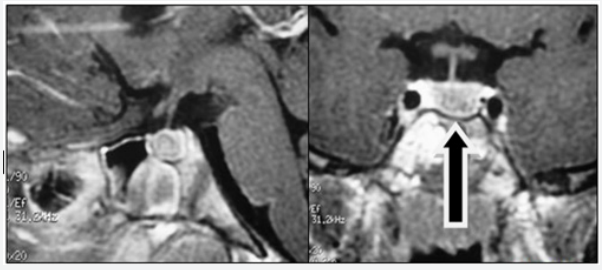

Figure 1: Preoperative pituitary MRI.

vTranssphenoidal surgery (TSS) was performed and a well-demarcated, fibrous and firm adenoma was excised. The pathologic specimen showed adenoma cells that were immunopositively only for TSH and chromogranin and negative for LH, FSH, PRL, ACTH, and GH. Eighteen hours after surgery, serum TSH and fT_4 descended to 0.53 and 1.8, respectively and goiter and thyrotoxicosis signs diminished as well. On the 3rd day postoperatively, acute adrenal insufficiency and transient diabetes ensued. Hydrocortisone and DDAVP were given and maintained for 2 and 14 months, respectively. Two months after TSS, ACTH was 12 (10-50 pg/mL) and IGF-1 64 (74-388 ng/mL). Peak GH and cortisol (µg/dL) on ITT were 0.2 and 26.9 respectively. PRL and TSH responses to TRH were blunted; however, RAIU was normal (23.8%). One year after surgery, BA was 11.5, TT_3, TT_4 and fT_4 were in the low-normal range for age, calorimetry was sub-normal and pituitary MRI showed no evidence of tumor.

He had gained weight, but growth velocity was <1 cm/yr despite adequate replacement dose of l-thyroxine (88 µg/day) He was put on rhGH (0,033 mg/kg/day) and growth velocity improved significantly (9.2 cm/yr). Three years after surgery, he is still pre-pubertal and growing normally (on both l-thyroxine and rGH). Last pituitary MRI was normal and aSU lower than 0.05 (aSU/TSH 0.61). His BA was 13.0 (chronological age 12.5) and peak LH and FSH after GnRH were 1.1 and 1.4 mU/mL, respectively. At that time, testosterone replacement was started and after 9 months, he was pubertal. Five years after surgery, rhGH was suspended, because he reached height above target height. Six months later, testosterone replacement was stopped. However, pubertal stage did not evolve and IGF-1 was 145 (226-903 ng/mL), testosterone (250 mg/month) and rhGH (0.6 mg/day) were re-started. At his last visit, at 16.3 yr.-old, height was 178.9 cm (0.59 SDS) and pituitary MRI was normal. Figure 2 shows his height and weight SDS during follow-up and table 3 summarizes main postoperative clinical and laboratory events.

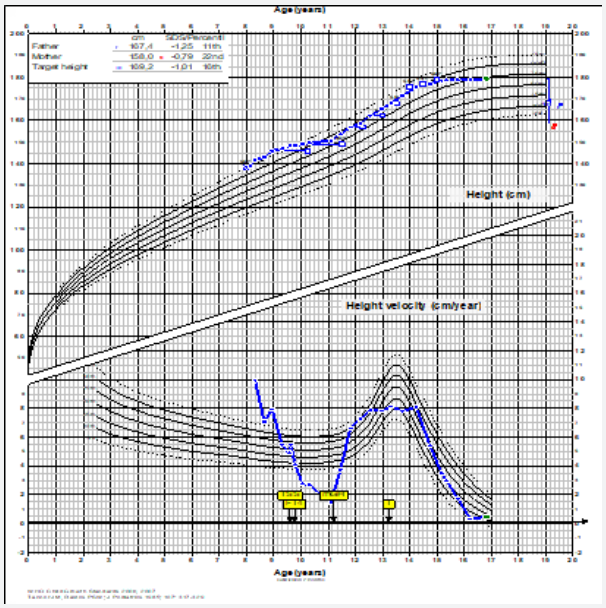

Figure 2: Height and height velocity chart during the follow-up. TSS = transphenoidal surgery; l-T4 = levothyroxine; rhGH = human recombinant growth hormone; T = testosterone.

Table 3: Main postoperative clinical and laboratory events.

TIME (after TSS)	Symptoms and signs	TT_3 (ng/dL)	TT_4 (mg/dL)	fT_4 (ng/dL)	TSH (mU/mL)	Treatment
3rd postoperative day*	Goiter reduction, weakness, anorexia, polyuria	115	8.7	1.3	0.28	Hydrocortisone DDAVP
2 months	Diminished goiter	117	8.9	1.47	0.78	
12 months	Weight gain, cool skin, growth failure, subnormal calorimetry	50.9	5.3	0.81	1.7	l-thyroxine
14 months	Growth failure					rhGH started
3 years	Growth acceleration, no puberal signs		10.2	1.5	0.86	l-thyroxine rhGH
3.4 years**	Growth acceleration, no pubertal signs		9.6	1.63		l-thyroxine rhGH Testosterone started
5 years	on puberty	57.1	10	1.24		rhGH suspended
5.5 years	Puberty not evolved		11.2	1.36	2.8	Testosterone suspended
6 years						Testosterone and rhGH re-started
Normal range		45-137	4.5-12	0.71-1.85	0.49-4.67	

*Basal cortisol = 3.43 mg/dL (6-19); urine density = 1005; ** Total testosterone = 106 ng/dL (<100); peak LH and FSH after GnRH = 1.1 and 1.4 mU/mL; CA = Chronological age; BA = bone age; rhGH = ecombinant human growth hormone.

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Discussion

Once inappropriate TSH secretion syndrome is identified, specific investigation to differentiate a TSH-oma of RTH is mandatory [2]. In our patient, TSH was not responsive to TRH stimulation test and both aSU and aSU/TSH molar ratio were high. In not previously treated subjects with RTH, the TSH response to TRH is preserved, and aSU/TSH is normal. Moreover, in RTH subjects a decreased secretion of TSH after supraphysiological doses of TH is usually accompanied by a reduction in RAIU [6], what was not observed in our patient. These findings suggest that RTH was not likely. TSH-omas are rare in adults and to our knowledge our patient is one of the youngest children with hyperthyroidism due to TSH-oma ever reported. Other 13 children or adolescents described were 8-yr. or older (8 to 16yr) and had macroadenoma except a 13 yr-old girl who had microadenoma and a 15 yr-old girl whose tumor size was not decribed [7-19].

In this case, pituitary MRI suggested microadenoma, although 88% of TSH-omas are usually large and invasive [2,20]. Patient underwent TSS because the primary goal of treatment of TSH-omas is, whenever possible, the complete removal of the tumor [2]. TSH, TH and aSU levels reduced soon after surgery and one week after, patient was euthyroid. TSS was successful in regard the complete removal of the tumor, although in the follow-up central hypothyroidism, and GH, PRL, LH and FSH deficiencies succeeded. Panhypopituitarism and diabetes insipidus also have been reported [14].

The first case of a patient with TSH-oma and normal aSU was described in 1991 [21]. Valdes-Socin et al. observed normal aSU in more than 60% of the cases. High aSU is often associated with bad prognosis and was found more frequently in macro than in microadenomas [4]. The high percentage of patients with normal aSU could difficult differential diagnosis with RTH. Absence of TSH response to TRH may be suggestive of presence of a TSH-oma. In difficult cases, genetic analysis looking for the presence of a mutation in TRβ gene may easily help to discriminate between the two disorders [2]. SHBG could also be a useful test yet its level was almost invariably normal in patients with RTH but often high in thyrotoxic patients with TSH-oma [2]. One challenging situation is those patients with an invisible adenoma on MRI and near-normal aSU, as initially occurred in our patient, whose diagnosis was done one year after inappropriate treatment with MTZ; possibly, that promoted tumor growth.

This case shows interesting aspects: the age of the patient at diagnosis; the finding of a normal MRI in contraposition to the elevated aSU/TSH molar ratio that was not adequately interpreted; growth of the tumor during MTZ, blunted TSH response to TRH in the post-operative phase in contradiction to diminished calorimetry, low-normal values of fT4, TT4 and TT3, and normal RAIU. We presented a comprehensive evaluation of a patient with TSH-oma followed for more than 8yr, who attained a final height, in accordance with the target height due to adequate therapeutic management.

Learning points

i. Once inappropriate TSH secretion syndrome is identified, specific investigation to differentiate a TSH-oma of RTH is mandatory, even in children.

ii. Patients who have TSH-oma could be misdiagnosed as having primary hyperthyroidism and, thus, mistakenly treated with antithyroid drugs or thyroid ablation.

iii. TSH-oma may be a microadenoma and be present even when aSU is near-normal or normal and it is a challenging situation.

iv. After surgery, follow-up should be prolonged and hormonal deficiencies should be diagnosed and treated.

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