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CASE REPORT

Thyrotoxicosis in a 13-year-old girl following pituitary adenectomy for Cushing's disease

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Key Clinical Message

Our objective is to report a case of thyrotoxicosis following pituitary adenectomy for Cushing's disease, the only pediatric case to our knowledge. No thyroid antibodies were detected, and the thyrotoxicosis was successfully treated for 3 months with no relapse after 5 years of follow-up. The cause of thyrotoxicosis remains unknown.

Keywords

Cushing's disease, pituitary, pituitary adenectomy, postoperative thyrotoxicosis, thyroid.

Introduction

Cushing's syndrome results from excess glucocorticoid steroids and is a rare condition in children and adolescents. Cushing's disease accounts for over 75% of pediatric causes of Cushing's syndrome, and it has a male predominance in prepubertal children but after the onset of puberty this equals out [1–3]. The disease is most often caused by a benign micro adenoma in the pituitary gland, secreting adrenocorticotrophic hormone (ACTH). The most prominent clinical symptoms and signs in children are growth failure, weight gain, virilization, headache, and hypertension [1, 2, 4]. As the disease has significant morbidity and mortality, early diagnosis is of utmost importance. To establish the pituitary as the source of excessive ACTH secretion, diagnosis involves a series of standardized biochemical and radiological investigations, such as 24-h urinary sampling for free cortisol, high-dose dexamethasone suppression test, imaging of the pituitary gland, and bilateral simultaneous inferior petrosal sinus sampling (BSIPSS) [1, 2, 5]. Transsphenoidal adenectomy is the primary treatment but in few cases accompanied by direct irradiation if hypercortisolemia persists.

Hyperthyroidism refers to overproduction of thyroid hormone by the thyroid gland, but thyrotoxicosis defines the clinical and biochemical picture of excessive thyroid hormones. Symptoms of thyrotoxicosis can be insidious and include growth acceleration, pubertal delay, ophthalmopathy, goiter, tachycardia, weight loss despite of increased appetite, heat intolerance, proximal muscle weakness, and changes in behavior. Causes of thyrotoxicosis are many, that is, toxic multinodular goiter, thyroiditis, toxic adenoma, and use of drugs, but Grave's disease is by far the most common cause [6, 7]. Grave's disease affects girls rather than boys (5:1) and has a peak incidence in adolescents. Most patients have a family history of autoimmune disease [8]. Grave's disease is caused by stimulation of antibodies to the thyroid-stimulating hormone (TSH) receptor and is diagnosed by high serum level of thyroxine (T4), triiodothyronine (T3), and low serum level of TSH as well as presence of antithyroid

antibodies. Therapy mainly includes antithyroid drugs, radioactive iodine, and surgery [8–10].

Case Report

An Icelandic girl was referred by the family to a pediatric endocrinologist at age 12 years because of growth failure. Growth had become slower the past 2.5 years (from 0 SD to −1 SD) as well as she had gained weight (from 0 SD to +1 SD). She had become lethargic, her face had become more swollen, and she had trouble with acne. Endocrine tests showed a substantial increase in both morning serum cortisol, 864 nanomol/liter (nmol/L) (reference range 193–773 nmol/L) and urine cortisol, 553 nmol/24 h (in totally 1.06 L urine) (reference range for age 9–12 years 7.2–102 nmol/24 h). Overnight high-dose dexamethasone test indicated a possible Cushing′s disease with serum cortisol before suppression measuring 530, 691, and 754 nmol/L and after suppression 78, 65, and 62 nmol/L and ACTH before suppression measuring 40, 47, and 43, and after suppression 12, 13, and 16 (prepubertal reference range 1.55–6.2 pmol/L) (three sets of blood tests, before and after high-dose dexamethasone test). MRI studies did not clearly demonstrate a pituitary adenoma and were seen as normal. A sinus petrosus catheterization on the other hand showed a high pituitary secretion of ACTH, especially on the right side as can be seen from following test results: pretest: right-side sample (RS) 224 and 348 nmol/L, left-side sample (LS) 71 and 93 nmol/L, and peripheral sample (PS) 11 and 12 nmol/L; after 5 min: RS 2790 nmol/L, LS 2279 nmol/L, PS 16 nmol/L; after 10 min: RS 2990 nmol/L, LS 3370 nmol/L, PS 37 nmol/L; after 15 min: RS >4000 nmol/L, LS 1900 nmol/L, PS 55 nmol/L; after 20 min: RS >4000 nmol/L, LS missing sample data, PS 63 nmol/L. For the catheterization, the patient received iopromide (*Ultravist*), 75 mL in total that makes up for 11 g of iodine. Subsequently, the girl underwent transsphenoidal surgery 3 months later where the pituitary was sliced from the right side and a 3 mm superficial adenoma was found and removed. Postoperatively, she was treated with hydrocortisone iv and then cortisone acetate po, which went well and the girl was discharged a few days later.

A week after surgery, she started to have headaches as well as loss of appetite, diarrhea, and vomiting. At first, this was thought to be myalgia and gastritis due to surgery and she was administered extra hydrocortisone and esomeprazole with little effect. Nearly 2 months later, she was still having these symptoms in addition to tachycardia and angina-like symptoms. Following blood tests, the girl was diagnosed with thyrotoxicosis with serum TSH measuring 0.02 milli-international units of activity (mIU)/L (reference range 0.3–4.2 mIU/L), free T4 measuring 63.9 picomol (pmol)/L (reference range 12–22 pmol/L) and free T3 measuring 24.8 pmol/L (3.5–6.7 pmol/L). Antibodies were negative, and she was successfully treated with carbimazole and propranolol. The thyrotoxicosis resolved after 3 months with no further treatment needed. Thyroid ultrasound performed one and a half year after the resolution of the thyrotoxicosis showed an enlarged lucent thyroid with a few ill-defined nodules. The cause of thyrotoxicosis was not established and remains unknown.

Discussion

To our knowledge, a pediatric case of thyrotoxicosis developing after transsphenoidal surgery has not yet been reported. There are however a few cases of adults developing thyrotoxicosis after surgery for Cushing′s syndrome. Yamakita et al. [11] report a silent thyroiditis after unilateral adrenalectomy in a patient with Cushing′s syndrome 9 months after surgery. They speculate that exposure to a large amount of endogenous and supplementary glucocorticoid protected the patient from thyroid antigens and that tapering of the prednisolone caused exacerbation of immune responses resulting in thyroid dysfunction. Another case report tells of an adult developing transient Grave′s disease after surgery for Cushing′s disease and the authors presume that a latent autoimmune process in the thyroid, suppressed by hypercortisolism, developed into overt Grave′s disease after abrupt reduction of plasma glucocorticoid levels after surgery [12]. Unlike our case, both of these cases postulate an antibody-positive thyroid dysfunction, and therefore, this pediatric case is unique. Iodinated contrast medium is known to induce thyrotoxicosis in adults but is very rare [13–15]. In this case, the first symptoms of thyrotoxicosis developed approximately 2 months after the use of iodinated contrast medium, and according to Conn et al. [16], the contrast may affect the thyroid as long as 8 weeks postinjection. Contrast medium injection does however not affect thyroid function tests (TFT) in patients with a normal thyroid. Patients at risk of developing thyrotoxicosis after contrast medium injection are patients with Grave′s disease and multinodular goiter with thyroid autonomy, especially elderly patients and patients living in areas of iodine deficiency [13, 17]. Iceland is considered an area without iodine deficiency, and it has been established that the girl did not have Grave′s disease as she was antibody negative. She did however have an enlarged thyroid with a few ill-defined nodules, whether that has any clinical importance has not been established. The only cases of contrast induced thyrotoxicosis in patients with autonomous nodules in the thyroid gland are of elderly patients, and no pediatric cases have been

reported to our knowledge. The amount of iodine that the girl received is also considerably low in relation to the adult cases presented. The cause of thyrotoxicosis therefore still remains unknown. The thyrotoxicosis needed short treatment with a thyreostatic drug (3 months), and now 5 years after surgery, there are no signs of reoccurrence of thyrotoxicosis, making antibody caused disease very unlikely.

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Authorship

AAS: Substantial contributions to conception and design, acquisition of data as well as analysis and interpretation of data, and drafting of the article as well as final approval of the version to be published. IHO: Substantial contributions in acquisition of data as well as analysis and interpretation of data and critical revising of article for important intellectual content as well as final approval of the version to be published. ÓK: Substantial contributions in acquisition of data as well as analysis and interpretation of data and critical revising of article for important intellectual content as well as final approval of the version to be published. RB: Substantial contributions to conception and design, acquisition of data as well as analysis and interpretation of data, and critical revising of article for important intellectual content as well as final approval of the version to be published.

Disclosure Summary

The authors have no relevant disclosures.

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