

Acromegaly and diabetes mellitus associated with hyperthyroidism

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Abstract

A 66-year-old woman with acromegaly and diabetes mellitus as well as primary hyperthyroidism is described. Serum GH Levels were inappropriately high. MRI revealed an enlarged sella turcica with intrasellar mass. Her HbA1c was 12.2% and fasting blood glucose 8.89 mmol/l. Thyroid hormone levels in serum and thyroidal radioiodine uptake values were elevated, while TSH measurements in serum were low. Anti TPO antibodies were negative, TSH receptor antibodies were normal. Thyrotoxicosis as the first presenting illness in acromegaly was particularly uncommon. An ultrasound thyroid scan showed a multinodular goiter. Histology of the pituitary lesion showed a typical eosinophilic adenoma which only secreted GH when tested with specific immunostain. Post-operatively, the patient's clinical conditions improved, however, secondary hypoadrenalism appeared.

INTRODUCTION

Hyperthyroidism can occur in about 3.5–26% of acromegalic subjects (Marzullo *et al.* 2000), and may be due to a concurrent TSH-secreting adenoma, or because of the effects of growth hormone (GH) excess on thyroid follicles (Kasagi *et al.* 1999). Various alterations in thyroid-function tests have been described in patients with acromegaly as well as an increased incidence of goiter (Hamilton & Maloof 1972). The precise cause of the hyperthyroidism could not be accurately determined before the development of radioimmunoassays to test thyroid function (Faglia *et al.* 1972). Impaired glucose tolerance or overt diabetes mellitus are well-recognized comorbidities in patients with

acromegaly, and found in up to 50% of cases at diagnosis (Colao *et al.* 2004). This report describes a patient with acromegaly, diabetes mellitus and primary hyperthyroidism.

CASE

The patient, a 66-year-old postmenopausal woman, was referred in June 2012 for acromegaly. She had mild body swelling, especially of the hands and feet. Her continuously swelling feet had led to frequent changes of shoes for 3 years. Other noted features included thickness of voice and enlargement of fingers. She had complained of intolerance to heat. She lost 6 kg in about 6 months but denied anorexia. In early 1992, features of acro-

megaly were first noted. The patient's history revealed gradual enlargement of acral and facial features along with increased perspiration. Polydipsia and polyuria occurred three years ago. Her fasting blood glucose concentration was 10.0mmol/l. She was treated with metformin (0.75g daily), glipizide sustained release tablets (2.5mg daily) and pioglitazone (15mg daily). Her fasting plasma glucose concentration ranged from 12 to 20mmol/l. There was no history of headache, vomiting, diplopia, trauma, fever, sleep disturbances or drug intake. On physical examination, her blood pressure was 160/90mmHg, and her pulse was regular 100/minute.

There was no exophthalmos or pretibial dermopathy. Her skin was moist. Her face and skull were big, broad and asymmetrical. A small diffuse goiter was

noted. There was a mild prominence of supra-orbital ridges, a broad nose and the malocclusion of the teeth. Her hands and feet appeared muscular. The lips were deeply fissured and her tongue increased in size in all dimensions. The secondary sex characters of the patient were normally present. The results from neurological examinations were negative, systemic examination displayed unremarkable results.

Investigations: The urine showed +4 sugar. Glucose tolerance test after 75 g of oral glucose load revealed the followings: 0 hr 8.89 mmol/L, 1/2 hr 8.94 mmol/L, 1 hr 10.50 mmol/L, 2 hr 13.06 mmol/L; Insulin release test results were 0 hr 16.15 μ IU/mL, 1/2 hr 19.82 μ IU/mL, 1 hr 23.47 μ IU/mL, 2 hr 43.06 μ IU/mL; C peptide releasing test found the following: 0 hr 1.16 ng/mL, 1/2 hr 1.42 ng/mL, 1 hr 1.71 ng/mL, 2 hr 2.99 ng/mL and HbA1c 12.20% (4–6%). Hormone assays were suggestive of acromegaly and hyperthyroidism (Table 1). Antithyroglobulin antibody 5.30 IU/mL (0.00–4.00), thyroid peroxidase autoantibodies 0.90 IU/mL (0.00–9.00), TSH receptor antibodies 4 U/L (<12), thyroglobulin 10.2 ng/mL (1.7–55.6). Repeated T_3 , T_4 , TSH were 3.80 mmol/L, 182.50 mmol/L, 0.020 μ IU/mL respectively. Fasting plasma human growth hormone (hGH) concentration was >40 ng/mL (0.06–5.00), and failed to become suppressed down to a normal level after oral glucose loading, confirming the diagnosis of acromegaly. The triglyceride level was 2.02 mmol/L (0.56–1.70 mmol/L). The islet cell antibody and insulin antibodies were negative. A thyroidal uptake of radioactive iodine of 48.5% percent at 24 hours, An ultrasound thyroid scan showed a multinodular goiter.the MRI pituitary revealed a 20×22×25 mm pituitary macroadenoma (Figure 1). The dual hands X-ray revealed osteoporosis (Figure 2). The X-ray of the skull was normal. X-ray imaging of feet showed the distal toe shape abnormality, obviously narrowed spaces between the toe joints, as well as the noticeable utricle bone absorption (Figure 3). The echocardiogram showed

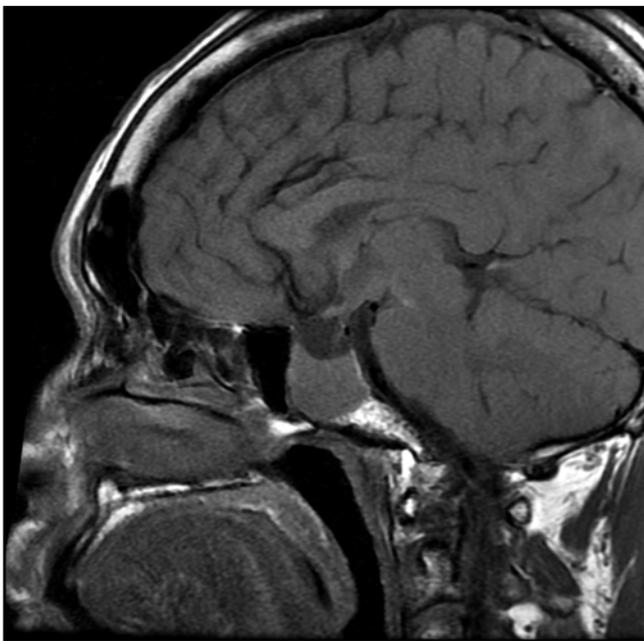


Fig. 1. Magnetic resonance imaging showing a sellar mass.



Fig. 2. X-ray showing osteoporosis.



Fig. 3. X-ray of feet.

aortic valve sclerosis, pulmonary hypertension (mild). The electrocardiogram showed T wave changes.

At this stage, The patient was treated initially with methimazole (30 mg/day). Metformin was prescribed at 1.5 g/day in combination with the insulin. A daily dose of 150 mg acarbose was also prescribed. The blood pressure was controlled at 125/70 mmHg with nifedipine controlled release tablets 30 mg/day. Fenofibrate (250 mg/day) was prescribed. Then she received X knife to the *sella turcica* as treatment for acromegaly from July 2012 to June 2013, but the serum growth hormone level did not decrease. Transsphenoidal hypophysectomy was performed in July 2013. Histology of the pituitary lesion showed a typical eosinophilic adenoma which only secreted GH when tested with specific immunostain. Post-operatively, methimazole administration continued (10 mg/day) and the insulin treatment stopped. She is presently maintained on metformin 500 mg daily and the current thyroid function tests and GH levels are normal. The FBG and HbA1c value decreased to 6.18 mmol/l and 5.5%, respectively. However, Gonadotropin and estrogen decline (Table 1).

DISCUSSION

Acromegaly is associated with a spectrum of thyroid abnormalities, the most common being goiter (70%) (Wuster *et al.* 1991). Most of these goiters are diffuse. The prevalence of goiter in acromegalics from iodine deficient areas reported to be 30% (Wuster *et al.* 1991). Thyrotoxicosis as the symptom of acromegaly is distinctly rare (Marzullo *et al.* 2000). The possibility that thyrotoxicosis preceded acromegaly is unlikely, considering that acromegaly becomes clinically apparent only after several years. It is plausible to conclude that thyrotoxicosis followed the of acromegaly. The patient developed hyperthyroidism years after the diagnosis of acromegaly had been made and therefore presented less of a diagnostic problem.

Current evidence favours a TSH independent mechanism in most cases (Marzullo *et al.* 2000). In addition, G protein abnormalities can constitutively activate GH releasing hormone (GHRH) receptors leading to acromegaly, as well as cause a constitutive TSH receptor activation leading to thyrotoxicosis (Spada *et al.* 1998). The most characteristic abnormality is a mutation in the gene encoding the alpha subunit of the Gs protein, which mediates the actions of TSH and GNRH. However, it is difficult to precisely pinpoint the molecular defects underlying the linkage between thyrotoxicosis and acromegaly in most cases.

In the report by Davidoff and Cushing (Davidoff & Cushing 1927) summarizing the findings in 100 cases of acromegaly, some 12% had an associated diabetes. Obviously then a high proportion of acromegalic patients have some disturbance in carbohydrate metabolism. This fact would suggest that the duration of the disturbance in pituitary function becomes an important

Tab. 1. Relevant laboratory data on the patient.

	At diagnosis	1 month after surgery	Reference range
hGH (ng/ml)	>40	1.01	0.06–5.00
HbA1c	12.20%	5.5	4–6%
Fasting blood glucose (mmol/l)	8.89	6.18	3.90–6.10
T ₃ (mmol/l)	3.95	1.60	0.92–2.79
T ₄ (mmol/l)	213.19	103.35	58.10–140.60
TSH (mIU/l)	0.020	1.720	0.550–4.780
Plasma ACTH (ng/l)	18.9	28.20	<46
Serum cortisol (8 a.m.) (nmol/l)	353.03	498.25	138–690
LH (IU/l)	23.85	5.88	15.9–54
FSH (IU/l)	24.22	9.8	23.6–116.3
TES (nmol/l)	1.57	0.10	8.36~28.77
E2 (pmol/l)	109.30	22.10	<114
Progesterone (nmol/l)	2.99	1.38	<2.32
Prolactin (µg/l)	7.96	7.59	1.8–20.3

element in the causation of diabetes. The present data also showed the insulin resistance present in chronic GH excess is accompanied by impaired muscle glucose uptake and nonoxidative glucose metabolism (Foss *et al.* 1991). The insulin sensitivity is reduced to a similar extent in acromegalic patients with normal glucose tolerance and those with impaired glucose tolerance or diabetes. The compensatory hyperfunction of β -cells appears to counterbalance the reduced insulin sensitivity in the acromegalic patients with normal glucose tolerance but not in those with impaired glucose tolerance or diabetes (Kasayama *et al.* 2000).

Thyroid hormones play an important regulatory role in growth, development, and metabolism. As early as 1909, studies have provided evidence suggesting that thyroid hormone has an oppositional effect on glucose utilization and catabolism (McCurdy 1909). The prevalence of glucose intolerance in patients with thyrotoxicosis has been reported to be as high as 44–72% (Paul *et al.* 2004). Although the specific mechanism remains obscure, these patients, in general, have been found to have insulin resistance, hyperinsulinemia, and impaired glucose tolerance (Jap *et al.* 1989). Impairment in insulin secretion, along with increased metabolic clearance of insulin, appears to contribute to both impaired fasting glucose and glucose intolerance to carbohydrate loads in the hyperthyroid state (Roubsanthisuk *et al.* 2006). In addition, alterations in gastric emptying, blunted insulin receptor binding, decreased glucose utilization, and enhanced lipid oxidation and hepatic glucose production via influence of catecholamines and glucagon have been demonstrated (Mitrou & Raptis 2010). Therefore,

regardless of the true mechanism of glucose intolerance in hyperthyroid patients, it is important to recognize the presence of this impairment in patients diagnosed with diabetes mellitus. The thyroid dysfunction should be considered, even in the absence of underlying symptoms or signs of hyperthyroidism.

On the basis of the results in our patient, conventional pituitary ablation therapy (surgery) appears to be the most effective treatment available. On the other hand, we should pay attention to adenohipophysitis hypofunction after surgery.

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