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Autoimmune polyendocrinopathy type II in a Chinese patient

一名華籍病人患有自體免疫多發性內分泌病II型

Autoimmune polyendocrinopathy type II is rarely reported in Chinese patients. A 42-year-old Chinese woman with a history of Hashimoto's thyroiditis and hypogonadotropic hypogonadism presented with pneumonia. During hospitalisation, she went into an adrenal crisis and diabetic ketoacidosis. Subsequent dynamic hormonal tests revealed primary and secondary adrenal insufficiency. She also had pernicious anaemia, possible alopecia areata, and myasthenia gravis. This constellation of multiple endocrine and non-endocrine disorders led to the diagnosis of autoimmune polyendocrinopathy type II. As the syndrome can be lethal, it is important to maintain a high index of suspicion, enabling early diagnosis and the appropriate replacement therapy, to ensure a successful outcome.

自體免疫多發性內分泌病II型在華籍病人中是罕見的。一名四十二歲本身有橋本氏甲狀腺炎和促性腺素缺乏性腺功能低下病史的華籍女子罹患肺炎。在住院接受診治期間，病者患上腎上腺危機和糖尿病酮症酸中毒。及後，動態性荷爾蒙測驗顯示腎上腺本體及腦下垂體腎上腺機能不全。她亦患有惡性貧血和可能患有油風和重肌無力症。這個多種內分泌和非內分泌疾患的組合促使自體免疫多發性內分泌病II型的診斷。因這個候群症能致命，加強對此病的警覺性有助及早診斷和適當的補充治療，達致良好的治療效果。

Introduction

Autoimmune polyendocrinopathy (APS) is a rare syndrome caused by immune-mediated destruction and involves the failure of both endocrine and non-endocrine organs. It is characterised by the insufficiency of at least two endocrine glands. The classification of APS remains controversial and two types have been identified—APS type I refers to chronic candidiasis, chronic hypoparathyroidism, and Addison's disease (at least two should be present); APS type II is more variable in its manifestation with the main components being Addison's disease, autoimmune thyroid disease, and type 1 diabetes.¹⁻⁴

Case report

A 42-year-old mother of two children being managed by her general practitioner for Hashimoto's thyroiditis had been receiving thyroxine replacement therapy since 2001. She had autoimmune antibodies (anti-microsomal antibody, 1:409 600; anti-thyroglobulin antibody, 1:100) and thalassaemia trait was noted incidentally at that time. In addition, she reported a history of sudden localised hair loss with subsequent spontaneous recovery. Her family history was unremarkable.

In February 2003, after the birth of her second child, she attended the gynaecology and obstetrics clinic because of amenorrhoea and axillary and pubic hair loss. Labour had been normal and the delivery spontaneous and uneventful. No blood transfusion was required but she was unable to breast-feed her baby. In February 2004, this patient was referred to our department with unsatisfactory control of her hypothyroidism with an elevated thyroid-stimulating hormone (TSH) level (6.52 mIU/L; reference range, 0.27-4.20 mIU/L). She complained of poor appetite and fatigue and her dose of thyroxine was increased. Her body weight (45.4 kg) and body mass index

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Table. Dynamic test results

Test*	Time (minutes)								
	0	30	60	90	120	150	210	240	300
Long synacthen test									
Cortisol (nmol/L)	<8.0	31.1	31.2	-	-	-	-	42.3	44.4
ACTH (pmol/L)	<2.2	-	-	-	-	-	-	-	-
Glucagon stimulation test									
Cortisol (nmol/L)	13	10	10	10	9	9	13	-	-
LHRH stimulation test									
FSH (IU/L)	6.0	8.9	10.8	-	-	-	-	-	-
LH (IU/L)	0.9	5.9	7.6	-	-	-	-	-	-
TRH stimulation test									
TSH (mIU/L)	1.09	6.39	6.03	-	3.94	-	-	-	-

* ACTH denotes adrenocorticotropic hormone, LHRH luteinising-hormone-releasing hormone, FSH follicle-stimulating hormone, LH luteinising hormone, TRH thyrotropin-releasing hormone, and TSH thyrotropin-stimulating hormone

(BMI) [19.1 kg/m²] remained unchanged but hypogonadotropic hypogonadism (oestradiol, 85 pmol/L; follicle-stimulating hormone, 6.8 IU/L; luteinising hormone, 2.7 IU/L; prolactin, 16 mIU/L) was diagnosed and hormone replacement therapy was commenced in April 2004.

Two months later, she was admitted to hospital with pneumonia. Clinically, she was thin (body weight, 35 kg; BMI, 14.7 kg/m²) and had pale skin. Haemostix for glucose was 5.2 mmol/L and blood tests revealed hyponatraemia (sodium 124 mmol/L, serum osmolality 261 mOsm/kg; spot urine sodium 60 mmol/L, osmolality 268 mOsm/kg). Her potassium level, renal function, and calcium level were normal. Hypochromic microcytic anaemia was noted with a haemoglobin level of 81 g/L. The TSH level was checked to monitor her thyroid status. Serial blood sampling revealed development of mild pancytopenia (white cell count, 3.8 x 10⁹ /L; platelet count, 121 x 10⁹ /L). Serum vitamin B12 and folate levels were also measured.

As the patient had low blood pressure (systolic blood pressure, 90-102 mm Hg), a short synacthen stimulation test (250 µg) was performed to exclude hypoadrenalism. The test revealed adrenal insufficiency (plasma cortisol, 16-51 nmol/L after 30 mins) and hydrocortisone 10 mg twice a day was commenced as hormonal replacement. Her TSH levels were normal (0.76 mIU/L). While in hospital, the patient developed nausea, vomiting, and increased malaise. Repeated blood tests demonstrated hyperkalaemia and impaired renal function (sodium, 132 mmol/L; potassium, 5.7 mmol/L; urea, 13.2 mmol/L; creatinine, 129 µmol/L). A differential diagnosis of adrenal crisis was made and she was prescribed high-dose hydrocortisone. Dextrose insulin (250 mL D10 plus 6 unit actrapid) was administered to lower the potassium. After 1 hour, the haemostix for glucose level was noted to be high. Plasma glucose was 37.8 mmol/L; blood gases revealed a metabolic acidosis (pH 7.07, PCO₂ 2.10 kPa, PO₂ 16.0 kPa, HCO₃ <6.0 mmol/L, BE -23.7 mmol/L) and urine stix for ketones showed 3+. The results were compatible with diabetic ketoacidosis. Intravenous fluid replacement and an insulin pump were commenced. Hydrocortisone was increased to a

stress dose (100 mg 8-hourly intravenously).

Her vitamin B12 level was subsequently shown to be low (89 pmol/L; reference range, 179-660 pmol/L). Both anti-parietal cell and anti-intrinsic factor antibodies were positive. Intramuscular vitamin B12 injection was prescribed and the patient's condition improved substantially. Clinically she also had mild bilateral ptosis, but no other symptoms and signs that might suggest myasthenia gravis. Her anti-acetylcholine receptor antibody level was elevated (0.61 ODU). Tests for anti-adrenal antibodies and anti-islet cell antibodies were negative. The patient was discharged from hospital on protaphane, hydrocortisone, thyroxine, and vitamin B12.

She later underwent investigations for adrenal insufficiency: morning adrenocorticotropic hormone (ACTH) and cortisol, long synacthen test (5 hours) and dynamic pituitary function tests (Table) were performed. A suppressed morning cortisol (<8.0 nmol/L) and ACTH (<2.2 pmol/L) were suggestive of secondary adrenal insufficiency and a flat response in the long synacthen test was possibly due to concomitant primary adrenal insufficiency. Dynamic pituitary function tests revealed subnormal cortisol and gonadotrophin axes but a normal thyroid axis. Magnetic resonance imaging of the pituitary in August 2004 was normal.

Discussion

Autoimmune polyendocrinopathy type II is a rare disorder: its prevalence in western populations has been reported as 1.5 to 4.5/100 000.⁵ This may be an underestimation if subclinical forms are taken into account. The age of onset is between 20 and 40 years, and females are over 3 times more likely to be affected than males. The main component diseases of APS type II are Addison's disease, autoimmune thyroid disease, and type 1 diabetes mellitus. Minor components include hypergonadotropic hypogonadism, alopecia areata, vitiligo, and pernicious anaemia. The time interval between manifestation of the first and second autoimmune disorder varies considerably, and may be longer than 10 years.⁶ The prevalence of the component

diseases also varies in studies because of different definitions of the syndrome and study populations. Among the component diseases, hypopituitarism is less often described in APS, but case reports have suggested an association between isolated ACTH, TSH, or gonadotrophin deficiencies with type 1 diabetes mellitus and Hashimoto's disease.⁷

Autoimmune polyendocrinopathy type I is a monogenic disorder that is determined by autosomal recessive mutation in the *AIRE* gene, whereas type II is polygenetically inherited.⁸ Genetic screening may thus be useful in APS type I but not type II.⁹ Functional and serological screening for autoimmune diseases is more useful in patients with APS type II and their first-degree relatives.⁶

Symptoms and signs of hypothyroidism and hypoadrenalism are often non-specific, especially in the elderly. Since early diagnosis and treatment of these hormonal insufficiencies are vital, it is essential to always consider an association. Adrenal insufficiency should be considered in patients with autoimmune thyroid disease or type 1 diabetes mellitus who develop non-specific illness or become seriously ill, or in diabetic patients whose insulin requirements fall inexplicably.

Treatment of APS is simple but vital and is dictated by the individual disorders. Glucocorticoids should be given before commencing thyroxine replacement in patients with both hypoadrenalism and hypothyroidism. This applies to all patients with adrenal insufficiency, not just those with APS, because thyroxine can precipitate an adrenal crisis in the presence of adrenal insufficiency by increasing cortisol clearance and the metabolic rate, thereby raising cortisol requirements. In addition, steroid replacement alone is capable of normalising the TSH level in some patients.

Our patient was typical of APS type II in terms of age and sex. The stress of pneumonia and hospitalisation is likely to have precipitated the adrenal crisis and diabetic ketoacidosis. The constellation of Hashimoto's thyroiditis, premature hypogonadism, adrenal insufficiency, type 1 diabetes mellitus, pernicious anaemia, and alopecia areata supported the strong suspicion of an autoimmune polyglandular syndrome. The results of the morning cortisol with ACTH testing and the long synacthen test

may have suggested concomitant primary and secondary adrenal insufficiency. A longer period of ACTH stimulation, for example 48 hours, is more helpful for distinguishing secondary from primary adrenal insufficiency. Adenohypophysitis with both secondary hypoadrenalism and hypogonadotropic hypogonadism was not reported in two previous large series of patients with APS type II.^{1,10} Tests for anti-adrenal antibodies and anti-islet cell antibodies were negative, which was not surprising since not all patients possess the relevant autoantibodies when clinical manifestations develop. Our patient continues to require regular monitoring for symptoms and signs of myasthenia gravis because of the presence of anti-acetylcholine receptor antibodies. We have found it important to maintain good rapport with our patient and keep her well informed about the syndrome to ensure good compliance with treatment.

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