CASE REPORT

Graves' Disease and Diabetes Mellitus

by

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Abstract

Thyroid hormones play an important role in the metabolic propesses. Its disturbances will involve several organs, conse-quently.

A 5 year old girl with Graves' diseases, after several weeks of treatment with porpylthiouracil (PTU), developed thyrotoxicosis crisis and diabetes mellitus with ketoacidosis; a condition which is usually fatal. Treatment toward the hyperthyroid state overcome the diabetic stage, eventually.

This report is an example of an endocrinological interaction in a hyperthyroid patient. Therefore, the diabetogenic effect of hyperthyroxinemia should not be overlooked.

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Introduction

Thyroid hormones play upon a great multiplicity on metabolic processes; as a consequence, no tissue escapes the adverse ef-fects of thyroid hormones excess or insufficiency [1].

Graves' disease has been known for over a hundred years but it has remain the most enigmatic of all thyroid diseases and from the clinical standpoint, the most important one. It occurs rarely in children less than ten years old [2].

The incidence in children less than 15 years old is 1 : 100. While 10-15% occurs in children less than 5 years old, and 20-25% in children between 5-10 years old. The incidence in children more than 10 years old is 50-75% *(Piersen, 1981)*. There is a strong relationship between sex and both the frequency as well as the clinical manifestations. The disorder is more common in women than in men, approximately 7 : 1 [1]. In the outpatient ward of the Endocrinology Subdivision, twelve cases of Graves' disease were found during the last 13 years from 1973 to 1986.

In broad outlines, the etiologic factors are immunologic and constitutional factors.

I. *Immunologic Factors*

There is evidence that the immune system, both humoral and cellular immunity, plays a role in the pathogenesis of Graves' disease.

Thyroid antibodies are found to be attached to the TSH receptor. They stimulate the endocrine cells, leading to thyroid autonomy and hyperthyroidism. These antibodies which are called as Human Thyroid Stimulating Immunoglobulins (HTSI), are a hete-rogenous group of antibodies such as Long Acting Thyroid Stimulator (LATS), Short Acting Thyroid Stimulator (SATS), etc. [3,4,5]. Their formation is a secondary process due to the sensitisation of the T cell-lymphocytes by the thyroid antigen (Schleusener, 1978; Brooks, 1981). The sensitized T cells modulate the activity of the B cell lymphocytes, inducing HTSI production.

II. *Constitutional Factors*

The emergence and subsequent course of the disease are modified by such factors as heredity, sex and perhaps emotion, nutritional state and iodine intake. Pathophysiologically, all aspects of thyroid hormones economy become abnormal, such as disruption of normal regulatory control of thyroid function; changes in the concentration, binding, and metabolism of the thyroid hormones. It may result in hyperfunction, leading to the lack of response toward TRH.

The effects of thyroid hormones on metabolic processes are calorigenic stimulation, increased lipid metabolism (the degradation process is more affected than the synthesis process), stimulation of carbohydrate metabolism (increased glycogenolysis, gluconeogenesis, glucose uptake usage, and insulin degradation enhancement)[6].

The endocrinological interactions reveal a close relation-ship between pituitary, thyroid, and adrenal gland [6].

The diabetogenic effect is due to overstimulation of carbohydrate metabolism and disturbances in the dynamic balance between the rate of insulin production and its requirement, decreased insulin sensitivity, together with the possibility of liver and pancreat-ic damage, leading to the thyrodiabetes condition [7,8].

The effect on the adrenal cortex will result in increased secretion and also degradation of the steroid hormones.

The clinical manifestations usually begin gradually, com-prising to diffuse thyroid gland enlargement, exophthalmus, to-gether with thyrotoxicosis symptoms which involve multisystem-organ, and other symptoms such as tremor, hypersensitivity to heat, etc.

Laboratory data reveal increased T4 and T3 concentration with low level of TSH, increased radioactive iodine uptake, metabolic impact (increased BMR and low cholesterol level), and the evidence of thyroid antibodies.

All major forms of treatment exert their effects by re-straining the rate of thyroid hormones secretion. Suppresion by antithyroid agents is considered to be effective. Thionamide is a strong inhibitor, and prophylthiourachil and methimazole are the agents commonly employed. Effective response will be acquired after the latent period has been overcome [1]. Corticosteroid can be used as an adjunctive treatment to achieve rapid alleviation. In severe thyrotoxicosis with pronounced tremor, tachycardia, palpitation, and severe restlessness, corticosteroid can be given together with an adrenergic antagonist. Surgical intervention should be considered in unresponsive cases or in cases with relapse after being given long term suppresive treatment. Remission rate with PTU is 25% in the first year of treatment and approximately reaches remission within 4,5 years of treatment [9]. Several factors which indicate good remission are, male sex, age 13 years, and T3 level (RIA) less than 645 ng/ml [9].

Case Report

L, a girl, 5.5 years old, was referred to the Pediatrics Endocrinology Subdivision of Cipto Mangunkusumo Hospital in October 1986, with struma. She had suffered from occasional diarrhea since December 1985 (10 months previously) and no weight gain inspite of increased appetite. Excessive sweating and heat intolerance seemed to happen long. She was given anti anemic treatment. In May, 1986, five months later, thyroid enlargement was noticed. Weight loss (23 kg to 21 kg) occurred despite more ravenous appetite. She drank a great deal and urinated very often. She was nervous and hyperactive, with decreased school performance. For those reasons, she was brought to an endocrinol-ogist, but the blood and urine findings revealed no abnormalities neither toward thyroid disorder nor diabetes mellitus. She was further referred to a pediatrician due to her anemic condition. After being treated for some time, marked palpitation was no-ticed, along with hypertention. She was then referred to a pedia-trician with struma.

History of pregnancy, delivery, and development, were nor-mal. Nutritional state was good. She was the second child of three siblings. No such disease was found within the family.

On the first physical examination, we found a girl, with a body weight of 21 kg, a height of 120 cm. She was alert, hyperactive, not dyspneic, not cyanotic, but slightly anemic. Heart rate was 120 x / minute, respiration rate 28 x / minute, blood pressure 135/70 mmHg, and body temperature 37.5^{O}C. The skin was moist and warm. No abnormalities were found in the eyes (no exophthalmus, no palpebral edema, no ophthalmoplegia). The thyroid gland was enlarged (4.8 x 3.3 cm), soft on palpation, with no thrill and bruits, and no signs of inflammation. Lymph nodes were not enlarged. ENT was normal. Heart and lung were normal. The abdomen was supple with slight liver enlargement and normal bowel sounds. There was no tremor in the extremities.

Laboratory data

- Peripheral blood findings : Hb 10,3 g/dl; leuco 7600/ul; diff.count (%) 1/-/49/3; platelets 224.000/ul.
- Erythrocyte sedimentation rate 20 mm/h.
- Liver function test : albumine 4,14 g/dl; globuline 2,13 g/dl; TTT 1,3 S McLagan; Kunkel 3,6 S MacLagan; Indirect bilirubine 0.2 mg/dl; direct bilirubine 0,1 mg/dl; SGOT 62 u/L (N 5-17); SGPT 76 (N 5-23) u/L : fosfatase alkali 33,5 U; cholesterol 93 mg/dl; triglice-ride 113 mg/dl (N 200); ureum 36 mg/dl; creatinine 1 mg/dl.
- Thyroid function : T4 19 (5-13) ug/dl; T3 uptake 35% (23-32); free thyroxine index 6,65 (1,15-4,16); TSH 0,5 (5,5) ul/ml. Thyroid scintiscanning, uptake NaJ^{131} (first 2 hours) was 30% , normal in the 24-48 hours (38-36%). Scintigram : diffuse en-largement.
- Skull X-ray : normal.
- Bone age : in accordance with a 7-7,5 year old child.

Based on complaints, clinical signs/symptoms, and laboratory data, the diagnosis was struma-diffusa. PTU was given starting with the dosis of 50 mg, three times a day.

The patient improved simptomatically after 6 weeks of treatment with PTU 75 mg, 3x/day. Body weight increased while thyroid size decreased. The blood pressure remained slightly high. A week later, she suffered from fever for 3 days, looked weak, had no appetite, and with marked palpitation.

She was brought to a cardiologist, who sent her back to the endocrinologist with the diagnosis of Graves' disease, hyperten-sion, and hyperdinamic heart. She was then hospitalized. On the following day she was apathetic and dyspneic. Blood gas analysis showed severe metabolic acidosis. Blood glucose level was 127-450 mg/dl, urine reduction positive 2-4. Thus, she fell into a ketoacidotic state. Treatment was given to overcome the ketoacidotic state, together with PTU 3x100 mg/day and propranolol 3x50 mg/day. Three days later, she was clinically improved, yet blood glucose level and urine reduction were still abnormal. Phaeochromocytoma was considered, but the urine VMA level was normal and there was no suprarenal enlargement according to the abdominal ultrasound examination. To assess the secretion ability of the pancreas, C peptide serum level was measured, [0.25 ng/ml (0.6-4.4 non diabetic)]. Chest X-raywas normal. She was discharged on the 20^{th} day of hospitalization and was further treated in the outpatient ward.

On follow up, insulin requirement gradually decreased. Several examinations were being carried on such as ophthalmology (normal): immunology : IgE 65 IU/ml (N 100), IgA 81 mg/dl (N 33-350), IgG 1616 mg/dl (N 350-1760), IgM 94 mg/dl (N 26-325); serum insulin level 39 uU/ml (N 5-40).

After 1.5 months, there were no complaints, she was in good clinical condition, with a body weight of 24 kg. The metabolic state was controlled by giving PTU 3x100 mg/day and antidiabetic therapy.

She was euthyroid then, and the dosage of PTU was gradually decreased. Four months later, we performed thyroid antibodies examination with negative results.

Discussion

This case was diagnosed as Graves' disease after 10 months of complaints. Thyroid supression was done by giving PTU. The main problem was the occurrence of Ketoacidotic - Diabetes mellitus after 4.5 months of treatment. This rare crisis is usually fatal. Several trigger factors are, infection, trauma, surgery, or diabetes mellitus it self (which was not clear in this case). Probably it happened because she was still in the latent period. It was very possible that this patient suffered from thyro-diabetes, which was a secondary condition due to the hyperthy-roidism itself. By overcoming the primary state, the diabetes mellitus was also overcome.

This case reminds us always to be cautious of the possibili-ty of secondary diabetes mellitus as an endocrinologic interac-tion, in a hyperthyroid patient.

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