CASE REPORT

A Case of Childhood Hyperthyroidism

by

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ABSTRACT

An unusual case of hyperthyroidism in a 4 years old girl is presented. The pathogenesis of this disease is still uncertain, but several possible pathogenesis are described.

The diagnosis is rarely difficult if the clinical manifestations are characteristic, but these signs and symptoms are usually found in adults and older children.

Several differential diagnosis are also considered and the treatment and prognosis discussed.

INTRODUCTION

Hyperthyroidism in childhood is uncommon and there are few reports regarding either its treatment or prognosis (Barnes, 1977; Brady and Greenberg, 1972; Breok, 1978; Crawford, 1981). The pathogenesis of this disease has not been precisely determined, though several reports :tated Grave's disease to be an autoimmune thyroid disease with an age related frequency of occurence and a female predominance (Bellanti, 1978; Brown et al., 1978; Kempe et al., 1981; Vaughan et al., 1980).

Though this disease is similar in many ways to its counterpart in adults, it seems less debilitating in children (Brook, 1978; Brown et al., 1978; Kempe et al., 1981; Vaughan et al., 1980).

Manifestation such as thyroid storms or apathetic hyperthyroidism are rare (Hayek et al., 1970; Kempe et al., 1981; Mc Kendrick and Newas, 1965). In addition psychic

trauma, psychologic malajustment, disturbances in pituitary functions and infectious diseases may play a part in triggering off the thyrotoxic state (Brook, 1978; Brown, 1978; Crawferd, 1981; Mc Kendrick and Newas, 1965). There is no agreement on whether medical or surgical therapy is better. In recent years, controversy has risen whether children are best treated with antithyroid drugs, by subtotal thyroidectomy or with radioactive iodine (I^{131}) (Barnes, 1977; Brown, 1978; Fisher, 1976; Kogut et al., 1965). The purpose of this report is to present an unusual case of hyperthyroidism in a four year old girl.

CASE REPORT

S.Y., a 4-year-old- Indonesian girl was admitted to the Department of Child Health, Dr. Soetomo Hospital on August 9, 1981 with the main complaints of excessive sweating, weight loss and severe hyperactivity. This patient was referred by a general practitioner from Samarinda with a possible diagnosis of Grave's disease.

She was the second child of three siblings and was fullterm normally delivered. Her father was an office clerk and he as well as the mother, and the two other children were healthy. Her grandmother underwent an operation for Grave's disease a few years ago in Surabaya.

One month before admission, the child suffered from fever and cough and was treated by her family doctor. But six months ago, her mother and grandmother noticed that the child had a voracious apetite, showed signs of hyperactivity, and also sweated profusely. Her voice also changed and sounded a little hoarse and there was an enlargement on the front side of her neck. Her body weight decreased despite the good appetite and her bowel habit became frequent namely 5 to 6 times a day, she passed urine normally. She also suffered from tremor of her fingers and insomnia. She had always been in a healthy condition since birth and had never had these symptoms before.

Physical examination on admission revealed a flushed and well nourished looking girl, with rather protruding eyes. Her body weight was 17 kg., pulse rate 164/min. and body temperature 37°C. There was an enlargement of the thyroid gland, with a size of 4 x 6 cm, it felt soft and diffuse with a smooth surface. Specific signs of exophthalmus, Moebius' sign, and Von Graefe sign, were all present and so were bruits of the thyroid gland heard on auscultation.

She had very red lips and on auscultation of her heart there was a tachycardia of 164/min.; respiratory rate was 40/min. Except tachycardia, no abnormality were observed on her heart and both lungs. Her blood pressure was 140/80. The liver and spleen were not palpable. A marked tremor of her fingers were noted, and she showed signs of nervousness with excessive sweating.

Laboratory examination on August 10, 1981 revealed the following : HB. 11,8 g/dl., Leucocyte 9.500/mm^3, Differential count 2/–/5/50/41/2, BSR 8–21.

The urine and stool examination were within normal limits. A working diagnosis of hyperthyroidism was made and she was managed with :

- high caloric diet
- restricted activity
- neomercazole 3 x 1 tabl. each day
- valium 3 x 5 mg/day
- multivitamins

On August 12, 1981, the Ophthalmologist confirmed the signs of Graves' disease. Laboratory examination on the same day revealed : HB. : 10g/dl., leucocyte 10.200/mm^3, differential count: –/–/–/80/19/1, Thrombocyte were sufficient in number and the blood smear showed no abnormality. Other more sophisticated examination revealed: T_3 concentration 4,0 μg/dl. (N: 0,75 – 1,6 μg/dl.) (Elisa); T_4 concentration 23,6 μg/dl. (N: 4,0 – 11,5 μg/dl.) (Elisa); TBG concentration 1,6 μg/dl. (N: 0,89 – 1,22 μg/dl.) (Elisa).

TSH concentration could not be evaluated due to technical difficulties. A thorax X-photo was made on the same day, with the following results :

- A soft tissue swelling on the anterior part of the neck (P A position).
- A mass was noted on the superior and anterior region of the mediastinum suggesting a struma or the thymus gland (lateral position).

On August 14, 1981 the basal metabolic rate assessment was made and the result was an increased BMR of (+) 54,7%, while the calculation of BMR with the Read method showed a positive rate of 72,5% (Body weight 17 kg., body heigh 113,5 cm). Her blood pressure was 120/70 before the test and 130/60 afterwards and the pulse rate was 148/min. before and 150/min. after. The clinical condition was the same as the day before.

On August 16, 1981 the pulse rate increased and signs of tachycardia was noted with:

- an active precordium and left ventricular thrill on palpation.
- marked tachycardia with a holosystolic murmur of grade 3/6 with the maximal point on the apex of the heart.
- ECG tracing showed an increased heart rate of 160/min. with normal tracing.

Lanoxin 1 tablet each day was added for two days and continued with 3/4 tablet/day.

On August 18, 1981 a second ECG was made and it showed an improvement of the heart condition, the heart rate became 140/min. and Lanoxin was continued.

In the mean time, neomercazole was still given and the child became more calm, she is able to sleep for a short time in the afternoon hours. After two weeks of treatment, her general condition improved well, she slept well during the nights. Her body weight increased to 18 kg and her grandmother insisted on taking the child home because of financial problems.

On August 25, 1981 the child was already in a good condition, her appearance was a lot better, but the flushing on her face was still observed . No visible tremor was noted and laboratory examination on that day revealed : Hb. concentration: 12,2 g/dl., leukocyte: 8.200/mm^3, differential count: 4/–/–/46/48/2, thrombocytes were sufficient in number and blood smear was normal.

On September 2, 1981 the patient was discharged on request of her grandmother. A second examination of T_3, T_4 and TBG concentration was not performed due to financial problems. The grandmother was advised to bring the child one month later for follow up. But only after three months did the child came again for follow up, and she was in a good condition, no visible tremor was noted and she looked calm, the enlargement of the thyroid gland seemed to regress and she gained weight of about 1 kg.

DISCUSSION

The classical features of Graves' disease are thyrotoxicosis, a goiter and infiltrative ophthalmopathy, but mostly in children the condition presents it self as a behavioral change or growth disorder (Bellanti, 1978; Brook, 1978; Kempe et al., 1978; Mc Kendrick and Newas, 1965). As in all thyroid diseases, it is more common in girls than in boys and the sex ratio is 3 – 4 : 1 (Bellanti, 1978; Brook, 1978; Brown et al., 1978; Vaughan et al., 1980). Patients are generally tall and thin and have a quite advanced bone age, but there may be no other sign at all (Brook, 1978; Brown et al., 1978; Kempe et al., 1981; Riggs et al. 1972). About 5% of all patients with hyperthyroidism are less than 15 years of age, and of these 20% are less than 10 years, the peak incidence occurs during adolescence (Brown et al., 1978; Vaughan et al., 1980; Kempe et al., 1981). Symptoms develop gradually and the usual interval between onset and diagnosis is 6 – 12 months (Bellanti, 1978; Brown, 1978; Kempe et al., 1981).

In our case the pathogenesis was still uncertain, though in accordance with several existing reports as has been previously mentioned the possible pathogenesis might be Graves' disease which, like Hashimoto's thyroiditis is considered to be an autoimmune phenomenon (Barnes, 1977; Belianti, 1978; Brook, 1978; Brown et al., 1978; Kempe et al., 1981; Vaughan et al., 1980). The autoimmune abnormality which actually causes the thyroid hyperfunction, wether by humoral or cell mediated mechanisms remains uncertain. (Barnes, 1977; Brady and Greenberg 1972; Brown et al., 1978; Vaughan et al., 1980). Recent reports though, stated that the hyperthyroidism in Graves' disease is probably caused directly by a specific autoimmune antibody or family of antibodies known as Thyroid Stimulating Antibodies (T.S.A.) (Bellanti, 1978; Brown et al., 1978; Kempe et al., 1981; Kogut et al., 1965; Mc Kendrick and Newas, 1965). However, some doubt exists whether T.S.A are true antibodies. These molecules have the property of binding to and stimulating TSH receptors of the thyroid follicular cells. Thus, the disorder appears to be an anti-receptor antibody disease. But in Graves' disease it is unique,

the antibodies stimulate rather than block cellular activity. The TSA, once attached to the TSH receptor, stimulates thyroid cells in the same way as does pituitary TSH. The increased secretion of thyroid hormones then results in feedback inhibition and suppression of endogenous TSH (Bellanti, 1978; Brook, 1978; Brown et al., 1978). Hyperthyroidism in the clinical setting is caused by the thyroid gland functioning independently of the normal pituitary thyroid axis control. This fact as demonstrated by the inability of exogenous thyroid hormone to suppress thyroid function, ultimately leads to hypermetabolic consequences (Bellanti, 1978; Brown et al., 1978; Vaughan et al., 1980).

Other investigations will demonstrate a high level of T_4, but levels of T_3 are usually more conspicuously elevated (Bellanti, 1978; Brown et al., 1978; Fisher et al., 1977; Kogut et al., 1965).

Our case represents a very unusual one, with many signs and symptoms, which were usually observed in older children or even in adults, such as : 1. restlessness and hyperactivity; 2. tremor of the fingers; 3. a voracious apetite combined with loss or no increase in body weight; 4. an enlarged thyroid which is visible, palpable with a smooth surface; 5. a slight exophthalmus (protruding of the eyes); 6. lagging of the upper eyelids as the eyes looked downward, which was known as the Von Graefe's sign; 7. inability of convergence of the eyes, which is called the Moebius sign; 8. a slight retraction of the upper eyelid and infrequent blinking, which is the Stellwag sign; 9. a smooth and flushed skin and face; 10. exessive sweating with tachycardia and palpitalion.

Diagnosis is rarely difficult, once it has been considered and extensive investigations is rarely necessary if the clinical manifestations are characteristic (Brook, 1978; Brown et al., 1978; Kempe et al., 1981; Vaughan et al., 1980). The evolution of Graves' disease is intriguing. The first thyroid stimulating immunoglobulin (TSI) was the Long Acting Thyroid Stimulator (LATS). About 70% of patients have a circulating LATS, which is an IgG immunoglobulin (Bellanti, 1978; Brown et al., 1978; Kempe et al., 1981). The role of LATS in the pathogenesis of the disorder is unsettled. Elevated levels of LATS may be found in only half of the patients. (Bellanti, 1978; Brook, 1978; Brown et al., 1978; Mc Kendrick et Newas, 1965). Due to lack of laboratory facilities, the LATS concentration was not performed in our patient. Radioimmunoassay of T_3 and T_4 is the most helpful test for the diagnosis of hyperthyroidism.

Serum T_4 level is usually elevated. At the time of presentation of disease the T_3 level is usually quite markedly elevated, making it the best single screening test for hyperthyroidism (Fisher et al., 1977; Kempe et al., 1981; Mitsunia et al., 1976). Since levels of T_3 and T_4 in children are generally higher than those in adults, one should be cautious in interpreting mild elevations.

Thyroid hormone levels are highest in infancy, gradually decline throughout childhood, and reach adult levels about the age of 15 (Brown et al., 1978; Fisher et al., 1977; Kempe et al., 1981). Laboratory examinations of T_3, T_4 and TBG concentrations in our case revealed abnormal high results, which were in accordance with reports of several authors.

Radioactive iodine uptake tests with measurements at 6 and 24 hours were the most reliable methods of diagnosis, prior to the availability of radioimmunoassay of T_3 and T_4 (Brook, 1978; Hayek et al., 1980; Kempe et al., 1981).

Radioactive iodine is later on more widely used in several centres as treatment of thyrotoxicosis in children (Hayek et al., 1970; Kempe et al., 1981; Vaughan et al., 1980). Many authors however, stated that the use of radioactive iodide must be restricted, more over because of two principal apprehensions (Brown et al., 1978; Kempe et al., 1981; Vaughan et al., 1980): a. the possibility of predisposing the development of cancer locally in the gland or as leukemia; b. it may cause genetic damage.

Radioactive iodine assay or treatment was not performed in our case. The Basal Metabolic Test (BMR) is of great value for differential diagnosis in highly neurotic or hyperactive individuals and several pathologic conditions can cause an increase in the BMR such as : 1. hyperthyroidism; 2. thyroiditis (normal or decreased); 3. malignancy of the thyroid (normal or decreased); 4. leukemias; 5. miscellaneous conditions (i.e. hypertension with cardio renal disease, pernicious anemia, pheochromocytoma, etc.).

There are many factors influencing the BMR, so the diagnosis of hyperthyroidism based only on an increase in the BMR should be made cautiously (Barnes, 1977; Brook, 1978; Brown et al., 1978; Kempe et al., 1981). Other specific tests of the thyroid gland are rapidly replacing the Basal Metabolic Test. The BMR of our case was also significantly increased (Normal value (+) 5% to (–) 15%).

There is no certain evidence on the pathogenesis of Graves' ophthalmopathy, but there are many clues suggestive of autoimmunity. It seems most likely that Graves' ophthalmopathy would have the same basic nature as Graves thyroid disease (Brown et al., 1978; Kempe et al., 1981; Mc Kendrick and Newas, 1965; Vaughan et al., 1980). Our case has a slight exophthalmus, which was suggestive for Graves ophthalmopathy.

Differential diagnosis : every tumor of the neck region, originating from the thyroid gland should be differentiated from Graves' disease, such as :

1. Endemic goiter. There is a chronic deficiency of iodine in endemic goiter, often accompanied by hypothyroidism and decompensation, besides a visible nodular enlargement of the gland (Brown et al., 1978; Kempe et al., 1981; Vaughan et al., 1980). The incidence of endemic goiter is greater in the mountain areas, because sea water is rich in iodine and shell fish is also high (Kempe et al., 1981; Vaughan et al., 1980). Endemic goiter is therefore rare among population living by the sea shores.

2. Lymphocyte thyroiditis (Hashimoto's disease) is the most common cause of thyroid disease in children and adolescents. In some countries the incidence is as great as 1% in school children (Kempe et al., 1981; Vaughan et al., 1980). The goiter may appear insidiously and vary in size, the thyroid is diffusely enlarged, firm and non tender and frequently nodular in 30 – 40 % of patients (Kempe et al., 1981; Vaughan etl., 1980). Most children affected are euthyroid or even with signs of hypothyrcidism without evidence of exophthalmia. There is an elevated level of TSH, which is common in lymphocytic thyroiditis.

3. Carcinoma of the thyroid gland. Malignancy of the thyroid gland in children is uncommon, and the cause is still unknown (Brook, 1978; Kempe et al., 1981; Patton et al., 1976). Exposure of the thyroid gland of the young to low doses of radiation, such as from radiation therapy to the neck and its adjacent areas has been known to be associated with the subsequent development of the thyroid neoplasms (Barnes, 1977; Brook, 1978; Brown et al., 1978; Fisher, 1976; Hayek et al., 1970). The types of carcinoma associated with radiation are usually papillary or papillary follicular and many of these nodules are easily palpable on clinical examination. Several authors reported malignancy of the thyroid gland in patients who received radioactive iodine for diagnostic purposes several years previously. Cervical lymphnodes involvement is usually present and the lungs are the most common site of metastasis, the thyroid gland is functionally euthyroid (Patton et al., 1976; Vaughan et al., 1980).

Therapy : the treatment of hyperthyroidism is still controversial, but it is commonly accepted that general supportive and medical therapy are the treatment of choice for the patient newly diagnosed as having Graves' disease (Barnes, 1977; Bellanti, 1978; Brook, 1978; Brown et al., 1978; Kempe et al., 1981).

1. General measures :
   Rest in bed is advisable only in severe cases, or in preparation for surgery, at the beginning of medical regimen. The diet should be high in calories, carbohydrates and vitamines (particularly vitamin B_1) (Barnes, 1977; Brook, 1978; Brown et al., 1978; Kempe et al., 1981). Propanolol may be useful in controlling symptoms of nervous instability or tachycardia, and even in lifethreatening cardiac complications that may occur in thyroid storm (Brook, 1978; Brown et al., 1978; Kempe et al., 1981; Reynolds and Woody, 1971; Smith and Howard, 1973).

2. Medical treatment :
   The increased thyroid hormone synthesis can be normalized by the administration of one of the thioamide drugs. Clinical response may be noted in 2–3 weeks and adequate control in 2–3 months after initiation of treatment (Barnes, 1977; Brown et al., 1978; Kempet et al., 1981; Kogut et al., 1965).

   The thyroid gland frequently increases in size after initiation of therapy, but usually will decrease in size within several months. (Hayek et al., 1970; Kempe et al., 1981; Kogut et al., 1965; Vaughan et al., 1980).

   a. Propylthiouracil, methimazole or carbimazole is commonly used. These drugs cause a blockage of organification of

iodine, thus decreasing the amount of thyroid hormone synthesized (Brown et al., 1978; Kempe et al., 1981; Vaughan et al., 1980). The dose of propylthiouracil is 5 mg./kg. B.W./day and symptomatic improvement may be observed in one to two weeks, though laboratory abnormalities may not return to normal until 4–6 weeks after initiation of therapy (Brown et al., 1978; Kempe et al., 1981; Vaughan et al., 1980). The dose of methimazole or carbimazole is one tenth the dosage of propylthiouracil (Brown et al., 1978; Kempe et al., 1981). It is important to monitor T_4 and T_3 serially dule) 3 x 1 tablet each day and improvement was noted within 2–3 weeks time. Monitoring of the blood count is indicated because of possible toxicity reaction of those drugs such as granulocytopenia, leukopenia, skin rashes, fever, and arthralgia. Remission occurs in the majority of children treated, and the average length of treatment before remission is about 3 years (Barnes, 1977; Brown et al., 1978; Kempe et al., 1981).

b. Radioactive iodine is the standard treatment for hyperthyroidism in adults in many clinics. The risk of radioactive iodide in pediatric patients are : genetic damage; thyroid cancer induced by radiation; development of hyperthyroidism.
Our patient did not receive any radioactive iodine treatment due to the possible risks involved and financial factors.

3. Surgical measures :
Subtotal thyroidectomy is considered by many to be the treatment of choice, especially where a close follow up of the patient is difficult or impossible (Brown et al., 1978; Kempe et al., 1981; Kogut et al., 1965). But surgery has its particular problems. First, the patient has to be well controlled with medical therapy and has to be pretreated with iodine a week or two before the operation (Brown et al., 1978; Kempe et al., 1981; Kogut et al., 1965; Voughan et al., 1980). The success of surgery depends a great deal upon the skill and experience of the surgical staff. Complications such as unintentional removal of the parathyroid glands or injury to the recurrent laryngeal nerve are more likely to occur (Brown et al., 1978; Kempe at al., 1981).
Keeping the above considerations in mind, the choice of an alternative mode of therapy to medical treatment is problematic

The risk and benefit of each procedure should be thoroughly explained to the family. Thus medical treatment is still the treatment of choice for hyperthyroidism in children where remission may occur within 2 to 3 years. If remission then is not achieved, surgery may be considered as an alternative therapy (Barnes, 1977; Brook, 1978; Kempe et al., 1981).

Prognosis

Improvement may occur without therapy in 30% of cases but with medical treatment alone, prolonged remission may be expected in 50–75% of cases (Brown et al., 1978; Kempe et al., 1981; Vaughan et al., 1980). The prognosis of our case was "dubious ad bonam", because improvement was observed after 2–3 weeks therapy, with carbimazole, but long term follow up has to be done to achieve significant results.

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