A case of infantile-onset Graves

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Summary

Graves’ disease is an autoimmune disorder presenting with hyperthyroidism and the disease is rare in the childhood. A two-year-old female patient was admitted to our clinic for her evident orbital puffiness. Physical examination revealed proptosis, tachycardia and a hyperpigmented spot with a diameter of 6x4 cm on the skin of the left hemithorax. Thyroid function tests were as follows: fT4: 4.00 ng/dl (N:0.8-1.9), fT3: 7.7 pg/ml (N:1.57-4.71), TSH:0.004 uIU/ml (N:0.4-5), anti-thyroglobulin: <20 IU/mL (N:0-50), anti-thyroid peroxidase: 45.7 IU/mL (N:0-50). To distinguish Graves’ disease and McCune Albright syndrome, TSH receptor antibody (TRAb) level and bone survey (X-ray) were evaluated. The TRAb level was 57 IU/L (N:0-9) and there was no finding consistent with fibrous dysplasia on bone X-rays. Propylthiouracil was started with a diagnosis of Graves’ disease. In her clinical follow-up, propylthiouracil was switched to methimazole because of a potential risk of hepatotoxicity. TRAb titers remained high and proptosis persisted. There was no evidence of ophthalmopathy on orbital magnetic resonance imaging (MRI). In this report, we described a patient with Graves’ disease who presented with proptosis because the disease and its ocular manifestations occur rarer in children compared to adults. McCune Albright syndrome was also discussed as a differential diagnosis.

Key words: Graves’ disease, ophthalmopathy, thyrotoxicosis

Introduction

Hyperthyroidism occurs considerably rarely in the childhood and the most common cause is Graves’s disease (1). Graves’ disease is an autoimmune disorder characterized with enlargement of the thyroid follicular cells and increase in synthesis and release of thyroid hormones as a result of development of stimulating antibodies against thyrotropin (TSH) receptors. Its prevalence has been reported to be 6.5/100 000 in the childhood and 0.1/100 000 below the age of five years (2,3). Although the first-line treatment is anti-thyroid drug treatment, remission with drug treatment has been reported to be approximately 30% in the childhood (4,5). Radioactive iodine (RAI) or surgical treatment are among the other treatment options. Two types of ophthalmopathy may be observed in Graves’s disease depending on thyrotoxicosis or involvement. The frequency of ophthalmopathy is considerably lower in the childhood and especially below the age of five compared to adults. In this article, a two-year-old female patient who had Graves’ disease with thyrotoxicosis and mild ophthalmopathy was presented because this disease is observed rarely in the childhood.

Case

A 2-year-old female patient presented to a health center because of orbital puffiness which had been present for one year. Her TSH value was found to be supressed and she was referred to us for further evaluation. When her history was questioned, growth failure, intermittent diarrhea, restlessness and difficulty in falling asleep were reported. Her personal history was normal. Her familial history revealed goitre in the grandmother. No other member of the family had similar disease. On physical examination, her body weight was found to be 10 kg (-1.65 SDS) and her height was found to be 88 cm (1.03 SDS).
Her general status was well and she was restless. She had mild proptosis (Picture 1). A hyperpigmented skin spot (café-au-lait) with a size of 6x4 cm was present in the midclavicular line on the left side of the thorax (Picture 2). The thyroid gland could not be palpated and no thrill was heard on the gland. The apical heart beat was found to be 180 beats/min, but the patient was crying. Other system examinations were found to be normal. Complete blood count, transaminases and renal function tests were found to be normal. Thyroid function tests were as follows: free thyroxin (FT4): 4.00 ng/dL (N:0.8-1.9 ng/dL), free triioditronin (FT3): 7.7 pg/mL (N:1.57-4.71 pg/mL), TSH: 0.004 IU/mL (N: 0.4-5 IU/mL), anti-tyroglobulin:<20 IU/mL (N:0-50 IU/mL), anti-thyroidperoxidase: 45.7 IU/mL (N:0-50 IU/mL). The bone age was compatible with below the age of 2 by Greulich-Pyle atlas. On thyroid ultrasonography, the right lobe was found to have a size of 10x11x23 mm and the left lobe was found to have a size of 6x11x20 mm. The total thyroid volume was found to be 2 mL (-0.27 SDS). The echogenicity of the gland was normal and homogenous. Bone graphies which were taken to investigate fibrous dysplasia observed in McCune Albright syndrome because of presence of Café-au-lait spot and to investigate craniosynostosis related with hyperthyroidism revealed no pathological finding. Propranolol was started at a dose of 2 mg/kg/day and propylthiouracil (PTU) was started at a dose of 6 mg/kg/day. In the follow-up, her tachycardia regressed and propranolol was discontinued. THS receptor antibody was found to be 57 IU/L (N:0-9 IU/mL) at first presentation. The patient was started to being followed up with a diagnosis of Graves’ disease. Na L-thyroxin (2.5 mcg/kg/day) was added to treatment, since FT4 values were found to be low, though the dose of PTU was decreased. PTU was discontinued in the 9th month of treatment considering the potential hepatotoxicity of the drug and metimazol was started at a dose of 0.25 mg/kg/day. High thyrotropin receptor antibody levels continued. Thyrotoxicosis was eliminated with treatment, but proptosis continued. Orbital magnetic resonance imaging revealed no finding of severe ophthalmopathy. The volumes of the periorbital muscles were normal and no treatment directed to ophthalmological findings was planned.

Considering that fact that prolonged medical treatment in the childhood decreases the risk of recurrence it was planned to continue antithyroid treatment for at least 24 months. It was thought to apply RAI if her age would be appropriate or else to perform surgical treatment if recurrence occurred or insensitivity to antithyroid drugs developed in the follow-up.

**Discussion**

Graves’ disease occurs rarely in the childhood and its frequency below the age of 5 years is not known. The rate of 0.1/100.000 given in the literature covers all causes of thyrotoxicosis (3). The disease is observed with the highest rate especially in adolescence in children (6) and the female/male ratio has been reported to be 9.7/1 (2). Our patient who had proptosis at least for one year presented at the age of two years and it was thought that the age at disease onset was approximately one year.

McCune Albright syndrome is a disease which occurs as a result of somatic mutation in the G protein α subunit, which is characterized with extensive café-au-lait spots on the skin and poliostatic or monostatic fibrous dysplasia and
which involves multiple systems. Autonomous excessive function involving especially the ovaries, adrenal glands and thyroid gland and related Cushing’s syndrome, increased growth hormone, hyperprolactinemia, peripheral puberty precox and hyperthyroidism may be observed (7,8). The frequency of hyperthyroidism is approximately 38% and a heterogenous appearance is present on ultrasonography of the thyroid gland. Our patient was investigated in terms of McCune Albright syndrome, when a large café-au-lait spot was observed on the thoracal wall on physical examination. However, bone survey which was ordered in terms of fibrous dysplasia was found to be normal. Pelvic ultrasonography performed to investigate autonomous activation which is observed in McCune Albright syndrome and serum estradiol levels were found to be compatible with the age of the patient. Thyroid receptor antibodies which are specific for Graves’ disease were found to be high. The diagnosis of McCune Albright syndrome was excluded in the patient in whom no finding supporting autonomous overfunction of the other endocrine glands developed in the clinical follow-up.

The frequency of ophthalmopathy related with Graves’ disease has been reported to be 37-67% in different studies (9,10). Ophthalmopathy observed in children is generally milder compared to adults and is considerably rare below the age of five years. The youngest patient reported in the literature was four months old (11). Ophthalmopathy may be observed as palpebral retraction, palpebral edema, proptosis, chemosis and periorbital edema. Severe ophthalmopathy characterized with chemosis, severe proptosis, periorbital ecchymosis, corneal ulceration, eye muscle paralysis and optic atrophy is observed rarely in the childhood and adolescence. The clinical findings of ophthalmopathy may occur together with thyroid dysfunction or months-years later. Since ophthalmopathy is milder in the childhood, it is generally self-limiting. Ophthalmological findings usually regress with control of hyperthyroidism (12,13). Puberty may worsen ophthalmopathy and the chance of regression of ophthalmopathy in patients who are diagnosed with ophthalmopathy in adolescence is lower (14). A relation has been found between thyrotropin receptor antibody levels and the severity of ophthalmopathy (15). Oral corticosteroid, orbital radiation or surgical decompression is rarely needed in treatment. We decided to monitor our patient and did not plan additional treatment, since orbital magnetic resonance imaging which was performed because proptosis did not regress did not reveal involvement compatible with ophthalmopathy and there was no increase in the volumes of the periorbital muscles which is the typical finding of chidhood ophthalmopathy.

In treatment of childhood Graves’ disease, the first-line treatment is anti-thyroid drug treatment and RAI and surgical treatment are the other treatment options (6,16). Anti-thyroid drugs act by inhibiting thyroid hormone synthesis at the steps of oxidation and iodine binding (6). Metimazol is stronger and has a longer action compared to PTU. Metimazol was started to be used as the first-line drug especially in the childhood age group after fatal hepatic failure cases related with propylthiouracil were reported (17). The cure rate with anti-thyroid drugs is low. The cure rate has been reported to be 33% after 10-year treatment (16). Another treatment method is RAI treatment and its cure rate is high (18). The risk of thyroid cancer related with radioactive iodine treatment is conversely related with age and RAI is not recommended below the age of five. The recommended dose is calculated according to the weight of the thyroid gland and a dose above 150µCi/g tissue is recommended. Lower doses increase the risk of thyroid cancer (6,16,19). In the 36-year follow-up of 116 patients who received RAI treatment in their childhood, it was shown that the risk of thyroid cancer related with RAI treatment did not increase. Surgical treatment is more successful in patients with a gland weight above 80 g (6,16). Performance of the surgical procedure by experienced surgeons and an older age of the child decrease the rate of complications. In our patient, PTU was started as the first-line drug at a dose of 6 mg/kg/day and L-thyroxin was added in the 7th month. After PTU was administered for 9 months, it was switched to metimazol because of potential side effects of PTU and improvement was provided with a metimazol dose of 0.25 mg/kg/day.

The risk of recurrence in Graves’ disease diagnosed in the childhood is higher compared to adults and recurrence is more frequently observed in the first 6 months after the drug is discontinued (6). The factors which increase the risk of recurrence of the disease include black race, young age, severity of the disease at the time of diagnosis, high TRAb and fT4 levels at the time of diagnosis and the time of usage of the anti-thyroid drug started (20). Our patient had a high risk of recurrence, since she was below the age of five at the time of diagnosis, her TRAb value at the time of diagnosis was 4-fold higher than the upper limit of normal and her fT4 value was high. Therefore, it was planned to continue anti-thyroid treatment at least for 24 months.

References


