Journal of Thyroid Disorders & Therapy
ISSN: 2167-7948

Saikiaand Choudhury, Thyroid Disorders Ther 2012, 1:3
DOI: 10.4172/2167-7948.1000113

Case Report Open Access

Hyperthyroidism in Down's Syndrome – A Report of Two Cases

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Abstract

Thyroid dysfunction in patients with Down's syndrome is well known. Hypothyroidism is the common abnormality documented. Hyperthyroidism is however, relatively rare. We report two cases of Down's syndrome with Graves' disease, one of whom succumbed to neutropenia and sepsis.

Keywords: Neutropenia; Sepsis; Down's Syndrome

Introduction

Down's syndrome is the most frequent genetic cause of mental retardation in men with an incidence of 1 in 750 live births [1]. Consequently physicians frequently encounter patients with Down's syndrome in their clinical practice and have to handle their medical problems. Autoimmune phenomenon like hypothyroidism, Celiac disease and type 1 diabetes mellitus are encountered more frequently in Down's syndrome than in the general population [2].

Hyperthyroidism though rare is more prevalent in patients with Down's syndrome than in the general population and has no gender predominance as shown in a study in Spain by Goday-Arno A et al. [3]. The study group included 1832 patients registered with the Catalan Down Syndrome Foundation in Spain. The incidence of Graves' disease in the Down syndrome population was 43 cases per 10,000 persons per year, as compared with 24 cases per 100,000 persons per year in the general population of Spain.

Despite advances in treatment, infections especially pneumonia and leukaemia are major cause of morbidity and mortality in Down's syndrome [4]. We report two adolescent girls of Down's syndrome with hyperthyroidism for the relative rarity of the condition and the intractable sepsis and mortality in one of them.

Case 1

A 14 year girl with Down's syndrome presented to the Endocrinology OPD with a history of hyperthyroidism for the last 2 years, detected when she had symptoms of weight loss and mild proptosis. She was started on Propyltiouracil (PTU) and was on a maintenance dose of 150 mg daily at presentation. She had developed fever, sore throat and arthralgia for the last one week and had consulted a local physician who had stopped PTU and had started a course of broad spectrum antibiotics. She presented to us on the third day after stopping PTU. She was found to be febrile, with mild tachycardia with pulse rate of 96/min and blood pressure of 110/70 mm of Hg. There was no goiter but mild proptosis was present. She had mouth ulcer and dysphagia. Her total leucocyte count was 2200/mm^3, absolute neutrophil count was 1000/mm^3 and ESR was 110 mm at the end of first hour. Haemoglobin was 8.5 gm%, platelet count was normal. She was started on intravenous fluconazole and intravenous antibiotics (Cefotaxime + Tazobactum). Her chest X-ray was normal and blood and urine culture were sterile. Throat swab culture revealed candidiasis. She became afebrile after 3 days and her total leucocyte count rose to 3400/mm^3 and ESR was 90 mm. Her ultrasonography of abdomen and echocardiography were normal. Serum T_4 was 15 mcg/dl and TSH < 0.01 mIU/L at admission. She was now started on methimazole 10 mg twice daily in view of reported preference of methimazole in adolescents.

Fever recurred on the 8th day. Her repeat total leucocyte count was 16,800/mm^3. She was started on Pipericillin + Tazobactum and Moxifloxacin. Her condition deteriorated with increasing tachycardia, tachypnoea and poor sensorium and she was shifted to the ICU where she was put on ventillatory support and also received iodine and iv hydrocortisone. She however succumbed to her condition on the 15th day.

Case 2

A 15 year old girl with Down's syndrome presented to the Endocrine OPD with history of weight loss, palpitation and tremulousness for last two months. She had a history of similar complaints two years back for which she had been treated with carbimazole for one year. She was apparently asymptomatic in the intervening period. She had attained menarche one year back and was having regular cycles. Examination revealed tachycardia (110/min) soft grade 1 goitre without any bruit. There was no clinical evidence of ophthalmopathy or dermopathy. Her serum T4 13.2 mcg/dl and TSH < 0.01 µIU/L. A diagnosis of Graves' disease was made and she was started on methimazole 10 mg twice daily.

Discussion

Thyroid disorders are frequent in patients with Down's syndrome. In a study of 140 patients aged 3 days to 13 yrs and 9 months with Down's syndrome, 40% had abnormal thyroid function of whom 37.9% had hypothyroidism and 20.1% had hyperthyroidism [5]. Subclinical hypothyroidism accounted for 32.9% of all cases. A review of 1105 cases of adolescents with Down's syndrome, analysed retrospectively in Spain, showed 216 with thyroid pathology (19.5%) of whom subclinical primary hypothyroidism was present in 168 cases, congenital primary hypothyroidism in 15, clinical primary hypothyroidism in 24 and hyperthyroidism in 5 cases [6]. In a longitudinal follow up of 85 patients with Down's syndrome in Upssala country up to the age of 25 years with TFT done at each yearly visit, hypothyroidism was documented in 30 patients and hyperthyroidism in 2 [7].

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Received April 03, 2012; **Accepted** June 25, 2012; **Published** June 26, 2012

Citation: Saikia UK, Choudhury BK (2012) Hyperthyroidism in Down's Syndrome – A Report of Two Cases. Thyroid Disorders Ther 1:113. doi:10.4172/2167-7948.1000113

The prevalence of Graves' disease has also been reported to be clearly higher in Down's syndrome children and adolescents (6.5%) than in the general population [3]. Graves' disease in Down's syndrome children and adolescent is also characterized by several peculiarities which include earlier presentation, no gender predominance, less severe clinical course, higher frequency of documented Hashimoto's thyroiditis antecedents and more frequent association with other autoimmune diseases [8]. In a paediatric population of 28 patients with Down's syndrome and Grave' disease compared with 109 controls without Down's syndrome, responsiveness to methimazole was significantly better in Down's syndrome patients as demonstrated by both the lower relapse rates after first cycle withdrawl (7.1% vs. 31.2%) and higher persistant remission rate after definite therapy withdrawl (46.4% vs. 26.7%). Moreover in Down's syndrome group, no patient needed surgery or radioactive iodine therapy whereas non-pharmacological treatment was needed in 11% of controls [8].

The occurrence of Graves' disease in adolescent females raises the speculation of the role of estrogen in the pathogenesis of Graves' disease. In a study by Wang et al. [9] estrogen receptor was detected in the thyroid tissues of 70% of patients with Graves' disease versus 13.3% in control group. The authors concluded that estrogen may be a promoting factor for Graves' disease. Kisiel et al. [10] noted that polymorphism of estrogen receptor beta gene is associated with susceptibility to Graves' disease. It is however difficult to give a definite comment on estrogen promoting susceptibility to Graves' disease.

Besides thyroid dysfunction Down's syndrome is associated with increased prevalence of other autoimmune phenomenon like celiac disease and type 1 diabetes mellitus [2]. Incidence of infections and risk of death due to sepsis is also high in Down's syndrome patients as compared to non Down's syndrome subjects [11]. The increased prevalence of autoimmune phenomenon in patients with Down's syndrome along with increased infections and leukaemia have lead to the formation of several hypothesis which if true would have consequences in everyday patient care. It is hypothesized that Down's syndrome is associated with an intrinsic defect in the immune system leading to a form of abnormal precocious ageing [12]. The thymus is smaller in Down's syndrome subjects, even in newborns and has an abnormal structure with a decreased proportion of phenotypically mature thymocytes expressing high levels of the αβ form of the T cell receptor and associated CD3 molecule and overexpression of tumour necrosis factor α and interferon gamma cytokines. Overexpression of these cytokines suggest a dysregulation in cytokine production in Down's syndrome [13]. The authors have also demonstrated T lymphocytopenia in all age groups that concerns $CD4^+$ helper as well as $CD8^+$ cytotoxic T lymphocytes with absence of the tremendous expansion seen in the first year of life suggesting a deficient reaction to antigenic stimulation. A profound B lymphocytopenia has also been observed in Down's syndrome even in fetuses. These may be due to an intrinsic B lymphocyte defect or due to deficient T helper lymphocyte function.

A considerable hypergammaglobulinaemia of IgG and IgA classes after the age of five years is described in Down's syndrome with IgM decreasing in adolescence [14-16]. Auto antibodies against human thyroglobulin and gliadin are observed more often in Down's syndrome children as are high titres against casein and beta lactoglobulin [14,17]. All these findings suggest a generalized immune dysfunction in Down's syndrome subjects involving both the T lymphocytes and B lymphocytes which makes them vulnerable to recurrent infection.

Conclusion

Down's syndrome patients are at an increased risk of infection and mortality due to severe sepsis. This is because of an inherent immune dysfunction in them. Physicians should keep this in mind while treating patients of Down's syndrome presenting with any infection.

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