Nigerian Journal of Clinical Practice
Dec. 2005: Vol. 8(2): 133 – 135.

FAMILIAL THYROTOXICOCIS IN FIVE NIGERIANS

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ABSTRACT

We describe the occurrence of thyrotoxicosis in four Nigerian families. Hitherto, the descriptions of familial thyrotoxicosis have been confined to the Caucasian population and only recently in a Chinese family. This is the first description of familial thyrotoxicosis in the Nigerian population. The mutation analysis of the genomic DNA of the TSH receptor of these patients is required to define the genetic mutations that caused the disease. We recommend that a high index of suspicion for familial thyrotoxicosis should be exercised in the clinical evaluation of patients who present with hyperthyroidism.

Key Words: Familial, thyrotoxicosis, thyrotropin receptor, genetic mutations

INTRODUCTION

Hyperthyroidism is common, affecting 2% of women and 0.2% of men[1]. It has a prevalence of 2.5-4.7 per 1000 female. The annual incidence is 1 per 1000 in the U. K., Scandinavia, Japan and the U. S. A[2]. The incidence of thyrotoxicosis is 4% - 8% of all thyroid disorders in the African population[3]. This description of five members of four families who were managed for thyrotoxicosis is the first report of familial thyrotoxicosis in the Nigerian population.

CASE REPORT

First Family.

The index patient of the first family, I. O., is the fourth of eight children. She is a 41-year-old female who presented with the clinical features of diffuse toxic goiter with exophthalmos. She became symptomatic at the age of 38 years and was commenced on Carbimazole and Propranolol but defaulted five months later. She presented again 27 months later with worse features of toxicity including systolic hypertension with cardiac failure. The serum T3 was 341.5 ng/dl (normal range, 100-190ng/dl), serum T4 was >12ug/dl (normal value, 5-12ug/dl) and the serum TSH was 0.1miu/l (normal value, 0.5-3.7miu/l). The serum calcium, phosphorus, albumin, electrolytes, urea and creatinine were normal. The electrocardiogram showed features of left atrial enlargement; left ventricular hypertrophy and non-specific T wave abnormality. Echocardiography showed normal heart valves and concentric (septal) hypertrophy. She was treated with tablets of Carbimazole, Propranolol, Diazepam, Amilodipine, Zestril, Aspirin and intravenous frusemide. She became euthyroid and normotensive with resolution of the cardiac failure. She had a subtotal thyroidectomy and the histology of the thyroid gland showed colloid goiter.

The seventh child of the family, I. O., is a 31-year-old female. She presented with diffuse toxic goiter at the age of 28 years and was commenced on tablets of Carbimazole, Propranolol and Diazepam. She stopped using the drugs after 18 months because she felt better. The symptoms recurred six months later. The serum T3 was 453.2 ng/dl (normal range, 100-190ng/dl), serum T4 was >20ug/dl (normal value, 5-12ug/dl) and the serum TSH was 0.3miu/l (normal value, 0.5-3.7miu/l). The serum calcium, phosphorus, albumin, electrolytes, urea and creatinine were normal. The electrocardiogram and echocardiogram were normal. She was rendered euthyroid on the same regimen and then had a subtotal thyroidectomy. The postoperative recovery period was uneventful and the histology of the thyroid specimen showed colloid goiter.

The first child of the family, A. O., is a 48-year-old female. She was noticed to have a goiter when she accompanied her two sisters to the clinic. She had noticed the goiter at the age of 20 years. There was no clinical feature of thyrotoxicosis. The serum T3 was 100 ng/dl (normal range, 100-190ng/dl), serum T4 was 9ug/dl (normal value, 5-12ug/dl) and the serum TSH was 37.7miu/l (normal value, 0.5-6.5miu/l). The other siblings do not have goitre. The late mother of the patients was reported to have had an anterior neck swelling.

Second Family.

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The index patient of the second family, O. A., is a 28-year-old female who presented with features of diffuse toxic goiter. She became symptomatic at the age of 27 years. She reported that her mother had died of a similar disease while being treated at another hospital fifteen months previously. Moreover, an older cousin had thyroidectomy performed for a similar disease in another hospital. The serum T3 was 254.3 ng/dl (normal range, 100-190ng/dl), serum T4 was 8.6ug/dl (normal value, 5-12ug/dl) and the serum TSH was 0.05miu/l (normal value, 0.5-3.7miu/l). The serum calcium, phosphorus, albumin, electrolytes, urea were normal. The electrocardiogram of the patient showed normal sinus rhythm with a first-degree atrioventricular block and nonspecific T wave abnormalities. She became euthyroid using Carbimazole and Propranolol. She had a total thyroidectomy and her postoperative recovery period was uneventful. The histology of the thyroid specimen showed focal lymphocytic thyroiditis. She was commenced on l-thyroxin 0.1mg daily, thereafter.

Third Family.

The index patient of the third family, F.A., is a 25-year-old female who presented with the clinical features of thyrotoxicosis of three years duration. She had had unsuccessful medical treatment elsewhere. The mother had thyroidectomy for thyrotoxicosis about 25 years before the patient presented. The serum T3 level was >800 ng/dl (normal range, 100-190ng/dl), serum T4 was >20ug (normal value, 5-12ug/dl) and the serum TSH was 0.01miu/l (normal value, 0.5-3.7miu/l). The E. C. G. showed tachycardia while the echocardiogram was normal. The serum calcium, phosphorus, albumin, electrolytes, and urea were normal. She became euthyroid on tablets of Carbimazole, propranolol and Bromazepam. The treatment was marked by intermittent neutropenia and Carbimazole was stopped intermittently. She had a near-total thyroidectomy complicated by a mild thyroid storm. This was managed with intravenous propranolol, diazepam, hydrocortisone, and cold compress. She made satisfactory recovery and was discharged home.

Fourth Family.

The index patient of the fourth family is a 38-year-old male who presented with features of thyrotoxicosis. One of his sisters had thyroidectomy performed for thyrotoxicosis elsewhere. The result of analysis of serum T3, T4 and TSH is being awaited. He has been commenced on tablet carbimazole, Propranolol and diazepam. He will undergo total thyroidectomy when he is euthyroid.

DISCUSSION

Familial predisposition has been noted in thyrotoxicosis but actual documentation of hereditary familial thyrotoxicosis is not common[2]. Familial Graves' disease is the commonest of this subset of patients and the contribution of both paternal haplotypes might be necessary for susceptibility to it[4]. Autosomal dominant non-autoimmune hereditary familial hyperthyroidism accounts for a very small proportion of the causes of hereditary familial thyrotoxicosis[2]. The mechanism is due to a congenital mutation of Thyroid Stimulating Hormone Receptor (TSH-R) causing persistent basal hyperfunction of the receptor and early onset of thyrotoxicosis[5]. It is characterized by a diffuse goiter with no thyroid stimulating antibodies -- a distinguishing feature from classical Graves' disease. These constitutively activating mutations also cause sporadic cases of congenital non-autoimmune hyperthyroidism and the majority of hyperfunctioning thyroid adenomas[6]. Takeshita et al[7] in their review concluded that its incidence appeared to be low in Japan. A study in a Chinese family associated mitral valve prolapse with this mutation[5]. Three of our patients in whom echocardiography was performed had normal mitral valves.

Thomas et al[8] described a non-autoimmune form of goitrous hyperthyroidism different from Graves' disease. The absence of exophthalmos and a rare presence of lymphocytic infiltration of the excised thyroid gland are characteristic. The index patient of the second family had a focal lymphocytic infiltration of the excised thyroid gland though she had exophthalmos. Rosler et al[9] reported Familial hyperthyroidism due to inappropriate thyrotropin secretion affecting six females in a family of three generations. The patients were successfully treated with tri-iodothyronine. However, our patients responded to conventional thyroid surgery following adequate preoperative preparation with Carbimazole, Propranolol, and sedatives.

Familial dysalbuminemic hyperthyroidism, a syndrome associated with abnormal binding of T4 in serum, has also been described and has an autosomal dominant mode of transmission[10].

The time course of thyrotoxicosis depends on the etiology and there are subtle differences in the clinical features of these various types of familial hereditary thyrotoxicosis. The clinical features of autosomal dominant non-autoimmune hyperthyroidism have been described[11]. The diagnosis is hinged on mutation analysis of genomic DNA.

The five patients in the four families we described may belong to any of the various types of Familial

hereditary thyrotoxicosis [4-12]. These include Familial Graves' disease, which has not been documented here before. The classification of these patients was hindered by lack of facility for genetic study. The subclinical hypothyroidism in the eldest child of the first family can also be caused by a homozygous mutation in the TSH receptor gene[13, 14].

The treatment of this group of patients, to be effective and permanent, will depend on ascertaining the basic defect. This is because a certain subset of patients, especially those with activating mutations of the TSH receptor gene, is characterized by disease persistence[12]. In our environment, a total thyroidectomy is recommended as the first line of treatment because of the present handicap with further categorization of these patients. This is especially for young patients in order to avoid relapse from residual thyroid tissue. Near-total or total thyroidectomy is safe and more effective than subtotal thyroidectomy in preventing recurrence of thyrotoxicosis and had been recommended for most patients referred for surgery[15]. We also recommend that a good family history should be obtained in the clinical evaluation of patients who present with features of thyrotoxicosis. This will increase the diagnosis of more cases of Familial thyrotoxicosis. We hope that further categorization with specific treatment of this subset of patients will be feasible in our practice in the near future.

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