FAMILIAL GRAVES' DISEASE AMONG THREE BLACK AFRICAN FAMILIES; CASE REPORT AND REVIEW OF LITERATURE.

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ABSTRACT
In the African setting with improvement in iodine supplementation by iodization of salt and drinking water; Graves disease may become more prominent as the main aetiology of thyrotoxicosis as toxic nodular goitre used to rank side by side in the causation of thyrotoxicosis. A report of Graves disease is being made among three black African Nigerian families. Graves' disease is an autoimmune disorder which is said not to be prevalent in the African continent because of the low prevalence of other autoimmune diseases. However, viruses and bacteria have been generally associated with its causation in genetically prone individuals. There is need for genetic analysis to be carried out in these types of cases as it will be of interest to document familial Graves' disease and its genetic nature in the blacks as not many cases have been reported. This will help to design the best treatment for each individual case.

Key words: *Familial Graves' disease, HLA haplotypes and polymorphisms.*

INTRODUCTION:

Graves' disease was first described in 1835 by an Irish Physician, Robert James Graves, to consist of goitre and exophthalmos. In 1840, the German Karl Adoph Von Basedow independently reported this association and noted same symptoms. Thus, it is also known as Basedow's disease on the European continent. Several earlier reports exist but were not circulated like those by Italians Giuseppe Flajani and Antonio Giuseppe Testa in 1802 and 1810 respectively. Prior to these, Caleb Hillier Parry, a Physician in England of the late 18th century, described a case in 1786, which was not published until 1825. Sayyid Ismail Al-Jurjani in the 20th century described the association between goitre and exophthalmos[1,2,3]

Graves' disease is more prevalent in females than males and the female to male ratio is 7 8:1[3,4,5].

The diagnostic features of Graves' disease are exophthalmos, which is due to immunoglobulins and lymphocytic infiltration. It is more common in smokers even after treatment in the smoker and can occur for the first time after radioiodine therapy. The second diagnostic feature of Graves' disease is pretibial myxoedema, which is also due to immunoglobulin and lymphocyte infiltration. This result in fluid retention and swelling of the skin of the shin. The third diagnostic criterion is the presence of diffuse goitre which may be small but visible and may be present in other causes of thyrotoxicosis[4,5].

Graves' disease is associated with the presence of thyrotropin receptor autoantibodies. These are thyroid stimulating immunoglobulins (TSI), thyroid growth immunoglobulins (TGI) and thyroid binding inhibiting immunoglobulins (TBII). Thyroid stimulating immunoglobulins act as long acting thyroid stimulant (LATS) activating the cells in a longer and slower way than (TSH) thyrotropin, leading to an elevated production of thyroid hormones[1]. Thyroid growth immunoglobulins bind directly to the thyrotropin receptors and have been implicated in the growth of thyroid follicles. Thyroid binding inhibiting immunoglobulins inhibit the normal union of thyrotropin and its receptors. By this inhibition, several other antibodies that normally would inhibit thyrotropin function, will actually act as if thyrotropin itself was binding to its receptor, thus, inducing increase in thyroid function.

There is a marked family preponderance which has led to speculation that there may be a genetic component[1]. However, no clear genetic defect has been found that would point at a monogenic cause. The trigger for auto antibody production is not known. Human leukocyte antigen, HLA DR (especially DR3) appears to play a significant role[7,8,9].

Since Graves' disease, autoimmune disease, appears suddenly, often quite late in life, it is thought that a viral or bacterial infection may trigger antibody formation which cross react with the human thyrotropin receptors[5, 6]. One possible culprit is thought to be the bacterium, *Yersinia enterocolitica*[3]. However, although, there is direct evidence for the structural similarity between the human thyrotropin receptor, direct causative evidence is limited. *Yersinia* seems not to be a major cause of this disease, although, it may contribute to the development of thyroid autoimmunity arising for other reasons in genetically susceptible individuals[9]. It has also been suggested that . It has also been suggested that *Y. enterocolitica* infection is not the cause of autoimmune thyroid disease but rather, is only an associated condition with both having a shared inherited susceptibility[3].

Genetic factors are important but not determinative in the development of Graves' disease. Twin studies show a 20% concordance with monozygotic twins and lower rates with dizygotic twins and other HLA-identicalsiblings[9]. Studies have found that several HLA *alleles* have been shown to predispose certain groups to the disease with regional and racial variations. These HLA *alleles* in British Caucasians include HLA Class II alleles DRB1- 0304, DQB1- 02 and DQA1- 0501 while North in American Caucasians, the susceptibility genes are DRB1*03/DRB3*0101 and DRB3*0202 while DRB1*07 is protective against Graves' disease in the North American Caucasians[1, 5, 6]. However, for African Americans, their susceptibility gene for Graves' disease is HLA DRB3*020/DQA1*0501[8]. The association of HLA alleles with susceptibility to Graves' disease is typical of an autoimmune disorder.

Genetic analysis has shown that polymorphism in the cytotoxic T-lymphocyte antigen 4 (CLTA - 4) gene, is associated with Graves' disease. CTLA - 4 is a receptor expressed on activated T cells proliferation by binding to the co-stimulatory B7 molecule and prevents further activation. The polymorphism corresponds with lessened effectiveness of this inhibitory receptor. CTLA - 4 has also been linked to organ - specific autoimmune diseases[7].

Another gene is the vitamin D - binding protein gene. Polymorphism of this gene has been associated with susceptibility to Graves' disease but mechanism of association is not known. Graves' disease patients have been shown to have low vitamin D in circulation[9].

CASE REPORTS:

First Family:

The index case of this family is M.V.M.V. was a 38 year old female school teacher who presented with a 9 month history of bulging of both eye balls, that were painful and there was an associated thyroid enlargement. She also had features of thyrotoxicosis, such as palpitations, shaking of the body, hyperdefaecation, and weight loss. She never had a spontaneous abortion. Patient's immediate elder sister had similar symptoms for which she was receiving treatment in a specialist hospital. She brought the sister later for further management. Examination revealed a young woman with coarse tremors of the whole body. She had exophthalmos with diffuse goitre that was not tender to touch. She had palmar erythema, onycholysis, warm moist palms, tachycardia of 120/minute regular and hypertension - 190/120mmHg. Her serum thyroid hormone levels were elevated (thyroxine = 327nmol/L, thyrotropin = 0.2m.i.u/L). Packed cell volume, white cell count, serum albumin and serum calcium and phosphorus were all within the laboratory's reference range for their assays. A diagnosis of Graves' disease was made.

This patient brought her elder sister with a three - month history of progressive bilateral protrusion of the eye balls and a goitre that was not painful. She had been prescribed carbimazole and propranolol from a peripheral hospital for one month which finished a month before she was brought by her sister. She claimed to be feeling better. No more palpitations, no more heat intolerance, no more sweatiness. So this second patient was examined and found to have a goitre, exophthalmos, but had no toxic features of warm sweaty palms, no tachycardia, blood pressure was 130/80mmHg supine. A diagnosis of euthyroid Graves' disease was made. Patient who had been off drugs for one month was not restarted on drugs. She was monitored by clinic follow-up visits and estimation of thyroid hormone concentration. Her hormones

had been within the laboratory's reference range and became elevated after 18 months. Patient was thereafter restarted on carbimazole and propranolol. The two patients have continue to come for follow-up in our hospital. The disease has been well controlled on antithyroids and they are on maintenance dosages. The exophthalmos has markedly regressed with prednisolone and the goitre has reduced in both patients.

Second Family:

O. O. was the index case of this family. She was a 26 year old married undergraduate student. She had had bilateral protrusion of the eye balls two years before presentation. She had gone to a peripheral hospital where she was placed on carbimazole and propranolol. A year after the protrusion of the eye balls, she became pregnant and she stopped the drugs on her own because she thought she was well. Four months after delivery, she presented to our hospital with worsening palpitations, heat intolerance, weight loss despite good appetite, worsening of the bulging of the eye balls and increase in size of the goitre. Patient's immediate younger sister and a paternal aunt also was said to be suffering from similar symptoms of bulging of the eye balls and goitre for which they were receiving treatment elsewhere.

Examination revealed a young woman that was not in distress. Her body mass index was 28kg/m^2. She had exophthalmos, diffuse goitre which was non-tender, warm moist sweaty palms, onycholysis, and palmar erythema. She had a tachycardia of 130/min, that was regular with a blood pressure of 120/60mmHg supine. Investigations done - Full blood count, serum proteins, calcium and phosphorus - were all within the laboratory's reference range, except for thyroid hormones that were elevated. (Thyroxine=293nml/L, triiodothyronine=8.1nmol/L, thyrotropin= 0.1m.i.u/L). A diagnosis of familial Graves' disease was made and patient was restarted on carbimazole and propranolol. She did well on the treatment and has continued with follow-up.

Third Family:

The index patient was NN. NN was a 22 year old female undergraduate student who presented to the ophthalmology clinic for progressive bilateral bulging of the eye balls. She had not been aware of any other symptom including goitre. She was referred to our medical unit because of the associated finding of elevated thyroid hormones by the ophthalmologist. Patient's younger brother and mother had earlier on visited a Doctor in a peripheral hospital for recent onset protrusion of the eye balls for which they had been placed on some tablet. Patient was found to have a diffuse goitre and exophthalmos with some features of thyrotoxicosis such as warm moist palms, onycholysis, palmar erythema and profuse sweating. Her thyroid hormone levels were markedly elevated with low serum thyrotropin.

DISCUSSION:

Among the three families, eight (8) persons had Graves' disease: seven women and one man. This finding brings out the ratio of 7:1. This ratio is similar to what other thyroid researchers[1, 4, 5] have documented. The presentation of these patients; diffuse goitre with bilateral exophthalmos led to the diagnosis of familial Graves' disease - the Graves' disease that is seen commonly in the population. This shows that these are the two common diagnostic features of Graves' disease. Pretibial myxoedema was not seen at all in any of these patients meaning that it is a rare finding even in thyrotoxicosis of Graves, disease.

These patients responded well to the ordinary antithyroid agents that are used for other patients. These are a combination of carbimazole in various dosages with propranolol also in various dosages depending on the heart rate - more in tachycardia. Patients never agreed for surgery even when thyroid gland was big. This response is different from that seen in other cases of familial hyperthyroidism because, these have a different aetiological agent. Rosler et al reported familial hyperthyroidism due to inappropriate thyrotropin secretion affecting six (6) females in a family of three generations. The patients were successful treated with triiodothyronine. Autosomal dominant non-autoimmune hereditary familial hyperthyroidism, accounting for a very small proportion of the causes of hereditary familial thyrotoxicosis, may not be successfully treated with antithyroid agents unless the aetiological factor is addressed. It is however, to be noted that Graves' disease may result from an interplay of more than one gene defects, contribution to it being probably a multifactorial disease.

Graves' disease has not been the leading cause of thyrotoxicosis in iodine-deficient areas of the world but toxic multinodular goitre[10,11,12]. With improvement in iodization of foodstuff like salt and drinking water, the prevalence of multinodular goitre that will eventually become toxic, will

reduce. Graves' disease, therefore will take pre-eminence as the leading cause of thyrotoxicosis because infection, still present in these areas of the world will trigger off a chain of antibody production leading to thyroid activation resulting in Graves' disease. However, familial Graves' disease is the commonest in a group of disorders called hereditary familial thyrotoxicosis .It has been reported among 4 families from Ibadan[9], but the patients in their report did not all have Graves' disease because some of the patients had diffuse goitre that may be present in other conditions and no exophthalmos, and pretibial myxoedema. The patients in this case report together with their relations all had Graves' disease as all had exophthalmos with goitre. However, exophthalmos distinguishes these patients with Graves' disease from those reported by Thomas et al. Thomas described a non-autoimmune form of the goitrous hyperthyroidism. Graves' disease can begin without exophthalmos but the exophthalmos may appear after the treatment has been initiated. Despite the presence of exophthalmos in these patients analysis is in no doubt necessary for susceptibility determinant or association. These genetic studies will help classify the type of genetic disorder whether it is HLA alleleic mutations, polymorphism in cytotoxic T-lymphocyte antigen 4 or the polymorphism in the vitamin D - binding protein gene. With this determination, solutions may be proffered to each individual patient accordingly.

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