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Original Article

Prevalence of Thyroid Dysfunction and Autoimmunity among First Degree Relatives of Patients with Graves' Disease at Aminu Kano Teaching Hospital, Kano, Nigeria.

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Abstract

Background: Graves' disease has a familial predisposition with about 15% of the patients having a close relative with the same disorder, while about 50% of the relatives of patients with Graves' have circulating thyroid autoantibodies. This study determined and compared the prevalence of thyroid dysfunction, and autoimmunity among healthy individuals, and first-degree relatives of patients with Graves' disease at Aminu Kano Teaching Hospital (AKTH), Kano.

Methodology: A cross-sectional descriptive study design was used to study 87 first degree relatives of patients with Graves' disease comprising of 5.7% fathers, 3.4% mothers, 29.9% brothers, 29.9% sisters, 16.1% sons, and 14.9% daughters; as well as 87 age and gender-matched controls selected using a systematic sampling technique. A pretested interviewer-administered questionnaire was administered to the eligible study participants. Anthropometric and clinical parameters were measured, and blood samples were assessed for TSH, fT3, fT4, anti-TPO, and anti-Tg antibodies. Data was analysed using SPSS version 22 for Windows with an α value of ≤0.05.

Results: The mean ±SD age of the study subjects and controls were 29.4±9.0 years, and 31.6±8.8 years respectively. About half 45 (51.7%) of the respondents were males among the study subjects and controls respectively. Up to 12.6% of study subjects had raised thyroid stimulating hormone (TSH). Overt hypothyroidism was observed among 5.7% of study subjects and none among the controls. Anti-thyroid peroxidase (anti-TPO) antibodies were positive among 4.6% of the study subjects while 1.1% of controls had positive anti-TPO antibodies. Anti-thyroglobulin antibody (anti-Tg) positivity was found among 23.0% of study subjects, while 9.2% of controls had positive anti-Tg antibodies.

Conclusion: Primary Hypothyroidism was the predominant thyroid dysfunction found amongst the relatives of patients with Graves' disease. The government and relevant stakeholders should develop a model that will mandate screening and follow-up amongst the first-degree relatives of patients with Graves' disease.

Keywords: Autoimmune Thyroid Disorder; First Degree Relatives; Graves' Disease; North-Western Nigeria; Thyroid Dysfunction.

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Introduction

Most patients with autoimmune thyroid disorders (AITD) have detectable circulating antibodies to a variety of thyroid-specific antigens like thyroglobulin (Tg), thyroid peroxidase (TPO), Na/I symporter protein, thyroid nuclei, and TSH receptor.[1]Out of these, anti-Tg and anti-TPO are the most prevalent and most useful in diagnosis.[1]Graves's disease (GD) is currently viewed as an autoimmune disease of unknown cause.[2]It has a strong familial predisposition, as 15% of the patients have a close relative with the same disorder and about 50% of relatives of patients with Graves' disease have circulating thyroid autoantibodies.[2]The thyroid auto-antibodies are inherited as an autosomal dominant trait in females, with incomplete penetrance among males.[1]The concordance rate is higher in monozygotic twins (40%) than in dizygotic twins (5%).[3]

Graves' disease was named in 1835after Robert J. Graves, who noted an association between exophthalmos, goitre, and palpitations.[4] It is an organ-specific autoimmune disorder characterised by hyperthyroidism, various degrees of diffuse goitre, ophthalmopathy, and less commonly pretibial myxoedema.[4] The thyroid Stimulating Immunoglobulins (TSI) bind and activate thyrotropin receptors causing the thyroid gland to grow and the follicles to increase the synthesis of thyroid hormones.[3] It represents 60-80% of all cases of thyrotoxicosis in different regions of the world and occurs in up to 2% of women. Females are involved five to ten times more commonly than males, and [3] can occur at any age with a peak incidence in the 20-40year age group. It can also occur among the elderly with no racial predilection.[3]

Studies on familial prevalence of AITD have reported familial clustering of autoimmunity ranging from 43% to 67%.[1] A significant proportion of first-degree relatives of patients with AITD have been found to exhibit overt (6%) and subclinical (22%) hypothyroidism, respectively.[1] Furthermore, anti-TPO antibodies were detected in 18% of the subjects.[1]

The prevalence of GD in Nigeria is about 4.0%.[5] Data on thyroid dysfunction among first degree relatives of patients with Graves' disease from developing countries are limited. This study therefore aimed to assess and compare thyroid autoimmunity and dysfunction in first degree relatives of patients with Graves' disease and controls at the Aminu Kano Teaching Hospital (AKTH), Nigeria. This study is essential to provide baseline information on the burden and potential risk factors associated with the condition. This can be of critical importance to the government and other stakeholders in terms of policy formulation, research, screening, and management of the individuals at risk of the disease.

Methods

Ethical consideration

Ethical clearance with approval number NHREC/21/08/2008/AKTH/EC/2689 dated 21st October 2019 was obtained from the Health Research Ethics Committee of Aminu Kano Teaching Hospital, Kano, before the commencement of the study. All the provisions of the HELSINKI declaration were respected throughout this study.

Study design and population

A hospital-based cross-sectional descriptive study design was used, conducted between January and April 2021.

The study subjects were first degree relatives of patients with Graves' disease attending the Endocrinology clinics of AKTH Kano. The control subjects were age and sex-matched apparently healthy hospital staff, who do not have first degree relatives with any known history of Graves' disease/thyroid disorder.

First degree relatives of patients with Graves' disease aged 18 years and above were included in the study. We excluded FDRs with any systemic illness (e.g. cardiac, renal, or liver disease) and/or those on drugs that could alter thyroid function. Apparently, healthy subjects were used as controls.

Study area

The hospital serves as a teaching hospital for Bayero University Kano. It serves the people of Kano State and is a referral centre for neighbouring States like Jigawa, and Katsina States. It has a bed capacity of 700 and is still expanding. The Hospital has several clinical departments supported by well-equipped laboratories (Chemical Pathology, Haematology, Microbiology, and Histopathology). There are facilities and human expertise for screening, diagnosis, and treatment of thyroid disorders including surgical management of patients. The study participants were recruited from the Endocrinology clinic of the hospital. The Endocrinology, Diabetes, and Metabolism (EDM) unit runs clinics twice per week (Thursdays and Fridays). The diabetes clinic is run every Thursday with an average attendance of 120 patients per week. The endocrinology clinic is run on Fridays. Approximately 30 patients attend the clinic every Friday, predominantly with thyroid disorders. Most of those attending the clinic have thyroid disorders with Graves' disease accounting for the cases (60% -70%).[6] The endocrinology clinics also render services to patients with Hypothalamo-pituitary disorders, obesity, and other related endocrine disorders. Each clinic is run by a team, comprising of consultants and resident doctors with support from the nurses.

Inclusion Criteria

For Study Subjects

First degree relatives (siblings, biological children, or parents) of patients with Graves' disease aged 18 years and above, consenting individuals.

Study Controls

Healthy individuals who do not have first degree relatives with any known family history of Graves' disease aged 18 years and above and consenting individuals.

Exclusion Criteria

For Study Subjects

Individuals (first degree relatives) with obvious systemic illnesses e.g. cardiac, renal, or liver diseases, and those on drugs that can alter thyroid function. e.g. Amiodarone, lithium, metoclopramide, interferon etc.

For Study controls

Individuals with a history of Thyroid disease, those with obvious systemic illness, and/or individuals on drugs that alter thyroid function.

Sampling Procedure

Participants who met the inclusion criteria were line-listed during each clinic day to obtain the weekly clinic sampling frame which was done over one month to obtain the monthly attendees. The sampling interval was obtained as the ratio of the sampling frame (over a month) to the calculated sample size.

The first respondent for the study in each arm was obtained by randomly selecting using balloting within the calculated sampling interval, thereafter; subsequent respondents were obtained by adding the calculated sampling interval in both arms of the study until the allocated sample size was obtained.

Procedure for data collection and instrument of data collection

Three trained research assistants (resident doctors and nurses), who speak at least Hausa and English, were used for data collection. A questionnaire with seven (7) sections namely biodata, clinical history, medical history, drug history, family history, social history, physical examination, and laboratory investigations was administered by the research assistants. Each study participant and control underwent a complete physical examination and the findings were recorded.

Sample Collection and Transportation

Five milliliters of blood were collected from each subject in the morning after an overnight fast, into a gel-activated bottle with the aid of a vacutainer needle from the antecubital vein while adhering to standard protocols by the researcher and research assistant. The collected sample was immediately transported to the laboratory and plasma was separated from the cells using a bench centrifuge at a speed of 1200 rev/min for 5 minutes. The centrifuged sample was immediately frozen and stored at -21^0cafter separation. All samples collected were analyzed by electrochemiluminescence-based immunoassay using Cobas E-400 automated analyzer (Roche Diagnostics) for TSH, fT_3, and fT_4. All collected samples further underwent antibody testing for TPO-ab and Tg-ab, lipid profile, and plasma glucose.[10] Normal precautions for handling all laboratory reagents, samples, laboratory wares, and machines were observed based on standard laboratory procedures. Quality control samples were assayed along with the test samples and assay batches and control values that fall outside ±2 standard deviation from the mean repeated.

Study participants with positive swallowing tests underwent a 2D-ultrasound scanning of the thyroid gland to confirm the presence of goiter and its nature. The thyroid ultrasound scan was carried out with the assistance of a consultant radiologist.

Data analysis and measurement of variables

The data generated was collated, and entered into Microsoft Excel, cleaned, and analyzed using Statistical Package for Social Sciences (SPSS) version 20.0 for Windows. Quantitative variables were summarized using mean and standard deviation while categorical variables were summarized using frequencies and percentages.

Patients were categorized as normal (euthyroid) or having thyroid abnormalities (hypothyroid or hyperthyroid) based on the following laboratory criteria; Hyperthyroidism → FT4 >21.9pmol/l (7.5-21.9pmol/l) and TSH values <0.25IU/ml (0.25 -4.2IU/ml). Hypothyroidism = FT4<7.5pmol/l (7.5-21.9pmol/l)[2] and/or TSH >4.2IU/ml (0.25 -4.2IU/ml) [2].

The Chi-squared test was used to compare proportions, while a two-sample t-test was used to compare means of the normally distributed continuous variables with a p-value of ≤ 0.05 considered statistically significant. For quality control, Preci Control Universal was used. This method has the following measuring range: TSH: 0.005 -100 μIU/ml [9], FT_3: 0.400-50.0 pmol/L or 0.260-32.6 pg/mL, [9] FT_4: 0.300-100 pmol/L or 0.023-7.77 ng/dl.[9]

Results

During the study period, a total of 174 participants who met the inclusion criteria were recruited, this is comprised of 88 study subjects and 87 study controls with a response rate of 98%, comprised of 5 fathers, 3 mothers, 26 brothers, 26 sisters, 14 sons and 13 daughters of patients with Graves' disease.

Clinical characteristics of the study participants

The clinical characteristics of the study participants are summarised in Table 1. The mean±SD age of the study subjects (Group 1) was comparable to that of the study controls (Group 2), 29.4± 9.0years vs.31.6 ± 9.0 years, p = 0.096. However, the mean BMI, heart rate, SBP, and DBP were higher among the study subjects than the control with p-values of 0.006, 0.022, 0.047, and 0.001 respectively.

Table 1: Clinical Characteristics of the study participants.

Clinical characteristics (Mean value)	Group 1	Group 2	P-value
Age (years)	29.38 ±8.95	31.63 ±8.81	0.096
Heart rate (bpm)	86.0± 9.7	82.0± 10.3	0.022*
SBP (mmHg)	114.0 ± 11.3	110.0 ± 9.8	0.047*
DBP (mmHg)	74.7 ± 8.4	70.6 ± 8.4	0.001*
Weight (Kg)	63.93±11.45	60.89±9.60	0.059
Height (m)	1.66±0.07	1.67±0.07	0.419
BMI (kg/m^2)	23.2 ± 3.97	21.8 ± 2.97	0.006*

Group 1= study subjects (first degree relatives of patients with Graves' disease); Group 2 =control subjects SBP - systolic blood pressure; DBP- diastolic blood pressure; BMI- body mass index.

Prevalence of Thyroid dysfunction

The prevalence of thyroid dysfunction among study participants was 11(12.6%) in group 1 and 2 (2.3%) in group 2. Elevated TSH was found in 6 (6.9%) males and 5 (5.7%) females among group 1, whereas 2 (2.3%) males with no single female were found to have elevated TSH among group 2. Six members (6.9%) in group 1 were found to have subclinical hypothyroidism, while five (5.7%) had overt hypothyroidism.

Prevalence of thyroid autoimmunity

The prevalence of thyroid autoimmunity among the study participants is as follows. The prevalence of anti-Tg antibody was 20 (23.0%) among the study subjects and 8 (9.2%) among the controls p= 0.023. while the prevalence of anti-TPO antibody was 4(4.6%) among the study subjects and 1(1.1%) among the controls, p = 0.364.

Prevalence of thyroid autoimmunity in thyroid dysfunction

The prevalence of thyroid autoantibodies among the group is shown in Table 2. Five (45.5%) study subjects with thyroid dysfunction had detectable anti-Tg antibodies compared to none among the controls, with a p-value of 0.04.

Table 2: Thyroid auto-antibody profile of those with thyroid dysfunction.

Parameters	Frequency of thyroid dysfunction		
	Group 1(n = 11)	**Group 2 (n = 2)**	***p*-value**
Anti-Tg	5 (45.5)	0 (0)	0.04*
Anti-TPO	1 (8.3)	0 (0)	0.33
Both anti-TPO and anti-Tg	2 (18.2)	0 (0)	0.23

Group 1= study subjects (first degree relatives of patients with Graves' disease); Group 2 =control subjects AntiTg-ab – antithyroglobulin antibody; AntiTPO-ab – antithyroid peroxidize antibody; n = frequency; % = proportion.

Thyroid autoantibody profile of the participants

The thyroid autoantibody profile of the study participants is shown in Table 3. Anti-Tg positivity was detected among 20 (23.0%) of group 1 comprising 3 fathers, 2 mothers, 5 brothers, 6 sisters, 2 sons, and 2 daughters respectively, as well as in 8 (9.2%) among group 2 with*a p*-value of 0.032. Anti-TPO-ab was detected among 4(4.6%) of group 1 (1 mother, 1 brother, 1 sister, and 1 son) and 1 (1.1%) among group 2 with a p-value of 0.368.

Table 3: Thyroid autoantibody profile of the study participants.

Parameters	Frequency n (%)		
	Group 1	**Group 2**	***P- value***
Age (Mean ±SD)	29.38 ± 8.95	31.63 ± 8.81	0.096
AntiTg-ab n (%)	20 (23.0)	8 (9.2)	0.032*
AntiTPO-ab n (%)	4 (4.6)	1 (1.1)	0.368

Group 1= study subjects (first degree relatives of patients with Graves' disease); Group 2 =control subjects AntiTg-ab – antithyroglobulin antibody; AntiTPO-ab – antithyroid peroxidise antibody; n = frequency; % = proportion.

Discussion

In this study, the mean age of the study subjects and the controls was comparable to the findings of Dayal *et al* [1] in their study of thyroid dysfunction among first degree relatives of patients with autoimmune thyroid disease. Strieder *et al* [11] however, reported a higher mean age among their study participants compared with the present study. The majority of the study subjects were traders, whereas most of the study controls were civil servants (hospital staff). This finding reflects the fact that Kano is widely regarded as the commercial nerve centre of Northern Nigeria. Most of the study subjects and controls in this study were married, but the difference was not statistically significant.

In this study, most of the study participants had either a secondary or tertiary level of education. However, the control subjects had more tertiary-level education compared to the study subjects. This is because the controls were hospital staff who had acquired tertiary education.

The prevalence of thyroid dysfunction in this study was 12.6% among the study subjects and 2.3% among the controls. Lower prevalence rate of 5%, 6.1%, and 8% were reported by Chopra *et al* [12] in Los Angeles-USA, Thomsen *et al*[13] in Sweden, and Akamizu *et al*[14] in Japan respectively. Dayal *et al* [1] in India, Kanga *et al* [15] in India, and Carey *et al* [16] in Chicago-USA reported a higher prevalence of 22%, 28.4%, and 36% respectively. The reason for the higher prevalence rates in the latter studies could be due to genetic/environmental factors including HLA DR3, B8, B17, iodine, infections, smoking, and medications [2]. Thyroid antibody positivity confers an increased risk for hypothyroidism1. Hypothyroidism was observed in 5.7% of the study subjects in our study. Similar rates were reported in other studies. [15], [17] The finding of hypothyroidism among the study subjects could be because both GD and HT are clustered as AITD, whereas there could be associated T-cell mediated immune mechanism from genetic and environmental factors [1], [2]. None of the study participants had features of hyperthyroidism. This finding is like reports from previous studies [1], [15], [17]. However, Strieder *et al* [11] and Hou *et al* [8] found the prevalence of hyperthyroidism to be 1.9% and 5.5% respectively, among their subjects. The difference could be due to the relatively smaller sample size in the index study compared with the latter studies.

We found the prevalence of anti-Tg antibodies (23.0%)) to be significantly higher among the study subjects versus the controls (9.2%). Likewise, the prevalence of anti-TPO was 4.6% among the study subjects versus 1.1% among the controls. Desai *et al* [17] reported a similar prevalence of 4.4% for anti-TPO antibodies in India. Dayal *et al* [1] reported a higher prevalence of 64% and 18% for anti-Tg and anti-TPO respectively, among their study subjects. Similarly, a higher prevalence for anti-Tg of 29.4% and 34% were reported by Kanga *et al* [15] and Chopra *et al* [12] respectively. In addition, higher prevalences of 9.4% and 24.0% for anti-TPO were reported by Kanga *et al* [15] and Strieder *et al* [11] respectively. The difference in the prevalence of thyroid autoimmunity may be because of environmental factors like iodine due to its immunomodulatory effect. Iodinated Tg molecules produce more immune responses as compared to less iodinated Tg molecules.[1], [18]. The raised TSH in 25% of anti-Tg-positive subjects suggests that autoantibody positivity may herald impending thyroid failure and warrant close monitoring of affected subjects. Thyroid autoimmunity is said to be commoner in females [1]. We found no gender difference in the prevalence of thyroid autoimmunity in the index study.

The limitation of our study includes the paucity of local studies on the subject for comparison and the inability to recruit a large population of first-degree relatives. Furthermore, the study could not test for TSHR-ab which is more sensitive and specific for Graves' disease.

Conclusion

The prevalence of thyroid dysfunction and thyroid autoantibody was found to be higher among first degree relatives of patients with Graves' disease when compared with age- and sex-matched controls. Auto-antibodies were similar in both males and females. The prevalence of thyroid dysfunction among first degree relatives of patients with GD demonstrates the importance of family history for developing AITD. Therefore, screening first-degree relatives of patients with Graves' disease for the presence of autoimmunity/thyroid dysfunction and following them up for subsequent development of overt thyroid disease is worthwhile.

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