Thyrotoxicosis, Etiology, Presentation and Management Challenges in Nigeria: A Review of Cases Seen Over a 5 Year Period

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Abstract

Background: Thyrotoxicosis is a common endocrine disorder worldwide with a female predominance. Graves disease is reported as the commonest cause of thyrotoxicosis by various authors in the Africa region. **Aims and Objectives:** The study evaluated patient characteristics, clinical and laboratory profile, co-morbidities, treatment modalities, response to therapy, side effects of anti-thyroid medications, treatment outcome and complications of the disease in patients with thyrotoxicosis. **Materials and methods:** This study was retrospective and observational. The records of patients diagnosed with overt thyrotoxicosis seen in the Endocrine unit (2013-2017) were pulled and relevant data compiled. Data was analyzed using SPSS V 21. **Results:** A total of 172 cases were studied; 33 males and 132 females (ratio 1:4). They were aged 18-70; 40.2 ±12.5 years. Graves Disease constituted 79 % 0f cases and toxic multinodular goiter made up 18%. Seven cases of Marine Lenhart syndrome were identified. Graves orbitopathy occurred in 54%, but was mild. All but 6 patients received anti-thyroid medication as initial therapy mainly carbimazole (90%). About 6% had thyroidectomy. Treatment default was high (52%), while 15% remitted and 19% relapsed. Total duration of illness was 1-380, 40.7 ± 52.6 months. Drug rash occurred in 5% and cholestatic hepatitis in 1.8%. Hypertension coexisted in 35%. Six pregnancies were recorded, four of which ended in miscarriages, two of which had thyroid storm. Heart disease complicated the disease in 36%. **Conclusion:** Thyrotoxicosis is a common clinical condition. Treatment with carbimazole is effective. However the treatment default rate was very high. Coexisting hypertension and pronlonged period of untreated disease exposed patients to a high burden of heart disease. Patient education and introduction of radioablation therapy will mitigate these challenges.

Keywords: Thyrotoxicosis, Presentation, Etiology, Treatment, Outcome, Complications, Heart disease

Introduction

Throtoxicosis is a common endocrine disorder worldwide. By definition, thyrotoxicosis refers to the clinical syndrome due to inappropriately raised circulating levels of thyroid hormones while hyperthyroidism implies increased synthesis and release of thyroid hormones by an overactive thyroid gland (Leo et al 2016). In general, the incidence of hyperthyroidism corresponds to population iodine nutrition. Various prevalence rates have been reported for hyperthyroidism in the general population in iodine sufficient areas of the world; 1-3% by Frankylen et al (2012) and 0.2% to 1.3% by Hollowell et al (2002). Higher rates of hyperthyroidism recorded in iodine deficient populations were ascribed to the excess of nodular thyroid disease in elderly patients (Laurberg et al 2006). Figures for the epidemiology of thyroid dysfunction in Africa are scarce due to absence of comprehensive population-based studies (Taylor et al 2018). Long-term variations in iodine intake do not influence the risk of disease; however rapid repletion especially in regions of moderate-severe iodine deficiency increases the incidence of overt hyperthyroidism from toxic adenoma, toxic multinodular goiter, and Graves' disease (Laurberg 2006). This was the case following successful universal salt iodization (USI) programs in Congo, (Bourdoux 1996) Zimbabwe (Todd et al 1995) and Ghana (Sarfo-Kantanka et al 2017). Prior to 1993, Iodine Deficiency Disorders (IDD) was recognized as a public health problem in Nigeria. In 1994, the program of Universal Salt Iodization (USI) came into force and by 2005, Nigeria was certified as USI compliant (SCN News 2007). It is to be expected that the profile of thyroid diseases should shift from that of iodine deficient to iodine sufficient. Graves disease has been reported as the commonest cause of thyrotoxicosis by various authors in the Africa region (Sarfo-Kantanka et al 2017, Ogbera et al 2011).

Aims and Objectives

The study evaluated the demographic socioeconomic, clinical and laboratory profile and co-morbidities in patients with thyrotoxicosis attending our endocrine clinic. It also studied modalities of treatment, response to therapy and the side effects of anti-thyroid medications, treatment outcome and complications of the disease.

Materials and methods

This was a retrospective observational study. The records of patients diagnosed with overt thyrotoxicosis seen in the Endocrine unit of the

University of Nigeria teaching Hospital (UNTH), Enugu, Nigeria over a 5 year period (2013-2017) were pulled and evaluated. Relevant data were compiled including patient demographics (age, gender, highest educational level attained, parity and occupation), presentation and clinical features, biochemical features (TSH, fT_4, fT_3, TRAb and TPO, FBC, serum urea and creatinine levels), treatment method, adverse drug reactions, duration of disease from inception, duration of treatment, disease status and treatment outcome. In addition, patients were assessed for co-morbidities and complications of therapy. Thyrotoxicosis was diagnosed based on suggestive clinical features in the presence of a suppressed TSH (<0.01 µU/mL) and elevated fT_4. Thyroid autoantibodies were requested for confirmation of cases of autoimmunity due to Graves Disease. Thyroid profile and auto-antibody results prior to starting medical therapy were used for analysis. Treatment status on intake was classified as naïve (never received ATDs), previously treated (had received ATDs in the past) or ongoing (was on ATDs at intake). Biochemical severity of the thyrotoxicosis was assessed using free fT_4 levels.

Treatment method

Only two methods of treatment were available; medical (ATD) and surgery (thyroidectomy). Carbimazole was the main and preferred ATD being the only drug readily available. All patients received carbimazole. Propylthioracil was used only in pregnancy or where carbimazole was not tolerated. The titration method was used starting with initial doses of 30-60mg/day and the dose tapered as the clinical features and biochemistry improved. Since 2015, the block and replace protocol was adopted to contain the arbitrary changes in ATD doses and chaotic thyroid function profile and therefore streamline the treatment algorithm. This problem arose because patients could not do their thyroid function tests as frequently and expeditiously as required. In this regime, Carbimazole was given at a steady dose of 30 mg daily with l-throxine 50-100 mg daily added when fT_4 level returned to normal (usually at 3 months). Treatment was discontinued after 18 months of ATD in those with controlled disease. They were then followed with thyroid function tests at one month and 3 monthly thereafter. The preferred beta blocker was propranolol which was used in all patients except where contraindicated. In such cases, atenolol was substituted. Patients who preferred surgery and those with nodular disease were referred to the surgical services. Surgery consisted of partial or total thyroidectomy.

Treatment outcome

The outcome of initial medical treatment was determined from biochemical response (fT_4 and TSH) and clinical assessment and recorded as follows:

1. Ongoing and controlled disease: normalization of biochemistry whilst on ATDs
2. Ongoing and uncontrolled disease: persistent symptoms or abnormal biochemistry despite ATDs
3. Disease remission: patients whose disease was controlled with ATDs and where control was maintained for at least a month after withdrawal of medical treatment or patients who remitted after thyroidectomy.
4. Defaulted: patients who did not complete the treatment schedule before discontinuing hospital attendance.
5. Relapsed: patients previously remitted or returned after defaulting
6. Unknown: where data or response were not available

Patients who relapsed after initial remission with ATDs or thyroidectomy were re-started on ATDs.

Data was analyzed using SPSS v 21 (SPSS, Inc, Chicago, IL, USA). Continuous variables were summarized using means and standard deviations. Categorical data was summarized using frequency tables and percentages. The relationship between variables was explored using 2 × 2 contingency tables to determine Chi squares and associated p-values. A *p*-value of <0.05 was considered statistically significant.

Result

Demographics

A total of 172 cases were studied; 33 males and 132 females (ratio 1:4). Table 1 and Figure 1 present the basic data on the patients. The ages of males and females were comparative (p = 0.332). Their diet consisted of local staples. Drinking water came from rivers, streams, boreholes, tap, sachet and bottled water. Family history of thyroid disease was present in 12%, affecting primarily first degree relatives. All patients used iodized salt. None of the patients was on lithium or amiodarone. Alcohol and tobacco use was very insignificant.

***Table 1**, Patient demographics*

Total, 172	Male, 33	
	Females, 132	
Age (years)	18-70; 40..2 ±12.5	
	M = 18-67; 41.6 ± 14.2	
	F = 19-70; 39.9.0 ± 11.7	
Variable	n	%
Education n=137		
Primary	22	20.5
Secondary	38	38.5
Tertiary	96	61.5
Marital status		
Single	54	31.4

Married	111	64.5
Widowed	7	4.0
*** Parity**	0-10 (4.0 ± 2.5)	
Occupation		
† Tech./Ass Prof	26	15.1
‡ Cler/Supp Workers	26	15.1
§ Craft Rel/Trade Workers	43	25.0
Students	36	20.9
Others	41	23.9
Family and social history		
|| Family hx goiter	21	12.2
Family hx thyrotoxicosis	2	1.2
Family hx vitiligo	2	1.2
Use iodized salt	169	98.3
Use extra iodized salt	3	1.7
Herbals	17	10.3
Supplements	23	13.9
Contraceptive use	1	0.6
Alcohol	2	1.2
Tobacco	2	1.2

***** Females only, † Technical and Associate professionals, ‡ Clerical and Support workers, § Craft Related and Trade workers, || hx-history

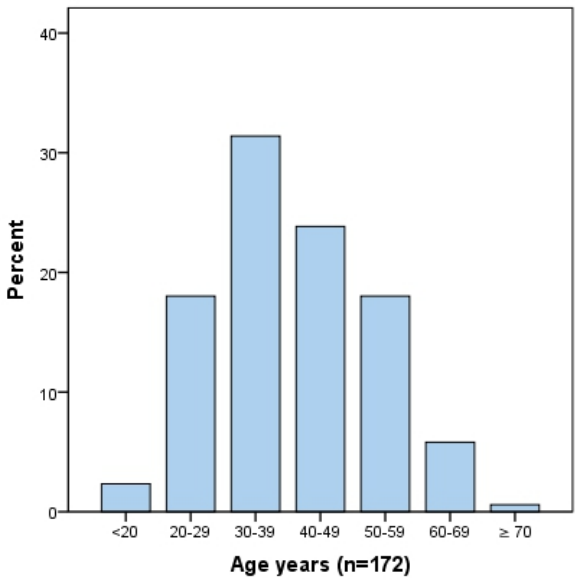

Figure 1, *Age distribution of patients*

Clinical presentation

The details of the presenting features are in Table 2 and 3 and Figure 2. The top ten symptoms were weight loss, heat intolerance, palpitations, hyper-defecation, excess sweating, goiter, increased appetite, bulging eyes,

fatigue, and nervousness. The frequencies would have been higher if all patients were treatment naïve. The stool count was 2-20/day (5± 3, median 4). BMI could be assessed in only a third of the subjects where records were available. Tachycardia was recorded in 100% in all treatment naïve subjects. Of the ten subjects with irregularly, irregular pulse, one was male aged 49 years and the rest were female aged 35-68 years (50.3 ± 10.4, median 51). Other common physical signs were goiter, eye signs, fine finger tremor, warm and moist palms. Pretibeal myxedema was observed in 4.1% and was of the diffuse and mixed (diffuse with nodules or plaque) types. No case of thyroid acropachy was recorded. Grade 0 goiters were observed in subjects on current or previous ATDs. Eye signs of Graves orbitopathy consisted of proptosis, periorbital edema and lid retraction. They were mild and regressed with ATD treatment except in two persons.

***Table 2**, Presenting symptoms*

Variable	n	%
Treatment Status at intake		
Naïve	98	59.4
Current	41	24.8
Previous	26	15.8
Symptoms (n=172)		
Weight loss	148	86
Heat intolerance	141	82
Palpitations	140	81.4
Hyperdefecation	128	74.4
Stool count	2-20; 5 ± 3	
Appetite changes	117	70.9
Same	30	18.2
Increased	101	61.2
Decreased	16	9.7
Excess sweating	116	67.4
Goiter	109	63.4
Hand tremor	107	62.2
Bulging eyes	94	54.7
Grittiness eyes	41`	23.8
Visual impairment	10	5.8
Fatigue	94	54.7
Nervousness	89	51.7
Insomnia	82	47.7
Shortness of breath	73	42.4
* Menstrual changes (n=132)	62	47
Hypomenorrhea	32	24
Amenorrhea	24	18
Menorrhagia	6	4.5
Postmenoupausal	24	18
Leg swelling	40	23.3
Muscle aches	37	21.5
Polydipsia	35	21.2
PMW	32	18.6

Polyuria	31	18
Cough	28	16.3
Mood swings	26	15.1
Orthopnea	21	12.2
PND	19	11.0
Skin hyperpigmentation	20	11.6
Hair loss	18	10.5
Pruritus	14	8.1
Persistent headache	11	6.4
Infertility	10	5.8
Vitiligo	4	2.3
Erectile dysfunction	3	1.7
Weight gain	2	1.2
Psychosis	2	1.2
Symptom duration before presentation	1-84; 18.6 ± 18.5, median 12 (months)	

***** Females only

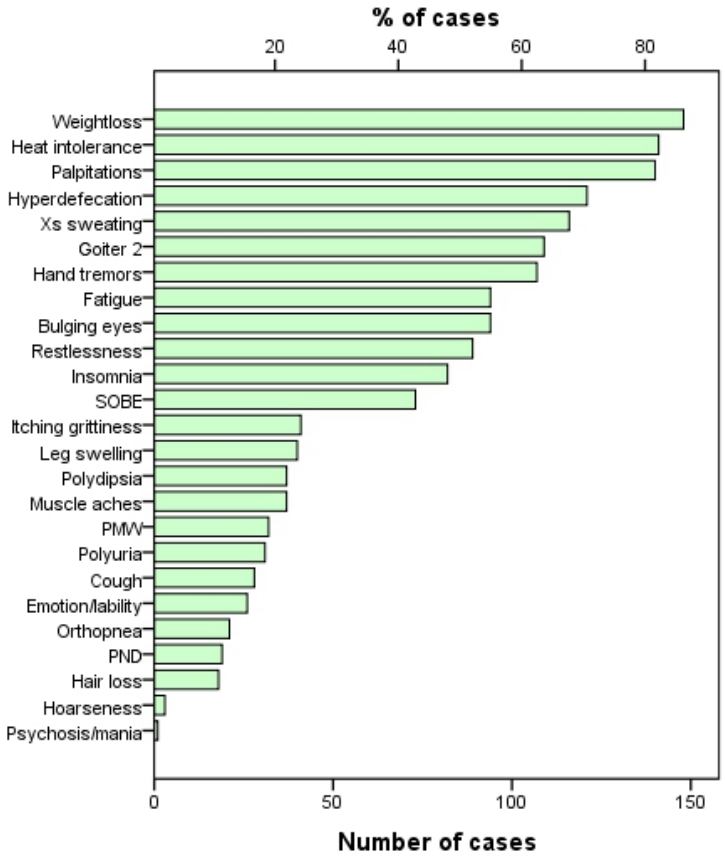

Figure 2, *Frequency of symptoms*

Table 3, *Physical and laboratory findings (n-172)*

Variable	n	%
Appearance		
Healthy calm	99	60
Anxious	47	28.5
Wasted	39	23.6
Acutely ill	4	2.4
Obese	2	1.2
Apathetic	2	1.2
BMI	15.6-33.2; 24.4 ± 4.2 median 23.9	
Pulse rate	92-148; 113 ±12.7, median 111	
Irregular pulse	10	6.9
Systolic blood pressure	80-190; 131 ± 20, median 130	
Diastolic blood pressure	40-120; 77 ± 13, median 80	
Goiter	147	89.1
Grade 2	135	78.5
Grade 1	18	10.5
Grade 0	19	11
Diffuse	127	73.8
Multinodular	24	14
Single nodule	2	1.2
Tender	4	2.4
Eye signs	102	59.3
Proptosis	92	53.5
Symmetrical	77	44.8
Asymmetrical	11	6.4
Unilateral	4	2.3
Chemosis	2	1.2
Ophthalmoplegia	4	2.3
Lid retraction	95	55.2
Lid lag	22	12.8
Sight loss	1	0.6
Fine finger tremor	95	55.2
Warm palms	73	42.4
Moist palms	38	22.1
Proximal myopathy	18	10.9
Pedal edema	17	10.3
Onycholysis	13	7.6
Pretibial myxedema	7	4.1
Vitiligo	4	2.3
Illness Severity		
Mild	53	42.1
Moderate	67	53.2
Severe	6	3.5
Laboratory data		
Hemoglobin	6.7-16.4; 11.9 ±1.6 g/dl	
WBC	2.9-14; 5.7 ± 1.8 x 10^9/l	
Urea	1.9-9.3; 4.1 ±1.5 mmol/l	
Creatinine	27-215; 967 ± 27.5µmol/l	

Etiologic Diagnosis

The etiologic causes of the thyrotoxicosis are presented in Table 4. GD was diagnosed in 79%, Toxic multinodular goiter (TMNG or Plummer's Disease) in 16.8% and Toxic adenoma (TA) in 1.8%. There were single cases of thyroiditis and secondary hyperthyroidism (all females). There was no significant difference in the etiologic factors between males and females (p = 0.910).

Table 4, *Etiologic diagnosis and illness severity (n=172)*

Etiologic Diagnosis		
Variable	n	%
GD	135	78.4
Males	29	16.8
Females	107	62.3
†MLS (females)	7	4.0
TMNG	31	17.6
Males	5	2.9
Females	26	15.1
Toxic Adenoma	3	1.8
Male	1	0.6
Female	2	1.2
Thyroiditis	1	0.6
2 Hyperthyroidism	1	0.6
Illness severity		
Mild	51	41.1
Moderate	57	54.0
Severe	6	3.5

Illness severity

Illness severity was classified using fT_4 cut off values according to Iglesias et al (2009) into Mild (fT_4 1.8-3.9 ng/dl or 23-50 pmol/l); Moderate (3.8-50 ng/dl or 50-99 pmol/l) and Severe Hyperthyroidism (> 3.9 ng/dl or > 100 pmol/l). This classification was only possible in subjects where fT_4 was measured and this is shown in Table 4. Illness severity was comparative between males and females (p = 0.214).

Thyroid auto-antibodies

The level of thyroid autoantibody testing was very low, but has picked up in later years. Testing was selective targeting subjects with Graves Disease features and was possible only in those who could afford the test. TPO Ab were positive in all 34 (19.8%) tested. (TRAb) in 32 (18.6%) tested. Seven cases of Graves Disease with nodular goiter MLS were picked us a result of such testing; all females aged 33-56 (41.1 ± 7.7) years.

Treatment and medication adherence

All subjects were offered ATD drugs except for 6 who defaulted before treatment could be started and the lone patient with thyroiditis (Table 5). In all, 163 (90.1%) received ATDs only, while 10 (6.1%) eventually underwent thyroidectomy. Carbimazole was commonly used (88.7%). Treatment resulted in rapid regression of symptoms (4-12 weeks). The total treatment duration on ATDs was 1-65 months (16.0 ± 15.2, median 12 months). Medication adherence was assessed as good in only 45%. Some subjects used their medication intermittently and in 16%, the status was unknown. The unknown cases were early defaulters where no meaningful assessment could be made. Adverse drug events with carbimazole resulted in pruritic, papular rash in 7.3% and hepatitis in 1.8%. The hepatitis was cholestatic. The events occurred within 3-12 weeks of commencement of therapy (Table 5). The skin reactions were controlled with antihistamines and a short course steroid therapy in one case. The hepatitis resolved spontaneously on drug withdrawal.

***Table 5**, Disease management and outcome*

Treatment		
Antithyroid medication	164	95.3
Carbimazol	154	89.5
Propylthiouracil	10	5.8
Symptom free (n=65)	4-12, 8.1 ± 3.0, median 4 weeks	
Treatment duration	1-65 (16.0 ±15.2) months, Median 12 months	
Medication adherence		
Good	77	44.8
Poor	45	26.2
Intermittent	27	15.7
Unknown	27	16.4
Complication ATD		
Rash	9	5.2
Hepatitis	2	1.2
Rash+hepatitis	1	0.6
Latent period	3-12 weeks	
Final treatment modality		
Medical	156	90.1
Surgical	10	5.8
No treatment	6	3.5
Disease status at assessment		
Controlled	98	57
Uncontrolled	68	39.5
No treatment	6	3.5
Treatment status		
Ongoing	50	29.1
Defaulted	89	51.7
Remitted	26	15.1
No treatment	6	3.5
Died	1	0.6
Relapses	24	14.0

Post-carbimazole	21	12.2
Post-thyroidectomy	3	1.7
No of relapses		
1	14	8.1
2	8	4.7
3	2	1.2
Duration of illness	1-380, 40.7 ± 52.6 month	

Disease and treatment status

As at the time of assessment, the disease was controlled in 57%, and uncontrolled in 39.5% of those treated (166). Of the 172 subjects, 52% had defaulted; treatment was ongoing in 29%, while 15% met the criteria for remission (Table 5). Remissions occurred in 10 who underwent thyroidectomy and in 14 on ATDs. There were 24 relapses in the series (3 post-thyroidectomy and 21 post-carbimazole). The relapses occurred once in 14 persons (including all previous thyroidectomies), twice in eight persons and three times in two cases. Relapses here refer to subjects who returned with the illness after an initial treatment episode whether or not they met the criteria for remission in that episode.

Co-existing conditions

Hypertension was the commonest co-morbidity occurring in 35% of which 52% had prior knowledge of this condition (Table 6). The hypertension was systolic (>140/<90 mm Hg) in only 12 of the 60 (20%). Diabetes mellitus (DM) with or without hypertension was coexistent in 3.6%. Others conditions are in listed in Table 6. The lone asthmatic patient was also hypertensive. Six pregnancies occurred during the illness.

Thyrotoxicosis associated complications

Thyrotoxicosis was associated with heart disease in 36% and overt heart failure in 9%. Screening for heart disease was not routine; being undertaken in subjects who were hypertensive or had suggestive features of heart failure or were preparing for surgery. Diagnosis was based on presence of compatible signs on plain chest radiography, electrocardiography or 2D echocardiography (cardiomegaly, AF, left atrial abnormalities, LVH, systolic or diastolic dysfunction). The vast majority of GO was mild. Moderate-severe disease occurred in 2 (1.2%). One was a lady aged 56 years with asymmetric disease, eye pain, chemosis and excess lacrimation. The other was a 64 years old man presenting solely with eye disease; proptosis, ophthalmoplegia, eye pain, chemosis, exposure keratitis, panophthalmitis and sight loss. These were the only ones requiring intervention. Two subjects came down with stroke and new onset Type 2 diabetes mellitus occurred in one subject. Of the 6 pregnancies that occurred during the illness, 4 ended in miscarriages and one

in preterm delivery of a live baby. Thyroid storm occurred in 2 (1.2%) of subjects who were pregnant. All the pregnant women unilaterally withdrew ATDs without physician knowledge fearing for the health of their baby. One death occurred in a subject whose disease was partially controlled, but died suddenly at home.

Table 6, *Co-morbidities and complications*

Co-existent conditions		
Hypertension	60	34.9
HPN + DM	3	1.7
DM	3	1.7
PUD	2	1.2
*DUB/Fibroids	4	2.3
Bronchial Asthma	1	0.6
Pregnancies	6	3.5
†CKD	1	0.6
Illness complications		
Heart Disease	61	35.5
Overt heart failure	15	8.7
Moderate-severe GO	2	1.2
Thyroid storm	2	1.2
Miscarriages	4	2.4
Preterm delivery	1	0.6
CVA	2	1.2
DM	1	0.6

* Dysfunctionsl uterine bleeding † chronic kidney disease

Discussion

Presentation

Thyrotoxicosis remains a disease affecting predominantly women. The age and gender distribution is similar to what is obtained in many developed countries which are iodine sufficient (Weetman 2000, Brent 2008). This is to be expected since population iodine nutrition in Nigeria has become optimal. The age distribution was unimodal.

The historical and examination findings are in keeping with the usual features of thyrotoxicosis found elsewhere; in the west, (Weetman 2000, Brent 2008, Smith et al 2016, DeGroot 2012), India, (Sahay 2011) Iran (Othman et al 2011) with local variations. Local researches have recorded similar findings including the series by Olurin as early as 1974 (Olurin 1974, Ogbera et al 2007, Sarfo-Kantanka et al 2018, Ayandipo et al 2018). Though 57% of the patients had GO, only two required attention. Other authors reporting from the region had noted that the majority of patients with GO have mild ocular symptoms and require only minimal intervention. Chemosis, severe proptosis and ocular motility disorder were very rare. This has been related to the low prevalence of smoking in the disease population (Ogun et al 2016). The severity of thyroid eye disease has been linked to cigarette smoking (Åsvold

et al 2007). Six variants of pretibial myxedema have been described; nodular, plaque, diffuse, tumor, mixed (combination of other variants) and elephantiasis types (Lan et al 2016). Two cases in this study were diffuse while the rest were of the mixed type. Vitiligo has a well known association with autoimmune diseases thyroid included and was present in 4 cases (Nunes et al 2011).

Etiology

Graves disease was the dominant cause of thyrotoxicosis in this report similar to other reports both local and global. It is possible that cases of thyroiditis with transient thyrotoxicosis may have resolved before patients could be referred to the Endocrine Clinic and therefore poorly represented in this report. One case of secondary hyperthyroidism due to thyrotrophin secreting pituitary adenoma was found and is awaiting surgery. Thyrotrophin secreting pituitary adenomas are notably rare (Beck-Peccoz 2000). The goiter in Graves disease is characteristically diffuse, but may not always be so. In the series by Bhargav (2014), the nature of the goiter can be nodular or atrophic. Goiter nodularity in Graves disease can also be due to simultaneous presence of toxic nodules; the Marine Lenhart Syndrome (Marine and Lenhart 1911, Charles 1973) Radioisotope scans may help in clarifying such cases. In this report, seven (4.0%) of such cases of multinodular goiter by ultrasound with elevated TRAb titers and proptosis were identified.

Treatment

ATDs are preferred primary treatment for thyrotoxicosis in most countries other than North America. The initial dose of carbimazole is 15–30 mg daily for mild hyperthyroidism and 20 –40 mg daily for moderate to severe disease. Block and replace and titration regimens are equally effective (Abraham 2010). The block and replace regimen suited the local setting. ATD was very effective in controlling the disease as was documented in an earlier report from our center (Modebe 1992). The treatment default rate in this study was very high. This was also noted in the report by Olurin (1974) and Ogbera et al (2007). Adherence to long time therapies is problematic in this culture. Since ATDs were very effective, many patients considered themselves cured and left without reference to the physician. Work stoppages due to workers strike action are common in Nigeria and may last as long as four months; and occur at least once a year. During these periods, patients seek help elsewhere, usually private establishments and may never return. A number of the patients were students who returned to base or gained admission to universities and continued their treatment elsewhere. Similarly, patients requiring surgery may decide to do so in a private hospital of their choice and are lost to follow up. Moreover, there is no existing system for patient recall. All these factors have

direct bearing on figures for treatment and disease outcome as outlined in the study. No categorical statement could be made about the remission rate under these circumstances which was only 15%. An earlier study from the same center in the 1990s by Modebe (1992) yielded a remission rate of 61% on ATDs and a patient default rate of 32%. Those with nodular goiter should proceed to surgery (total or near total thyroidectomy) as definitive treatment, but again quite a number could not be stabilized for surgery, cannot afford surgery or do not want surgery. Radioablation therapy would have been the most suitable alternative especially as the pharmaco-ecocomics is favorable (Ogunjobi et al 2015). However, both surgery and radioablation result in hypothyroidism requiring lifelong treatment with l-thyroxine. This in itself presents another major problem. Again, hypothyroidism presents with nondescript signs and symptoms and more difficult to recognize than hyperthyroidism. For those with recurrent Graves Disease, some recent studies have reported that compared with radioactive iodine or thyroidectomy, a second course of ATD or prolonged low dose ATD treatment led to prolonged remission while minimizing the risk of side effects (Azizi et al 2005, Liu et al 2015, Villagelin et al 2015). Long-term continuous treatment of hyperthyroidism with methimazole is reported as safe (Hussain et al 2017). These treatment modalities are viable alternatives for such cases. Identification of patients at high risk for relapse (male sex, large goiters, a high fT_3, low TSH levels, high TRAb and smoking) will assist in counseling patients on the best treatment approach (Hussain et al 2017, Liu et al 2017).

Adverse drug reaction

About 5% of patients using ATDS will experience some drug related side effect most commonly a drug rash (Cooper 2005) Hepatotoxicity and agranulocytosis are uncommon. Cholestatic hepatitis occurred 1.8% of cases and resolved following drug withdrawal. Macula-papular rash and cholestatic hepatitis is typical of carbimazole induced drug reactions. No case of agranulocytosis was encountered.

Thyrotoxicosis, hypertension and heart disease

Thyroid hormones have profound effects on the heart and vascular system. T_3 effect on heart function is mediated by genomic and non-genomic pathways (Biondi 2012). Thyrotoxicosis is characterized by an increase in resting heart rate, blood volume, stroke volume, myocardial contractility, and ejection fraction. Cardiac dysfunction is manifested by left ventricular hypertrophy, heart rhythm disturbances, heart chamber dilation and heart failure, pulmonary hypertension, systolic and diastolic dysfunction (Vargas-uricoechea et al 2017). It is estimated that the prevalence of hypertension with thyrotoxicosis is 20–30% (Prisant et al 2006). Thyrotoxicosis typically causes

isolated systolic hypertension. However, in this study only in 20% of cases was the hypertension systolic suggesting pre-existing diastolic hypertension. The large burden of cardiac disease seen in thyrotoxicosis in Africa has been noted by several authors (Ogbera et al 2007, Anakwue et al 2015). This was attributed to some genetic susceptibility. However, analysis of present date as shown in Figures 3-5, demonstrate three factors to be highly contributory; namely coexistent hypertension ($p < 0.001$), duration of the disease ($p = 0.039$) and age of the patient ($p = 0.020$. Older patients would have harbored the disease and hypertension for a longer period of time. Patients with partially or poorly treated thyrotoxicosis and hypertension, drift in and out of hospital for many years, in some cases for more than thirty years. Gender difference ($p = 0.081$) and etiologic diagnosis ($p = 0.638$) were not significant contributors. Patients with heart failure responded rapidly to ATD and anti-failure treatment.

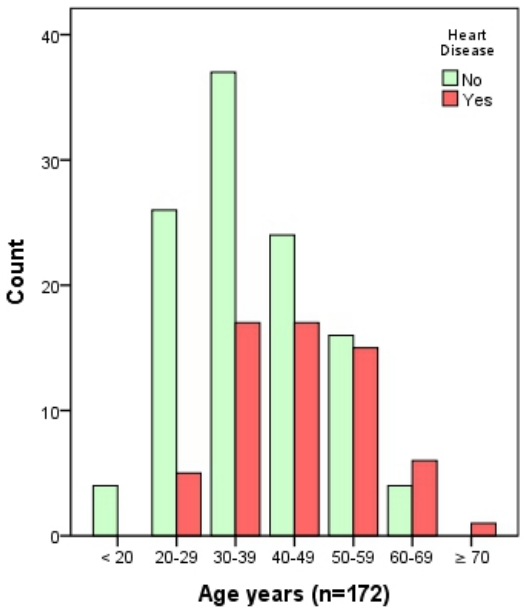

***Figure 3**, Heart disease and age of patients*

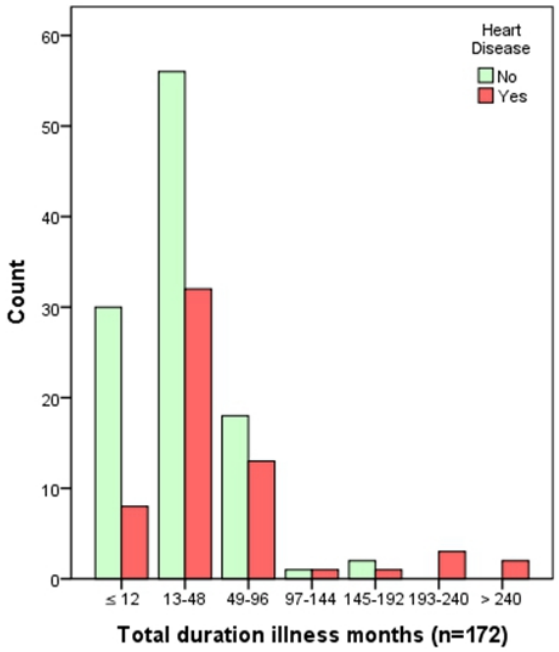

Figure 4, *Heart disease and total duration of illness*

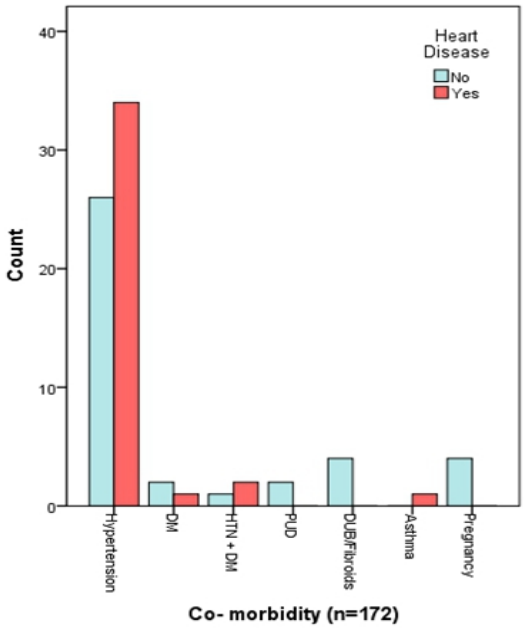

Figure 5*, Heart disease and hypertension*

Conclusion

Thyrotoxicosis is a common clinical condition. Treatment with carbimazole was effective but treatment outcome was marred by a high default

rate. Coexisting hypertension and a prolonged period of untreated disease exposed patients to a high burden of heart disease. Patient education on the disease process, available treatment modalities and timeline and introduction of radioablation therapy will mitigate these deficiencies.

Study limitation

This study is limited by its retrospective nature and the lack of a complete dataset. Some of the folders could not be traced and in some folders, data was incomplete.

Conflict of interest

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