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Original Research Article

Resistance to Thyroid Hormones Syndrome among Sudanese Patients with Thyroid Disorders

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ABSTRACT

Objective: The resistance to thyroid hormone (RTH) is a syndrome of reduced responsiveness of target tissues to thyroid hormone (TH). This study aimed to screen for RTH and among Sudanese patients presented with thyroid disorders.
Materials and Methods: The study encompassed 104 patients with thyroid disorders referred to the national cancer institute (NCI), at Gezira University. Experimental procedure implemented on mutual RIA for total T3 (TT3), free T4 (FT4), and the IRMA for thyroid stimulating hormone (TSH).
Results: The preliminary data and hormonal analysis represent 91 (87.5%) females as the prime susceptible patients with thyroid problems. The adults' category (16-30 years) was the most vulnerable age group in females, comprises 42.3%. Patients reside in rural area constitutes 64.4% compared to urban residents, and Ga'alia tribe constituted the majority 70.2% over the rest of other seven tribes. The mean levels of total TT3, FT4, and TSH were significantly high ($P<0.001$) compared with the normal levels (2.65 ±3.78 nmoles/L; 16.31±12.71 pmoles/L; 8.27±17.20 mIU/L vs. 0.6- 3.0 nmol/L; 6.0-20.0 pmol/L; 0.3-6.0 mIU/L, respectively). Over the total study subjects, 5 (5.2%) unrelated patients matched the RTH features. Tachycardia, sweating, weight loss, and anxiety were the most frequent clinical presentations among study subjects. Thyroid function test indicate 8 out of 34 patients clinically diagnosed hyperthyroidisms.
Conclusions: This study shed light on the presence of RTH among 5% of study patients, and the dominance of thyroid disorders among Sudanese females and Ga'alia tribe. There was discrepancy between clinical features and biochemical thyroid function tests.

Key words: Thyroid hormone, Thyrotoxicosis, THR beta, RTH, Sudan.

INTRODUCTION

Thyroid problems are common affecting aged people and are more prevalent in females than males. [1,2] The resistance to thyroid hormone (RTH) is a syndrome of reduced responsiveness of target tissues to thyroid hormone (TH), characterized by elevated free thyroid hormones with in appropriately normal, or elevated levels of thyroid stimulating hormone (TSH). [3] The difference in the clinical presentations of RTH (hyper, hypo, and euthyroid states) is due to the variability in the responsiveness of tissues to thyroid hormones. [4,5] The association of RTH with persistent goitre, tachycardia, and hyperactivity has frequently resulted in erroneous diagnosis of thyrotoxicosis. [6] In the present study we screened for RTH among Sudanese patients with different physical and clinical presentation of thyroid problems and to determine relationship between clinical features the biochemical thyroid function tests. Among the study population, 5% were compatible to RTH features, and there is discrepancy between

the clinical features and laboratory tests for thyroid hormones.

MATERIALS AND METHODS

Patients

One hundred and four patients (91 females; 13 males, their mean age 33.15±12.99 years) with thyroid disorders referred to the National Cancer Institute, at the University of Gezira, Central Sudan between December 2011-2012. They were divided into three groups (Hypothyroidism, Hyperthyroidism, and Euthyroidism) based on the physical and the clinical examinations conducted by an endocrinologist. A questionnaire was designed to obtain demographic information, physical presentation, in addition to the clinical examination and laboratory investigations. Once the patient agreed to participate, a written informed consent was issued prior to data and samples collections. Patients with pituitary or thyroid tumours, subjected to recent surgery, and received anti-thyroid hormone therapy or any drugs affecting thyroid hormones levels were excluded from the study. Laboratory tests were carried out at the RIA laboratory, Molecular Biology Unit. Serum for TT3 and FT4 using radioimmunoassay (RIA) and for TSH using immunoradiometric assay (IRMA) protocols (skybio Ltd. UK).

Quantitative measures of TT_3 and FT_4

The assay methods used were the ones in operation at NCI for routine practice. Thus, all had serum TT3, FT4, and TSH measurements made using radioisotopes. Seven millilitre blood samples were obtained from each patient; serum was processed for hormonal analysis. Total T3 (TT3), FT4, and TSH were measured by Radioimmunoassay (RIA) (Tythe Farm WY Boston Bedfordshire, UK). In brief, 50 µl of the sample, standards, or QCs were added to labeled assay tubes, and 500 µl of assay buffer to each tube. One anti- TT3 or Anti- FT_4 coated bead were added to all tubes (except the total count tubes) and vortex for 30, 2 ml of wash buffer was added to all tubes (except the total count tubes) followed by aspiration of solution to all tubes (except the total count tubes), the last two steps were repeated twice. Five hundred micro letter of tracer solution ^{125}I - T4 or T3 was added to each tube, and 200 µl tracer solution was added to total counts tubes. After the mix for 2 hours using a rotating tube holder, 2 ml wash solution was added followed by aspiration to all the tubes except total counts tubes. This step was repeated twice or more to ensure thorough washing of the tubes. The bound radioactivity was counted for 60 seconds using the gamma counter and plotted a graph of % (Bound/Total) Counts vs. log TT_3 or FT_4 concentration for the standards. The samples and QCs results were interpolated from the standard curve automatically by using a data reduction software package. The reference values used for serum TT_3, and FT_4 were 0.6- 3.0 nmol/L, and 6.0-20.0 pmol/L respectively (skybio Ltd.UK).

Quantitative measures of TSH

Hundred microliter of TSH, standards, or QCs were added to labeled assay tubes, followed by 200 µl of tracer solution ^{125}I Anti-TSH. One anti- TSH coated bead were added to all tubes (except the total count tubes) and vortex for 30 minutes, after that 2 ml of wash buffer was added to all tubes (except the total count tubes) in the next day, followed by aspiration to solution to all tubes (except the total count tubes), the last two steps were repeated twice. The bound radioactivity was counted for 60 seconds using the gamma counter and plotted a graph of % (Bound/Total) Counts vs. TSH concentration for the standards. The samples and QCs results were interpolated from the standard curve automatically by using a data reduction software package. The reference values used for serum TSH was 0.3-6.0 mIU/L respectively (skybio Ltd.UK).

Statistical analysis

The statistical analyses were performed using SPSS version 20. Descriptive statistics such as mean and

frequency distribution were used to describe the baseline demographic, clinical profile, and laboratory investigations of patients. Unpaired t test was used to compare the means of various quantitative variables for thyroid hormones. P value less than 0.05 was considered statistically significant.

RESULTS

A total of 104 patients were recruited in this study, all encountered subjects have thyroid problems, and they underwent medical and physical examinations by acquainted endocrinologist and further by addressing specialized medical laboratory investigations at the NCI. Basic essential data was abstracted from well-designed questionnaire, filled by the aid of resident health providers at the NCI. The male to female ratio of study subjects was 1:14.3, 13 (12.5%) males and 91 (87.5%) were females. Their mean age was 33.15±12.99 years, the most frequent age ranged between 16-30 years, and the total number of patients less than 45 years old was found to be almost 85% of the total study subjects. The rural population is representing 64.4% compared to 35.6% urban (Table 1).

Table 1: Distribution of gender, age, and residency among study subjects

Item			Frequency	Percent
Gender	M		13	12.5
	F		91	87.5
Age (years)	≤ 15	M	3	2.9
		F	1	1.0
	16-30	M	2	1.9
		F	44	42.3
	31-45	M	4	3.8
		F	35	33.7
	≥ 46	M	4	3.8
		F	11	10.6
Residence	Rural		67	64.4
	Urban		37	53.6

M= Male, F= Female

As shown in figure 1, the Ga'alia was the biggest tribe representing 70.2% of other ascertains tribes, followed by Johyna (16%), and Baggara (6%).

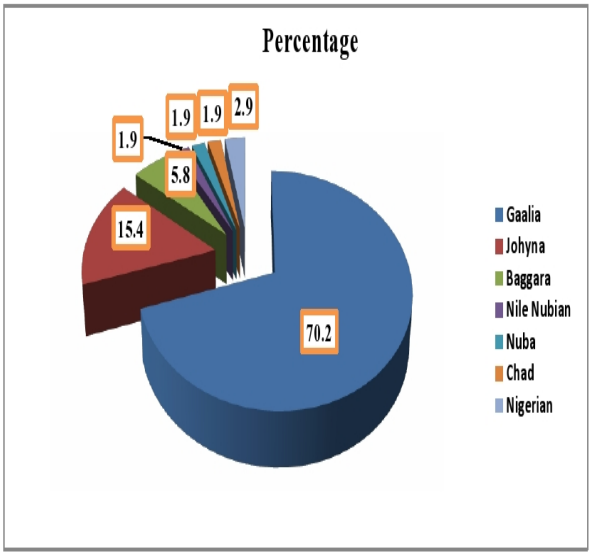

Fig.1: Frequency of the Sudanese resident tribes among study population

Nearly half (44.2%) the study subjects were presented with tachycardia, (39.4%) with sweating, (36.5%) weight loss, (33.7%) with anxiety, 29.8% with hyperactivity, and (11.5%) characterized by physical appearance of goitre. Owing to the clinical diagnosis, 32.7% were diagnosed hyperthyroidism, and 11.5% with goitre. The mean levels of TT3, FT4, and TSH were significantly high (P <0.001) among the patients compared with reference range (Table 2).

The data in Table 3 indicates the association between the clinical examinations and laboratory findings. The clinical diagnoses indicate 34 patients are hyperthyroidism, they are further categorized based on the laboratory investigation into 17 (16.3%) normal, 8 (7.7%) hyperthyroidisms, and 5 (4.8%) unrelated patients characterized by high TT3, high FT4, and normal TSH, which is most likely the criteria for RTH.

The demographic and clinical information of the 5% THR patients showed most of them their ethnic origin belong to Ga'alia tribe, they are misdiagnosed having thyrotoxicosis, characterized by elevated thyroid hormones and normal TSH, and they present with symptoms of goiter, hyperactivity and anxiety (Table 4).

Table 2: Clinical features and laboratory investigation for study thyroid patients

Feature		Frequency	Percentage
Clinical Symptoms			
Hyperactivity		31	29.8
Weight	Loss	38	36.5
	Gain	28	26.9
Tremor		29	27.9
Anxiety (nervousness)		35	33.7
Heat intolerance		27	26.0
Cold intolerance		34	32.7
Sweating		41	39.4
Constipation		17	16.4
Menstruation*	Regular	49	53.9
*Note No. of females = 91	Irregular	30	33.0
Physical Examination			
Pulse rate	<70	17	16.4%
	70-80	39	37.5%
	>80	48	46.1%
Blood Pressure	L	22	21.1%
	N	61	58.7%
	H	21	20.2%
Tachycardia		46	44.2%
Eye signs		28	26.9%
Clinical Diagnosis			
Euthyroid		31	29.8%
Hyperthyroid		34	32.7%
Hypothyroid		27	26.0%
Goitre		12	11.5%
Laboratory Investigation			
Hormones	Levels: Mean ± SD		
TT3 mmol/L	L: 0.13 ± 0.15	15	14.4
	N: 1.75 ± 0.60	74	71.2
	H: 9.58 ± 6.37	15	14.4
FT4 pmol/L	L: 4.00 ± 0.01	3	2.9
	N: 12.15 ± 3.22	84	80.8
	H: 39.03 ± 17.85	17	16.3
TSH mIU/L	L: 0.15 ± 0.07	6	5.8
	N: 1.82 ±1.26	78	75.0
	H: 35.89 ± 24.55	20	19.2

L= low, N= normal, H= high

Table 3: The association between the laboratory findings and clinical diagnosis in study subjects

		Clinical Diagnosis				
		Euthyroid	**Hyperthyroid**	**Hypothyroid**	**Goitre**	**Total**
Laboratory Investigatio	Normal	27 (26 %)	17 (16.3%)	16 (15.4%)	11 (10.6%)	71 (68.3%)
	Hyperthyroidism	2 (1.9%)	8 (7.7 %)	0 (0%)	1 (1.0%)	11 (10.6%)
	Hypothyroidism	2 (1.9%)	4 (3.8 %)	11 (10.6%)	0 (0%)	17 (16.3%)
	High TT3 and FT4, normal TSH	0 (0 %)	5 (4.8%)	0 (0%)	0 (0%)	5 (4.8%)
Total		31 (29.8%)	34 (32.6%)	27 (26.0%)	12 (11.6%)	104 (100%)

Table 4: Demographic and clinical information in patients with RTH

Patients ID		**Patient-1**	**Patient-2**	**Patient-3**	**Patient-4**	**Patient-5**
Sex		**M**	**F**	**F**	**M**	**F**
Ethnic origin		**Gaalia**	**Gaalia**	**Gaalia**	**Baggara**	**Gaalia**
Age at presentation (yr)		43	18	24	31	29
Initial diagnosis		Hyperthyroidism	Hyperthyroidism	Thyrotoxicosis	Hyperthyroidism	RTH
Symptoms	Tremor	No	No	Mild	No	No
	Hyperactivity	Yes	No	Yes	No	Yes
	Tachycardia	Yes	Yes	No	Yes	Yes
	Anxiety	No	No	Yes	Yes	No
	Other Symptoms	Non	Non	Non	Sweating	Cold intolerance
Thyroid gland size		3X	2X	2X	1.5%	3X
TT3 (Normal range = 0.6- 3.0 nmol/L)		5.2 nmol/L	7.1 nmol/L	11.8 nmol/L	6.5 nmol/L	14.0 nmol/L
FT4 (Normal range = 6.0-20.0 pmol/L)		21.1 pmol/L	26.9 pmol/L	34.6 pmol/L	29.0 pmol/L	55.3 pmol/L
TSH (Normal range = 0.3-6.0 mIU/L)		3.8 mIU/L	8.2 mIU/L	6.1 mIU/L	5.4 mIU/L	9.0 mIU/L

DISCUSSION

In this study, we screened 104 patients presented with different signs and symptoms of thyroid disorders; they were evaluated in respect to the prevalence of different thyroid phenotypes, and the interrelationship between the clinical and laboratory findings.

Our results indicates the prevalence of thyroid disorders among females, they are in the middle age and reside in rural areas. This observation is a clear indication to the fact that, females were actually the vulnerable gender, this agrees with study conducted in the United States indicated females predilection. [7] Also in Africa, goitre was prevalent among the rural poor people, mostly women. [8] Another studies reported that, thyroid problems are common in middle aged people and are more prevalent in females than males. [1,2]

Ga'alia was found the biggest tribe having patients suffering from thyroid problems followed by Johyna, and Baggara. The rationale behind the determination of distribution of study population among different tribes is the conceptual hypothesis that some tribes in our country are more prone to develop thyroid diseases than others. This in fact needs proof and further investigation.

The patients in this study represent the central Sudan, and they showed levels of thyroids hormones and TSH above the upper limit of normal, in addition to sound symptoms of anxiety, tachycardia, sweating, and goitre compared with patients from southern Sudan. [8] where they reported low prevalence of anxiety (4%), tachycardia (3%), and sweating (3%); but goitre was by far the most common finding constituting (95%); however our findings were consistent with results reported by Refetoff's and Dumitrescu in 2007. [9]

Resistance to thyroid hormones (RTH) is a syndrome of reduced responsiveness of target tissues to thyroid hormone (TH). It is characterized by elevated thyroid hormones levels in association with a high or normal TSH level and goitre. [10,11] The first case of RTH was described in Refetoff in 1067, [3] it was found to link with mutations with the TH receptor (TR) β gene located at chromosome 3. The mutant TRβ genes have either a reduced affinity for thyroid hormones or impaired interactions of cofactors mediate the TH action. [12-14] Variability in the responsiveness of tissues to TH explains the different in clinical presentations of RTH (hyper, hypo and euthyroid states). The association of RTH with persistent tachycardia and hyperactivity has frequently resulted in erroneous diagnosis of thyrotoxicosis lead to false treatment. Unfortunately, Sudan still lacks comprehensive data on the specific clinical features of thyroid dysfunction. However, the largest experience with these prognostic variables is coming from the African continent.

In this study, we represent five unrelated patients express the phenotype of RTH. Referring to the literature, the phenotypes of RTH in these subjects is not clearly different from that of individuals with RTH due to TRβ gene mutations. Since, we didn't identify the TRβ gene mutations related to this phenotype, because such knowledge, could assist in prenatal diagnosis and genetic counselling, also it was not important diagnostically or in the management. Although, we are consistent with other studies demonstrate the occurrence of RTH without structural TRβ gene mutation. [15-18]

CONCLUSION

This study demonstrates the presence of RTH phenotype among five Sudanese patients presented with thyroid problems, and the controversy between the clinical examination and laboratory findings which enhance the erroneous diagnosis and treatment as well. Further genetic and family related studies are needed to correlate between the phenotypes and genetic manifestations.

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