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Original Research Article

Aetiological sub-classification of thyrotoxicosis and relevance of TT3/TT4 ratio in sub-classification of patients with thyrotoxicosis: an Indian cross-sectional study

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ABSTRACT

Background: Thyrotoxicosis is a common endocrine problem. Sub-classification and rapid diagnosis of disease is crucial in the management.
Methods: In this prospective cross-sectional study from India, newly diagnosed thyrotoxicosis patients were enrolled. All patients were sub classified into Graves' disease, (GD), sub-acute thyroiditis (SAT) and toxic nodular goiter (TNG) based on diagnostic criteria. Clinical features were noted and TT3, TT4 and TSH level were measured. A thyroid scan was also done.
Results: In the present study 84.21%, 11.84% and 3.95% were suffering from GD, SAT and TNG, respectively. Mean± SD age for GD, SAT and TNG were 36.88±10.55, 37.44±5.96 and 61±11.36 years, respectively. Most of patients were female (77.63%). Goiter was present in 81.25%, 55.56% and 100% of GD, SAT and TNG patients, respectively. Mean TT3/TT4 ratio was higher (20.15±5.45 verses 12.72±0.77) in GD as compared to SAT patients. The area under ROC curve of the TT3/TT4 for diagnosis of GD was 0.964. Cut off level of TT3/TT4 ratio >14.1 offered best sensitivity, specificity, PPV (positive predictive value) and accuracy.
Conclusions: This first report from India on sub-classification of thyrotoxicosis shows that GD is the most common cause of thyrotoxicosis. TT3/TT4 ratio of >14.1 may help in differentiating the cause of thyrotoxicosis.

Keywords: Thyrotoxicosis, Graves' disease, Sub-acute thyroiditis, Toxic nodular goiter, Sub-classification, Thyroid associated ophthalmopathy

INTRODUCTION

Thyrotoxicosis is a common endocrine disorder worldwide and the prevalence is increasing.[1-4] The incidence and prevalence of thyrotoxicosis depends upon age, sex, ethnicity, stress, geographical area and iodine intake.[5] Thyrotoxicosis is more common in females as compared to male and this is because they are more prone to develop autoimmune disease.[6,7] As the age increases, prevalence of toxic multi-nodular goiter also increases.[5] This is because of fact that toxic multi-nodular goiter develops in nontoxic nodular goiter after many years. In non-Hispanic blacks prevalence of thyrotoxicosis is 3 times more as compared to non-Hispanic whites and this is due to different heritable and environmental exposures.[8] Winsa et al for the first time showed that in patients with newly diagnosed Graves' disease (GD), there are more negative life events in the 12 months preceding the diagnosis and higher negative life

events score than matched controls.[9] This may be due to the fact that stress hormone suppresses IL-2 production by antigen presenting cells and enhances the secretion of IL-4, IL-10 and IL-10 production and thus GD develops. Philips et al in their study from seven towns of England showed that there is wide geographical variation in percentage of positive TSH-Receptor thyrotoxic patients (Southampton 92% verses Preston 35%).[10] GD accounts for 70-80% of patients with hyperthyroidism in iodine sufficient area while in area with iodine deficiency Graves' disease constitute about half of all cases of hyperthyroidism.[11,12] The clinical and biochemical profile of thyrotoxicosis patients also varies with subtype of thyrotoxicosis. GD presents at younger age, have higher thyroid hormone level and are more overt type hyperthyroidism as compared to toxic multi-nodular goiter.[11] Clinical presentation also shows geographical variation. Sahara African patients suffer a disproportionate more cardiovascular disease burden as compared to whites.[13] Though we do not know the exact cause but could be due to genetic variation, late diagnosis and poor disease control. Disease complication also shows ethnic variation. Graves ophthalmopathy is 6 times more common in Caucasians than in Asians.[14] Thyrotoxic periodic paralysis is significantly more common in Asian men.[15,16]

Treatment of various type of thyrotoxicosis varies according to etiology. Treatment of choice for GD is ATD but for toxic nodular goiter (TNG) surgery is the treatment of choice. Sub acute thyroiditis (SAT) is usually treated symptomatically by steroid, NSAID and supportive medicine. Therefore, accurate sub classification of thyrotoxicosis is very much important so as to avoid wrong use of anti-thyroid drugs to thyroiditis patients as this could leads to hypothyroidism and drug related side effects. Besides this, outcome of therapy and prognosis varies with subtype of thyrotoxicosis. No study till now has been performed to know the proportion of different type and clinical profile of thyrotoxicosis from India. Besides these, Indian thyroid patients differ from other countries patients in terms of high prevalence rate, more rapid progression to overt hypothyroidism and clinical features.[4,17,18] The objective of this study was to know the etiologic and clinical profile of thyrotoxicosis patients from eastern part of Uttar Pradesh, India. Further, our aim was to know the relevance of TT3/TT4 ratio in sub classification of thyrotoxicosis patients.

METHODS

In this prospective cross sectional study, all patients were enrolled from Endocrine Clinic and Hospital, Varanasi, India. A total of 81 consecutive thyrotoxic patients were recruited between January 2021 to June 2023. Inclusion criteria were age >15 years and raised total T3 (TT3), total T4 (TT4) and suppressed TSH. Subjects with history intake of thyroid hormone, amiodarone, lithium or having history of radioactive iodine intake were excluded from study. Pregnant patients were also excluded from the study. A total of 5 patients were excluded from study, as they do not meet the inclusion and exclusion criteria. Graves' disease was diagnosed by presence of TSH Receptor antibody (TSHR Ab) or positive thyroid scan (99 m Tc-pertechnate). SAT was diagnosed on basis of clinical presentation (neck pain and biochemical evidence of thyrotoxicosis) and supported by suppressed thyroid scan. Toxic nodular goiter (TNG) was diagnosed based on clinical presentation (nodular thyroid and biochemical evidence of thyrotoxicosis) and supported by typical thyroid scan and/or USG.

The criteria for diagnosis of TAO were eyelid retraction in conjunction with thyroid dysfunction or exophthalmos or optic nerve dysfunction or extra-ocular muscle involvement. If eyelid retraction is absent, thyroid dysfunction in association with exophthalmos or optic nerve dysfunction or extra-ocular muscle involvement was the diagnostic criteria. We chose TT3 and TT4 over Free T3 (FT3) and Free T4 (FT4) because TBG (Thyroid binding globulin) can interfere with the immunoassay of FT3 and FT4 and many patients with GD have elevated TBG and many SAT patients are complicated by liver dysfunction and thus increased TBG. Besides this cost of TT3 and TT4 test is cheaper than FT3 and FT4 test and is readily available. Test was performed by immunoassay analyzer. The reference ranges of TT3, TT4 and TSH were 80-200 ng/dl, 5.1-14.1 µg/dl and 0.27-4.2 µIU/ml, respectively. Ethical committee of Opal hospital approved this study. Ethical committee waived requirement for informed consent as it does not required intervention. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Statistics

The data were tabulated and analyzed using SPSS version 16 software. Continuous data were expressed as mean± standard deviation. Categorical data were expressed as numbers and percentages for their analysis. Categorical variables of data were compared by Chi-square test and continuous groups were compared by Student's test. ROC curve analysis was used to detect cut-off values for TT3/TT4 ratio with optimal sensitivity and specificity in differentiating between GD and sub-acute thyroiditis. A p value of <0.05 was considered as significant in this study.

RESULTS

Baseline demographic data

A total of 76 patients with newly onset thyrotoxicosis were enrolled in this study. Mean± SD age for GD, SAT and TNG were 36.88±10.555 years, 37.44±5.96 years and 61±11.36 years respectively. Of these 76 patients, 17 (22.37%) were male and 59 (77.63%) were female. Female to male ratio was 3.47. For GD, SAT and TNG female to male ratio were 3.57, 3.5 and 2, respectively. In the present study, 64 (84.21%) were diagnosed with GD, 9 (11.84%) with SAT and 3 (3.95%) with TNG. 59 (77.63%) patients had goiter in the present study. Goiter was present in 52 (81.25%), 5 (55.56%) and 3 (100%) of GD, SAT and TNG

patients, respectively. TAO was present in 10 (15.63%) patients of GD. Neck pain was present in all patients with SAT. None of the patients were suffering from acropathy and pretibial myxedema (Table 1). TT3, TT4 and TSH test were done at time of diagnosis in all patients. Additional tests such as TSH Rab, USG and thyroid scan were also done at time of diagnosis. Mean± SD values of TT3, TT4 and TSH in GD patients were 380.54±148.03 ng/dl, 18.59±3.59 µg/dl and 0.006±0.013 µIU/ml, respectively. Mean±SD values of TT3, TT4 and TSH in patients with SAT were 204±31.83 ng/dl, 16.21 µg/dl and 0.029±0.05 µIU/ml, respectively. In patients with TNG the mean± SD values of TT3, TT4 and TSH were 303±93.62 ng/dl, 16.18 µg/dl and 0.002±0.002 µIU/ml, respectively. TT3 and TT4 value were significantly higher in GD patients as compared with SAT patients (Table 1).

Thyroid associated ophthalmopathy and associations

Of the 64 patients with GD, 10 (15.62%) had TAO. Female to male ratio of TAO was 2.33 while ratio was 3.9 in patients without TAO. Mean± SD age of patients with TAO and patients without TAO were 39.8±11.81 and 36.33±10.33 years, respectively. Mean± SD value of TT3, TT4, TSH and TT3/TT4 ratio values were similar in two groups. 50% TAO patients had history of smoking while history of smoking was present in 7.41% of patients without TAO. Lid retraction (LR) was present in 7(70%) patients, exophthalmos was present in 6 (60%) patients and restrictive ocular myopathy was present in 2 (20%) and none had optic neuropathy. Five combinations of sign of TAO were as follows: 3 (30%) had only LR with hyperthyroidism, 2 (20%) had LR, hyperthyroidism plus exophthalmos, 1(10%) had LR, hyperthyroidism, exophthalmos and restrictive ocular myopathy, 3 (30%) had only exophthalmos and hyperthyroidism and 1 (10%) had thyrotoxicosis, LR and exophthalmos (Table 2).

TT3/TT4 ratio for differentiating between GD versus SAT

Mean±SD ratio of TT3/TT4 was 20.15±5.49 in patients with GD, 12.72±0.77 in patients with SAT and 18.76±3.18 in patients with TNG. TT3/TT4 ratio was significantly ($p<0.001$) higher in GD patients as compared to SAT patients (Table 1 and Figure 1). The area under ROC curve for TT3/TT4 ratio for diagnosis of GD was 0.964 (95%CI, 0.924-1.00) (Figure 2). A cut off value of 14.1 offered a sensitivity of 92.19%, specificity of 100%, accuracy of 93.15% and PPV of 100%. If we lower the TT3/TT4 cut off value to 13.6 than sensitivity remains the same (92.19%) but specificity, accuracy and PPV are reduced to 66.67%, 89.04% and 95.16% respectively. However if we increase the cut off value to 20.1 than sensitivity and accuracy is reduced to 50% and 56.16%, respectively however specificity (100%) and PPV (100%) remains the same. We propose that TT3/TT4 ratio of 14.1 and not 20 (as proposed by Amino et al) is best ratio to differentiate between GD verses SAT (Table 3).

Table 1: Baseline characteristics in patients with GD, SAT and TMG.

Variables		GD (64)	SAT (9)	TNG (3)	P value*
Male		14(21.87%)	2(22.22%)	1(33.33%)	0.000
Female		50(78.13%)	7(77.78%)	2(66.67%)	
Age		36.88±10.55	37.44±5.96	61±11.36	
Age	<25	10.94%	11.11%	0%	
	25-34.9	29.69%	22.22%	0%	0.98
	35-44.9	39.06%	55.55%	0%	
	>45	20.31%	11.11%	100%	
Goiter		52(81.25%)	5(55.56%)	3(100%)	0.08
TAO		10(15.6%)	0	0	
Acropathy		0	0	0	0.000
Pretibial MYX		0	0	0	
Neck pain		0	9(100%)	0	0.000
TT3		380.54±148.03	204.67±31.83	303±93.62	0.001
TT4		18.59±3.59	16.21±2.79	16.18±4.02	0.001
TSH		0.006±0.0013	0.029±0.05	0.002±0.002	0.2
TT3/TT4 ratio		20.15±5.45	12.72±0.77	18.76±3.18	0.001

Note:*- p value is between GD and SAT patients.

Table 2: Baseline characteristics of patients with TAO and patients without TAO.

Variables	TAO (present) N (%)	TAO (absent) N (%)	P value
Age	39.8±11.8	36.33±10.33	0.402
Male	3 (30)	11 (20.37)	0.49
Female	7 (70)	43 (79.63)	
Smoker	5 (50)	4 (7.45)	0.0003

Continued.

Variables	TAO (present) N (%)	TAO (absent) N (%)	P value
Non-smoker	5 (50)	50 (92.59)	
Lid retraction	7 (70)	0	0.000
Exophthalmos	6 (60)	0	0.000
Restrictive eye movement	2 (20)	0	0.000
Optic neuropathy	0	0	0
T3	411.84±200.7	374.74±137.79	0.586
T4	18.7±4.79	18.56±3.38	0.924
TSH	0.009±0.018	0.005±0.011	0.575
TT3/TT4	21.07±6.7	19.97±5.29	0.63

Table 3: Sensitivity, specificity, accuracy and PPV at different TT3/TT4 ratio.

TT3/TT4 ratio	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)
>13.6	92.19	66.67	89.04	95.16
>14.1	92.19	100	93.15	100
>20.1	50	100	56.16	100

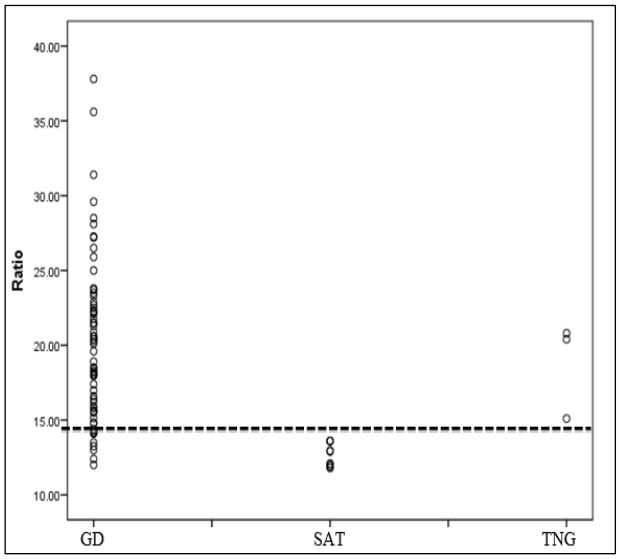

Figure 1: Scatter plot showing the ratio of TT3/TT4 for differential diagnosis of thyroxicosis.

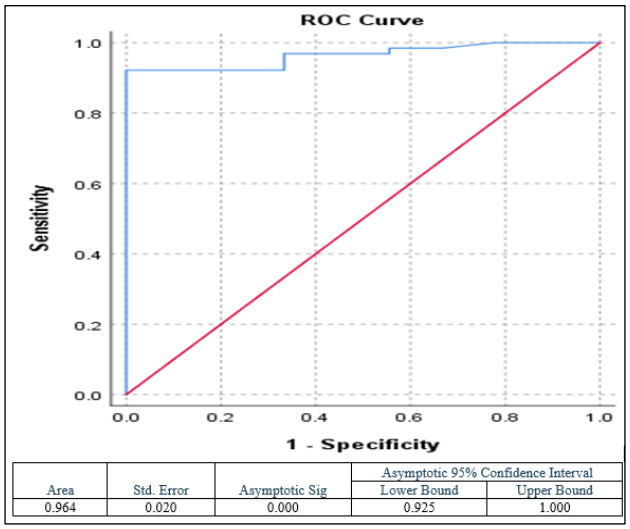

Figure 2: ROC curve for performance of TT3/TT4 ratio in diagnosis of thyrotoxicosis.

DISCUSSION

The present study shows that GD is the most common cause of thyrotoxicosis from eastern part of Uttar Pradesh of India. Of the total 76 patients of thyrotoxicosis, 84.21% were suffering from GD, 11.84% were suffering from SAT while 3.95% were diagnosed with TNG. Similar result were also found in countries that are iodine sufficient and in these countries GD account for 70-80% patients with hyperthyroidism.[11] However, in areas with iodine deficiency, half of the cases of hyperthyroidism is attributable to nodular thyroid disease and other half is due to GD.[12] Laurberg et al further support these differences in a landmark epidemiological study from Iceland and Denmark in ethnically identical North European population.[12] Their result showed that high prevalence of GD in iodine sufficient Iceland and high prevalence of TMG in Denmark with low iodine intake. This indirectly proves that India has become iodine adequate country. Iodine Global Network (IGN) 2021 also endorses the same.

Overall female to male ratio in present study was 3.47:1. Others have also reported the same ratio of.[19] This study reconfirms that thyrotoxicosis is the disease predominantly affecting females. This is because females are more prone to develop autoimmune disease.[7] Many genes originating from X chromosome make the possibility of more mutations to occur. Since women have two X chromosomes as compared to men and this double dose of gene puts women at more risk for development of autoimmune disease. Besides this, estrogen directly influences the expression of a few genes involved in immunity.[20]

Clinical phenotype of GD varies from TNG. As compared to patients with TNG, GD patients are younger and have higher thyroid hormone levels. This study also proves the same. Usually, TNG patients are one to two decades older than GD patients. SAT is a self-limiting type of thyrotoxicosis and its prevalence in present study is like

what we find in data from Woolner et al and Hamburger et al.[21,22] In their study, Hamburger et al 10% of patients presented as SAT and in Woolner et al study 12.5% were suffering from SAT. All SAT patients had neck pain at time of diagnosis while none of the GD and TNG patients had neck pain at time of diagnosis. Pain is due to sudden inflammation and swelling of thyroid gland. No cases of silent thyroiditis were seen in the present study, and this could be due to referral bias.

Prevalence of TAO in GD patients was low (15.62%) in the present study. This could be due to fewer smokers in the present study. Tellez et al also noted a low prevalence of TAO in Asian GD patients.[14] They found that prevalence of TAO in patients with GD was 42% in Europeans and 7.7% in Asians. In the present study, lid retraction was the most common sign followed by exophthalmos. Others have also reported the same.[14] However, in a study by Lim et al, it was the exophthalmos, which was the most common eye sign followed by lid retraction.[23]

The TT3/TT4 ratio is more in GD patients as compared to SAT patients in present study. Others have also reported the same.[24] The reason for high TT3/TT4 ratio in GD patients is due to increment of thyroidal deiodinase activity, namely, Type 1 and Type 2 iodothyronine deiodinase (D1 and D2).[25,26] This increase activity could be due to higher cAMP level produced in thyroidal cell by TSHR Ab. Besides this prompt release of T3 due to TG hydrolysis is also responsible for higher TT3/TT4 ratio. Amino et al has proposed that ratio of >20 are useful in differentiation of GD from SAT.[24] However, we find that ratio of >14.1 is most appropriate for that.

If we take criteria as >20 than sensitivity and accuracy reduced to 50% and 56.16%, respectively. But if we reduce the ratio to >13.6, then specificity and PPV are reduced to 66.67% and 95.16%, respectively. So, for optimal sensitivity (92.19%), specificity (100%), accuracy (93.15%) and PPV (100%) a ratio of >14.1 is the best ratio. The reason for lower cut off value in our study as compared to Amino et al study could be due to different age of patients. All know that when age increases the deiodinase activity decreases.[27]

The average age of patients in our study was higher (36.88 years verses 32 years) as compared to Amino et al study patients. In fact, when we stratified the TT3/TT4 ratio based on age (age <37 verses >37 year) we find lower mean±SD TT3/TT4 ratio (age<37: 20.4±5.99 verses age >37: 19.6±4.46) in older patients as compared to younger. Besides this iron deficiency also suppress the deiodinase activity and prevalence of iron deficiency is more in Indian population as compared to Japanese population.[28] We propose that there should be an age specific and ethnic specific TT3/TT4 ratio to differentiate between GD and SAT. For this, a large multi-centric and multi-national study should be done to make the criteria.

Limitation

The limitation of the present study was the low number of SAT patients. So, our finding at best can be hypothesis generation. The low number of SAT patients is due to rarity of disease. We know that thyroid scan is the gold standard test to diagnose different type of patients with thyrotoxicosis, however this is not readily available everywhere in India and worldwide. Besides this, it is a costlier investigation. If a ratio is confirmed in a larger number of patients, then it will be helpful in diagnosing etiology of thyrotoxicosis in low-income countries. The strength of the present study is that, it is first study from India which sub classifies the different type of thyrotoxicosis patients and proposes TT3/TT4 ratio criteria to differentiate between GD and SAT.

CONCLUSION

The study shows that GD and SAT are the two common causes of thyrotoxicosis. A higher TT3/TT4 (>14.1) ratio suggestive of GD while low ratio (<14.1) supports the diagnosis of SAT. In conclusion, if this is proved in a larger study, then this will be a rapid and cost-effective method to differentiate between the two.

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