ORIGINAL RESEARCH

Predictors of time to remission and treatment failure in patients with Graves' disease treated with propylthiouracil

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Manuscript submitted 6th March, 2009

Manuscript accepted 26th March, 2009

Clin Invest Med 2009; 32 (3): E199-E205.

Abstract

Purpose: Propylthiouracil is one of the thionamides used in the treatment of Graves' disease. The drug has serious side effects and long-term treatment might be needed to achieve remission.

We designed this study to evaluate the clinical and thyroid Doppler characteristics that might predict time to remission and treatment failure in propylthiouracil treated Graves' patients.

Methods: 26 patients, among 134 presenting to our university hospital outpatient clinic between Feb -July 2007 and with first time diagnosis of clinical thyroid dysfunction, were clinically and ultasonographically diagnosed with Graves' disease. Doppler parameters, serum thyrotropin, free thyroxine and free triiodothyronine were measured at the beginning of the study and thyroid studies were repeated every 4 weeks until remission. Propylthiouracil 300 mg/day was started for each patient at the time of diagnosis and doses were titrated according to repeat thyroid studies. Patients were treated and followed up for 18 months.

Results: Treatment failure was associated with smoking ($P = 0.001$) and male gender ($P = 0.037$). Stepwise multiple regression analysis revealed that age, free thyroxine and superior thyroid artery flow rate were predictors of time to remission ($P = 0.001$, 0.002 and 0.003 , respectively).

Conclusion: The time to remission in Graves patients treated with propylthiouracil can be predicted using age, serum free thyroxine and superior thyroid artery flow rate. This may help early consideration of alternative treatment for the patients requiring prolonged treatment for remission or for those who fail medical treatment. This would decrease unnecessary, long-term propylthiouracil exposure with its serious side effects.

Graves' disease is the most common form of hyperthyroidism.¹ Treatment options are antithyroid drugs, radioiodine and surgery.² Initial treatment choice varies with geographic location. Medical treatment is the preferred therapy in Europe and Asia while radioactive iodine is the treatment of choice in the USA.³ Antithyroid drugs have been used to treat hyperthyroidism with variable remission rates and frequent relapses.⁴ In addition to high relapse, antithyroid drugs have serious side effects including agranulocytosis, hepatic necrosis that might require liver transplantation, cholestatic hepatitis and vasculitis. Due to high relapse rates, patient compliance and se-

rious side effects, antithyroid drug treatment for Graves' disease has even been considered obsolete.⁶

Clinicians have sought clinical and laboratory predictors to select patients most likely to have a remission.⁷ This would subject only these patients to the potential risks and inconvenience of antithyroid drug treatment. Retrospective studies showed that patients with more severe hyperthyroidism, large goitre and higher serum free T4/T3 ratios were less likely to enter remission after a course of drug treatment. Other predictors including age, sex, smoking, presence or absence of ophthalmopathy and duration of symptoms before diagnosis revealed inconsistent findings.⁷

Our clinical practice area is located in an endemic goitre region and antithyroid drug side effects are relatively frequent in our practice. As a universal problem related to medical treatment of Graves' disease, treatment compliance and monitoring for the potentially serious side effects of antithyroid drugs are also important problems faced in our region. We observed that the duration of initial antithyroid drug therapy to achieve remission varied considerably among patients. We designed this study to find clinical and laboratory predictors of how long a Graves' disease patient should be treated with antithyroid drugs to achieve remission (time to remission) and who will fail medical treatment. This would help initial treatment planning and provide early consideration of alternative therapy, such as radioiodine ablation and surgery, in predicted late or non-responders.

Methods

Patients

The study population was selected from 134 patients presenting to Duzce University School of Medicine internal medicine outpatient clinic between Feb- July 2007 and receiving a new diagnosis of clinical thyroid dysfunction. Thirty-five patients had clinical hyperthyroidism. Among these, 26 were diagnosed with Graves' disease and were included in the study. In-

formed consent was obtained from all patients. Patients had at least one of the clinical symptoms related to hyperthyroidism including palpitations (55%), weight loss (45%), heat intolerance (35%) and nervousness (25%). Three patients had ophthalmopathy related to Graves' disease.

Study Design

This is a prospective cohort study based on Duzce University internal medicine outpatient clinic patient population. Patients received routine clinical approach of our clinic according to the guidelines of diagnosis and treatment of Graves' disease.⁴

Clinical Assessment

History and physical examination were performed in all patients upon presentation. Fasting morning blood glucose, BUN, creatinine, serum electrolytes, AST, ALT, alkaline phosphatase, total bilirubin, fasting lipid profile were measured using a p800 system (Roche Diagnostics, Indianapolis, IN, USA). TSH (thyrotropin), free T4 (FT4), free T3 (FT3) were measured using e170 modular analytics (Roche/ Hitachi, Indianapolis, IN, USA) system while Sysmex XT 2000i was used for CBC&differential (Roche Diagnostics, Indianapolis, IN, USA). The diagnosis of Graves' disease was made on the basis of clinical signs including hyperthyroidism, ophthalmopathy and laboratory findings. All patients had thyroid scintigraphy to exclude toxic nodular goitre. None of the patients had been treated for Graves' disease before inclusion. Failure to achieve free T3 and/or free T4 within the normal laboratory limits of our hospital (2.8 to 7.1 ng/dL and 0.27 to 4.2 ng/dL, respectively) was accepted as treatment failure. The maximum propylthiouracil dose was 600 mg/day and no further increments were given above this.

After preliminary ultrasound examination for gross abnormalities such as parenchymal nodules, Doppler and grey-scale measurements were performed, after a 10-min rest, by using Hitachi EUB-

6500 ultrasound device (Hitachi Medical Corporation, Tokyo, Japan) with a 14-MHz linear transducer in thyroid mode. With the patient in the supine position with his/her neck hyperextended and rotated away from the examiner, the thyroid was scanned. The width, length, and thickness of each lobe was measured and the volumes of the lobes were calculated using an ellipsoid model formula ($\text{width} \times \text{length} \times \text{thickness} \times 0.52$ for each lobe). The thyroid isthmus was not included in the volume calculation. Doppler ultrasound was performed immediately after the grey-scale examination.

Measurements were performed at the superior thyroid artery along a horizontal segment in the sagittal plane with the Doppler insonation angle at a standard 60° . The sampling volume was maximum and included most of the vessel lumen. Three consecutive blood velocity waveforms of a similar pattern were considered as correct spectral samples. The peak systolic velocity (PSV), resistance index (RI), pulsatility index (PI) and flow rate (FR) were obtained automatically from both superior thyroid arteries and the mean values were recorded (Figure 1).

FIGURE 1. Flow velocity measurement in the superior thyroid artery by Doppler ultrasonography.

Statistical analysis

Baseline and descriptive data were presented as mean $\pm$ SD for normally distributed data and median and interquartile range for non-normally distributed data. Chi-square test was used for analysis of data when both dependent and independent variables were categorical. Multiple logistic regression analysis was used for analysis of categorical dependent variable and continuous independent variables. Multiple stepwise linear regression was used when the dependent and independent variables were continuous. All *P* values were calculated as two-tailed. *P* < 0.05 was set as statistically significant. SPSS 15.0 was used for statistical calculations (SPSS Inc., Chicago, IL, USA).

Results

Twenty-six patients with Graves' disease were examined. Baseline clinical and laboratory characteristics of the patients as well as after treatment measurements are presented in Table 1.

There were 22 females (84.6%) and 4 males (16.4%). The mean thyroid volume and flow parameters did not differ between the lobes of the thyroid

gland in either sex and, thus, data were expressed as the mean of the values for the two lobes. Mean thyroid volume was 29 mL and was increased in all but 4 patients. Despite remarkable improvement in thyroid hormone levels and thyrothyropin, complete remission could not be achieved in 4 patients. Male sex and smoking were associated with treatment failure (Table 1).

The results were used to construct a model with binominal logistic regression to predict the occurrence of failure of remission based on thyroidal artery Doppler parameters, namely PSV, RI, PI and FR (Table 2). None of the Doppler parameters predicted the failure of remission. Assumptions of binary logistic regression analysis were met.

Further analysis of data included stepwise multiple regression analysis with the dependent variable "time to remission". The model had three independent predictors and an *R*² of 52 % and a predicted *R*² of 47.7%. Predictors for time to remission were age, serum free T4 and arterial flow rate (Table 3). Addition of PSV, RI, PI, serum TSH or free T3 did not further increase the fit of the model. Distribution of dependent and independent variables were first checked by using runs

TABLE 1. Baseline and clinical characteristics of twenty-six patients with Graves' disease

	Before treatment	After treatment	χ^2 , <i>P</i>
Age, mean (SD)	46.7 (16)		
Male / female	4 / 22		4.351, = 0.037
TSH, median (IR), (uIU/mL)	0.005 (0.005 to 0.09)	0.59 (0.01 to 1.74)	
Free T4, median (IR) (ng/dL)	25 (15 to 100)	14.5 (11.75 to 17)	
Free T3, mean (SD) or median (IR) (ng/dL)	18.62 (16.38)	4 (3.5 to 5.5)	
Time to remission, mean (SD) (months)	10.8 (4.7)		
Hypertension, <i>n</i> (%)	12 (46.1)		0.028, = 0.867
Diabetes Mellitus, <i>n</i> (%)	1 (3.8)		0.189, = 0.664
Coronary artery disease, <i>n</i> (%)	4 (15.4)		0.839, = 0.36
Smoking, <i>n</i> (%)	6 (23.1)		7.18, = 0.001
Peak systolic velocity (PSV), mean (SD) or median (IR)	37.4 (11.7 to 95)	39.52 (19.86)	
Resistance index (RI), mean (SD)	0.58 (0.15)	0.19 (0.58)	
Pulsatility index (PI), median (IR)	0.96 (0.3 to 4)	0.92 (0.7 to 1.13)	
STA-Flow rate (FR), median (IR) (L/min)	0.02 (0.001 to 0.2)	0.02 (0.01 to 0.04)	
Thyroid volume, mean (SD) or median (IR) (mL)	32.1 (20.16)	26 (16.5 to 40.5)	

SD: standard deviation, IR: interquartile range STA: Superior thyroid artery

TABLE 2. Multiple logistic regression analysis of superior thyroidal artery Doppler parameters.

Variable	Coefficient (β)	Standard Error	Wald χ^2	P Value	Odds Ratio	95% CI
Intercept	-2.329	2.185	—	—	—	—
PSV	0.048	0.047	1.023	0.312	1.05	0.96 to 1.151
RI	0.028	0.087	0.103	0.748	1.028	0.867 to 1.22
PI	-0.094	0.181	0.267	0.605	0.911	0.638 to 1.3
STA-FR	-0.075	0.084	0.806	0.369	0.928	0.788 to 1.093

PSV: peak systolic volume, RI: resistance index, PI: pulsality index, STA-FR: Superior thyroid artery flow rate (L/ min)

test and assumptions of multiple linear regression model were met. The regression equation for the model was: Time to remission = - 1.50 + 0.202 Age + 0.092 FT4 - 54.5 FR.

Discussion

The results from this study showed that age, serum free T4 and superior thyroid artery flow rates are predictors for time to remission in PTU treated Graves' disease patients. Also, male sex and smoking are associated with failure of remission while superior thyroid artery Doppler parameters PSV, PI, RI and FR are not. Age, serum free T4 and thyroid artery flow rate may be used to predict time to remission in these patients to consider alternative treatment earlier for the expected late responders. This would prevent exposing these patients to unwanted side effects of PTU and increase patient compliance starting from the initial mutual planning of the treatment.

The study was based on data from 26 Graves' disease patients who were treated and have been followed for 18 months. There was a female preponderance as expected in Graves' disease. We demonstrated the association of sex and smoking with failure of treatment, but failed to show such an association with

logistic regression perhaps due to an alpha error. A larger study may have been able to demonstrate these associations with a logistic regression model and would have increased the ability to generalize conclusions from our study. Nevertheless, a model that explained 52% of the variation in time to remission was constructed and this revealed three independent predictors. Thus, we believe our results may be generalized.

The time to remission in Graves' disease has been a concern in children.^{8,9} With a similar intent, these investigators studied the time to remission in oral anti-thyroid medication treated children, for early consideration of alternative treatment and avoidance of exposure to drug side effects. They found that time to remission tended to be longer in prepubertal children. On the other hand, they did not evaluate Doppler ultrasound characteristics as predictive factors and their study population did not include adults.

Allahabadia et al. reported that male sex, younger age and large goitres were associated with failure to respond medical treatment.¹⁰ We found similar results with regard to male sex and treatment failure, but our results revealed that increased age was predictive for increased time to remission. We did not find that thy-

TABLE 3. Stepwise multiple linear regression model with the explanatory variables age, free T4 and superior thyroid artery flow rate.

Variable	Coefficient (β)	Standard Error	95% CI	P
Intercept	-0.319	2.65		
Age	0.188	0.049	0.087 to 0.29	0.001
FT4	0.086	0.024	0.036 to 0.136	0.002
STA-Flow rate	-55.472	16.814	-90.342 to -20.6	0.003

FT4: Free thyroxine, STA: Superior thyroid artery

roid size predicted failure of treatment but this might be related to smaller patient number of our cohort.

Our results that thyroid artery flow rate are predictive for the time to remission can be explained by increased thyroidal blood flow related to more active disease in Graves' patients. This is supported by Huang et al, who showed that thyroid artery blood flow was related to intrathyroid microvessel density, glandular weight, and histopathologic microscopic pattern.¹¹ Increased thyroid vascularity and, thus, thyroid blood flow is largely explained by increased vascular-endothelial growth factor which plays an important role in intrathyroidal angiogenesis in Graves' disease.¹² More recently, angiogenesis markers angiopoietin-2 and Tie-2 were reported to be higher in Graves' disease than in controls and to participate in the pathogenesis of Graves' disease.¹³

We also found that FT4 was a predictive factor for time to remission. This does not seem to be related to the direct effect of FT4 on the thyroid gland as thyroid vascularity and blood flow were found to be independent of thyroid hormone concentrations but related to stimulatory effect of thyrotropin and/or TSH-receptor antibody.¹⁴ Our finding of FT4 as a predictive factor for time to remission in Graves disease might be related to disease activity.

Other studies including thyroid Doppler characteristics mainly concerned relapse of Graves' disease. Some researchers reported that Doppler quantification of thyroid blood flow might have been predictive for relapse of Graves' disease after withdrawal of medical treatment.^{15,16} Cappelli et al. reported that thyrotropin receptor autoantibodies at the time of diagnosis or rate of fall in titers could predict remission after antithyroid drug therapy in Graves' patients¹⁷ and a recent study reported that large thyroid size and high free T3/T4 ratios, in addition to thyrotropin receptor autoantibodies, were also prognostic factors in the relapse of Graves' disease.¹⁸

This is the first study evaluating clinical and thyroid artery Doppler characteristics to predict time to remission in Graves' disease. Predicting time to re-

mission by age, free T4 and thyroid artery flow rate is relatively easy. Male sex and smoking might further modify treatment planning, as treatment failures were more common in this group. Considering the importance of patient compliance and possible serious side effects of antithyroid drugs, it is worthwhile trying to decrease unnecessary drug exposure in adult patients with Graves' disease as in children. Our findings may help the planning process at the beginning of treatment by increasing patient compliance and early consideration of alternative treatment such as radioactive iodine ablation and surgery.

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