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Original Article

Prognostic Factors in the Relapse of Graves' Disease Following Treatment with Antithyroid Drugs

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Abstract

Background: Patients with Graves' disease exhibit a considerable rate of relapse after treatment with antithyroid drugs and require ablative therapy.

Objective: The purpose of this study was to evaluate variables which can be used as prognostic factors in predicting the outcome of Graves' disease after treatment with antithyroid drugs.

Methods: Age, sex, duration of antithyroid drug therapy, pretreatment T3 and T4 values, T3 to T4 ratio, size of thyroid gland before and after treatment, and the effect of salt iodination were determined in 439 patients at an endocrine clinic in southern Iran during a 15-year period. The patients included 338 (77%) females and 101(23%) males with a mean age of 34.1±11.2 years.

Results: Overall, the relapse rate was 62%. The relapse rates were 58% and 76% in females and males, respectively (P=0.001). The mean age was 35.0±11.6 years in the relapse group (n=275) and 32.6±11.3 in the remission group (n=164) (P=0.03). T4 was 20.4±6.3 and 18.1±5.4 μg/dl in the relapse and remission groups, respectively (P=0.000). In the relapse group, T3 was 443.0±189.5 ng/dl and in the remission group, it was 373.4±182 ng/dl (P=0.009). T3 to T4 ratio was higher in the relapse group (21.8±8.3 *vs* 18.6±7.0 ng/μg, P<0.005). Larger pre- and post-treatment thyroid size were associated with higher relapse rate (P<0.05 and P=0.001, respectively). Logistic regression analysis showed that male sex, old age, higher pretreatment T4, T3, and T3 to T4 ratio, and larger pre- and post-treatment thyroid size were associated with higher relapse rates. Iodinated salt consumption and duration of treatment beyond 12 months had no effect on the relapse rate.

Conclusion: Patients with male gender, older age, higher pretreatment T3, T4 higher T3/T4 ratio, and larger thyroid size before and after treatment have higher risk of relapse.
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Keywords • Graves' disease • relapse • iodized salt • Iran

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Introduction

Three different modalities of treatment are used for Graves' disease: antithyroid drugs (ATDs), radioactive iodine, and surgery. ATDs maintain the patients euthyroid, however, because they are not curative, 20-40% of cases will remain in remission after ATD's are discontinued and the rest relapse and need ablative therapy.[1]

The treatment policy for Graves' disease varies considerably in different centers; in USA, radioactive iodine is the treatment of choice after the control of thyrotoxic state, while in other countries, a course of 12-18 months of ATD is used first and radioablation is given if the disease relapses.[2] Since the response to treatment with ATD is unpredictable, it would be helpful to identify factors that might predict the outcome in order to prescribe the most appropriate form of therapy for each patient. Several studies have tried to solve this issue but their results, as will be discussed later, are contradictory. These contradictions have been attributed to differences in iodine intake.[3,4] Fars province in the South of Iran had been an iodine deficient area up to 1991[5], but after implementation of national salt iodination program, more than 98% of the population have been supplied with iodinated salt and daily iodine intake is estimated at 150 µg/day.[6] The purpose of this study was to determine factors that could predict the relapse of Graves' disease after a course of ATD in our region and compare the relapse rates before and after mass iodination program.

Patients and Methods

439 patients with Graves' disease were treated and followed at the out-patient clinics of Shiraz University of Medical Sciences, Shiraz, Iran. The diagnosis of Graves' disease was based on signs and symptoms of thyrotoxicosis, non-nodular thyroid enlargement, categorized according to WHO goiter classification[7]. Presence of Graves' ophthalompathy was assessed by presence of eye signs in categories 2-6 of NOSPECS classification[8], elevated free T4 and T3 indices, and suppressed TSH. T3, T4, and T3 Ru were measured by RIA method. TSH was assayed by RIA up to 1992 and thereafter by IRMA. In cases without Graves' ophthalompathy, thyroid radioactive iodine uptake was measured to rule out thyroiditis and other causes of thyrotoxicosis with suppressed iodine uptake. In these cases 99mTc thyroid scan was also performed to exclude toxic nodular goiters. Remission was determined by disappearance of signs and symptoms of thyrotoxicosis and normalization of serum T3 and T4. Relapse was defined as reappearance of signs and symptoms of thyrotoxicosis and elevation of serum T3 and T4 after discontinuation of ATD. Our policy over the period of study was to treat the patients with methimazole or propylthiouracil for 12 to 18 months followed and reassessed at 3-month intervals for relapse of the disease. The duration of follow-up after initial remission was at least 3 years. The relation between age, sex, pretreatment T4, T3 and T3/T4 ratio, pre- and post-treatment thyroid size, duration of treatment with ATD, and the effect of salt iodination program on relapse rate were analyzed.

Statistical Methods

Chi square test was used to test the association between two categorical factors and unpaired T test was used to analyze the relation between continuous factors. For continuous data which were not normally distributed, Mann-Whitney test was used to confirm the results of T test. Statistical analysis was done using SPSS version 8.

Binary logistic regression analysis was used to determine the independent predictors of the relapse.

Results

Overall, the relapse rate was 62%. Factors effective in the relapse rate comprised:

Sex: Of 439 patients, 338(77%) were female and 101 (23%) were male. The relapse rates were 58% and 76% in female and male groups respectively (P<0.001).

The association between gender and relapse was shown to be another variable, using logistic regression (estimated odds ratio 2.6; P = 0.005).

Age: The mean age of relapse group was 35.0±11.6 years and that of the remission group was 32.6±11.3 (P:0.03).

For analysis, patients were divided into those under and over 40 years of age. Patients in the younger age group had significantly higher mean total T4 (20.1±4.8 versus 17.8±5.2 µg/dl, P<0.01). The younger group also tended to have larger goiters (P < 0.001). Age at the onset of disease remained a significant predictor for relapse allowing for association with other variables in using logistic regression. Patients older than 40 years were more likely to incur a relapse after medical therapy (odds ratio 1.82; P = 0.01).

T3 and T4 level: Pretreatment serum T3 in the relapse and remission groups were 443.0±189 ng/dl and 373.4±182.9 ng/dl, respectively (P:0.009). Pretreatment serum T4 in the relapse group was 20.4±6.3 µg/dl versus 18.1±5.4µg/dl in the remis-

Table 1: Relapse rates according to pretreatment thyroid size

Outcome	Size		
	1a, 1b	II	III
Relapse rates according to pretreatment size	45%	66%	73%
Relapse rates according to post treatment size	49%	60%	85%

sion group (P<0.0001). Patients with T4 more than 21 μg/dl had 90% chance of relapse. T3 to T4 ratios were 21.8 ± 8.3 ng/μg and 18.6 ± 7.0 ng/μg in the relapse and remission groups, respectively (P<0.005).

These variables remained significant predictors of relapse after logistic regression analysis. The odds ratio for relapse in patients with T4 more than 20 μg/dl, T3 more than 300 ng/dl, and T3 to T4 ratio above 20 ng/μg were 1.54 (P=0.01), 1.48 (P=0.008), and 1.60 (P=0.02) respectively.

Thyroid size: Considering the size of thyroid before and after treatment, the patients with larger pretreatment and post-treatment goiters had higher relapse rates (P<0.01 and P<0.001, respectively; Table 1).

Although large goiters were associated with other variables such as higher T4, T3, and T3/T4 ratio, it remained a significant predictor of relapse in regression analysis. The ratios for relapse in patients with grade II or larger goiters before and after treatment were 1.82 (P=0.01) and 3.4 (P=0.001), respectively.

Duration of treatment with ATD: There was no significant difference in relapse rate between patients who received 12 months of treatment and those who were treated for 18 to 24 months.

Time of relapse: Of patients who relapsed, 28% did so in the first 6 months, 58% in the first year and 81% within 2 years after cessation of treatment.

Effect of salt iodination: 234 patients referred before and 204 after implementation of salt iodination program; the remission rates were 63 and 61 percent, respectively and the difference was not statistically significant (P>0.5). There was also no significant difference in variables such as age at disease onset, goiter size, and levels of thyroid hormones.

Discussion

It is generally believed that ATDs do not alter the course of the underlying disease process, and persistence of remission after the course of treatment will occur only if the disorder has entered a latent or inactive phase along its natural evolution.[9] If relapses were reliably predictable, rational choice could be adopted for determining early ablative therapy. In spite of many investigations, however, there is still no consensus about reliable markers of outcome after ATD treatment.

Age: There are different results: Chiou[10] and, Torring[11] reported no relationship between age and relapse rate, whereas Winsa[12], Allahabadia[3], and Vitti[13] reported higher relapse rate in younger patients. In our patients, relapse rate increased with older age.

In areas with a past history of iodine deficiency, autonomous hyper-functioning foci develop in the thyroid with advance age, and may contribute to relapse after withdrawal of ATD's [14]

Sex: In the study by Chiou[10] no correlation was reported between the sex and relapse rate, whereas in our study, the relapse rate was higher in male patients, and this is in accordance with the results reported by Vitti[13] and Allahabadia.[3]

Pre-treatment T3 and T4 levels: Torring[11], and Allanic[15] reported no relation between these two factors and relapse rate while Winsa[12], noticed a strong association was found similar to our study. Chiou[10], in another survey, suggested T3 but not T4 as a predictive value of relapse.

T3 to T4 ratio: Allanic[15], Chiou[10], Tajiri[16] and Torring[11], showed that this index was not useful to determine relapse, while Gauna[17,] as in this study, reported a positive correlation between this ratio and relapse.

Thyroid size: Ikinoue[18], Schleusener[19], Laurberg[20] Kimball[21-23]and Winsa[12] found a significant correlation between pretreatment thyroid size and relapse, which is similar to our results.

Duration of Treatment:[22] Schumm-Draeger[24] and Weetman[25], showed that beyond 12 months, there was no correlation between duration of treatment and outcome which is in keeping with our study.

Iodine intake: The iodine intake of patients may influence the response to ATD and this may account for different results in different areas.[4,26] Excess iodine ingestion may precipitate or aggravate thyrotoxicosis by providing iodine substrate for excess hormone synthesis in autonomously functioning thyroid gland.[27,28] Iodine excess is also related to the altered immunologic surveillance characteristic of Graves' disease. Iodine promotes IgG synthesis in human lymphocytes[29], increases thyroglobulin antigenicity[30], and enhances autoimmune mechanisms in thyroid.[31,32] Solomon et al pointed out that as daily iodine intake in the United States decreased from 750 μg/day in 1973 to

200µg/day in 1985, the remission rate of Graves' disease after medical therapy increased from 14% to 50.1%.[33] In our region, increased iodine intake after salt iodination program did not adversely affect the remission rate of Graves' disease and this is in accordance with the result of some other studies.[34,35] It seems that the effect of iodine intake on remission rate of Graves' disease is dose dependent and a moderate daily intake of about 100-200µg has no adverse effect in this regard.

Conclusions

In our region, patients who are elderly males have higher serum T3 and T4, higher T3/T4 ratio, and larger size of thyroid before and after treatment run a high risk of relapse after withdrawal of ATD therapy. For these patients early ablative therapy should be considered. The duration of treatment beyond 12 months has no significant influence on outcome.

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