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Risk Factors for the Relapse of Graves' Disease Following Withdrawal of Antithyroid Drugs

Antitiroid İlaçların Kesilmesini Takiben Graves' Hastalığının Nüksü ile İlişkili Risk Faktörleri

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Abstract

Objective: The treatment of Graves' disease (GD) with antithyroid drugs (ATD) is associated with a risk of relapse. The rate and predictive factors of GD are controversial. This study aimed to assess the relapse rate after the withdrawal of ATD in patients with GD, as well as to identify its predictive factors. **Material and Methods:** This was a retrospective cohort study covering 35 patients with GD that were treated with ATD. Relapse was defined as the state when hyperthyroidism was detected after the withdrawal of medical therapy. Relapse was studied by establishing the survival curve according to Kaplan-Meier's method. The Log-Rank test was used to compare the survival curves according to the clinical, biological, and therapeutic parameters of the patients. **Results:** The mean follow-up time after the withdrawal of ATD was 32.8±28.8 months. Relapse was observed in 13 patients (37%) after an average time of 7.8±8.8 months of ATD discontinuation. Factors associated with the risk of relapse were smoking (p=0.08), family history of thyroid disease (p=0.03), the presence of a triggering factor (p=0.004), FT4 level at the time of diagnosis at >2.3 times the normal range (p=0.002), thyroid-stimulating hormone level less than 0.76 mIU/L at three months after ATD withdrawal (p=0.05), and a benzylthiouracil dose of >125 mg/day at the time of ATD discontinuation (p=0.02). **Conclusion:** Relapse in patients with GD after the withdrawal of ATD is observed in almost a third of the patients. Identification of patients at a high risk of relapse is necessary to indicate radical treatment.

Keywords: Graves' disease; antithyroid drugs; recurrence

Özet

Amaç: Graves hastalığının [Graves' disease (GD)] antitiroid ilaçlarla [antithyroid drugs (ATD)] tedavisi nüks riski ile ilişkilidir. GD'nin oranı ve prediktif faktörleri tartışmalıdır. Bu çalışmada, GD'li hastalarda ATD'nin kesilmesinden sonraki nüks oranını değerlendirmek ve ilgili prediktif faktörleri belirlemek amaçlanmıştır. **Gereç ve Yöntemler:** ATD ile tedavi edilen GD'li 35 hastayı kapsayan bu retrospektif kohort çalışmasında, nüks medikal tedavinin kesilmesinden sonra hipertiroidinin saptanması durumu olarak tanımlanmıştır. Nüks, Kaplan-Meier yöntemine göre sağkalım eğrisi oluşturularak incelenmiştir. Log-Rank testi, hastaların klinik, biyolojik ve terapötik parametrelerine göre sağkalım eğrilerini karşılaştırmak için kullanılmıştır. **Bulgular:** ATD'nin kesilmesinden sonraki ortalama takip süresi 32,8±28,8 aydır. ATD'nin kesilmesinden ortalama 7,8±8,8 ay sonra 13 hastada (%37) nüks gözlenmiştir. Nüks riski ile ilişkili faktörler sigara (p=0,08), ailede tiroid hastalığı öyküsü (p=0,03), tetikleyici faktör varlığı (p=0,004), tanı anındaki FT4 seviyesinin normalin >2,3 katı olması (p=0,002), ATD'nin kesilmesinden sonraki 3 ayda tiroid stimüle edici hormon düzeyinin 0,76 mIU/L'den düşük olması (p=0,05) ve ATD'nin kesilmesi sırasında benziltiyourasil dozunun >125 mg/gün olması (p=0,02) olarak bulunmuştur. **Sonuç:** GD'li hastalarda, ATD'nin kesilmesinden sonra hastaların yaklaşık 1/3'ünde nüks görülmektedir. Radikal tedavi endikasyonu için yüksek nüks riski taşıyan hastaların belirlenmesi gereklidir.

Anahtar kelimeler: Graves hastalığı; antitiroid ilaçlar; nüks

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Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism, with an annual incidence of around 1%. It is an autoimmune disease that progresses in flare-ups interspersed with periods of remission. The treatment is either radical, with radioactive iodine or less commonly by surgery, or medical, with antithyroid drugs (ATD) (1). Several factors influence the choice of treatment. Six decades after their introduction, ATDs continue to play an important role in disease management. Despite some side effects and the need for close monitoring, their use remains simple, non-invasive, and inexpensive. The main disadvantage associated with ATD treatment is the risk of relapse following the discontinuation of treatment. The ability to predict the risk of relapse before the initiation of ATD would be of great value in the choice of treatment. Factors that can predict relapse after the discontinuation of ATD are controversial (2-4). Hence, our work aimed to assess the relapse rate during the follow-up of patients with GD that were treated with ATD, as well as to analyze the factors that influenced the recurrence.

Material and Methods

This was a retrospective cohort study conducted at the endocrinology department of La Rabta hospital (Tunis-Tunisia). It included all the patients with GD in remission after the discontinuation of ATD between January 2000 and December 2013.

The diagnosis of GD was made in the presence of a biologically confirmed hyperthyroidism [suppressed thyroid-stimulating hormone (TSH) with normal or elevated FT4 levels] associated with at least one of the following criteria: clinically obvious Graves' orbitopathy, an elevated thyroid-stimulating hormone receptor antibody (TRAB), or increased uptake of diffuse isotope on thyroid scintigraphy.

Remission was defined as achieving normal FT4 and TSH levels after the discontinuation of ATD. Relapse was defined as the state when hyperthyroidism was detected after the withdrawal of ATD. The duration of remission was defined as the period between ATD withdrawal and relapse.

Sociodemographic characteristics (age, gender, smoking status), clinical (personal and family pathological history, triggering factor of the disease as bereavement, divorce, separation, dismissal or other emotional stress, the presence of Graves' orbitopathy, and goiter size), paraclinical (FT4 and TSH levels, TRAB levels, and thyroid ultrasound results) and therapeutic (type and dose of ATS used, the evolution of the thyroid workup under ATS, and duration of treatment) parameters were obtained from the medical file.

Statistical Analysis

The study was conducted in accordance with the Helsinki declaration principles and was approved by the ethic committee of La Rabta Hospital (Approval number: CEBM. EPS.HR 22/2021).The data were analyzed using the statistical software SPSS version 20.0. Quantitative variables were expressed as mean±standard deviation, and qualitative variables were expressed as percentages (%). Relapse was studied by establishing the survival curve according to Kaplan-Meier's method. The Log-Rank test was used to compare the survival curves according to the clinical, biological, and therapeutic parameters of the patients. The quantitative variables were transformed into dichotomous variables. Receiving Operating Curves (ROC) curves were created, allowing the determination of the optimal cutoff values for age (</>33 years), gender (female/male), smoking (never/ever), family history of thyroid disease (no/yes), disease trigger (no/yes), orbitopathy (no/yes), goiter (no/yes), initial FT4 level (</>2.3 times the normal range), ATD type (methimazole/benzylthiouracil), the occurrence of hypothyroidism during treatment (no/yes), benzylthiouracil dose during the withdrawal of medical treatment (>/<125 mg/day), methimazole dose during the withdrawal of medical treatment (>/<15 mg/day), TSH level 3 months after discontinuing ATD (>/<0.76 mIU/L). The dependent variable in the ROC analyses was "relapse." A p value of <0.05 indicated statistical significance.

Results

A total of 35 patients met the inclusion criteria. The mean age of the patients at diagnosis was 34.9±14.2 years. The sex ratio (men/women) was 0.3. The ATDs used were benzylthiouracil (77% of patients) and methimazole (23% of patients). The mean dose of benzylthiouracil used was 210±67.5 mg/day, and that of methimazole was 33.2±19.7 mg/day. The mean duration of treatment before ATD withdrawal was 23.4±19.9 months.

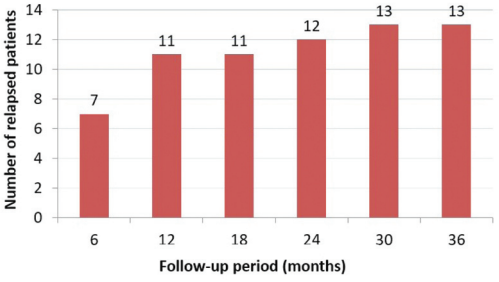

Figure 2. Cumulative relapse rate over 36 months of follow-up after antithyroid drugs withdrawal.

Relapse Rate

The mean follow-up time after the discontinuation of ATD was 32.8±28.8 months. Relapse was observed in 13 patients (37%) after a mean of 7.8±8.8 (1-33) months from the discontinuation of ATD. In 54% of these (7 patients), relapse occurred within the first six months after stopping ATD.

Figure 1 presents the Kaplan-Meier curve of relapse after ATD withdrawal, while Figure 2 represents the cumulative relapse rate over 36 months of follow-up after ATD withdrawal.

Factors Associated With Relapse

Age (< or ≥33 years) and gender were not associated with relapse (p=0.65 and 0.73, respectively). Smoking was associated with the risk of relapse (p<0.05) (Figure 3A). Relapse was more frequent in patients with a family history of thyroid disease and the presence of a disease trigger (Figure 3B) (Figure 3C). The presence of an orbitopathy was not associated with an increased risk of relapse (p=0.89), as was the presence of goiter at diagnosis (p=0.8).

Biologically, the risk of relapse was higher if the initial FT4 level was >2.3 times the normal range (Figure 3D). The level of TSH at baseline and the end of treatment did not correlate with the risk of relapse. A TSH level <0.76 mIU/L at three months after stopping ATD was associated with relapse (Figure 3E). The initial levels of TSH receptor antibodies and the thyroid volume on cervical ultrasound were not associated with the risk of relapse (p=0.6 and p=0.5, respectively).

Therapeutically, a dose of benzylthiouracil higher than 125 mg/day at the time of stopping medical treatment was associated with a higher risk of relapse (Figure 3F). The methimazole dose at the time of stopping medical treatment was not associated with the risk of relapse (p=0.6). The type of ATD and treatment duration were not associated with the risk of relapse (p=0.9 and p=0.9, respectively). Relapse was less frequent if hypothyroidism occurred during medical treatment, although the relationship was not statistically significant (p=0.09).

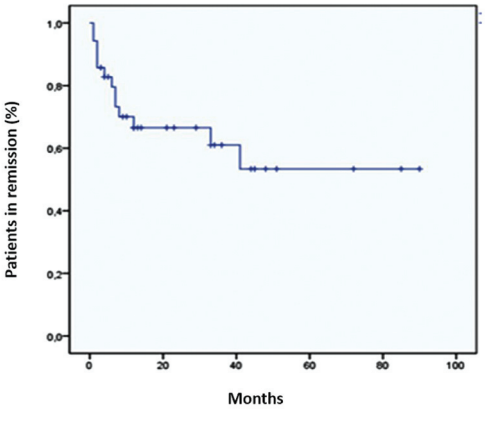

Figure 1. Kaplan-Meier survival curve showing time to relapse after antithyroid drugs withdrawal in patients who had gone into remission.

Discussion

The rate of relapse of GD after the withdrawal of ATD affected approximately one-third of the patients after a mean follow-up of 32 months. Recurrences were most frequently observed within the first six months after stopping treatment (20%) and were rarely observed after two years (3%).

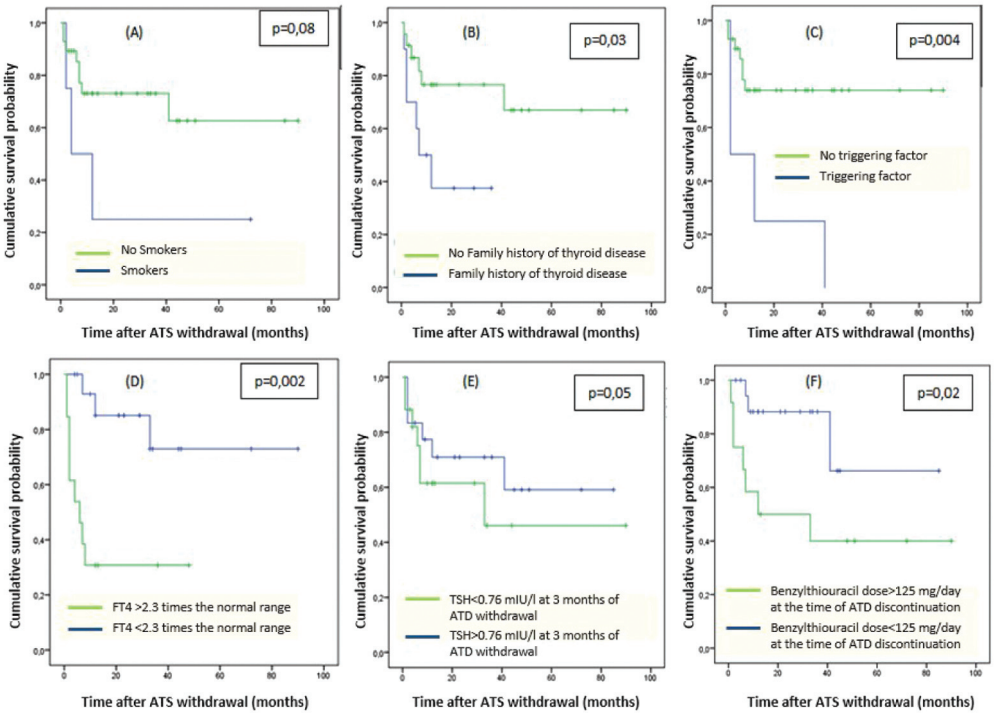

Figure 3. Patient survival curves according to (A) smoking, (B) the presence of a family history of thyroid disease, (C) the presence of a triggering factor, (D) the FT4 level at diagnosis, (E) the TSH level at 3-months after ATD withdrawal, (F) the dose of benzylthiouracil at the time of ATD withdrawal.
ATD: Antithyroid drugs; TSH: Thyroid-stimulating hormone.

We observed an increased risk of recurrence in patients with a family history of thyroid disease and if a triggering factor was present. Biologically, an FT4 level at diagnosis of >2.3 times the normal range and a TSH level of <0.76 mIU/L at 3-months after ATD withdrawal were associated with a higher rate of relapses. Therapeutically, a benzylthiouracil dose of >125 mg/day at the time of ATD discontinuation was associated with higher rates of relapse.

This study has some methodological limitations. The main limitation is the small sample size of the study. Moreover, it would have been interesting to assess the involvement of other factors, such as the level of TSH receptor antibodies during the treatment with and after the discontinuation of ATD, in the occurrence of relapses.

Despite these limitations, several clinical and biological factors have been identified to be associated with relapse. The estimation of the survival function by the Kaplan-Meier method allowed us to factor the subjects lost to follow-up, as well as the fact that some patients had a longer follow-up period than others.

The relapse rate of GD reported in the literature is highly variable, with an average of about 50% (2-4). According to our survival curve, the immediate relapses were significant. Almost 50% of the relapses occurred within the first six months after the discontinuation of ATD. Previous studies have also established that relapses usually occur within the first three to six months after the withdrawal of ATD (5-8).

Predictive factors such as age and gender were not associated with relapse in our study. The majority of previous studies agree that gender does not predict the risk of relapse in GD (9-11). However, the role of age is more controversial (11-13). In some studies, young age is associated with a higher risk of relapse (5,14-16). Several studies have also reported that relapses were more fre-

quent among smokers (17,18). In our study, this relationship was statistically significant. This observation may be explained by an increase in interleukin-2 receptors in smokers (19).

Clinically, a family history of thyroid disease and the presence of a disease-triggering factor at the time of diagnosis were associated with a higher risk of relapse. These factors have been scarcely studied in the literature (20). According to Fukao et al., depression, hypochondria, paranoia, and mental fatigue were the risk factors for relapse after an average of three years of treatment with ATD (20). Unlike many other studies (5,10,17,18,21-24), the size of the goiter and the presence of an orbitopathy were not associated with the risk of relapse in our study.

Biologically, an initial FT4 level of >2.3 times the normal range was significantly associated with more subsequent relapses in this study. However, our results diverge from those of other studies (12,25). Nevertheless, the overall chance of remission is better when the initial biological intensity of hyperthyroidism is moderate (10,14,17, 23,24). The relationship between the level of anti-TSH receptor antibodies and the subsequent risk of relapses has been extensively studied with highly conflicting results. An accurate prognosis in itself could not be satisfactorily predicted by the antibody levels. In our study, the level of TSH receptor antibodies was not associated with the risk of subsequent relapses; however, antibodies were measured only at the time of diagnosis. A meta-analysis including ten pros pective studies demonstrated a significant relationship between the risk of relapse and the presence of anti-TSH receptor antibodies after the discontinuation of ATD. However, the positive and negative predictive values were low (22). Furthermore, it was interesting to note that TSH levels of <0.76 mIU/L at 3-months after stopping ATD predicted the subsequent risk of relapse.

Therapeutically, neither the type of ATD nor the duration of treatment was associated with the risk of relapse. However, a higher dose of ATD at the time of stopping medical treatment appeared to be associated with a higher risk of subsequent relapses. In our study, a dose of benzylthiouracil of >125 mg/day at the end of treatment was associated with a higher risk of relapse. However, this finding contrasts those reported in the literature (22).

Conclusion

According to our study, about a third of the patients treated are at risk for the relapse of GD after ATD withdrawal. This risk is significant during the first six months after stopping treatment, due to which it is essential to monitor the thyroid function closely during this period. The main predictive factors of relapse are smoking, a family history of thyroid disease, the presence of a triggering factor for the disease, severe biological hyperthyroidism, and a high treatment dose at the end of treatment. These factors must be considered when initiating treatment and during follow-up for timely radical treatment.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Meriem Yazidi; Design: Nadia Ben Mansour; Control/Supervision: Meriem Yazidi, Melika Chihaoui; Data Collection and/or Processing: Rym Ben Othmane; Analysis and/or Interpretation: Nadia Ben Mansour, Meriem Yazidi; Literature Review: Rym Ben Othmane; Writing the Article: Meriem Yazidi; Critical

Review: Melika Chihaoui, Ibtissem Oueslati, Fatma Chaker; References and Fundings: Melika Chihaoui; Materials: Rym Ben Othmane.

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