Thyroid disease and haemostasis: a relationship with clinical implications?
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Chapter 14

The effect of thyroid autoantibodies on warfarin stability

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Abstract

Introduction: An influence of overt thyroid dysfunction on the sensitivity to oral vitamin K antagonists has been described. Data on the effect of thyroid dysfunction on warfarin stability are currently sparse and not conclusive. To our knowledge, no data have ever been published on the interaction between thyroid antibodies and warfarin. The aim this study was therefore to test the hypothesis of an effect of thyroid autoantibodies on warfarin stability.

Methods: A retrospective inception cohort study was carried out in a population of 100 consecutive adult outpatients with provoked or unprovoked deep venous thrombosis followed at the Anticoagulation Clinic of the Department of Clinical Medicine of the University Hospital of Varese, Italy, and treated with warfarin to achieve therapeutic range of the international normalized ratio (INR) between 2.0 and 3.0. Thyroid autoantibodies, i.e. anti-thyroid peroxidase (AbTPO), anti-thyroglobulin (AbTg), and anti-TSH receptor antibodies (AbTR), were measured in all patients. We compared warfarin stability in patients with elevated antibodies levels to those with antibodies within the normal range. Stability of oral anticoagulation was evaluated during a period of three months, before or after the date of antibody measurement, and presented as the percentage of time in range and the standard deviation (SD) of the mean INR values.

Results: Overall, 36 patients, 12 with elevated antibody levels (5 women; mean age 71.0 years) and 24 with normal antibody levels (10 women; mean age 66.5 years) with available INR values were analysed. Eight patients had elevated AbTPO levels (one also elevated TrAb), four elevated AbTg, and none isolated elevated TrAb. Percentage of time in range was slightly lower, although not significantly, in patients with elevated antibodies (61.9% vs 70.1%, p=0.16), whereas the SD of the INR values was higher in patients with elevated antibodies (0.83 vs 0.65, p=0.05), suggesting that thyroid autoantibodies may be responsible for the instability of the INR control.

Conclusions: The presence of thyroid autoantibodies may be associated with an increased instability of the INR control and, therefore, deserves further investigation in prospective clinical trials.
**INTRODUCTION**

A large proportion of patients on warfarin treatment spend up to half of their time outside the therapeutic range, with resultant increased risk of either thromboembolic or bleeding complications\(^1\). While changes in concurrent medications, comorbidities, and patient’s compliance affect the quality of control of anticoagulant therapy in a predictable way, intraindividual variability in the response to warfarin treatment remains often unexplained\(^2\). Thyroid disorders are not uncommon in patients on warfarin therapy, in particular because atrial fibrillation may be secondary to hyperthyroidism or because patients develop amiodarone-induced hypothyroidism. An influence of overt thyroid dysfunction on the sensitivity to oral vitamin K antagonists has been described\(^3\). The effect of vitamin K antagonists is potentiated in thyrotoxicosis and is attenuated in hypothyroidism. This disease-drug interaction has been described in a number of case reports and in animal studies, in particular for overt hyperthyroidism, where a change in thyroid function appears to be associated with a change in warfarin sensitivity, irrespectively of the nature of the underlying thyroid disease\(^4\). However, data on the effect of thyroid dysfunction on warfarin stability are currently sparse and not conclusive\(^5\). To our knowledge, no data have ever been published on the interaction between thyroid antibodies and warfarin.

**METHODS**

The aim of our retrospective inception cohort study was therefore to test the hypothesis of an effect of thyroid autoantibodies on warfarin stability. The study was carried out in a population of 100 consecutive adult outpatients with provoked or unprovoked deep venous thrombosis who were enrolled in an etiological cross-sectional study\(^6\). Subjects and methods have been previously described\(^6\). Briefly, all patients were followed at the Anticoagulation Clinic of the Department of Clinical Medicine of the University Hospital of Varese, Italy, and treated with warfarin to achieve therapeutic range of the international normalized ratio (INR) between 2.0 and 3.0. Thyroid autoantibodies, i.e. anti-thyroid peroxidase (AbTPO), anti-thyroglobulin (AbTg), and anti-TSH receptor antibodies (AbTR), were measured in all patients. The following commercial test were used: AbTPO, DYNOtest anti-TPOn, Brahms, Germany; AbTg, Anti-Tgn RIA, Brahms; TRAb, TRAK human RIA, Brahms. Reference values in our laboratory are as follows: AbTPOb60 U/mL; AbTgb60 U/mL; TRAb, b1 IU/L. Both cases and controls signed a written informed consent for the original study. For the purpose of this study, we compared warfarin stability in patients with elevated antibodies levels to those with antibodies within the normal range. For each case, we randomly selected two controls matched for age, gender and cause of deep venous thrombosis (provoked/unprovoked). Stability of oral anticoagulation was evaluated during a period of three months, before or after the date of antibody measurement, and presented as the percentage of time in range and the standard deviation of the mean INR values. INR values within the first month of treatment following the acute thrombotic event were not included in the analysis. A period of three months was arbitrary selected, based on the mean available anticoagulation period. The difference in measures of variability of anticoagulation (percentage time in range and standard deviation...
of INR) between cases and controls were calculated. Percentage of time in range was estimated by linear interpolation between successive INR measurements, calculating the proportion of time during each interval that was spent in-range, summing across all intervals, and then dividing by the total duration of therapy\(^7\). Unpaired t tests were used to calculate the mean difference in measures of stability of anticoagulation (percentage time in range and standard deviation of INR during the study period) between the two groups. Results are presented as means unless stated otherwise. A P-value below .05 was considered statistically significant.

**Results**

Overall, 36 patients, 12 with elevated antibody levels (5 women; mean age 71.0 years) and 24 with normal antibody levels (10 women; mean age 66.5 years) with available INR values were analysed. Eight patients had elevated AbTPO levels (one also elevated TrAb), four elevated AbTg, and none isolated elevated TrAb. Five patients with elevated antibody levels were excluded because blood sample was obtained far distant from anticoagulation period. All other patients had antibodies within the normal range. One patient with elevated antibodies and two controls temporary discontinued warfarin treatment to undergo an invasive procedure. New medications were administered in none of the patients with elevated antibodies and in 5 (20.8%) of the controls. In particular, one patient received long-term atorvastatin, and a brief course of levofloxacin and N-acetylcysteine, one long-term chlorthalidone, one amoxicilline for few days, and the last two a brief course of an unspecified non-steroidal antiinflammatory drug and an antibiotic, respectively. Two patients with elevated antibodies had a subclinical hypothyroidism; one of the controls had a euthyroid goiter. Percentage of time in range was slightly lower, although not significantly, in patients with elevated antibodies (61.9% vs 70.1%, \(p=0.16\)), whereas the SD of the INR values was higher in patients with elevated antibodies (0.83 vs 0.65, \(p=0.05\)), suggesting that thyroid autoantibodies may be responsible for the instability of the INR control.

**Discussion**

Several mechanisms can be advocated to explain the potential interference of thyroid autoantibodies on warfarin stability. Thyroid autoantibodies may interfere with warfarin metabolism, clearance, absorption, or transportation; another possibility is that thyroid autoantibodies exert an in vitro effect, thus altering the quality of laboratory control. This mechanism could be similar to that observed in patients with antiphospholipid antibodies, which largely depends on the type of thromboplastin used\(^8\). Our study results are limited by some methodological drawbacks. First, we did not routinely measure lupus anticoagulant in each patient, therefore an influence cannot be excluded. Second, there is limited sample size. Third, well-known factors that influence the quality of control of anticoagulant therapy – such as drugs and interruption for surgical procedure – were not taken into account in the analysis. However, these factors were more prevalent in the control group. Moreover, as warfarin was self-administered, drug compliance could not be analysed as additional confounding factor.
Fourth, the lack of a power calculation limited our study quality, but it was not possible to perform given that it is the first study investigating a possible association. Finally, a antibody-specific effect could not be explored given the low sample size.

In conclusion, although these findings are hampered by the limited sample size of the study and are not statistically significant, our hypothesis - that the presence of thyroid autoantibodies may be associated with an increased instability of the INR control – deserves further investigation in prospective clinical trials.

REFERENCES