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ORIGINAL ARTICLE

Thyroid Dysfunction Coexistence in Patients with Acute and Subacute Deep Vein Thrombosis

Akut ve Subakut Derin Ven Trombozu Hastalarında Tiroid Disfonksiyonu Birlikteliği

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ABSTRACT

Objective: Coagulation anomalies in patients with thyroid dysfunction may vary from subclinical disorders in laboratory tests to life threatening thrombotic events or bleeding. We aimed to determine the effect of thyroid dysfunction on thrombophilia in patients with acute and subacute deep vein thrombosis (DVT).
Materials and Methods: A number of 30 patients with the diagnosis of DVT between November 2015 and June 2016 included in this case - control study. The patients divided into two groups as provoked (with known ethiology, n = 13) and unprovoked (with un-known ethiology, n = 17) patients. Provoked patients group divided as the patients with acquired risk factors (predisposition) and/or the patients with genetic risk factors.
Results: The difference of the rate of the thyroid dysfunction between the provoked and unprovoked groups was not significant (p=0.844). The PAI – 1 gene mutation was detected in 70% of the study cohort and none of the patients had prothrombin gene mutation. The most provocative factors for DVT were male gender and undergoing a major surgery in the last three months.
Conclusions: There was no correlation between acute – subacute DVT and thyroid dysfunction in this study. Therefore, we think that the 'provocative factors' may support the relation of thyroid dysfunction and venous thromboembolism (VTE). We think that more studies with larger cohorts and prospective should be conducted about this subject.

Keywords: deep vein thrombosis, thyroid dysfunction, thrombophilia

ÖZ

Amaç: Tiroid disfonksiyonu olan hastalarda koagülasyon bozuklukları, subklinik laboratuvar anormalliklerinden hayatı tehdit eden kanamalara veya trombotik olaylara kadar uzanır. Çalışmamızda, akut-subakut DVT tespit edilen hastalarda, trombofili sebebi olarak tiroid disfonksiyonu araştırılması amaçlanmıştır.
Gereç ve Yöntem: Kasım 2015 ile Haziran 2016 arasında DVT tanısı almış 30 hasta bu vaka kontrol çalışmasına dahil edilmiştir. Hastalar provoke (bilinen etiyolojisi olan, n = 13) ve provoke edilmemiş (bilinmeyen etiyolojisi olan n = 17) hastalar olarak iki gruba ayrıldı. Provoke hasta grubu edinsel risk faktörleri (yatkınlık) ve / veya genetik risk faktörleri olan hastalar olarak ayrıldı.
Bulgular: Proveke grup ve Unprovake gruplar arasında tiroit disfonksiyonu sıklığı arasında istatistiksel olarak anlamlı fark bulunamamıştır (p=0.844). DVT geçiren hastalarımızın %70'inde PAI-1 gen mutasyonuna rastlanırken, Protrombin gen mutasyonu hastaların hiçbirinde tespit edilememiştir. Provake eden faktörler arasında en sık erkek cinsiyet ve 3 ay içinde majör cerrahi geçirmiş olma bulunmuştur.
Sonuç: Çalışmamızda akut-subakut DVT teşhis edilen hastalar ile tiroit disfonksiyonu birlikteliği arasında net bir ilişki bulunamamıştır. Bu nedenle 'provokatif faktörlerin' tiroid disfonksiyonu ile venöz tromboembolizm (VTE) ilişkisini destekleyebileceğini düşünüyoruz.Bu konuda prospektif ve daha geniş kohortlu çalışmaların yapılması gerektiğini düşünüyoruz.

Anahtar Kelimeler: Derin ven trombozu, tiroid disfonksiyonu, trombofili

Introduction

Venous thrombosis (VT) is an important cause of morbidity and mortality in developed countries. Various risk factors have been identified for both genetic and acquired VT to date (1). But no significant risk factor can be identified in 25% to 50% of the cases (2). Identifying additional risk factors associated with VT will improve prevention of this disease. Studies on thyroid dysfunction among acquired risk factors, especially in the patient population with DVT, started to attract attention after the 2000s.

Thyroid dysfunction and autoimmunity are among the pathophysiological mechanisms leading to primary or secondary hemostatic disorders (3). Both

hyperthyroidism and hypothyroidism are known to influence the initiation of coagulation disorders (4). However, the clinical implications of its effects on the hemostatic system have received relatively little attention. Limited data exist about the association between thyroid dysfunction and the risk of venous thromboembolism (VTE). The aim of the present study is to disclose the prevalence of any kind of thyroid dysfunction in patients having acute or subacute deep venous thromboembolism (DVT).

Material and methods

This case-control study was conducted between November 2015 and June 2016, on 30 patients diagnosed as having DVT in our clinic Department of Cardiovascular Surgery. The study was approved by the local ethical committee with the protocol number of 2014-179-25/11. The study was conducted in accordance with the Declaration of Helsinki Ethical Principles.

Patients:

The study population was composed of 30 patients with acute or subacute DVT. All of the participants have given their informed consents. The diagnosis of DVT was made by compression ultrasound technique of the legs using a 9 MHz probe (Siemens S3000, Germany). Patients were divided into two groups as provoked (n=13) and unprovoked (n=17) according to the presence or absence of the criteria in Table-1. Patients with DVT having the criteria mentioned in Table-1 were classified as provoked DVT. All of the patients had DVT for less than 2 weeks. We have examined the patients for inherited genetic factors of thrombophilia. The demographic data of the patients were summarized in Table-2. All of the patients in our provoked and unprovoked groups were free of previously diagnosed thyroid disease or any previous use of thyroid hormone therapy.

Table 1: Predisposing factors for deep venous thrombosis

Patient age ≥ 60 years
Patients with History of DVT*
Patients with Malignancy
Patients with Obesity (BMI** ≥25)
Immobilized patients for more than 6 months
Varicose veins or venous insufficiency, recurrent DVT
Use of hormone replacement therapy or oral contraceptive agents
Chronic diseases such as atherosclerotic cardiovascular disease, acute respiratory diseases, cerebrovascular accidents or spinal injuries
Major surgery in less than 3-month time
Pregnancy or puerperium related DVT

*DVT: Deep vein thrombosis, **BMI: Body mass index

Table 2. Demographic data

	Unprovoked (n=13)	Provoked (n=17)	P value
Age (years)	54.5±13.9	46.2±18.3	0.185
Gender (M/F)	9/4	6/11	0.05
BMI	25.27 ± 2.34	26.35 ± 3.75	0.375
Distal DVT	13	15	0.123
Proximal DVT*	10	13	0.977
Concomitant Superficial Thrombosis	8	9	0.638
Smoke	1	1	0.845
Medications			
Corticosteroids	0	2	0.123
Antipsychotics	2	3	0.869
Antihypertensive drugs	1	7	0.007
Antidiabetics	3	4	0.869
COPD** drugs	1	1	0.845
Risk factors (%)			
Major surgery (in less than 3 months)	0	7	0.007
Trauma or fracture	1	2	0.845
BMI*** ≥ 25	7	10	0.785
Immobilisation	0	2	0.123
Pregnancy/Puerperium	0	2	0.123
Oral contraceptive use	0	1	0.304
Acute infection	1	2	0.845
Age (>60)	5	4	0.869
Malignant disease	0	2	0.123
Systemic disease	2	1	0.845
Recurrent DVT	2	0	0.123

*DVT: Deep Vein Thrombosis

**Chronic obstructive pulmonary disease (COPD)

***BMI: Body Mass Index

Determination of thyroid dysfunction and thyroid function tests:

We have screened all of the patients for abnormalities of thyroid hormone levels. Hyperthyroidism was defined as a suppressed level of thyroid stimulating hormone (TSH) with or without an increase in free thyroxine (FT4) levels in blood. Hypothyroidism was defined as an elevated level of TSH either with or without decreased levels of FT4. Blood samples were taken from antecubital vein following a 12h of fasting. Free triiodothyronine (FT3), FT4 and TSH levels were measured by direct chemiluminescence method (Advia Centaur XP, Siemens, Dublin, Ireland). Normal range were 2 to 4.3ng/mL for FT3, 0.5 to 1.2ng/mL for FT4 and 0.3 to 5,6µIU/mL for TSH. Anti-thyroid peroxidase antibodies

(Ab-TPO) and anti-thyroglobulin antibodies (Ab-Tg) were measured by ELISA method (Orgentek ELIZA kit, Diagnostika, GmbH, Mainz, Germany and ELIZA Reader, Bio-Tek Instrument Inc. ELx800, USA). Normal range were <60 U/ml for Ab-TPO and Ab-Tg. All of the patients in our provoked and unprovoked groups were free of previously diagnosed thyroid disease or any previous use of thyroid hormone therapy.

Definition of genetic tests:

DNA Extraction: Genomic DNA was extracted from peripheral blood leucocytes using SNPure Genomik DNA extraction kit, according to the manufacturer's instructions. Extracted DNAs have been preserved at -20 ° until amplification by Real Time PCR.

FV Leiden Gene Mutation: Factor V Leiden point mutation was detected through "Factor V Leiden Mutation Real Time PCR device" (ABI Prism 7500 Real-Time PCR System, USA) using "Factor V Leiden Mutation Real Time PCR Kit" (SNP Biotechnology, Turkey).

FV Cambridge Gene Mutation: Factor V Cambridge point mutation was detected through "Factor V Cambridge Mutation Real Time PCR device" (ABI Prism 7500 Real-Time PCR System, USA) using "Factor V Cambridge Mutation Real Time PCR Kit" (SNP Biotechnology, Turkey).

MTHFR 1298 Gene Polymorphism: MTHFR 1298 gene polymorphism was detected through "Real Time PCR device" (ABI Prism 7500 Real-Time PCR System, USA) using "MTHFR 1298 Mutation Real Time PCR Kit" (SNP Biotechnology, Turkey).

MTHFR 677 Gene Polymorphism: MTHFR 677 gene polymorphism was detected through "Real Time PCR device" (ABI Prism 7500 Real-Time PCR System, USA) using "MTHFR 677 Mutation Real Time PCR Kit" (SNP Biotechnology, Turkey).

FII G20210A (Prothrombin) Gene Mutation: Prothrombin G20210A point mutation was detected through "Real Time PCR device" (ABI Prism 7500 Real-Time PCR System, USA) using "Prothrombin G20210A Mutation Real Time PCR Kit" (SNP Biotechnology, Turkey).

PAI-1 (4G/5G) Gene Polymorphism: PAI-1 (4G/5G) gene polymorphism was detected through "Real Time PCR device" (ABI Prism 7500 Real-Time PCR System, USA) using "PAI-1 (4G/5G) Mutation Real Time PCR Kit" (SNP Biotechnology, Turkey).

Definition of clotting factors:

The plasma levels of clotting factors 7, 8, protein C, protein S, activated protein C resistance, anti-thrombin III, Von Willebrand factor and fibrinogen were measured using Instrumentation Laboratory ACLTOP 500 (Perkin Elmer, Massachusetts, USA) and same brand of kits. The normal value ranges of the tests are as follows: F7 %70-120, F8 %70-150, protein C %70-140, protein S %60-130, active protein C resistance <2.5, vWF 50-200 IU/dL, fibrinogen 200-400mg.

Statistical analysis:

Statistical analysis was carried out using SPSS for Windows (version 11.0, Chicago, IL, USA). Variables were presented as mean ± standard deviation (SD). Mann Whitney U test was used to compare mean values between groups. P< 0.05 was considered as statistically significant. Group comparisons were made by one-way ANOVA (Kruskall–Wallis), followed by Mann–Whitney U-test in case of significance.

Results

In the unprovoked DVT patients group, one patient had an elevated level of TSH and one had an elevated level of FT4 with a suppressed level of TSH. One patient in the provoked DVT group had a decreased level of TSH. Anti-TPO was positive in two patients, one from each of the study groups, Anti-TG was positive in only one patient in the unprovoked group. One patient with subclinical hyperthyroidism were included in the provoked group. One patient with clinical hyperthyroidism and one patient with subclinical hypothyroidism were included in the unprovoked group. The frequency of thyroid dysfunction for all patients was %10 (3/30). The laboratory findings of the groups were presented in Table 3 and the distribution of the pathological laboratory values was presented in Table 4. All of the patients had a genetic predisposition for deep venous thrombosis in the provoked group. The PAI -1 gene mutation was detected in 70% (21/30) of the study cohort but there was no significant difference between the groups (p=0.623). The distribution of the gene mutations in the study cohort was presented in Table-5.

Table 3. Laboratory Findings

	Unprovoked	Provoked	p value
Factor 7	78.77 ± 24.93	79.29 ± 28.12	0.958
Factor 8	155.62 ± 31.77	141.94 ± 38.22	0.220
Protein C	94.00 ± 30.23	100.53 ± 36	0.603
Protein S	71.36 ± 30.77	67.19 ± 15.61	0.631
Active protein C resistance	1.63 ± 0.84	1.90 ± 0.76	0.369
Anti-thrombin 3	89.45 ± 9.64	99.91 ± 12.30	0.017
Fibrinogen	513.31 ± 201.85	441.06 ± 135.22	0.250
von Willebrand factor	187.68 ± 48.77	179.82 ± 28.54	0.584
FT3	2.92 ± 0.37	2.91 ± 0.52	0.969
FT4	0.97 ± 0.27	.97 ± 0.24	0.976
TSH	2.69 ± 2.66	1.72 ± 1.14	0.187
TPO antibody	8.64 ± 31.15	2.61 ± 10.74	0.462
Thyroglobulin antibody	24.62 ± 88.75	0	0.260

All values are presented as mean ± standard deviation. FT3: Free triiodothyronine; FT4: free thyroxine; TSH: Thyroid stimulating hormone; TPO: Thyroid peroxidase.

Table 4. Laboratory values disorders

	Unprovoked	Provoked	P value
F7 disorder	2 (15.38)	5 (29.41)	0.360
F8 disorder	5 (38.46)	6 (35.29)	0.858
Protein C disorder	2 (15.38)	3 (17.64)	0.869
Protein S disorder	5 (28.46)	6 (35.29)	0.858
Active protein c resistance	9 (69.23)	12(70.58)	0.936
Anti-thrombin 3 disorder	2 (15.38)	1 (5.88)	0.391
Fibrinogen disorder	11 (84.61)	11 (64.70)	0.212
vWF disorder	4 (30.76)	2 (11.76)	0.198
FT3 disorder	0	0	NA
FT4 disorder	1 (7.69)	3 (17.65)	0.415
TSH disorder	2 (15.38)	1 (5.88)	0.391
Anti-TPO disorder	1 (7.69)	0	0.190
Anti-Thyroglobulin disorder	1 (7.69)	0	0.190

All values are presented as counts and percentages (%). F7: Factor 7; F8: Factor 8; vWF: von Willebrand factor; FT3: Free triiodothyronine; FT4: free thyroxine; TSH: Thyroid stimulating hormone; TPO: Thyroid peroxidase. NA: Not-applicable.

Table 5: The distribution of the gene mutations found in the study patients

		Provoked	Unprovoked	P (value)
MTHFR*	carrier	15	10	0.41
	negative	2	3	
Prothrombin gene mutation	carrier	1	0	0.34
	negative	16	13	
Factor V Leiden gene mutation	carrier	8	4	0.367
	negative	9	9	
PAI-1**	carrier	12	9	0.623
	negative	5	4	

* Methylenetetrahydrofolate Reductase gene mutation

** Plasminogen activator inhibitor-1 gene mutation

Discussion

The major clinical presentation forms of venous thromboembolism are DVT and pulmonary thromboembolism (PTE). Therefore, it is said that the most common cause of non-cardiac sudden deaths is PTE (5). The major source of thromboembolic material in PTE is the deep veins of the lower extremities. It is obvious that the better the knowledge of DVT and PTE ethiology and predisposing factors, the better the results of preventive and treatment strategies will be.

Thyroid hormones can directly affect the synthesis of the coagulation factors and the immune system. There are some clinical studies (3-9) about the relation between thyroid dysfunction and DVT which are hypothesizing some pathophysiologic mechanisms of the effect of thyroid dysfunction on hemostasis, but a strong evidence is not presented yet. Hypercoagulability and hypofibrinolysis can be seen concomitantly with hypothyroidism (10,11). On the contrary, there are some studies reporting a hyperfibrinolysis in deep hypothyroidism (11,12). Also an increase in the activity of immune system was reported in thyroid diseases (13,14). It can be foreseen that the risk of venous thromboembolism (VTE) may vary when the functions of the immune system diminish in elderly patients. We think that the controversy between the reports of these studies may be due to the changes of the fibrinolytic activity and/or the changes of auto-immune activity along with the increased age.

There was no difference in the prevalence of thyroid diseases in the provoked and unprovoked groups of patients in our study. We found the rate of thyroid gland dysfunction in DVT patients as 10%. Also, we found that the most provocative factors were male gender and having a major surgery in the last 3-months period in contrary to literature. There was no significant effect of age and obesity in the groups. According to our results, we can say that the changes in thyroid hormone levels do not affect risk of VTE. We found no strong evidence of correlation between thyroid hormone levels and the risk of DVT in general population. Therefore, we think that the 'provocative factors' may support the relation of thyroid dysfunction and VTE.

As the positive aspect of our study, besides its prospective design, since the observation period started simultaneously with VTE, the relationship between thyroid dysfunction and the short-term risk of VTE was clearly evaluated. Thus, temporary thyroid dysfunction was not allowed to be overlooked due to the time elapsed from the diagnosis of DVT to the evaluation of thyroid function.

One of the limitations of our study is the small population and low statistical power. Statistical power is critical for the correct interpretation of risk estimates. The low prevalence of individuals with thyroid dysfunction, as in our study, led to limited statistical power for risk assessment in these groups. Layered analyzes could not be performed for provoked/unprovoked DVT because there was little or no thyroid dysfunction. The reason for the small patient population is the lack of technical infrastructure and cost in our clinic. There was a problem with the supply of test kits in our hospital. When test kits were provided, the patients were out of the appropriate period for the study because they

passed the acute period.

The main purpose of our study was to detect thyroid dysfunction among the causes of DVT. It was not designed as a genetic study. However, the two subheadings reached were on genetic predisposition. The first one is the positivity of the PAI-1 gene mutation in all of the patients in our study. It can be thought that patients with PAI-1 gene mutation have a high risk of DVT. Therefore, we suggest the utilization of PAI-1 gene mutation analysis as a monitoring test in the high risk patient groups to decrease the morbidity and mortality rates and DVT prophylaxis in case of a positive test result.

Indeed, in a large-scale meta-analysis, it was supported that the PAI-1 rs17999889 polymorphism might be one of the predisposing factors of VTE in the Caucasian-East Asian population, particularly in those with DVT and Factor V Leiden mutation (15). The second one is the negativity of the Prothrombin gene mutation in all of the patients in our study. In the western population, the prevalence of hereditary thrombophilia for prothrombin gene mutation and Factor V Leiden is 4% (16). In a thrombophilia study including 58 Turkish patients under 45 years of age who presented with VTE, prothrombin gene mutation was detected in 16 (27%) patients (17). This is a relatively high frequency compared to our study and general literature. Large-scale genetic studies are needed for definitive conclusions about these genetic mutations in the patient population we selected.

Conclusion

There is no relation between the thyroid gland dysfunction and VTE in the patients with acute / subacute DVT according to the results of this prospective study. We think that larger scale studies should be conducted on this subject.

Conflict of Interest: The authors declared no conflict of interest.

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