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Differences in autoimmunity factors based on the activity of thromboangiitis obliterans

Tromboangiitis obliterans aktivitesine bağlı olarak otoimmünite faktörlerindeki farklılıklar

Abbas Shapouri-Moghadam, M.D., Ph.D.[1], Seyed Jalil Tavakkol Afshari, M.D., Ph.D.[1], Mohammad-Hadi Saeed Modaghegh, M.D.[2], Mahmoud Mahmoudi, M.D., Ph.D.[1], Hamid Reza Rahimi, M.D., Ph.D.[3], Seyed Morteza Ehteshamfar, M.D., PhD.[1]

[1]Immunology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Vascular and Endovascular Surgery Research Center, Mashhad University of Medical Sciences Alavi Hospital, Mashhad, Iran
[3]Department of Medical Genetics and Molecular Medicine, Mashhad University of Medical Sciences Faculty of Medicine, Mashhad, Iran

ABSTRACT

Objective: The treatment of Buerger's disease (BD) presents a medical problem as its etiology is still unclear. In this study, our objective was to evaluate the serum levels of autoimmune markers in patients with different clinical features of BD.

Methods: In this study, 80 BD patients were categorized in three groups using a cross-sectional design: migratory thrombophlebitis, cold sensitivity, and skin discoloration (mild symptoms); chronic ulcers, claudication, and burning pain of the feet at night (moderate symptoms); pain at rest and spontaneous gangrene (severe symptoms). Enzyme-linked immunosorbent assay was performed to measure antibodies against immunoglobulin M rheumatoid factor (IgM RF), anti-nuclear antibodies (ANA), antibodies against cyclic citrullinated peptide (anti-CCP), antiphospholipid antibodies (APA), anti-cardiolipin antibodies (ACLA), anti-double stranded DNA (anti-dsDNA), and extractable nuclear antigen (ENA) profile.

Results: Patients with severe symptoms showed the lowest age (p=0.031), ESR (p<0.001), and highest prevalence of ischemia (p<0.001). In all the patients, the serum levels of ANA and IgM RF were higher than 1 U and 15 IU/mL, respectively. However, the progression of the disease from mild to moderate did not affect these markers significantly (p>0.05). Other markers were negative in patients with BD.

Conclusion: The findings of this study indicate that BD may closely be correlated to transient autoimmune phenomena, despite the fact that further research is required to investigate how transient unspecific autoimmune reactions contribute to the BD pathogenesis.

ÖZET

Amaç: Buerger hastalığının (BH) tedavisi, etiyolojisi hala net olmadığı için tıbbi bir sorun teşkil etmektedir. Bu çalışmanın amacı, farklı BH klinik özellikleri olan hastalarda otoimmün belirteçlerin serum seviyelerini değerlendirmektir.

Yöntemler: Bu çalışmada, 80 BH hastası, kesitsel bir tasarım kullanılarak üç gruba ayrıldı: göçmen tromboflebit, soğuğa duyarlılık ve ciltte renk değişikliği (hafif semptomlar); kronik ülserler, topallama ve geceleri ayaklarda yanma ağrısı (orta dereceli semptomlar); istirahatte ağrı ve spontan kangren (şiddetli semptomlar). İmmünoglobulin M romatoid faktöre karşı antikorlar (IgM RF), anti-nükleer antikorlar (ANA), siklik sitrüline peptide karşı antikorlar (anti-CCP), antifosfolipid antikorları (APA), anti-kardiyolipin antikorları (ACLA), anti-çift sarmallı DNA (anti-dsDNA) ve ekstrakted nükleer antijen (ENA) profili ölçmek için ELISA yöntemi kullanıldı.

Bulgular: Şiddetli semptomları olan deneklerde en düşük yaş (p=0.031), ESR (p<0.001), en yüksek iskemi prevalansı (p<0.001) gözlendi. Tüm hastalarda serum ANA ve IgM RF seviyeleri sırasıyla 1 U ve 15 IU/mL'den yüksekti. Ancak hastalığın hafif evreden orta evreye ilerlemesi bu belirteçleri anlamlı olarak etkilemedi (p>0.05). BH hastalarında diğer belirteçler negatifti.

Sonuç: Bu çalışmanın bulguları, BH'nin geçici otoimmün fenomenlerle yakından ilişkili olabileceğini göstermektedir. Bununla birlikte, geçici spesifik olmayan otoimmün reaksiyonların BH patogenezine nasıl katkıda bulunduğunu araştırmak için daha fazla araştırma yapılması gerekmektedir.

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Correspondence: Seyed Morteza Ehteshamfar, M.D., Immunology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
Tel: +98 915 314 0112 e-mail: drehteshamfar@yahoo.com

Thromboangiitis obliterans (TAO) or Buerger's disease (BD) refers to a recurring and progressive vasculitis that starts with ischemia in small distal arteries and veins, and further involves segmental inflammatory conditions.[1] Smoking, genetic predisposition, immune reactions, and coagulation have been investigated in relation to the development of BD.[2] This disease is associated with symptoms, such as ischemic pain, intermittent claudication, and skin ulcers. Moreover, less than half of patients with BD develop thrombophlebitis as well as Raynaud's phenomenon.[3,4] The clinical presentation of critical limb ischemia often consists of rest pain, ulcerations, and digital gangrene and is observed in more advanced patients. BD mainly affects the arteries of the extremities, but there is some evidence for the involvement of the cerebral, coronary, renal, mesenteric, and pulmonary arteries.[5] The etiology of BD is still unclear and may be related to autoimmune response. In fact, several studies have identified circulating autoreactive antibodies having effects on endothelial cells and the walls of the blood vessels when the disease is active.[6,7] Previous reports have shown that HLA class I and II alleles correlate to BD. In this study, we aimed to investigate whether changes in the clinical presentation of BD are associated with autoimmune reactions.

METHODS

Procedure

In this study, 91 patients were initially recruited on the basis of a call to action in the vascular and endovascular research center (VERC) in 2012. There is a regional data bank in the VERC consisting of clinical features, blood parameters, and gene profile of patients with or suspicious for BD. For this study, the data of 91 previously confirmed patients were extracted from the registry. After the first contact with them, only 80 patients agreed to give a blood sample of 10 mL for more immunological analyses. Shionoya's clinical criteria were used to diagnose BD.[8,9] Thus, all the participants were evaluated to have a score of 4 or 5. As for the exclusion criteria, this study did not include reluctant patients and those with additional autoimmune disease (i.e., scleroderma or the CREST syndrome, systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, antiphospholipid antibody syndrome, and vasculitis), malignancy, viral diseases, and allergies. Of note, there was one female patient who was excluded from the study to avoid confounding effects related to the sex differences on clinical and laboratory findings.

Abbreviations:

ACLA	*Anti-cardiolipin antibodies*
ANA	*Anti-nuclear antibodies*
ANOVA	*One-way analysis of variance*
Anti-CCP	*Antibodies against cyclic citrullinated peptide*
anti-dsDNA	*Anti-double stranded DNA*
anti-nRNP	*Anti-ribonuleoprotein*
anti-Sm	*Anti-Smith*
anti-SS-A	*Anti-Sjögren's syndrome A*
anti-SS-B	*Anti-Sjögren's syndrome B*
APA	*Antiphospholipid antibodies*
BD	*Buerger's disease*
CI	*Confidence intervals*
ELISA	*Enzyme-linked immunosorbent assay*
ENA	*Extractable nuclear antigen*
ESR	*Erythrocyte sedimentation rate*
IgM RF	*Immunoglobulin M rheumatoid factor*
IQ	*Interquartile range*
IQR	*Interquartile range*
Jo-1	*Histidyl-tRNA synthetase*
NR	*Not reported*
nRNP	*Ribonuleoprotein*
Scl-70	*Scleroderma-70*
SD	*Standard deviation*
Sm	*Smith*
SS-A	*Sjögren's syndrome A*
SS-B	*Sjögren's syndrome B*
TAO	*Thromboangiitis obliterans*
VERC	*Vascular and endovascular research center*

The patients signed informed consent documents, and the demographic data as well as clinical symptoms were collected using a researcher-made questionnaire. This was designed as a cross-sectional study approved by the medical research committee of Mashhad University of Medical Sciences on July 1, 2016 (Ethical code: IR.MUMS.REC.1393.197). A specialist was responsible for recording the participant's characteristics. A 10-mL blood sample was then obtained from each patient to measure the serum levels of antibodies to immunoglobulin M rheumatoid factor (IgM RF; Rheumatoid factor enzyme-linked immunosorbent assay (ELISA) Kit; Euroimmun, Germany), anti-nuclear antibodies (ANA; ANA-Ease ELISA Kit; Genesis, Biocompare, USA), anti-cyclic citrullinated peptide (anti-CCP; Autoantibodies against CCP; Euroimmun, Germany), antiphospholipid antibodies (APA; Autoantibodies against phospholipids; Euroimmun, Germany), anti-cardiolipin antibodies (ACLA; Cardiolipin-GM ELISA Kit; AESKU, Wendelsheim, Germany), anti-double stranded DNA (anti-dsDNA; Autoantibodies against dsDNA; Euroimmun, Germany), and extractable nuclear antigen (ENA; ENA ELISA Kit; antibodies-online, England) profile by the ELISA method. The normal range for RF (<15 IU/mL), ANA (<1 IU), anti-CCP (<20 U/mL), APA (<20 SGU or <20 SMU), ACLA (<40 GPL or <40

Table 1. Categorical characteristics of patients with BD

Variables	Disease severity			p
	Mild (n=11)	Moderate (n=46)	Severe (n=23)	
Smoking status, n (%)				0.639*
Successful smoking cessation	4 (36.36)	15 (38.46)	4 (19.05)	
Unsuccessful quitting activity	1 (9.09)	8 (20.51)	5 (23.81)	
No change in cigarette use	2 (18.18)	9 (23.08)	6 (28.57)	
Smoking reduction	4 (36.36)	7 (17.95)	6 (28.57)	
Amputation, n (%)	8 (72.73)	19 (41.30)	11 (47.83)	0.172†
Superficial thrombophlebitis, n (%)	1 (9.09)	4 (8.70)	0 (0.00)	0.328*
Cold sensitivity, n (%)	7 (63.64)	34 (73.91)	20 (86.96)	0.278†
Ischemia, n (%)	0 (0.00)[a]	40 (86.96)[b]	23 (100)b	<0.001*

BD: Buerger's disease.
*Fisher's exact test: 20% or more cells have an expected count less than 5. Small different letters in each row indicate significant differences in ischemia between different symptoms at the 0.05 level in the Fisher's exact test.
†Pearson chi-squared.

MPL), anti-dsDNA (<30 IU/mL), and ENA profile (<1 U) was considered based on the manufacturer's instructions. The ENA profile includes anti-Sjögren's syndrome A (anti-SS-A), anti-Sjögren's syndrome B (anti-SS-B), anti-Smith (anti-Sm), anti-ribonuleoprotein (anti-nRNP), anti- anti-histidyl-tRNA synthetase (anti-Jo-1), and anti-scleroderma (anti-Scl70).[10]

Statistical Analysis

Data were collected and fed into the SPSS version 13 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented in the form of mean, standard deviation (SD), median, interquartile range (IQ), frequency, and percentage. The normal data distribution was evaluated by the Shapiro-Wilk test. If the p value was less than 0.05, the data did not follow a normal distribution. Therefore, a two-step approach was applied to transform the continuous variables to normal as described by Templeton.[11] Non-parametrical tests were selected when a normal distribution was less likely to occur even after transformation. The one-way analysis of variance (ANOVA) or the Kruskal-Wallis test was used to explore the effect of the severity of the disease on the patient's characteristics and autoimmune markers. The Welch ANOVA was used when the homogeneity of variances were not met according to Levene's test. If the P value of parametrical or non-parametrical variance analysis was less than 0.05, the Schiffe's post-hoc test was applied as the number of patients at each stage of the disease was not equal. Furthermore, analysis of covariance was performed to adjust for the confounding variable, on which the disease severity had a significant effect, such as age and erythrocyte sedimentation rate (ESR). Finally, the Pearson chi-squared test or the Fisher's exact test was applied to compare these autoimmune markers as dichotomous variables among patients with BD with mild to severe clinical presentations. The Bonferroni correction was applied for controlling Type I error. All statistical analyses were considered significant at a p value <0.05 with the 95% confidence intervals (CI).

RESULTS

This study consisted of 80 patients with BD. A total of 13.75% (n=11) was diagnosed with migratory thrombophlebitis, cold sensitivity or Raynaud's phenomenon, and skin discoloration, which were classified as mild symptoms. Forty-six patients (57.5%) developed moderate symptoms, including chronic ulcers, claudication, and burning pain of the feet at night, whereas more than one fourth (n=23, 28.75%) presented with pain at rest and spontaneous gangrene as severe symptoms. The smoking status, amputation, and clinical presentations in our patients are summarized in Table 1. In the patients with mild symptoms, successful smoking cessation and smoking reduction were the prevailing smoking status (72.72%). The highest amount of amputation was observed in the patients with mild symptoms (72.73%). Interestingly,

Table 2. Continuous characteristics of patients with BD

Variables	Disease severity			p
	Mild (n=11)	Moderate (n=46)	Severe (n=23)	
Mean age, (SD), years	48.68 (2.99)[b]	42.43 (1.20)[ab]	40.43 (1.48)[a]	0.031*
Mean age at onset (SD), years				
Untransformed	40.78 (2.99)	34.60 (1.04)	33.89 (1.59)	NR†
Transformed‡	41.13 (3.05)	34.50 (0.92)	33.91 (1.54)	0.123§
Median smoking time (IQR), years	25.00 (11.00)	17.00 (18.00)	20.00 (13.50)	0.061‖
Median cigarette number (IQR)	20.00 (7.50)	20.00 (2.50)	20.00 (0.00)	0.620‖
Mean ESR (SD), mm/hour				
Untransformed	13.44 (3.53)	11.00 (3.27)	34.62 (7. 34)	NR†
Transformed‡	20.22 (6.45)[ab]	12.69 (3.56)[a]	38.36 (5.10)[b]	<0.001*

BD: Buerger's disease; ESR: erythrocyte sedimentation rate; NR: not reported; SD: standard deviation; IQR: interquartile range.
*Analysis of variance: Small different letters in each row indicate significant differences in age and ESR between different symptoms at the 0.05 level in the Schiffe's post-hoc test.
†P value for untransformed variables is not reported. ‡The variable follows normal distribution after a two-step transformation; §Welch ANOVA; ‖Kruskal-Wallis test.

none of the patients with severe symptoms had superficial thrombophlebitis. At least 60% of the patients with BD experienced cold sensitivity. There was a significant difference in ischemia (p<0.001) among the three categories of the BD symptoms. Of the patients, 86.96% with moderate symptoms and 100% of the patients with severe symptoms suffered from ischemia.

As can be seen in Table 2, these three categories of the patients are homogeneous in terms of age at onset (p=0.123), smoking duration (p=0.061), and cigarette numbers (p=0.620); however, there are significant differences in age (p=0.031) and ESR (p<0.001). Patients with severe symptoms were youngest (40.43±1.48 years) and had the earliest age at onset (untransformed mean: 33.89±1.59 years; transformed mean: 33.91±1.54 years). Their ESR (untransformed mean: 34.62±7.34 mm/hour; transformed mean: 38.36±5.10 mm/hour) was about twice as much as 15 mm/hour.

Table 3 demonstrates the mean levels of the autoimmune markers in patients with BD. Overall, the progression of the symptoms from mild to severe caused no significant change in the immunomarkers (p>0.05). Even adjustment for the confounding variables (i.e., age and ESR) did not alter this finding (p>0.05). Of the factors tested for autoimmunity, the mean values of anti-CCP, ACLA-G, ACLA-M, APA-G, APA-M, anti-dsDNA, and ENA profile were within the normal reference range; and the severity of the symptoms failed to increase these values above the cutoff points. Applying the normal transformation to these data had no effect on these results, although patients with BD showed mean ANA and IgM RF levels more than the normal limits irrespective of their symptom category. The first category of the patients with mild clinical presentations was found to have the highest ANA (untransformed mean: 6.05±0.94 U; transformed mean: 7.54±3.80 U) and IgM RF (41.15 (IQR: 21.78) IU/mL); however, these values did not reach the significant level.

Table 4 shows that a conversion of the immunomarker scale from continuous to dichotomous indicates no significant differences among the patients (p>0.05).

DISCUSSION

The main findings of this study were that the majority of patients with BD were at the moderate stage of the disease with chronic ulcers, claudication, and burning pain of the feet at night. This observation shows neurologic involvement among our patients. Studies confirm that neurological symptoms largely develop at all stages of the disease. It begins with paresthesia and cold sensation and subsequently progresses toward the manifestation of claudication and eventually ischemic rest pain.[12-14] Our study also demonstrated that when BD progressed from mild to severe

Table 3. Immunomarkers (continuous parameters) and adjusted differences in patients with BD with different clinical presentations

Variables	Disease severity				Difference in mean (95% CI)[c]		
	Mild (n=11)	Moderate (n=46)	Severe (n=23)	p	Comparison between mild and moderate levels	Comparison between and severe mild levels	Comparison between moderate and severe levels
Median anti-CCP (IQR)	1.90 (3.99)	1.35 (2.90)	1.45 (2.35)	0.790* 0.965†	0.13 (-19.39 to 19.65)	-1.41 (-22.82 to 20.00)	-1.54 (-16.29 to 13.20)
Mean ACLA-G (SD)							
Untransformed	11.69 (2.29)	9.67 (1.66)	9.84 (1.47)	NR	0.09 (-8.67 to 8.86)	0.64 (-9.30 to 10.57)	0.54 (-6.32 to 7.41)
Transformed	13.03 (10.10)	10.71 (9.03)	10.92 (9.59)	0.759‡ 0.869§			
Mean ACLA-M (SD)							
Untransformed	3.03 (1.77)	1.17 (0.37)	1.96 (0.66)	NR	0.15 (-2.87 to 3.17)	-0.74 (-4.07 to 2.58)	-0.89 (-3.32 to 1.53)
Transformed	2.11 (1.06)	1.84 (0.44)	2.66 (0.74)	0.605‡ 0.660§			
Mean APA-G (SD),							
Untransformed	1.81 (0.66)	3.44 (2.26)	1.85 (0.60)	NR	-2.73 (-11.89 to 6.44)	1.23 (-8.88 to 11.3)	3.96 (-3.73 to 11.64)
Transformed	2.49 (2.64)	6.10 (1.75)	2.06 (2.38)	0.319‡ 0.423§			
Mean APA-M (SD),							
Untransformed	2.37 (1.21)	1.79 (0.23)	1.64 (0.21)	NR	-0.02 (-0.97 to 0.94)	-0.22 (-1.27 to 0.84)	-0.20 (-0.96 to 0.56)
Transformed	1.80 (0.64)	2.20 (0.27)	1.82 (0.40)	0.668‡ 0.796§			
Mean ANA (SD),							
Untransformed	6.05 (0.94)	5.51 (1.24)	6.04 (3.22)	NR	1.76 (-6.98 to 10.50)	3.04 (-6.71 to 12.79)	1.28 (-6.17 to 8.74)
Transformed	7.54 (3.80)	7.20 (1.37)	7.49 (2.24)	0.991‡ 0.746§			
Mean Anti-dsDNA (SD),							
Untransformed	4.52 (1.39)	8.22 (2.15)	10.04 (4.61)	NR	-9.04 (-21.69 to 3.61)	-12.38 (-26.87 to 2.12)	-3.34 (-14.69 to 8.02)
Transformed	3.11 (4.44)	10.94 (2.28)	12.98 (2.99)	0.190‡ 0.106§			
Median IgM RF (IQR),	41.15 (21.78)	30.99 (46.99)	23.38 (14.64)	0.065* 0.080†	8.36 (-10.08 to 26.80)	17.06 (-3.17 to 37.29)	8.70 (-3.88 to 21.29)
Mean Sm (SD),							
Untransformed	0.17 (0.02)	0.16 (0.02)	0.16 (0.01)	NR	-0.02 (-0.11 to 0.07)	-0.04 (-0.14 to 0.06)	-0.02 (-0.09 to 0.06)
Transformed	0.18 (0.04)	0.18 (0.02)	0.18 (0.04)	0.911‡ 0.654§			

Table 3. Immunomarkers (continuous parameters) and adjusted differences in patients with BD with different clinical presentations (Continue)

Variables	Disease severity				Difference in mean (95% CI)[c]		
	Mild (n=11)	Moderate (n=46)	Severe (n=23)	p	Comparison between mild and moderate levels	Comparison between and severe mild levels	Comparison between moderate and severe levels
Mean nRNP (SD),							
Untransformed	0.15 (0.02)	0.17 (0.03)	0.18 (0.03)	NR	-0.07 (-0.21 to 0.06)	-0.06 (-0.21 to 0.09)	0.01 (-0.10 to 0.12)
Transformed	0.15 (0.05)	0.19 (0.02)	0.22 (0.03)	0.523‡ 0.407§			
Mean SS-A (SD),							
Untransformed	0.25 (0.07)	0.21 (0.01)	0.21 (0.01)	NR	-0.02 (-0.13 to 0.08)	-0.02 (-0.13 to 0.09)	0.01 (-0.08 to 0.09)
Transformed	0.22 (0.04)	0.22 (0.02)	0.23 (0.02)	0.951‡ 0.862§			
Mean SS-B (SD),							
Untransformed	0.17 (0.07)	0.14 (0.03)	0.16 (0.02)	NR	0.05 (-0.09 to 0.19)	-0.01 (-0.16 to 0.15)	-0.05 (-0.17 to 0.07)
Transformed	0.20 (0.04)	0.16 (0.02)	0.19 (0.03)	0.585‡ 0.490§			
Mean Scl-70 (SD),							
Untransformed	0.13 (0.01)	0.15 (0.02)	0.18 (0.04)	NR	-0.04 (-0.16 to 0.08)	-0.07 (-0.21 to 0.06)	-0.04 (-0.14 to 0.07)
Transformed	0.14 (0.03)	0.17 (0.02)	0.20 (0.03)	0.558‡ 0.391§			
Mean Jo-1 (SD),							
Untransformed	0.16 (0.03)	0.19 (0.03)	0.19 (0.04)	NR	-0.05 (-0.18 to 0.09)	-0.09 (-0.23 to 0.06)	-0.04 (-0.15 to 0.07)
Transformed	0.17 (0.04)	0.21 (0.02)	0.22 (0.03)	0.673‡ 0.311§			

ACLA: Anti-cardiolipin antibodies; Anti-CCP: Antibodies against cyclic citrullinated peptide; Anti-dsDNA: Anti-double stranded DNA; ANA: Anti-nuclear antibodies; APA: Antiphospholipid antibodies; BD: Buerger's disease; CI: Confidence intervals; IgM RF: Immunoglobulin M rheumatoid factor; Jo-1: histidyl-tRNA synthetase; nRNP: Ribonuleoprotein; Scl-70: Scleroderma-70; SD: Standard deviation; SS-A: Sjögren's syndrome A; SS-B: Sjögren's syndrome B; Sm: Smith. c indicates (Quade's) ANCOVA adjusting for age and ESR.
*Kruskal-Wallis test.
†Quade's analysis of covariance (ANCOVA) adjusting for age and ESR.
‡one-way ANOVA.
§ANCOVA adjusting for age and ESR.

symptoms, there was a statistically significant difference in the amount of ischemic limbs. The patients at the moderate and severe stages of the disease greatly suffered from ischemia as opposed to those at the earlier stage. Despite the highest prevalence of ischemic limbs at the advanced stages of BD, less amounts of amputation were found in these patients. It has been documented that amputation must be delayed until the patients have stopped smoking,[15] which justifies the highest amount of amputation in the patients with mild symptoms. Indeed, these patients achieved successful smoking cessation or reduced smoking. Another factor worthy of attention was age at onset. The patients who presented with BD at younger ages would experience the worst symptoms. Probably, an early age at diagnosis could impact the progression of the disease from mild to severe stages. Some reports exist concerning the effect of early age at onset on the worst prognosis and course of some autoimmune diseases.[16] ESR is one of the acute phase reactants

Table 4. Proportion of normal immunologic outcomes (dichotomous parameters) in patients with BD with different clinical presentations

Variables	Disease severity			
	Mild (n=11)	Moderate (n=46)	Severe (n=23)	p†
Anti-CCP (< 20 U/mL)*, n (%)	10 (90.9)	44 (100.0)	20 (100.0)	0.147
ACLA-G (< 40 GPL), n (%)	11 (100.0)	44 (95.7)	23 (100.0)	0.665
ACLA-M (< 40 MPL), n (%)	11 (100.0)	46 (100.0)	23 (100.0)	-
APA-G (< 20 SGU), n (%)	11 (100.0)	43 (93.5)	23 (100.0)	0.710
APA-M (< 20 SMU), n (%)	11 (100.0)	46 (100.0)	23 (100.0)	-
ANA (< 1 U), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Anti-dsDNA (< 30 IU/mL), n (%)	11 (100)	40 (90.9)	18 (90.0)	0.714
IgM RF (< 15 IU/mL), n (%)	0 (0.0)	14 (37.8)	6 (46.2)	0.138
Sm (< 1 U), n (%)	11 (100.0)	46 (100.0)	23 (100.0)	-
nRNP (< 1 U), n (%)	11 (100.0)	46 (100.0)	23 (100.0)	-
SS-A (< 1 U), n (%)	11 (100.0)	46 (100.0)	23 (100.0)	-
SS-B (< 1 U), n (%)	11 (100.0)	46 (100.0)	23 (100.0)	-
Scl-70 (< 1 U), n (%)	11 (100.0)	46 (100.0)	23 (100.0)	-
Jo-1 (< 1 U), n (%)	11 (100.0)	46 (100.0)	23 (100.0)	-

ACLA: Anti-cardiolipin antibodies; Anti-CCP: Antibodies against cyclic citrullinated peptide; Anti-dsDNA: Anti-double stranded DNA; ANA: Anti-nuclear antibodies; APA: Antiphospholipid antibodies; BD: Buerger's disease; CI: Confidence intervals; IgM RF: Immunoglobulin M rheumatoid factor; Jo-1: histidyl-tRNA synthetase; nRNP: Ribonuleoprotein; Scl-70: Scleroderma-70; SD: Standard deviation; SS-A: Sjögren's syndrome A; SS-B: Sjögren's syndrome B; Sm: Smith.
*Normal range.
†Fisher's exact test: 20% or more cells have an expected count less than 5.

that was normal or less than 15 mm/hour in more than half of the patients (i.e., those at the moderate stage). The progression of BD to the development of severe symptoms significantly increased ESR up to twice the normal limit. False results commonly occur when measuring ESR. Furthermore, it responds less quickly to changes in clinical features.[17] As evident in our findings, the significant increase in ESR was found in the severe stage of BD.

It is widely accepted that autoimmune diseases are more likely to be diagnosed within years of the presence of their related autoantibodies.[18] As a result, there is a possibility that autoantibodies can predict certain diseases and their level of progression.[19] Therefore, the goal of this study was to identify these markers and their effect on clinical presentations in BD.

All the patients with BD with migratory thrombophlebitis, cold sensitivity, and/or skin discoloration (mild symptoms) had positive ANA and IgM RF. Only one patient in early stage was found with positive anti-CCP. For chronic ulcers, claudication, and/or burning pain of the feet at night (moderate symptoms), 100% and 62.2% of patients with BD were observed with abnormal ANA and IgM RF levels, respectively. Positive ACLA-G, APA-G, and anti-dsDNA occurred in two (95.7%), three (93.5%), and six (90.9%) patients at the moderate stage, respectively. Moreover, the presence of pain at rest and/or spontaneous gangrene (severe symptoms) in patients with BD was associated with positive ANA. At the severe stage, as many as 10% and 53.8% showed high serum levels of anti-dsDNA and IgM RF. These differences in the clinical presentations of BD at different stages did not reach significant levels.

The existing literature links the role of ANA to the progression of immunolesion caused by TAO as follows; ANA can trigger neutrophils to produce reactive oxygen species and lytic enzymes, which in turn lead to the lysis of endothelial cells and neutrophils.[20,21] ANA IgG can affect several functions of neutrophils, including the improvement of a proinflammatory phenotype that enables neutrophils to increase the collateral impairment to endothelial and other cells.[22] Finally, it is possible that ANA disturbs the

T-cell compartment and changes the T-cell subsets that effectively contribute to the T-cell immunological function and directly impair endothelial cells.[23]

Except for ANA and IgM RF, the mean levels of other immunological markers were within the normal range among all the patients with BD. Although these events imply that transient autoimmune phenomena might be involved in the BD activity, these immunological tests did not indicate that the patients with positive results tended to go on to the advanced stages of the disease. There are some reports with conflicting results related to these immunological tests. For example, Jorge et al.[15] have described a case of BD with negative ANA, anti-ds DNA, SS-A, SS-B, nRNP, Sm, Scl-70, and other immunological markers. Piazza and Creager[24] have recorded the clinical features of a patient with BD and negative ANA and Scl-70. Johnson and Enzenauer[25] revealed an elevated ESR and positive ANA titer with a negative RF titer for a BD case.

In addition, Guo et al.[26] have figured out that the serum levels of various immune complexes, such as anti-endothelial cell antibodies, ANA, and ACLA were notably high in patients with BD compared with those in the healthy control. In another study, Maslowski et al.[27] have pointed out the increased level of ACLA in TAO. Moreover, they showed that the high antibody titer led to increased morbidity, such as major limb amputation; although some symptoms, for example, upper limb involvement, digital necrosis, superficial thrombophlebitis (or deep venous thrombosis), were not considerably connected to the presence of ACLA. The study by Schenkein et al.[28] have demonstrated that patients with BD who developed generalized periodontitis had a significantly marked titer of immunoglobulin G (IgG) or IgM ACLA. Therefore, the presence of various auto-antibodies supports the theory of the autoimmune character of BD. However, these immunological tests are not appropriate markers for the diagnosis of BD. Many other autoimmune diseases have showed positive results.[29]

Limitations

The main strength of this study was the recruitment of the patients with BD from a single center. Accordingly, our patients represented a relatively homogeneous BD population. The limitations of this study included the fact that as VERC was a tertiary referral center, there could be a bias toward more severe patients. In the clinical diagnosis, we could not exclude probable cases with cannabis arteritis as it is indistinguishable from BD. Furthermore, our study lacked of a control group of healthy participants and had a small sample size. This could increase the probability of type II errors, especially when no differences or associations were found between the study categories. More importantly, there were unavoidable changes in the severity of BD stages in our patients from the time of the disease onset. Not all of our participants were in the active phase of BD. The amount of tissue loss because of ulcers and gangrene and medications received by the patients during the course of the disease are other factors worthy of note that could influence inflammation and its subsequent responses.

Conclusion

Increased ANA and IgM RF levels were common among all patients with BD irrespective of their clinical features and BD progression. Patients with BD with serious symptoms presented with a significantly elevated ESR, whereas they did not show significant changes in ANA and IgM RF. Therefore, transient unspecific autoimmune reactions can be implicated in developing or progressing BD. These may be appropriate targets for novel molecular therapies to restore the immunologic homeostasis damaged during the disease.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Mashhad University of Medical Sciences (Approval Date: July 1, 2016; Approval Number: IR.MUMS.REC.1393.197).

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REFERENCES

1. Seebald J, Gritters L. Thromboangiitis obliterans (Buerger disease). Radiol Case Rep 2015;10:9-11. [Crossref]
2. Cacione DG, Baptista-Silva JCC, Macedo CR. Pharmacological treatment for Buerger's disease. Cochrane Database of Systematic Reviews 2016;10.1002/14651858.CD011033.pub2. [Crossref]
3. de Godoy JM, de Godoy MF, Braile DM. Recurrent thrombosis in patients with deep vein thrombosis and/or venous thromboembolism associated with anticardiolipin antibodies. Angiology 2006;57:79-83. [Crossref]
4. Olin JW, Young JR, Graor RA, Ruschhaupt WF, Bartholomew JR. The changing clinical spectrum of thromboangiitis obliterans (Buerger's disease). Circulation 1990;82:IV3-8.
5. Olin JW. Thromboangiitis obliterans (Buerger's disease). N Engl J Med 2000;343:864-9. [Crossref]
6. Keramat S, Sadeghian MH, Keramati MR, Fazeli B. Assessment of T helper 17-associated cytokines in thromboangiitis obliterans. J Inflamm Res 2019;12:251-8. [Crossref]
7. Ketha SS, Cooper LT. The role of autoimmunity in thromboangiitis obliterans (Buerger's disease). Ann N Y Acad Sci 2013:19:15-25. [Crossref]
8. Dargon PT, Landry GJ. Buerger's disease. Ann Vasc Surg 2012;26:871-80. [Crossref]
9. Igari K, Inoue Y, Iwai T. The epidemiologic and clinical findings of patients with Buerger disease. Ann Vasc Surg 2016;30:263-9. [Crossref]
10. Malik S, Bruner GR, Williams-Weese C, Feo L, Scofield RH, Reichlin M, et al. Presence of anti-La autoantibody is associated with a lower risk of nephritis and seizures in lupus patients. Lupus 2007;16:863-6. [Crossref]
11. Templeton GF. A two-step approach for transforming continuous variables to normal: implications and recommendations for IS research. Communications of the Association for Information Systems 2011;28. [Crossref]
12. Fazeli B, Dadgar Moghadam M, Niroumand S. How to Treat a Patient with Thromboangiitis Obliterans: A Systematic Review. Ann Vasc Surg 2018;49:219-28. [Crossref]
13. Fazeli B, Ravari H. A disease-specific activity score for Thromboangiitis obliterans. Vascular 2014;22:336-40. [Crossref]
14. Qaja E, Muco E, Hashmi MF. Buerger Disease. [Updated 2021 Aug 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430858/
15. Jorge VC, Araújo AC, Noronha C, Panarra A, Riso N, Riscado MV. Buerger's disease (thromboangiitis obliterans): a diagnostic challenge. Case Reports 2011;2011:bcr0820114621. [Crossref]
16. Amador-Patarroyo MJ, Rodriguez-Rodriguez A, Montoya-Ortiz G. How does age at onset influence the outcome of autoimmune diseases? Autoimmune Dis 2012;2012:251730. [Crossref]
17. Harrison M. Abnormal laboratory results: erythrocyte sedimentation rate and C-reactive protein. Aust Prescr 2015;38:93-4. [Crossref]
18. Lorber M, Gershwin ME, Shoenfeld Y. The coexistence of systemic lupus erythematosus with other autoimmune diseases: the kaleidoscope of autoimmunity. Semin Arthritis Rheum 1994;24:105-13. [Crossref]
19. Hawa M, Beyan H, Leslie RD. Principles of autoantibodies as disease-specific markers. Autoimmunity 2004;37:253-6. [Crossref]
20. Kallenberg CG, Heeringa P, Stegeman CA. Mechanisms of disease: pathogenesis and treatment of ANCA-associated vasculitides. Nat Clin Pract Rheumatol 2006;2:661-70. [Crossref]
21. Noel LH. Antineutrophil cytoplasm antibodies (ANCA): description and immunopathological role. Ann Med Internet 2000;151:178-83.
22. Savage CO. Pathogenesis of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. Clin Exp Immunol 2011;1:23-6. [Crossref]
23. Schultz DR, Diego JM. Antineutrophil cytoplasmic antibodies (ANCA) and systemic vasculitis: update of assays, immunopathogenesis, controversies, and report of a novel de novo ANCA-associated vasculitis after kidney transplantation. Semin Arthritis Rheum 2000;29:267-85. [Crossref]
24. Piazza G, Creager MA. Thromboangiitis obliterans. Circulation 2010;121:1858-61. [Crossref]
25. Johnson JA, Enzenauer RJ. Inflammatory arthritis associated with thromboangiitis obliterans. J Clin Rheumatol 2003;9:37-40. [Crossref]
26. Guo Y, Dai Y, Lai J, Fan Y. Study about correlation of anti-neutrophil cytoplasmic antibodies and anticardiolipin antibodies with thromboangiitis obliterans. Vascular 2013;21:363-8. [Crossref]
27. Maslowski L, McBane R, Alexewicz P, Wysokinski WE. Antiphospholipid antibodies in thromboangiitis obliterans. Vasc Med 2002;7:259-64. [Crossref]
28. Schenkein HA, Berry CR, Burmeister JA, Brooks CN, Barbour SE, Best AM, et al. Anti-cardiolipin antibodies in sera from patients with periodontitis. J Dent Res 2003;82:919-22. [Crossref]
29. Castro C, Gourley M. Diagnostic testing and interpretation of tests for autoimmunity. J Allergy Clin Immunol 2010;125:S238-S47. [Crossref]

Keywords: Thromboangiitis obliterans; disease progression; antibodies; autoimmune diseases

Anahtar Kelimeler: Tromboangiitis obliterans; hastalık progresyonları; antikorlar; otoimmün hastalıklar

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ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Associations of F2 (G20210A), F5 (G1691A), F7 (G10976A), F13 (G13T), FGB, ITGA2, ITGB3, and PAI-I gene polymorphisms with cardiovascular and thrombotic complications in patients with Takayasu arteritis from the Urals population

Urallar popülasyonundaki Takayasu arterit hastalarında kardiyovasküler ve trombotik komplikasyonlarla ilişkili F2 (G20210A), F5 (G1691A), F7 (G10976A), F 13 (G13T), FGB, ITGA2, ITGB3, PAI-I gen polimorfizmleri

Irina Borodina, M.D., Gezel Salavatova, M.D., Lubov Shardina, M.D.

Department of Internal Medicine, Ural State Medical University, Yekaterinburg, Russia

ABSTRACT

Objective: Cardiovascular complications, especially thrombotic events, are characteristic for Takayasu arteritis (TA). These events significantly deteriorate the patients' quality of life and cause disability and preterm death. Coagulation factor II (F2, G20210A), coagulation factor V (F5, G1691A, Leiden), coagulation factor VII (F7, G10976A), coagulation factor XIII (F13, G13T), fibrinogen (FGB), platelet alpha subunit of transmembrane receptor for collagens and related proteins (ITGA2), platelet glycoprotein (ITGB3), and plasminogen activator inhibitor-1 (PAI-I) gene polymorphisms coexist with TA, and their pathophysiologic interaction needs to be studied.

Methods: A total of 43 patients with TA were examined for nucleotides polymorphism in F2 (G20210A), F5 (G1691A, Leiden), F7 (G10976A), F13 (G13T), FGB, ITGA2, ITGB3, and PAI-I genes using polymerase chain reaction. Moreover, 130 sex- and age-adjusted healthy controls without a history of any thrombotic complications were enrolled.

Results: Among the patients with TA, there were 34 women aged between 17 and 77 (mean 49, median 49; Q1-Q3, 36-61) years and 9 men aged between 20 and 66 (mean 37.8, median 38; Q1-Q3: 31-45) years. Thrombotic complications were recorded in 22 (51%) patients with TA. Comparison of thrombophilia markers genotypes in patients with TA and healthy controls revealed homozygous and heterozygous mutation in ITGA2 ($p<0.0001$) and PAI-I genes ($p=0.026$). The frequency of occurrence of hereditary thrombophilia markers in patients with TA was assessed. Detection of the PAI-I gene mutation was significantly more frequent ($p=0.032$) in patients with TA with a history of thrombotic events than in those with no thrombosis history. Detection of multiple (more than 4 genes) simultaneous mutations of thrombophilia markers was significantly ($p=0.0001$) more frequent in patients with TA with a history of thrombotic events.

ÖZET

Amaç: Kardiyovasküler komplikasyonlar, özellikle trombotik olaylar Takayasu arteriti (TA) için karakteristiktir. Bu olaylar, hastaların yaşam kalitesini önemli ölçüde bozar ve sakatlığa ve erken ölüme neden olur. Koagülasyon faktörü II (F2, G20210A), koagülasyon faktörü V (F5, G1691A, Leiden), koagülasyon faktörü VII (F7, G10976A), koagülasyon faktörü XIII (F13, G13T), fibrinojen (FGB), kollejen ve ilişkili proteinlerin transmembran reseptörlerinin trombosit alfa alt birimi (ITGA2), trombosit glikoprotein (ITGB3) ve plazminojen aktivatör inhibitörleri (PAI-I) genleri polimorfizmleri TA ile birlikte bulunur ve bunların patofizyolojik etkileşiminin çalışılması gerekmektedir.

Yöntemler: F2 (G20210A), F5 (G1691A, Leiden), F7 (G10976A), F13 (G13T), FGB, ITGA2, ITGB3, PAI-I nükleotid polimorfizmleri polimeraz zinciri reaksiyonu ile TA'lı toplam 43 hastada incelendi. Ayrıca herhangi bir trombotik komplikasyon öyküsü olmayan, cinsiyete ve yaşa göre ayarlanmış 130 sağlıklı kontrol dahil edildi.

Bulgular: TA hastaları arasında 17-77 yaş arası 34 kadın (ortalama 49, medyan 49 yıl; Q1-Q3 36-61) ve 20-66 yaş arası 9 erkek (ortalama 37.8, medyan 38 yıl; Q1-Q 3: 31- 45) hasta vardı. Yirmi iki TA hastasında (%51) trombotik komplikasyonlar kaydedildi. TA hastalarında ve sağlıklı kontrollerde trombofili belirteçleri genotiplerinin karşılaştırılması, ITGA2 geni ($p<0.0001$), ve PAI-I geni homozigot ve heterozigot mutasyonlarını ($p=0.026$) ortaya çıkardı. TA hastalarında kalıtsal trombofili belirteçlerinin görülme sıklığı değerlendirildi. PAI-I gen mutasyonunun saptanması, trombotik olay öyküsü olan TA hastalarında, tromboz öyküsü olmayan TA hastalarına göre anlamlı olarak daha sıktı ($p=0.032$). Trombotik olay öyküsü olan TA hastalarında, trombofili belirteçlerinin aynı anda birden fazla mutasyonunun (4'ten fazla gen) saptanması anlamlı derecede ($p=0.0001$) daha sıktı.

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Correspondence: Irina Borodina, M.D., Department of Internal Medicine, Ural State Medical University, Yekaterinburg, Russia
Tel: 89122657283 e-mail: borodysik@mail.ru

Conclusion: Assessment of hereditary thrombophilia genetic markers reveals additional (genetic) risk markers of thrombotic complications in patients with TA and may help in decision making for antiplatelet and/or anticoagulant treatment in patients with TA to reduce the risk of thrombotic complications.

Sonuç: Kalıtsal trombofili genetik belirteçlerin değerlendirilmesi, TA hastalarında trombotik komplikasyonların ek (genetik) risk belirteçlerinin ortaya çıkarılmasına olanak sağlar ve trombotik komplikasyon riskini azaltmak için TA hastalarında antiplatelet ve/veya antikoagülan tedaviye karar vermede yardımcı olabilir.

Takayasu arteritis (TA) refers to granulomatous inflammation of the aorta and its large branches. The disease occurs mainly in Asian and South American countries, but quite a number of TA cases have been reported to occur globally.[1] TA prevalence varies from 0.8 to 2.6 cases per 1,000,000, depending on the region of residence and ethnic group.[2] There are no epidemiological data on the actual prevalence of TA in the Russian Federation.

Typical TA complications are major cardiovascular events, which negatively affect the patients' quality of life and often cause disability and preterm death. Immunological activity, propensity to thrombosis, and changes in the arterial wall in TA contribute to the development of cardiovascular complications.

Genetic associations of immune response regulators, pro-inflammatory cytokines encoding genes may be involved in pathogenic mechanisms of the disease. TA non-HLA susceptibility loci include FCGR2A/FCGR3A, IL12B, IL6, and RPS9/LILRB3 and a locus on chromosome 21 near PSMG1.[3]

The strongest association with TA has been found to be located within the class I sub region, with rs12524487 (located between HLA-B and major histocompatibility complex (MHC) class I polypeptide-related sequence A; *MICA*) (p=1.92E-16, odds ratio [OR]=3.70). IL12B is a well-established risk gene for TA.[4]

The G allele at rs763780 (IL-17F) was significantly associated with TA (p=0.014), the rs763780 showed a tendency toward association with TA (p=0.08), and the magnitude and direction of the OR were consistent with the results of phase 1. In phase 1, the genomic DNA of 120 patients with TA and 119 healthy controls were genotyped for single-nucleotide polymorphisms (SNPs) rs1800795 (interleukin [IL]-6), rs763780 (IL-17F), rs1800871, rs1800872, rs1800896 (IL-10), rs1800468, rs1800469, and rs1800470 (transforming growth factor-β). In the combined analysis, protective association of the G allele of rs763780 with TA was also reported as significant (OR=0.44, 95% confidence interval [CI]=0.25-0.77; p=0.0029). The G allele was associated (p<0.05) with underlying tuberculosis (TB) and occurrence of syncope in patients with TA.[5]

Abbreviations:

4G4G	*Homozygous mutations*
5G4G	*Geterozygous mutations*
AA	*Homozygous mutations*
AT III	*Antithrombin III*
CC	*Homozygous mutations*
CI	*Confidence interval*
F5	*Factor V Leiden gene defect*
FGB	*Fibrinogen*
GA	*Geterozygous mutations*
HT	*Hereditary thrombophilia*
MHC	*Major histocompatibility complex*
OR	*Odds ratio*
PAI-I	*Plasminogen activator inhibitor-1*
RAS	*Renin–angiotensin system*
RR	*Relative risk*
SNPs	*Single-nucleotide polymorphisms*
TA	*Takayasu arteritis*
TB	*Tuberculosis*
TT	*Homozygous mutations*
CT	*Geterozygous mutations*

No significant differences were found in the distribution of allele and genotype frequencies of IL-12, IL-12R, IL-23, and IL-23R genes between patients with TA and healthy controls.[6] Patients with TA carrying the rs582054/rs568408 haplotype (p=0.019) appeared less likely to progress to a more severe form of the disease, and the C allele (p=0.082) of IL23R rs1004819 appeared to be a protective factor for a refractory disease.[6]

During the last 20 years, spontaneous thrombosis investigation has been focused on hereditary thrombophilia (HT). HT refers to a rather heterogeneous group of hereditary and acquired conditions with a propensity to intravascular blood clotting. HT includes arterial, arteriolar, microcirculatory (capillary bed), venous, and mixed (damage to various types of vessels) thrombosis.

Since 1965, lack of antithrombin III (AT III) was considered as a genetic cause of venous thrombosis. Between 1981 and 1982, Leiden's mutation was described.[7] Further on, other gene polymorphisms have been found for the development of thrombosis.

A number of genetic mutations in the thrombophilia genes have been reported as risk factors for myocardial infarction thrombotic complications, polycythemia, and other arterial conditions as well as venous thrombosis in young individuals.[7-9]

A genome-wide association study on 633 patients with TA and 5928 controls found a number of unreported loci, particularly concerning non-HLA susceptibility genes (PTK2B, LILRA3/LILRB2, DUSP22, and KLHL33).[10] A novel association of PTPN22 single-nucleotide polymorphism (R620W) has been linked to susceptibility for TA in a study including 111 patients.[11]

In 1999, Shin and Godwin[12] have reported the first case of TA associated with the Factor V Leiden gene defect (F5). They reasoned that hereditary hypercoagulable states could coexist with acquired vasculitides and that further investigation into these associations and their pathophysiologic interaction was warranted.

In this study, we evaluated the effect of the presence of hereditary thrombophilia genetic markers on the development of thrombosis in patients with Takayasu Arteritis.

METHODS

A cross-sectional study enrolled all consequent patients presenting with TA during the period from January 01, 2016, to December 31, 2018, at the regional clinical hospital No. 1. All the patients signed an informed consent form for depersonalized data processing.

Nucleotide polymorphisms in the pro-thrombin genes coagulation factor II (F2, G20210A), coagulation factor V (F5, G1691A, Leiden), coagulation factor VII (F7, G10976A), coagulation factor XIII (F13, G13T), fibrinogen (FGB), platelet alpha subunit of transmembrane receptor for collagens and related proteins (ITGA2), platelet glycoprotein (ITGB3), and plasminogen activator inhibitor-1 (PAI-I) [A1] gene polymorphisms have been investigated using polymerase chain reaction in 43 patients with TA.

TA was verified according to the American College of Rheumatology criteria (1990):[13]

1. Age at disease onset <40 years

2. Claudication of extremities (muscle fatigue and discomfort occurring or worsening on effort in 1 or more extremities, especially the upper ones)

3. Lack of brachial artery pulse (decreased pulsation of 1 or both brachial arteries)

4. Difference of >10 mmHg in systolic blood pressure between the arms

5. Bruit over subclavian arteries or aorta (bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta)

6. Arteriogram abnormality (arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or low extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental).[13]

There were also 130 healthy age- and sex-adjusted controls without a history of thrombotic complications. All the controls were the residents of Middle Urals region and were recruited during a scheduled periodic examination at the general medicine department of the regional clinical hospital No. 1 with the support of medical centers of the city of Yekaterinburg.

The study was approved by the Ethics Committee of Urals State Medical University (Approval Date: November 23, 2018; Approval Number: 9/2018).

Statistical analysis

STATISTICA 7 software (StatSoft Inc. 1984-2004, version 7.0.61.0, Tulsa, USA) was used to process the data. For statistical analysis of normal distribution data, Student t test was used. The results were expressed as relative risk (RR) with 95% CI. All the statistical tests were 2-sided and a $p<0.05$ was considered to be statistically significant. Continuous variables were presented as mean, median, and Q1-Q3 (quartile 1-quartile 3). The statistical significance of the differences between the groups when comparing the proportions was assessed by the Fisher exact test.

RESULTS

Among the patients with TA, there were 34 women aged between 17 and 77 (mean 49, median 49; Q1-Q3 36-61) years and 9 men aged between 20 and 66 (mean 37.8, median 38; Q1-Q3: 31-45) years. Symptomatic disease duration varied from 0.6 to 64 (mean 14.5 years; median 11.5; Q1-Q3: 5-20) years in women and from 2 to 12 (mean 5.22, median 5; Q1-Q3: 3-16) years in men (Table 1).

Among healthy controls, there were 105 women aged between 27 and 65 (mean 36.6, median 34; Q1-Q3: 31-39) years and 25 men aged between 23 and 69 (mean 41, median 38.5; Q1-Q3: 35-49) years.

Table 1. General characteristics of patients

Indicators	Patients with TA	Healthy controls	*p*
Sex			
Female/male	34 (79%)/9 (21%)	105 (80%)/25 (20%)	0.00445
Age, Q1-Q3, years			
Female/male	49 (36-61)/38 (31-45)	34 (31-39)/38.5 (35-49)	1.000
Duration of disease, median, Q1-Q3, years			
Female/male	11.5 (5-20)/5 (3-6)	-	-
TA vessel impairment types (Moriwaki)			
1	18 (42%)		
2 a	4 (9.3%)		
2 b	0 (0%)		
3	1 (2.3%)		
4	7 (16.2%)		
5	13 (30.2%)		
Involved arteries			
Subclavian	23 (52%)		
Carotid	25 (57%)		
Axillary	5 (11%)		
Brachial	5 (11%)		
Vertebral	8 (18%)		
Pulmonary	1 (3%)		
Coronary	4 (9%)		
Upper mesenteric	11 (25%)		
Celiac trunk	10 (22%)		
Renal	17 (39%)		
Femoral	7 (16%)		
Iliac	8 (8%)		
Operations	14 (32%)		
Aortofemoral bypass surgery	2 (14%)		
Renal artery stenting	5 (36%)		
Thrombectomy of infrarenal aorta	1 (7%)		
Endarterectomy of the vertebral artery	1 (7%)		
Aorto-coronary artery bypass grafting	1 (7%)		
Stenting of the common carotid artery	1 (7%)		
Endarterectomy of emergency	1 (7%)		
Thoracoabdominal bypass surgery with plastic surgery of the left renal artery	1 (7%)		
Femoral artery bifurcation prosthetics	1 (7%)		
Thoracoabdominal shunting with prosthetics of the celiac trunk, superior mesenteric artery, and left renal artery	1 (7%)		
Renal artery autotransplantation	1 (7%)		
Stenting of the right descending artery	1 (7%)		
Prosthesis of the left brachial artery	1 (7%)		
Autovenous iliac-femoral bypass	1 (7%)		

TA: Takayasu arteritis.

Table 2. Gene polymorphisms of thrombophilia in F2 (G20210A), F5 (G1691A), F7 (G10976A), F13 (G13T), FGB, ITGA2, ITGB3, and PAI-I in patients with TA and in healthy controls

Genes		Patients with TA (n=43)	Healthy controls (n=130)	*p*	OR	95% CI
F2	GA+AA	0 (0%)	2 (1.5 %)	1.000	0.000	-
F5	GA+AA	1 (2.7%)	6 (5%)	0.682	0.492	0.058-4.206
F7	GA+AA	9 (21%)	15 (11%)	0.132	2.029	0.816-5.045
F13	GT+TT	14 (32%)	51 (39%)	0.472	0.748	0.361-1.550
FGB	GA+AA	13 (30%)	48 (37%)	0.466	0.740	0.353-1.555
ITGA2	CT+TT	31 (72%)	56 (24%)	0.001	3.414	1.610-7.237
ITGB3	TC+CC	14 (32%)	48 (37%)	0.714	0.825	0.397-1.712
PAI-I	5G4G+4G4G	36 (84%)	86 (66%)	0.033	2.631	1.083-6.391

4G4G: homozygous mutations; 5G4G: geterozygous mutations; AA: homozygous mutations; CC: homozygous mutations; CI: confidence interval; GA: geterozygous mutations; OR: odds ratio; TA: Takayasu arteritis; TT: homozygous mutations; CT: geterozygous mutations.

Table 3. Polymorphisms of thrombophilia in F2 (G20210A), F5 (G1691A), F7 (G10976A), F13 (G13T), FGB, ITGA2, ITGB3, and PAI-I genes in patients with TA with or without a history of cardiovascular and thrombotic complications

Genes		History of thrombosis (n=22)	No history of thrombosis (n=21)	*p*	OR	95% CI
F2	GA+AA	0 (0%)	0 (0%)	-	-	-
F5	GA+AA	0 (0%)	1 (5%)	0.488	-	-
F7	GA+AA	6 (27%)	3 (14%)	0.456	2.250	0.482-10.505
F13	GT+TT	5 (23%)	9 (43%)	0.202	2.250	0.283-1.311
FGB	GA+AA	5 (23%)	8 (38%)	0.331	0.679	0.319-1.445
ITGA2	CT+TT	17 (77%)	14 (66%)	0.509	1.316	0.627-2.763
ITGB3	TC+CC	6 (27%)	8 (38%)	0.525	0.777	0.390-1.546
PAI-I	5G4G+4G4G	21 (95%)	15 (71%)	0.045	4.083	0.651-25.595

4G4G: homozygous mutations; 5G4G: geterozygous mutations; AA: homozygous mutations; CC: homozygous mutations; CI: confidence interval; GA: geterozygous mutations; OR: odds ratio; TA: Takayasu arteritis; TT: homozygous mutations; CT: geterozygous mutations.

Thrombotic complications were recorded in 22 (48%) patients with TA. A total of 3 (13%) patients had a history of myocardial infarction, 9 (41%) had ischemic stroke, 2 (9%) had a history of renal artery thrombosis, 1 (4.5%) had brachial artery thrombosis, 1 (4.5%) had femoral artery thrombosis, 2 (9%) had femoral artery shunt thrombosis, 1 (4.5%) had abdominal aorta thrombosis, 1 (4.5%) had pulmonary embolism, 1 (4.5%) had thrombosis of the sural and small saphenous veins, 1 (4.5%) had foot artery thrombosis, 1 (4.5%) had sinus thrombosis, and 2 (9%) had repeated thrombosis.

Comparison of thrombophilia markers genotypes in patients with TA and healthy controls revealed the presence of homozygous and heterozygous mutation in the ITGA2 ($p<0.001$) and PAI-I genes ($p=0.033$) in patients with TA (Figure 1, Table 2).

Detection of the PAI-I gene mutation was significantly more frequent ($p=0.040$) in patients with TA with a history of thrombotic events than in those with no history of thrombosis (Table 3).

Detection of multiple (more than 4 genes) simultaneous mutations of thrombophilia markers was significantly ($p=0.024$) more frequent in patients with TA than in the control group (Table 4).

There was no difference in the quantity of thrombophilia marker-altered genotypes between patients with TA with and without a history of thrombosis (Table 5).

DISCUSSION

The data obtained confirmed that thrombosis was a frequent complication of TA, and therefore, the es-

Table 4. Comparison of altered genotypes of thrombophilia quantity in patients with TA and healthy controls

Number of mutations	Patients with TA (n=43)	Healthy controls (n=130)	*p*	OR	95% CI
0	0 (0%)	14 (11%)	0.024	0.000	-
1	4 (9%)	34 (16%)	0.020	0.290	0.096-0.871
2	17 (39.5%)	26 (20%)	0.010	2.615	1.239-5.522
3	9 (21%)	34 (16%)	0.434	0.747	0.325-1.718
4	12 (28%)	17 (13%)	0.024	2.573	1.112-5.955
5	1 (2%)	4 (3%)	0.798	0.750	0.082-6.899

CI: confidence interval; OR: odds ratio; TA: Takayasu arteritis.

Table 5. Comparison of altered genotypes of thrombophilia in patients with TA with and without a history of thrombosis

Number of mutations	History of thrombosis (n=22)	No history of thrombosis (n=21)	*p*	OR	95% CI
0	0 (0%)	0 (0%)	1.000	-	-
1	2 (9%)	2 (9.5%)	0.961	0.950	0.121-7.440
2	9 (41%)	8 (38%)	0.850	1.125	0.331-3.826
3	5 (23%)	4 (19%)	0.776	1.250	0.285-5.473
4	6 (27%)	6 (28.5%)	0.924	0.938	0.247-3.555
5	0 (0%)	1 (4.7%)	0.234	-	-

CI: confidence interval; OR: odds ratio; TA: Takayasu arteritis.

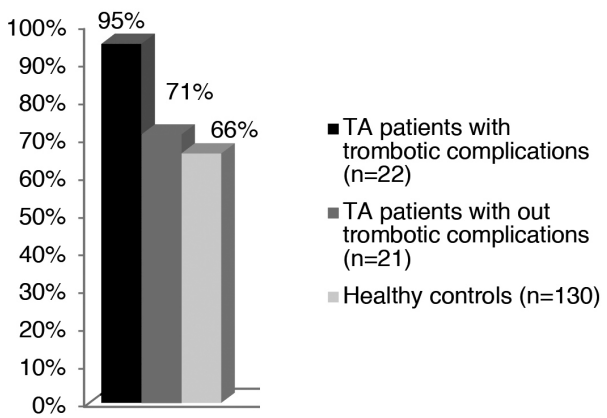

Figure 1. Plasminogen activator inhibitor-1 PAI-I (5G4G+4G4G) [A1] genotype distribution in patients with Takayasu arteritis with and without a history of thrombosis and in healthy [A2] controls.
TA: Takayasu arteritis.

tablishment of additional thrombosis risk factors is of paramount importance in this setting.

Meanwhile, a number of gene mutations known as thrombophilia markers have not been discussed earlier as additional risk factors for thrombotic complications in patients with TA . The comparison of thrombophilia marker genotypes in patients with TA with and without a history of thrombotic complications has revealed a statistically significant PAI-I gene frequency difference between the subgroups (p=0.032). Previously, only prothrombin genes (F2) and the Leiden (F5) mutations have been reported to be the most significant for TA thrombotic complications.[14,15]

In our study, the simultaneous detection of 4 or more mutations of the thrombophilia markers genes was associated with thrombosis risk in patients with TA.

Frequency of simultaneous F7, ITGA2, ITGB3, and PAI-I detection in patients with TA was significantly higher than that in the control group. These data support the view that thrombophilia marker genotypes should be investigated in all patients with newly diagnosed TA to better predict the risk of both hypercoagulation resulting in thrombosis and consumption hypocoagulation leading to bleeding com-

plications. Moreover, some mutations, namely, F7 gene, may be directly associated with hypocoagulation.[14,15]

It should be noted that when comparing patients with TA with developed thrombosis and without thrombotic complications, statistically no significant differences in the mutation of the ITGA2 and ITGB3 genes were revealed. Meanwhile, these genes are responsible for platelet-derived genesis, which is particularly significant for the choice of therapy. Furthermore, the presence of the mutation of ITGB3 reduces the sensitivity to aspirin.[16] Statins have been shown to decrease platelet aggregation, inhibit tissue factor and PAI-1 expression, and increase tPA, which lead to a decrease in the susceptibility to coagulation and thrombosis.[17] Considering the fact that PAI-1 is closely related to the renin-angiotensin system (RAS), an important contributor to the development and progression of vascular diseases,[18] therapeutic strategies can also target angiotensin II inhibition to reduce the effects of PAI-1.[19] Identification of genetic markers of thrombophilia allows a personalized approach to prescribing therapy to patients with a high risk of thromboembolic complications.

These changes undoubtedly require further studies to properly assess their clinical significance. Better understanding and clinically relevant interpretation of these findings may require thorough hemostasis investigations in patients with different mutations patterns.

At least one pro-thrombotic gene mutation detection in nearly every patient with TA is a strong argument in favor of investigating markers of HT during the baseline examination of patients with TA for better treatment tailoring and recurrent thrombosis prevention.

Limitations

Due to the small sample size, this study may lack statistical power and both overestimate and underestimate the magnitude of the registered association. Data relevance interpretation is complicated owing to the absence of previous appreciable epidemiological studies of TA in the Russian Federation.

However, Regional Clinical Hospital No. 1, being the largest hospital in the Urals, is the reference center for all regional patients with a suspicion of TA. Therefore, TA diagnosis verification and treatment strategy initiation appear to be more or less standardized. Unfortunately, logistic issues and psychological and administrative obstacles negatively affect patients' compliance and further follow-up.

Conclusion

Thrombotic events are typical TA complications. They negatively affect the patients' quality of life and cause disability and preterm death. In this study, we assessed thrombophilia marker genotypes in patients with TA in relation to personal history of thrombotic complications.

The study data allow to suggest that investigation of thrombophilia markers may be acknowledged to be mandatory in patients with TA. Typical TA onset age being under 40, the proposed approach may prevent early major cardiovascular events (myocardial infarction, ischemic stroke, and large arteries thrombosis) as well as avoid a number of surgical vascular interventions.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Urals State Medical University (Approval Date: November 23, 2018; Protocol no. 9/2018).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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REFERENCES

1. Nasonov EL, Nasonova EL. Rheumatology. National guidelines. Moscow: Media; 2010.
2. Volosnyakov DK, Glazyrina GA, Serebryakova EN, Kolyadina NA, Vasilyeva EL, Letyagin EI. Nonspecific aortoarteritis (arteritis Takayasu) in children and adolescents: literature review and clinical case. Difficult Patient 2015;1:36-9.
3. Renauer P, Sawalha AH. The genetics of Takayasu arteritis. Presse Med 2017;46:179-87. [Crossref]
4. Carmona D, Coit P, Saruhan-Direskeneli G, Hernández-Rodríguez J, Cid MC, Solans R, et al. Analysis of the common

genetic component of large-vessel vasculitides through a meta-Immunochip strategy. Sci Rep 2017;7:43953. [Crossref]
5. Danda D, Goel R, Danda S, Mohan H, Joseph G, Kabeerdoss J, et al. Interleukin-17F and interleukin-6 gene polymorphisms in Asian Indian patients with Takayasu arteritis. Hum Immunol 2017;78:515-20. [Crossref]
6. Yang KQ, Yang YK, Meng X, Zhang Y, Jiang XJ, Wu HY, et al. Lack of association between polymorphisms in interleukin (IL)-12, IL-12R, IL-23, IL-23R genes and Takayasu arteritis in a Chinese population. Inflamm Res 2016;65:543-50. [Crossref]
7. Shikhbabaeva DI, Polushkina LB, Shuvaev VA. Genetic markers of hereditary thrombophilia and the risk of thrombotic complications in patients with true polycythemia. Clinical oncohematology. Fundamental Res Clin Practice 2017;10:85-92.
8. Hubert A, Gueret P, Leurent G. Myocardial infarction and thrombophilia: do not miss the right diagnosis! Rev Port Cardiol 2018;37:89. [Crossref]
9. Pascual-Camps I, Hernandez-Martinez P, Dolz-Marco R. Systematic study of retinal vein occlusion in young patients. Case report and review of the literature. Arch Soc Esp Oftalmol 2016;91:130-3. [Crossref]
10. Terao C, Yoshifuji H, Matsumura T, Naruse TK, Ishii T, Nakaoka Y, et al. Genetic determinants and an epistasis of LILRA3 and HLA-B*52 in Takayasu arteritis. Proc Natl Acad Sci USA 2018;115:13045-50. [Crossref]
11. Soto ME, Montufar-Robles I, Jimenez-Morales S, Gamboa R, Huesca-Gomez C, Ramirez- Bello J. An association study in PTPN22 suggests that is a risk factor to Takayasu's arteritis. In Amm Res 2019;68:195-201. [Crossref]
12. Shin DD, Godwin JE. Takayasu's arteritis associated with factor V Leiden. Am J Hematol 1999;60:237-8. [Crossref]
13. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990;33:1129-34. [Crossref]
14. Cunha ML, Bakhtiari K, Peter J, Marquart JA, Meijers JC, Middeldorp S. A novel mutation in the F5 gene (factor V Amsterdam) associated with bleeding independent of factor V procoagulant function. Blood 2015;125:1822-5. [Crossref]
15. Gemmati D, Serino ML, Ongaro A, Tognazzo S, Moratelli S, Resca R, et al. A common mutation in the gene for coagulation factor XIII-A (VAL34Leu): a risk factor for primary intracerebral hemorrhage is protective against atherothrombotic diseases. Am J Hematol 2001;67:183-8. [Crossref]
16. Xu ZH, Jiao JR, Yang R, Luo BY, Wang XF, Wu F. Aspirin resistance: clinical significance and genetic polymorphism. J Int Med Res 2012;40:282-92. [Crossref]
17. Cappelletti RM. Statins therapy: effects on plasma fibrinogen levels and fibrinolysis. Nutrition Disorder Ther 2011;6:1-23.
18. Matsumoto T. Angiotensin-converting enzyme inhibition augments coronary release of tissue plasminogen activator in women but not in men. Hypertension 2010;56:364-8. [Crossref]
19. Baluta MM. PAI-1 inhibition - another therapeutic option for cardiovascular protection. Maedica (Buchar) 2015;2:147-52.

Keywords: Takayasu arteritis; thrombophilia; thrombosis; genes

Anahtar Kelimeler: Takayasu arteriti; trombofili; tromboz; genler

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ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Characteristics of a large-scale cohort with accessory pathway(s): A cross-sectional retrospective study highlighting over a twenty-year experience

Aksesuar yolu bulunan geniş ölçekli bir kohortun karakteristikleri: Yirmi yılı aşkın deneyimi vurgulayan retrospektif kesitsel bir çalışma

Suat Görmel, M.D.[1], Salim Yaşar, M.D.[1], Serkan Asil, M.D.[1], Erhan Bozkurt, M.D.[2], Serdar Fırtına, M.D.[1], Hatice Tolunay, M.D.[1], Veysel Kutay Vurgun, M.D.[3], Erkan Yıldırım, M.D.[1], Yalçın Gökoğlan, M.D.[1], Barış Buğan, M.D.[1], Murat Çelik, M.D.[1], Uygar Çağdaş Yüksel, M.D.[1], Hasan Kutsi Kabul, M.D.[1], Basri Amasyalı, M.D.[4], Cem Barçın, M.D.[1], Sedat Köse, M.D.[3]

[1]Department of Cardiology, Gülhane Training and Research Hospital, Ankara, Turkey
[2]Department of Internal Medicine, Afyonkarahisar Health Sciences University School of Medicine, Afyonkarahisar, Turkey
[3]Department of Cardiology, Liv Hospital, Ankara, Turkey
[4]Department of Cardiology, TOBB Economics and Technology University School of Medicine, Ankara, Turkey

ABSTRACT

Objective: Catheter ablation following electrophysiologic study (EPS) is the mainstay of diagnosis and treatment for patients with atrioventricular reentrant tachycardia (AVRT), demonstrating excellent long-term outcome and a low rate of complications. In this study, our aim was to assess our experience in patients with accessory pathway (AP) and to compare our data with the literature.

Methods: We included 1,437 patients who were diagnosed and treated for AP in our hospital between 1998 and 2020. The demographic data of all the patients, AP location, and periprocedural results were recorded.

Results: Of the 1,437 patients, 1,299 (90.4%) were men; and the mean age of the population was 26.67 years. The location of 1,418 APs were along the left free wall (647 [45.6%] patients), in the posteroseptal region (366 [25.3%] patients), in the anteroseptal region (290 [20.4%] patients), and along the right free wall (115 [8.1%] patients). The ratio of the second AP existence was 3.0% and AVNRT co-existence was 2.0%. A total of 55 (3.8%) patients had recurrent sessions for relapse. Our center's total success rate was 95.5%, and total complication rate was 0.26%.

Conclusion: According to our retrospective analysis, EPS is a highly functional tool in the diagnosis and management of arrhythmias such as AVRT for high-risk patient groups like military personnel with the aim of risk stratification and medical management.

ÖZET

Amaç: Elektrofizyolojik çalışmayı (EPS) takiben kateter ablasyonu, Atriyoventriküler Reentrant Taşikardisi (AVRT) olan hastalar için tanı ve tedavinin temel dayanağıdır ve mükemmel uzun vadeli sonuç ve düşük bir komplikasyon oranı gösterir. Çalışmamızın amacı, aksesuar yolaklı hastalardaki deneyimlerimizi değerlendirmek ve verilerimizi literatür ile karşılaştırmaktı.

Yöntemler: Hastanemizde 1998-2020 yılları arasında aksesuar yol (AP) tanısı alan ve tedavisi olan 1437 hastayı dahil ettik. Tüm hastaların demografik verileri, aksesuar yolun konumu ve işlemle ilgili sonuçlar kaydedildi.

Bulgular: 1437 hastanın 1299'u (%90.4) erkekti ve çalışma popülasyonun ortalama yaşı 26.67 idi. 1418 AP'nin lokasyonu; sol serbest duvar boyunca (647 hasta, %45.6), posteroseptal bölgede (366 hasta, %25.3), anteroseptal bölgede (290 hasta, %20.4) ve sağ serbest duvar boyunca (115 hasta, %8.1) idi. İkinci AP var olma oranı %3.0 ve AVNRT birlikte var olma oranı %2.0 idi. 55 (%3.8) hastada relaps sebebiyle tekrarlayan işlemler yapıldı. Merkezimizin toplam başarı oranı %95.5 ve toplam komplikasyon oranı %0.26 idi.

Sonuç: Retrospektif analizimizin ışığında elektrofizyolojik çalışma, risk sınıflandırması ve tıbbi karar amacıyla askeri personel gibi yüksek riskli hasta grupları için AVRT gibi aritmilerin tanı ve yönetiminde oldukça işlevsel bir araçtır.

Patients with accessory pathway (AP) have an alternative conduction to the atriventricular (AV)-His-Purkinje system, bypassing the AV node and typically resulting in pre-excitation in the electrocardiogram (ECG). The types of APs are classified as AV bypass tracts (best known, Kent fibers), atrionodal tracts (James fibers), atriohisian tracts (Brechenmacher fibers) and Hisian-fascicular tracts (Mahaim fibers).[1]

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Correspondence: Suat Görmel, M.D. Department of Cardiology, Gülhane Training and Research Hospital, Ankara, Turkey
Tel: +90 530 691 10 24 e-mail: suatgormel@yahoo.com

The clinical significance of these APs is AV re-entrant tachycardias (AVRT) by re-entrant circuits. These circuits consist of two anatomically defined limbs; AV-His-Purkinje system and AP, with different refractoriness and conduction times, which may initiate an AVRT with a critically timed premature atrial or ventricular beat.

In 1930, Wolff, Parkinson, and White first described the bundle of Kent causing pre-excitation on an ECG through an AV bypass tract and named it the "Wolff-Parkinson-White (WPW) pattern."[2] In case of paroxysmal tachyarrhythmias, it is called the WPW syndrome.

In the general population, the prevalence of a WPW pattern on surface ECG which means "manifest AP," ranges from 0.15%-0.25 %; however, concealed AP is not rare,[3] and not all patients develop supraventricular tachycardia (SVT). Compared with the other SVTs, the pre-excitation population is generally younger, predominantly male, and has less comorbidity.[4,5] Nowadays, AVRTs are among the most frequently referred SVTs for catheter ablation to specialized centers after atrial fibrillation (AF)/atrial flutter and AV node re-entrant tachycardia (AVNRT).[6-8] Radiofrequency (RF) catheter ablation or cryo-ablation are the optimal medical procedures for AVRT with high procedural success, which result in significant improvements in the patients' quality of life.[9,10]

Although AVRTs are well-known SVTs, most of the studies defining its characteristics are from the beginning of the electrophysiological studies (EPS) consisting of smaller populations. Therefore, the epidemiological studies over the characteristics AVRTs are scarce and insufficient. To address and complete the gaps in evidence, we investigated an AVRT cohort consisting of mainly military personnel with over 8,000 patients for over 20 years retrospectively, and this study represents the results.

METHODS

Our study was a retrospective analysis, and our population consisted of 1,437 consecutive children and adult patients (1,299 [90.4%] men; 26.67±10 years) who underwent EPS between January 1998 and June 2020 at our center. The study group was evaluated for AVRT including clinical and electrophysiologic characteristics. There was no exclusion criterion. The study protocol was approved by the Clinical Research Ethics Committee of Gülhane Training and Research Hospital (Approval Date: June 30, 2020; Approval Number: 2020-314) and conformed with the principles defined in the Declaration of Helsinki. Written informed consent was obtained from all the individual participants included in the study.

Abbreviations:

AF	*Atrial fibrillation*
AP	*Accessory pathway*
AS	*Anteroseptal*
AV	*Atrioventricular*
AVNRT	*AV node re-entrant tachycardia*
AVRT	*AV re-entrant tachycardias*
CHD	*Congenital heart disease*
ECG	*Electrocardiogram*
EPS	*Electrophysiological studies*
HRA	*High right atrium*
LA	*Left anterior*
LAL	*Left anterolateral*
LL	*Left lateral*
LP	*Left posterior*
LPL	*Left posterolateral*
LPS	*Left posteroseptal*
MS	*Midseptal*
RA	*Right anterior*
RAL	*Right anterolateral*
RF	*Radiofrequency*
RL	*Right lateral*
RP	*Right posterior*
RPL	*Right posterolateral*
RPS	*Right posteroseptal*
SVT	*Supraventricular tachycardia*
WPW	*Wolff-Parkinson-White*

EPS Procedure

All antiarrhythmic drugs were discontinued four to five half-lives before the procedure. EPS was performed under local anesthesia in a fasting state. Three catheters were introduced through the right femoral vein and were positioned at high right atrium (HRA), coronary sinus, and His region. The catheter at His position was also used for ablation, or the catheter at HRA was shifted to right ventricle when necessary. Intracardiac signals were filtered at 20-500 Hz, amplification gains were 10-80 mm/mV. All signals were displayed and acquired on an electrophysiological recording system. After obtaining baseline basic cycle length (BCL), atrial-His interval (AH), and His-ventricle interval (HV) measurements,interval measurements, programmed electrical atrial and ventricular stimulation was performed. Anterograde and retrograde conduction properties were analyzed. If no tachycardia was inducible, the stimulation protocol was repeated after atropine administration. Ablations were carried out using 7F non-irrigated multicurve ablation catheter (steerable 4-mm tip ablation catheter, Marinr®, Medtronic, Minneapolis, USA) and Medtronic Atakr II® (Medtronic Inc., Mpls., MN, USA) radiofrequency generator. Patients who had undergone ablation were hospitalized overnight and discharged the day after the procedure. Follow-up visits were performed in the outpatient clinic at one month after ablation.

Statistical Analysis

This was a descriptive study in which the categorical variables were represented as absolute numbers and

percentages. Continuous variables were represented as mean±standard deviation. Statistical analyses were performed using SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Between 1998 and 2020, we evaluated 8,233 patients who underwent EPS. The characteristics of the patients are summarized in Table 1. Among all the patients, we established 1,437 patients with 1497 APs. Our population was unusually predominant of the male sex (90.4%) and consisted of young adults (26.67±10 years) (Figure 1). Most of the patients had manifest AP (69.2%).

In our study, we found two (0.14%) patients with Ebstein anomaly as congenital heart disease in our population. Both patients had right-sided APs, a right posteroseptal AP and a right midseptal AP, which were ablated successfully.

The periprocedural results of the 1,437 patients who underwent EPS for diagnostic evaluation or ablation therapy are displayed in Table 2. We classified the AP distribution according to location, and 1,418 APs are illustrated in Figure 2. In addition, there were 36 patients with atrio-fasicular pathway. AP localization of 43 patients was unknown because of missing data. Of the 1,418 APs, 647 (45.6%) were located along the left free wall, 366 (25.3%) in the posteroseptal region, 290 (20.4%) in the anteroseptal region, and 115 (8.1%) along the right free wall respectively.

Among 1,437 cases, 1,352 patients had single AP, and 42 patients had double APs; the ratio of the second AP existence was 3.0%. Co-existence of AVNRT was observed in 30 (2.0%) patients. For most of the patients (1,382 [96.1%]), a single EPS procedure was enough for diagnosis and/or ablation. However, for complete evaluation, 50 (3.5%) patients had to undergo a second procedure and five (0.3%) patients a third procedure.

We classified our population according to EPS indications and showed that 17.3% asymptomatic patients with pre-excitation had undergone EPS for medical evaluation. Considering the EPS results of 1,437 patients, 999 (69.0%) had successful ablation and 47 (3.2%) had failed ablation; 143 (9.9%) patients with indistinct complaints and borderline ECG findings who were admitted for assessing health sufficiency for military service had innocent APs not causing any inducible tachycardia; and therefore, ablation was deferred. Seventy nine (5.4%) patients who were military staff at the same time had undergone diagnostic EPS for medical evaluation but did not demand ablation at our center, and 122 (8.4%) patients had para-hisian AP and did not prefer any high-risk procedure. As a result, our success rate for catheter ablation in the treatment of AVRT was 95.5%.

Our overall total major complication rate was 0.26%. The most common complication encountered after procedure was persistent AV block requiring pacemaker implantation in two patients. Another major complication in one patient was anaphylactic shock against the local anesthetic drug, who recovered after medical treatment. Finally, one patient with cardiac tamponade who had hemodynamic instability underwent surgical pericardial drainage.

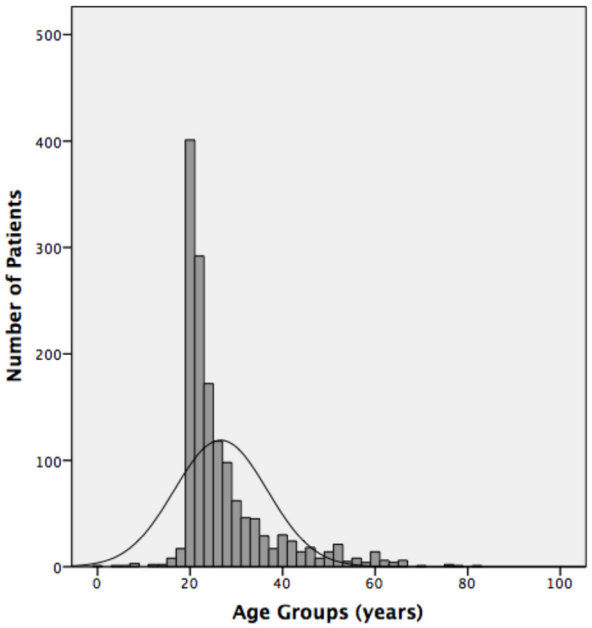

Figure 1. Histogram showing age-specific prevalence of AP existence in our population.

Table 1. Baseline characteristics of population

Population, n	1,437
Accessory pathway, n	1,497
Sex, male, n (%)	1,299 (90.4)
Age (years)	26.67±10
Pre-excitation existence, n (%)	891 (69.2)
CHD	
Ebstein anomaly, n (%)	2 (0.14)

CHD: congenital heart disease.

Table 2. Periprocedural results

AP number (n=1,437)	No. of patients	% of patients
Single AP	1,352	94.1
Double AP	42	2.9
Missing data	43	3.0
AVNRT co-existence (%)	30	2.0
Recurrent EPS (1,437)		
Single	1,382	96.1
Twice	50	3.5
Thrice	5	0.3
EPs indications (n=1,497)		
WPW patients with cardiac arrest and pre-excited AF	7	0.4
Symptomatic patients with documented SVT	287	19.0
Patients with complaints and induced tachycardia	938	62.0
Asymptomatic patients with pre-excitation and innocent AP	260	17.3
No data	5	0.3
EPS results (n=1,437)		
Successful ablation	999	69.0
Failed ablation	47	3.2
İnnocent AP	143	9.9
Diagnostic EPS	79	5.4
Postponed ablations	39	2.7
High risk procedure - ablation canceled	122	8.4
No data	8	0.5
Complications (n=1437)		
Third-degree AV block	2	0.13
Cardiac tamponade	1	0.06
Anaphylactic shock	1	0.06

AP: accessory pathway; AV: atrioventricular; AVNRT: AV node re-entrant tachycardia; EPS: electrophysiological study; SVT: supraventricular tachycardia.

DISCUSSION

Our hospital used to be a military hospital, and every 20-year-old male military service candidate plus military staff were referred here nationwide for further medical evaluation until August 2016. Therefore, our center's archives contain one of the largest and longest series of patients with AVRT in Turkey.[11] Because it was a military hospital, the patient population here was unusually predominantly male. However, similar to previous literature of Taiwanese (mean age 26.8 years) and Spanish (mean age 20.9 years) cohorts and differently from the Swedish (mean age 41.0 years) cohort, our population's mean age was 26.67±10 years.[4,6,8]

Approximately one-third of the AP tachycardias are because of concealed Aps with an incidence of 15%-42%.[12] In our study, 546 (30.8%) patients had concealed AP which is consistent with the literature.

Most APs in Ebstein's are associated with the tricuspid valve. As we expected, the AVRTs in both of our patients with Ebstein anomaly were right-sided; a right posteroseptal AP and a right midseptal AP. Because of lower acute success rates and higher recurrence rates compared with the general population, ablation in this population is challenging. The leading causes for difficulties are altered right heart anatomy and common electrophysiological problems such as

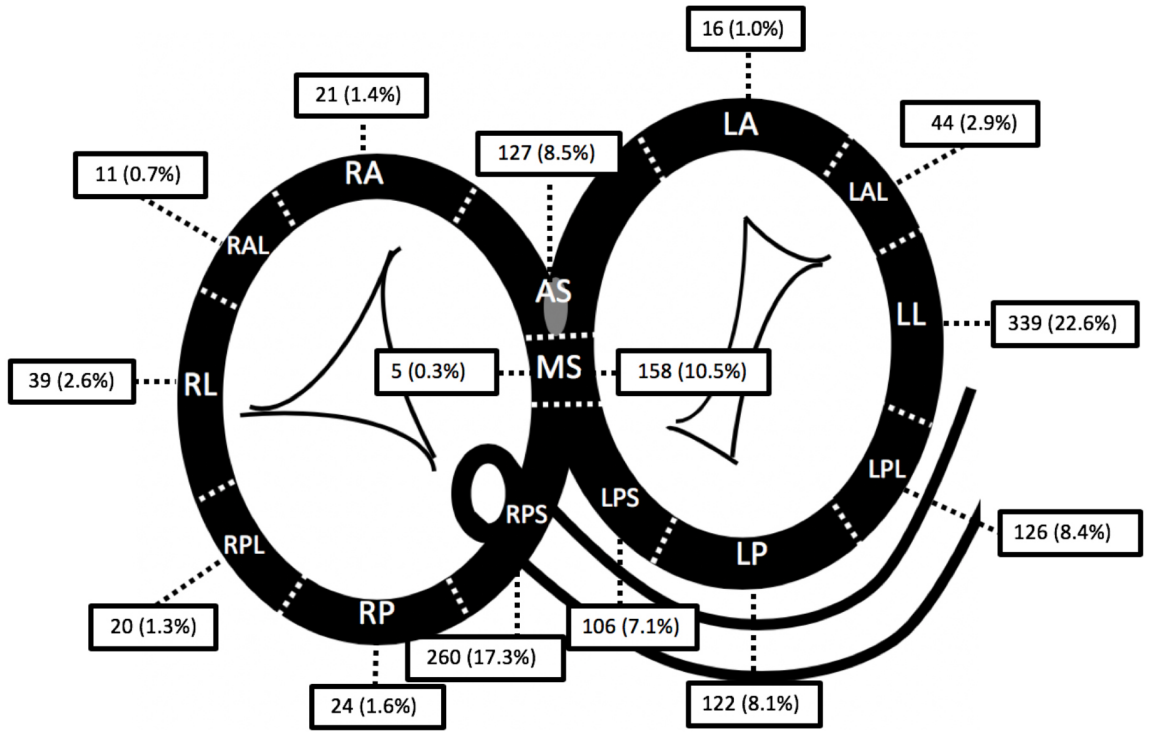

Figure 2. Distribution of accessory pathway location. Schematic of tricuspid, mitral atrioventricular rings and coronary sinus in a left anterior oblique projection.
AS: anteroseptal; MS: midseptal; LA: left anterior; LAL: left anterolateral; LL: left lateral; LP: left posterior; LPL: left posterolateral; LPS: left posteroseptal; RA: right anterior; RAL: right anterolateral; RL: right lateral; RP: right posterior; RPL: right posterolateral; RPS: right posteroseptal.

additional APs, AP variants such as Mahaim fibers, other tachycardia mechanisms, and so forth.[13-15]

Aps are commonly located along the tricuspid or mitral annulus or within the subepicardial pyramidal space in the inferoseptal region.[16] In this study, we classified the APs according to anatomical localizations and demonstrated that the most common AP area was the septal area and the area surrounding the coronary sinus, referring to nearly two-third of all the APs. This was similar to previous studies, which have demonstrated the most frequent AP distribution was along the left free wall, in the posteroseptal region, in the anteroseptal region, and along the right free wall, respectively.[17] Rarely, an AP has an alternative conduction from the atria to the ventricles other than atriventricular (AV)-His-Purkinje system, bypassing the AV node; atrionodal tracts, atriohisian tracts and Hisian-fascicular tracts. We had 36 (2.4%) patients with fascicular pathway, which was more frequent in our population in comparison to the previous results. However, our population consisted of mainly incidental patients admitted for medical evaluation and few symptomatic patients. Fascicular pathways seldom cause an inducible arrhythmia and are generally encountered incidentally. This paradigm was demonstrated by LaRocca et al.[18] in their study with similar results; fascicular pathway existence in incidental APs was 12.2% and 1.1% in patients with WPW syndrome.

Multiple Aps can be identified in 3%-13% of the patients undergoing EPS for tachycardias mediated by APs, and its prevalence is as high as 52% in patients with Ebstein anomaly. According to literature, a high prevalence of multiple APs has been observed, especially in pediatric populations with structural heart disease (SHD) predominance.[19,20] Our study population had a majority of adults and very few patients with SHD. As a result, we had relatively less patients (3%) with multiple APs.

Sometimes, AVRT and AVNRT may present concurrently up to 8% as reported by Zardini et al.[21] in a retrospective analysis of 402 patients. Although our cohort had a larger study group, co-existence was lower than expected (2%). This inconsistency may be owing to the retrospective design of both studies. Our

clinic's repeat ablation rate for AVRT was compatible with the previous studies.[8]

In asymptomatic patients, catheter ablation of APs successfully eliminates the low risk of sudden death associated with the condition. However, a generalized referral of every asymptomatic patient for ablation could also carry serious and potentially life-threatening complications.[22] Therefore, to date, the decision to refer an asymptomatic patient with pre-excitation for ablation remains a dilemma. Currently, there is no agreement among the European and American Cardiology Societies in the management of asymptomatic athletes or high-risk professionals with a WPW ECG pattern. The consensus recommends that upon discovery of ventricular pre-excitation, first line non-invasive diagnostic methods like exercise stress test should be done to assess the persistence of pre-excitation. However, if the results of first line methods are not satisfactory, risk stratification with invasive methods is recommended.[23,24] Our population consisted of a large number of asymptomatic military staff with WPW ECG pattern referred for medical evaluation. Therefore, the asymptomatic patient ratio enrolled for diagnostic assessment was as high as 17.3% in our study group unlike the general EPS populations.[6-8]

In our study group, there was a patient population of 17.3% with pre-excitation on the surface ECG but clinically asymptomatic. In this group, although the indications for diagnostic EPS were not clear according to the current literature, the majority were military personnel working in the high-risk business group, which increased our diagnostic EPS rate. These patients were pre-diagnosed with incidental arrhythmia during routine periodic examinations and had no previous cardiac history. Therefore, we aimed to prevent possible adverse cardiac events by basic medical evaluation, including standard 12-lead ECG followed by EPS evaluation if needed. In countries with compulsory military service as in our country, a baseline resting ECG is an important tool in the diagnosis and management of arrhythmias such as AVRT for discriminating the high-risk group.

Radiofrequency catheter ablation (RCA) for APs is often considered as a first-line approach because of its high success rates (approximately 95%) and low-risk profile (complication rates of 3%).[25-27] Our center's total success rate (95.5%) and total complication rate (0.26%) were consistent with the previous studies.

Limitations

This study was a single-center retrospective study in which the epidemiological characteristics of the patients and the findings of electrophysiological procedures were retrieved from institutional archives. Therefore, it lacked follow-up data and did not include long-term outcomes. In addition, a vast majority of our study group was male military staff referred for medical evaluation, inconsistent with the general population.

Conclusion

To the best of our knowledge, this study is probably the largest and the longest to demonstrate a nationwide epidemiological profile of military service patients with APs in Turkey. We investigated the patient characteristics, AP location, and periprocedural results in our population. Our outcomes of EPS and RCA showed acceptable success rates, similar to those in the literature. The complication rate in our cohort was as low as shown in other studies. As a result, based on our retrospective analysis, EPS seems to be a functional tool in the diagnosis and management of arrhythmias, such as AVRT for high-risk patient groups like military personnel.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee of Gülhane Training and Research Hospital (Approval Date: June 30, 2020; Approval Number: 2020-314)

Informed Consent: Written informed consent was obtained from all the individual participants who participated in this study.

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REFERENCES

1. de Alencar Neto JN, Ramalho de Moraes SR, Back Sternick E, Wellens HJJ. Atypical bypass tracts: can they be recognized during sinus rhythm? Europace 2019;21:208-18. [Crossref]
2. Wolff L, Parkinson J, White PD. Bundle-branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia. 1930. Ann Noninvasive Electrocardiol 2006;11:340-53. [Crossref]
3. Vidaillet HJJ, Pressley JC, Henke E, Harrell FEJ, German LD. Familial occurrence of accessory atrioventricular pathways (preexcitation syndrome). N Engl J Med 1987;317:65-9. [Crossref]

4. Lu CW, Wu MH, Chen HC, Kao FY, Huang SK. Epidemiological profile of WolffParkinsonWhite syndrome in a general population younger than 50 years of age in an era of radiofrequency catheter ablation. Int J Cardiol 2014;174:530-4.[Crossref]
5. Skov MW, Rasmussen PV, Ghouse J, Hansen SM, Graff C, Olesen MS, et al. Electrocardiographic preexcitation and risk of cardiovascular morbidity and mortality. Results from the Copenhagen ECG Study. Circ Arrhythm Electrophysiol 2017;10:e004778. [Crossref]
6. Garcia-Fernandez FJ, Ibanez Criado JL, Quesada Dorador A; collaborators of the Spanish Catheter Ablation Registry; REGISTRY COLLABORATORS. Spanish Catheter Ablation Registry. 17th Official Report of the Spanish Society of Cardiology Working Group on Electrophysiology and Arrhythmias (2017). Rev Esp Cardiol (Engl Ed) 2018;71:941-51.
7. Hosseini SM, Rozen G, Saleh A, Vaid J, Biton Y, Moazzami K, et al. Catheter ablation for cardiac arrhythmias: utilization and in-hospital complications, 2000 to 2013. JACC Clin Electrophysiol 2017;3:1240-8. [Crossref]
8. Holmqvist F, Kesek M, Englund A, Blomström-Lundqvist C, Karlsson LO, Kenneback G, et al. A decade of catheter ablation of cardiac arrhythmias in Sweden: ablation practices and outcomes. Eur Heart J 2019;40:820-30. [Crossref]
9. White J, Withers KL, Lencioni M, Carolan-Rees G, Wilkes AR, Wood KA, et al. Cardiff cardiac ablation patient-reported outcome measure (C-CAP): validation of a new questionnaire set for patients undergoing catheter ablation for cardiac arrhythmias in the UK. Qual Life Res 2016;25:1571-83. [Crossref]
10. Brachmann J, Lewalter T, Kuck KH, Andresen D, Willems S, Spitzer SG, et al. Long-term symptom improvement and patient satisfaction following catheter ablation of supraventricular tachycardia: insights from the German ablation registry. Eur Heart J 2017;38:1317-26. [Crossref]
11. Kanat S, Tütüncü A. Wolf Parkinson White sendromu (WPW) ablasyonu yapılan hastaların özellikleri: tek merkez vaka serisi. Turk J Clin Lab 2019;10:85-91. [Crossref]
12. Ross DL, Uther JB. Diagnosis of concealed accessory pathways in supraventricular tachycardia. Pacing Clin Electrophysiol 1984;7:1069-85. [Crossref]
13. Reich JD, Auld D, Hulse E, Sullivan K, Campbell R, for the Pediatric Electrophysiology Society. The pediatric radiofrequency ablation Registry's experience with Ebstein's anomaly. Pediatric Electrophysiology Society. J Cardiovasc Electrophysiol 1998;9:1370-7. [Crossref]
14. Roten L, Lukac P, Groot DE, Nielsen JC, Szili-Torok T, Jensen HK, et al. Catheter ablation of arrhythmias in ebstein's anomaly: a multicenter study. J Cardiovasc Electrophysiol 2011;22:1391-6. [Crossref]
15. İnanç MT, Eryol NK, Zencir C. Catheter ablation of accessory pathway tachycardias in three patients with Ebstein's anomaly. Turk Kardiyol Dern Ars 2010;38:125-30.
16. Ernst S, Ouyang F, Antz M, Cappato R, Kuck KH. Catheter ablation of atrioventricular reentry. In Zipes DP, Jalife J, editors: Cardiac Electrophysiology from Cell to Bedside, ed 4, Philadelphia, 2004, WB Saunders, pp 1078-86. [Crossref]
17. Jackman WM, Wang XZ, Friday KJ, Roman CA, Moulton KP, Beckman KJ, et al. Catheter ablation of accessory atrioventricular pathways (Wolff-Parkinson-White syndrome) by radiofrequency current. N Engl J Med 1991;324:1605-11. [Crossref]
18. LaRocca TJ, Beyersdorf GB, Li W, Foltz R, Patel AR, Tanel RE. Comparison of electrophysiologic profiles in pediatric patients with incidentally identified pre-excitation compared with Wolff-Parkinson-White syndrome. Am J Cardiol 2019;124:389-95. [Crossref]
19. Cappato R, Schlüter M, Weiss C, Antz M, Koschyk DH, Hofmann T, et al. Radiofrequency current catheter ablation of accessory atrioventricular pathways in Ebstein's anomaly. Circulation 1996;94:376-83. [Crossref]
20. Zachariah JP, Walsh EP, Triedman JK, Berul CI, Cecchin F, Alexander ME, et al. Multiple accessory pathways in the young: the impact of structural heart disease. Am Heart J 2013;165:87-92. [Crossref]
21. Zardini M, Leitch JW, Guiraudon GM, Klein GJ, Yee R. Atrioventricular nodal reentry and dual atrioventricular node physiology in patients undergoing accessory pathway ablation. Am J Cardiol 1990;66:1388-9. [Crossref]
22. Obeyesekere MN, Sy RW, Modi S. When can ablation be considered a reasonable option in young asymptomatic patients with a Wolff-Parkinson-White ECG? Expert Rev Cardiovasc Ther 2012;10:1451-3. [Crossref]
23. Cohen MI, Triedman JK, Cannon BC, Davis AM, Drago F, Janousek J, et al. Pediatric and Congenital Electrophysiology Society (PACES); Heart Rhythm Society (HRS); American College of Cardiology Foundation (ACCF); PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the American Academy of Pediatrics (AAP), and the Canadian Heart Rhythm Society (CHRS). Heart Rhythm 2012;9:1006-24. [Crossref]
24. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomström-Lundqvist C, et al. 2019 ESC Guidelines for the management of patients with supraventricular tachycardia: The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). Eur Heart J 2020;41:655-720. [Crossref]
25. Pappone C, Santinelli V, Manguso F, Augello G, Santinelli O, Vicedomini G, et al. A randomized study of prophylactic catheter ablation in asymptomatic patients with the Wolff-Parkinson-White syndrome. N Engl J Med 2003;349:1803-11. [Crossref]
26. Pappone C, Santinelli V, Rosanio S, Vicedomini G, Nardi S, Pappone A, et al. Usefulness of invasive electrophysiologic testing to stratify the risk of arrhythmic events in asymptomatic patients with Wolff-Parkinson-White pattern: results from a large prospective long-term follow-up study. J Am Coll Cardiol 2003;41:239-44. [Crossref]
27. Pappone C, Vicedomini G, Manguso F, Saviano M, Baldi M, Pappone A, et al. Wolff-Parkinson-White syndrome in the era of catheter ablation: insights from a registry study of 2169 patients. Circulation 2014;130:811-9. [Crossref]

Keywords: Accessory conducting pathways; preexcitation syndrome; supraventricular tachycardia

Anahtar Kelimeler: Aksesuar iletim yolakları; preeksitasyon sendromu; supraventriküler taşikardi

ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Time in therapeutic range values of patients using warfarin and factors that influence time in therapeutic range

Varfarin kullanan hastalarda terapötik aralıkta geçen zaman ve terapötik aralıkta geçen zamanı etkileyen faktörler

Lale Dinç Asarcıklı, M.D.[1], Habibe Kafes, M.D.[2], Taner Şen, M.D.[3], Esra Gucuk İpek, M.D.[4], Muhammet Cebeci, M.D.[5], Murat Gül, M.D.[6], Selçuk Kanat, M.D.[7], Ahmet Temizhan, M.D.[2]

[1]Department of Cardiology, Dr. Siyami Ersek Cardiovascular and Thoracic Surgery Research and Training Hospital, İstanbul, Turkey
[2]Department of Cardiology, Health Sciences University Ankara City Hospital, Ankara, Turkey
[3]Department of Cardiology, Dumlupınar University School of Medicine, University Hospital, Kütahya, Turkey
[4]Department of Cardiology, Polatlı State Hospital, Ankara, Turkey
[5]Department of Cardiology, Söke State Hospital, Aydın, Turkey
[6]Department of Cardiology, Aksaray University School of Medicine, Aksaray, Turkey
[7]Department of Cardiology, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

ABSTRACT

Objective: The time in therapeutic range (TTR) of international normalized ratio (INR) is essential for the safety and efficacy of warfarin treatment. In this study, we aimed to determine TTR and the factors that affect TTR in patients using warfarin.

Methods: Patients taking warfarin for valvular and nonvalvular atrial fibrillation (AF) or prosthetic heart valves who were admitted to our cardiology outpatient clinic were enrolled. TTR was calculated using the linear interpolation method. The patients were analyzed according to warfarin indications and TTR efficiency (TTR ≥60%). Weekly warfarin dose, the duration of warfarin use, the frequency of INR visits per year, and the awareness of patients regarding target INR were noted.

Results: The TTR of 248 patients (aged 57.21±12.45 years, 33.1% male) was 55.92±27.84%, and 48.0% patients exhibited efficient TTR. Clinical and demographic characteristics (age, sex, socioeconomic status, and comorbidities) exerted no effect on TTR and TTR efficiency. The frequency of INR visits per year was 10.02±3.80. TTR was related to the frequency of annual INR visits (r=0.131, p=0.039). Only one-third (30.2%) of patients were aware of their target INR. The literacy of the patients and duration of warfarin use exerted a positive effect on awareness (p=0.011 and p=0.024, respectively).

Conclusion: The findings of our study demonstrated that TTR and TTR efficiency were low and not associated with the characteristics of patients or indications. Unfortunately, in patients with valvular AF and prosthetic valves, warfarin is the sole drug that can be used. Thus, awareness and knowledge regarding target INR are essential to overcome poor anticoagulation monitoring with frequent INR visits.

ÖZET

Amaç: Uluslararası normalleştirilmiş oranın (INR) terapötik aralıkta geçen zamanı (Time in therapeutic range - TTR) varfarin tedavisinin etkinliği ve güvenliği için zorunludur. Bu çalışmada, varfarin kullanan hastalarda TTR değerlerini ve TTR'yi etkileyen faktörleri belirlemeyi amaçladık.

Yöntemler: Kardiyoloji polikliniklerine başvuran valvüler-valvüler olmayan AF veya prostetik kalp kapağı için varfarin kullanan hastalar çalışmaya alındı. Terapötik aralıkta geçen süre doğrusal interpolasyon yöntemi ile hesaplandı. Hastalar varfarin endikasyonlarına ve TTR etkinliğine (TTR ≥%60) göre analiz edildi. Haftalık varfarin dozu, varfarin kullanım süresi, yıllık INR kontrol sıklığı ve hastaların hedef INR değeri konusunda farkındalıkları not edildi.

Bulgular: Katılan 248 hastanın (ortalama yaş: 57.21±12.45 yıl, %33.1'i erkek) TTR değeri %55.92±27.84 idi ve hastaların % 48.0'i etkin TTR'ye sahipti. Klinik ve demografik özelliklerin (yaş, cinsiyet, sosyoekonomik durum, komorbiditeler) TTR ve TTR etkinliği üzerinde etkisi gösterilemedi. Yıllık INR kontrolü sıklığı 10.02±3.80 idi. Yıllık INR kontrolü sıklığıyla TTR ilişkili bulundu (r=0.131, p=0.039). Hastaların sadece 1/3'ü (%30.2) hedef INR değerinin farkındaydı. Hastanın okur-yazarlık durumu ve ilaç kullanım süresi farkındalık üzerinde olumlu etki sağladığı görüldü (sırasıyla p=0.011 ve p=0.024).

Sonuç: Çalışmamız TTR ve TTR etkinliğinin düşük olduğunu ve bu iki parametrenin hastaların karakteristikleri ve varfarin endikasyonunuyla ilişkili olmadığını gösterdi. Maalesef valvüler AF ve protez kapak varlığında kullanılabilecek tek ilaç varfarindir. Bu nedenle kötü antikoagulasyon izleminin üstesinden gelmek için sık INR kontrolleri ile takip olmak, varfarin hakkında bilgi sahibi olmak ve farkındalık gereklidir.

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Correspondence: Lale Dinç Asarcıklı, M.D. Department of Cardiology, Dr. Siyami Ersek Cardiovascular and Thoracic Surgery Research and Training Hospital, İstanbul, Turkey
Tel: +90 216 542 44 44 e-mail: mdlaledinc@gmail.com

Anticoagulation with warfarin in patients with atrial fibrillation (AF) prevents stroke by 64% compared with placebo; however, there exist ischemic and bleeding risks owing to the fluctuation of the international normalized ratio (INR).[1] The management of warfarin therapy is rather difficult because of its narrow therapeutic window, drug–drug interactions, inter-individual variability, pharmacogenetic differences, intake of vitamin K with foods, close monitoring requirement, and serious complications owing to warfarin itself that restrict its effective use.

Nowadays, direct oral anticoagulants (DOACs) are being used widely in patients with nonvalvular AF (NVAF). However, patients with valvular AF and prosthetic mechanical heart valves have no choice other than warfarin. Thus, warfarin is the only option for preventing thromboembolic events in these patients; however, it necessitates lifetime monitoring. The most important parameter that determines the efficiency of the therapy in patients using warfarin is the time in therapeutic range (TTR). As the TTR value decreases, the therapeutic effect of warfarin diminishes. Warfarin efficiency could not be demonstrated when TTR was less than 58%.[2,3] Unfortunately, studies conducted in Turkey revealed that the mean TTR of patients using warfarin was lower than the target range.[4-6] Warfarin itself is a complex drug, and it is difficult to predict its response. Various individual factors and the duration of warfarin treatment affect TTR.[7]

In the history of warfarin, the focus has always been on the difficulty in monitoring it and its complications. This study aimed to determine the mean TTR values of patients using warfarin and to describe the factors affecting the mean TTR values and TTR efficiency.

METHODS

Study design

Between June and December 2012, patients who were 18 years of age or older and admitted to our hospital for INR control with indications of NVAF, valvular AF, and mechanical heart valves were enrolled in the study. The valvular AF group was composed of only patients with moderate-to-severe mitral stenosis, excluding those with mild stenosis or any degree of mitral regurgitation and aortic valve pathological conditions. Patients with a follow-up duration of more than 6 months and those who had registered at least 4 INR values in the hospital database in the previous 6 months of enrollment were included. Patients with a history of stroke, malignancy, or hospitalization in the previous 6 months; warfarin interruption for any reason, active infection, active hepatitis, or chronic liver disease and those who were not regularly admitted to INR visits and had less than 6 total INR controls until the inclusion period was over were excluded. The enrolled patients were assigned to 3 groups according to warfarin indications as follows: valvular AF (33 patients), NVAF (56 patients), and prosthetic heart valves (159 patients). Socioeconomic status, clinical history, frequency of INR visits, awareness regarding target INR values, and previous hemorrhagic and embolic complications during warfarin treatment were noted. Written informed consent was obtained from all participants.

Abbreviations:

AF	*Atrial fibrillation*
CAD	*Coronary artery disease*
CKD	*Chronic kidney disease*
DOAC	*Direct oral anticoagulant*
GFR	*Glomerular filtration rate*
INR	*International normalized ratio*
NVAF	*Nonvalvular atrial fibrillation.*
TTR	*Time in therapeutic range*

The study was conducted in accordance with the ethical standards stated in the Declaration of Helsinki and was approved by the Ethics Committee of Turkey Yüksek İhtisas Hospital (registration number: EPKK-619-00370).

Data collection

Clinical history, cardiovascular risk factors, medications including antiplatelets (acetylsalicylic acid, clopidogrel, and dipyridamole), non-steroidal anti-inflammatory drugs that affect warfarin and can cause warfarin-associated complications, frequency of INR visits, presence of warfarin interruption, and previous bleeding and thromboembolic events were interrogated and recorded. At the index visit, 12-lead electrocardiography was performed (Nihon Kohden Cardiofax ECG-9132K). Transthoracic echocardiographic evaluation was performed using a Vivid 7 (General Electric, Norway) echocardiography device with a 2.5-3.5-MHz transducer. Cardiac chamber quantification was performed as recommended in the guideline.[8] After a 12-hour fast, venous blood samples were drawn for evaluating plasma glucose, high-density lipoprotein, triglycerides, total cholesterol, INR value, complete blood count, and serum

creatinine. Physical examination was performed after 10 min of rest. The blood pressure of the patients was measured using an appropriate sphygmomanometer as suggested by the guidelines.[9]

Definitions

Educational level (illiterate/literate and the last graduated school degree) and monthly income (low: <350 EUR, moderate: 350–750 EUR, and high: >750 EUR) were recorded. The mean monthly income of a family was calculated in Turkish Lira (TRY) and then converted to EUR. Low income is defined as <350 EUR/month and corresponds to the minimum wage. Moderate income is defined as twice the minimum wage (350–750 EUR); high income is defined as three times the minimum wage (>750 EUR). A patient was classified as an active smoker even if they smoked 1 cigarette per day for at least 1 year. Weekly warfarin dose was calculated as the total dose of warfarin during the week before the last visit. The patients were asked about the frequency of hospital admission for INR control in the last 1 year; the awareness regarding INR target was queried with simple yes/no questions, and the answers were noted.

Hypertension was defined as systolic and/or diastolic blood pressures ≥140/90 mmHg or the use of any antihypertensive drug.[10] Diabetes mellitus was defined according to the criteria of the American Diabetes Association Diabetes Guideline, i.e., fasting blood glucose levels ≥126 mg/dL or glycated hemoglobin (HbA1c) ≥6.5 or the use of any antidiabetic drug.[11] Dyslipidemia was diagnosed if the patients' total cholesterol level was more than 200 mg/dL or if the patients were using antihyperlipidemic drugs. Coronary artery disease (CAD) was diagnosed if the patient had a history of previous acute coronary syndrome or revascularization or both or if there was ≥50% stenosis in any coronary artery. Chronic kidney disease (CKD) was defined according to the estimated glomerular filtration rate (eGFR) calculated using the modification of diet in renal disease formula.[12] If the eGFR value was <60 mL/min/1.73m^2, the patients were diagnosed with CKD. Heart failure was diagnosed if the patients' left ventricular ejection fraction was ≤40% and the signs and symptoms of heart failure were present.

Target INR ranges were defined according to recent guidelines.[13] The mean TTR value was calculated using the Rosendaal linear interpolation method.[14] The patients' INR values in the hospital database were recorded with their dates (day/month/year), and target INR and INR ranges were entered into an electronic program called INR Desk 2.0.[15]

At the index visit, the patients were asked about the complications associated with warfarin. They provided information regarding their history of complications. Such complications were classified as clinically relevant non-major bleeding (bleeding that does not meet the criteria for major bleeding and that does not require any medical or surgical intervention, e.g., gingival bleeding, hematuria, epistaxis, etc.), major bleeding (bleeding with a decline in hemoglobin level >2g/dL, with the transfusion of ≥2 units of erythrocyte or whole blood, that occurs in a critical location such as intracranial, intraocular, or retroperitoneal areas, or that causes death),[16] and peripheral and cerebral embolic events.

Statistical analysis

Statistical analysis in this study was performed using the SPSS 13.0 statistical package program (SPSS Inc., Chicago, IL, USA). The KolmogorovSmirnov normality test and the Levene test were performed to check the distribution of normality of the variables. Descriptive statistics of continuous variables were shown as mean±standard deviation, and categorical variables were shown as the percentage (%) of patients within the category. Continuous variables were compared across the groups using independent samples t-test or Mann-Whitney U test according to the distribution of variables. One-way ANOVA and post-hoc Bonferroni tests were used for comparing continuous variables between more than 2 groups. The categorical variables were compared using the chi-square test. The Pearson and Spearman correlation tests were used for correlation analysis according to the state of the variables. A p value less than 0.05 was considered statistically significant.

RESULTS

A total of 274 patients were included in this study. Of the 274 patients, 26 patients were excluded owing to irregular INR control or warfarin interruption or insufficient registered INR values in the hospital database (<6 INR values). The remaining 248 patients were analyzed. The mean age of the study

population was 57.21±12.45 years, and 33.1% were men. The socioeconomic status and comorbidities of the participants are listed in Table 1. The mean TTR value of the patients was 55.92±27.84%, and TTR efficiency (TTR >60%) was found in 48.0% of the patients. Among the patients, 49.6% had a history of thromboembolic and bleeding complications (31.5% had clinically relevant non-major bleeding, 11.7% had major bleeding, 2.4% had cerebral emboli, and 4.0% had peripheral emboli). Only 30.2% of the patients (75 patients) were aware of their INR target values. The average weekly warfarin dose of the patients was 33.33±15.38 mg, and the duration of warfarin use was 7.48±6.18 years (8 months-35 years) (Table 1).

Characteristics of the patients according to warfarin indications

The study patients were divided into 3 groups according to warfarin indications (159 patients had prosthetic heart valves, 33 patients had valvular AF, and 56 patients had NVAF). There existed no statistically significant difference between the groups in terms of education level, monthly income, and smoking status (Table 1). The mean TTR value and TTR efficiency (TTR ≥60%) of the patients were also similar in the 3 groups (p=0.668 and p=0.901, respectively).

Patients in the NVAF group were significantly older, and the prevalence of men, hypertension, and CAD was higher in this group than in the other groups (p<0.001, p<0.001, p<0.001, p=0.004, respectively). The total weekly warfarin dose was lower in the NVAF group than in the other 2 groups (p=0.004). In addition, weekly warfarin dose was negatively correlated with age (r=-0.277, p<0.001).

In the prosthetic heart valve group, the presence of a history of warfarin-associated complications was significantly higher than that in the other 2 groups (p=0.027). The duration of warfarin use was longer and weekly warfarin dose was significantly higher than that in the other groups (p<0.001, p=0.004, respectively). The ratio of patients who were aware of target INR values was higher in the prosthetic heart valve group (p<0.001).

Factors that affect the mean TTR value and TTR efficiency

No significant difference was observed in the mean TTR values (55.20±26.73% in women and 57.38±30.07% in men) and TTR efficiency in terms of sex (p=0.564 and p=0.209, respectively) (Table 2). No significant relationship was found between the education level and monthly income level of the patients and the mean TTR value (p=0.718 and p=0.168, respectively) and TTR efficiency (p=0.494 and p=0.125, respectively) (Table 2 and Table 3). No statistically significant relationship was observed between the mean TTR value, TTR efficiency, and the presence of comorbidities such as diabetes, hypertension, hyperlipidemia, CAD, smoking status, CKD, and heart failure (p>0.05 for all, Table 3). No statistically significant difference was observed between the weekly warfarin low-dose (<15 mg/week) users and high-dose (≥15 mg/week) users in terms of mean TTR (p=0.711) and TTR efficiency (p=0.623). The mean TTR value was positively correlated with the frequency of INR visits per year (r=0.131 and p=0.039) (Figure 1).

Presence of a history of hemorrhagic and embolic complications

Among the patients, 49.6% had a history of hemorrhagic or embolic complications. Of these, 31.5% had clinically relevant non-major bleeding, 11.7% had major bleeding, 2.4% had cerebral emboli, and 4.0% had peripheral emboli.

Awareness of INR target value

Although the mean TTR value of the patients who were aware of the target INR value was

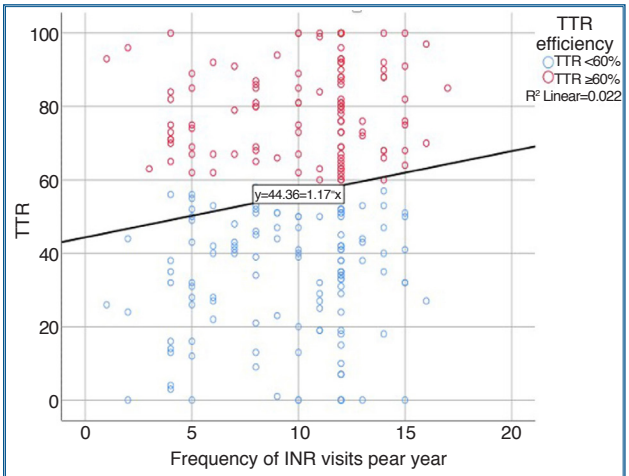

Figure 1. Relation between mean TTR, TTR efficiency and the frequency of INR visits per year.
TTR: time in therapeutic range; INR: international normalized ratio.

Table 1. Characteristics of the patients according to warfarin indications

Characteristics	All patients (n=248)	Prosthetic heart valve (n=159)	Valvular AF (n=33)	Nonvalvular AF (n=56)	*p*
Age (year±SD)	57.21±12.45	52.96±11.24	57.97±11.96	68.82±7.77	0.013
Male sex, n (%)	82 (33.1)	56 (35.2)	1 (3.0)	25 (44.6)	<0.001
Educational level					
Illiterate, n (%)	58 (22.2)	34 (21.4)	7 (21.2)	14 (25.0)	0.225
Elementary school, n (%)	133 (53.6)	78 (49.1)	23 (69.7)	32 (57.1)	
Secondary school, n (%)	24 (9.7)	18 (11.3)	3 (9.1)	3 (5.4)	
High school, n (%)	26 (10.5)	21 (13.2)	0 (0.0)	5 (8.9)	
University, n (%)	10 (4.0)	8 (5.0)	0 (0.0)	2 (3.6)	
Monthly income					
Low, n (%)	110 (44.4)	62 (39.0)	15 (45.5)	33 (58.9)	0.082
Moderate, n (%)	108 (43.5)	73 (459)	15 (45.5)	20 (35.7)	
High, n (%)	30 (12.1)	24 (15.1)	3 (9.1)	3 (5.4)	
SBP (mmHg±SD)	123.93±18.56	122.56±18.21	124.24±18.03	127.64±19.63	0.906
DBP (mmHg±SD)	78.08±10.59	76.95±9.77	79.70±11.24	80.32±12.07	0.610
Hypertension, n (%)	127 (51.2)	64 (40.3)	15 (45.5)	48(85.7)	<0.001
Dyslipidemia, n (%)	77 (31.0)	44 (27.7)	12 (36.4)	21(37.5)	0.306
Diabetes, n (%)	31 (16.9)	19 (11.9)	9 (27.3)	3 (25.0)	0.019
Smoking					
None, n (%)	152 (61.3)	95 (59.7)	25 (75.8)	32 (57.1)	0.167
Quit smoking, n (%)	75 (29.0)	45 (28.3)	6 (18.2)	21 (37.5)	
Active smoker, n (%)	24 (9.7)	19 (11.9)	2 (6.1)	3 (5.4)	
Coronary artery disease, n (%)	58 (23.4)	32 (20.1)	4 (12.1)	22 (39.3)	0.004
Heart failure, n (%)	18 (7.3)	8 (0.05)	1 (3.0)	9 (16.1)	0.014
Chronic kidney disease, n (%)	48 (19.4)	28 (17.6)	5 (15.2)	15 (26.8)	0.483
Creatinine clearance*	79.61±23.02	82.90±23.97	74.55±19.12	73.23±20.68	0.010
Weekly warfarin dose (mg)	33.33±15.38	35.58±16.90	31.68±11.05	27.92±11.18	0.004
The duration of warfarin use (year)	7.48±6.18	9.49±6.58	3.82±2.47	3.91±3.31	<0.001
Complication history (%)	123 (49.6)	89 (56.0)	13 (39.4)	21 (37.5)	0.027
Awareness of target INR value (%)	75 (30.2)	64 (40.39)	4 (12.1)	7 (12.5)	<0.001
Frequency of INR visits per year	10.02±3.80	9.99±3.94	10.52±4.10	9.82±3.19	0.558
The mean TTR (%±SD)	55.92±27.84	55.24±28.53	61.48±25.90	54.59±27.01	0.668
Efficient TTR (TTR ≥60%), n (%)	119 (48.0)	75 (47.2)	17 (51.5)	27 (48.2)	0.901

*(mL/min/1.73m^2).
AF: atrial fibrillation; SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; INR: international normalized ratio; TTR: time in therapeutic range.

60.31±28.11%, the mean TTR value of the patients who were not aware of the target INR value was 54.02±27.58%. No statistically significant difference was observed between these 2 groups (p=0.103). The ratio of the patients who were aware of the target INR value was higher in the literate group (p=0.011) (Figure 2). A statistically significant relationship was found between the duration of warfarin use and the awareness of the target INR value (p=0.024) (Figure 3).

Table 2. The mean TTR value of the patients according to their characteristics

		Patient n, (%)	Mean TTR (mean±SD)	*p*
Sex	Male	82 (33.5)	57.38±30.07	0.564
	Female	166 (66.5)	55.20±26.73	
Educational level	Illiterate	55 (22.2)	53.62±27.85	0.718
	Elementary school	133 (53.6)	55.39±26.81	
	Secondary school	24 (9.7)	56.17±32.35	
	High school	26 (10.5)	59.50±32.01	
	University	10 (4.0)	65.80±19.08	
Monthly income	Low	110 (44.4)	53.07±26.45	0.168
	Moderate	108 (43.5)	59.72±28.59	
	High	30 (12.1)	52.70±29.30	
Smoking status	None	152 (61.3)	55.34±26.26	0.698
	Quit smoking	72 (29.0)	55.64±32.14	
	Active smoker	24 (9.7)	60.50±24.14	
Diabetes	Absent	206 (83.1)	56.13±28.22	0.795
	Present	42 (16.9)	54.90±26.16	
Hypertension	Absent	121 (48.8)	54.60±26.80	0.464
	Present	127 (51.2)	57.19±28.84	
Dyslipidemia	Absent	171(69.0)	54.58±27.51	0.260
	Present	77 (31.0)	58.90±28.50	
Coronary artery disease	Absent	190 (76.6)	56.99±27.74	0.276
	Present	58 (23.4)	52.43±28.09	
Chronic kidney disease	Absent	200 (80.6)	57.15±27.37	0.157
	Present	48(19.4)	50.81±29.43	
Heart failure	Absent	230 (92.7)	56.18±27.68	0.646
	Present	18 (7.3)	52.67±30.36	

SD: standard deviation; TTR: time in therapeutic range.

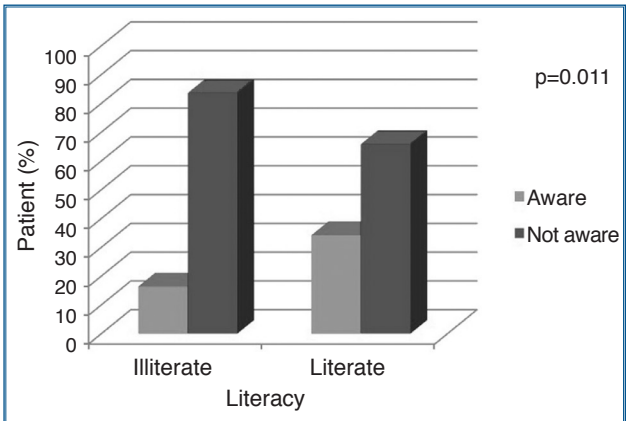

Figure 2. Awareness of the target INR value according to literacy.
INR: international normalized ratio.

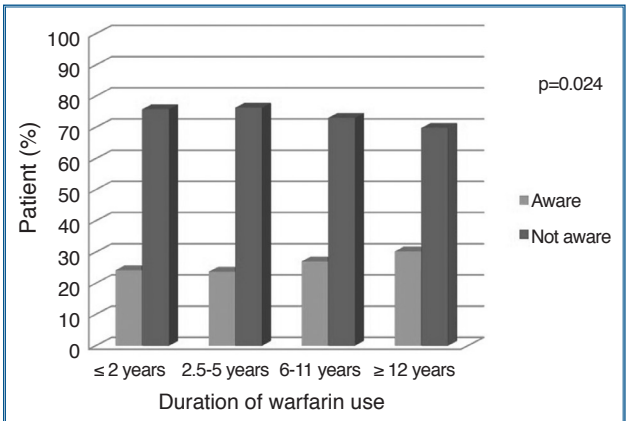

Figure 3. Awareness of the target INR value according to the duration of warfarin use.
INR: international normalized ratio.

Table 3. The efficient TTR distribution according to patients' characteristics

Characteristics	TTR <60% (n=129)	TTR ≥60% (n=119)	*p*
Age (year±SD)	57.91±12.85	56.45±12.01	0.360
Male sex, n (%)	38 (29.5)	44 (37.0)	0.209
Educational level			
Illiterate, n (%)	32 (24.8)	23 (19.3)	0.494
Elementary school, n (%)	70 (54.3)	63 (52.9)	
Secondary school, n (%)	13 (10.1)	11 (9.2)	
High school, n (%)	10 (7.8)	16 (13.4)	
University, n (%)	4 (3.1)	6 (5.0)	
Monthly income			
Low, n (%)	65 (50.4)	45 (37.8)	0.125
Moderate, n (%)	49 (38.0)	59 (49.6)	
High, n (%)	15(11.6)	15(12.6)	
SBP (mmHg±SD)	123.53±17.03	124.37±20.16	0.349
DBP (mmHg±SD)	77.82±10.01	78.35±11.22	0.306
Hypertension, n (%)	64 (49.6)	63(52.9)	0.600
Dyslipidemia, n (%)	36 (27.9)	41(34.5)	0.256
Diabetes, n (%)	25 (19.4)	17(14.3)	0.285
Smoking			
None, n (%)	84 (65.1)	68 (57.1)	0.367
Quit smoking, n (%)	35 (27.1)	37 (31.1)	
Active smoker, n (%)	10 (7.8)	14 (11.8)	
Coronary artery disease, n (%)	33 (25.6)	25 (21.0)	0.395
Heart failure, n (%)	9 (7.0)	9 (7.6)	0.872
Chronic kidney disease, n (%)	27 (20.9)	20 (16.8)	0.436
Creatinine clearance (mL/mn/1.73m^2±SD)	77.88±22.07	81.48±23.96	0.965
Weekly warfarin dose (mg)	32.39±12.95	34.36±17.65	0.314
The duration of warfarin use (year)	7.77±6.34	7.17±6.02	0.448
Complication history, n (%)	63 (48.8)	60 (50.4)	0.886
Awareness of target INR value, n (%)	36 (27.9)	39 (32.8)	0.411
Frequency of INR visits per year	9.60±3.75	10.48±3.81	0.070

TTR: time in therapeutic range; SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; INR: international normalized ratio.

DISCUSSION

The mean TTR value of the patients admitted to our cardiology outpatient clinic was 55.92±27.84%. Efficient TTR (TTR ≥60%) was present in 48.0% patients. Only 30.2% patients were aware of their target INR values. Contrary to previous studies, comorbidities (CAD, hypertension, congestive heart failure [CHF], and smoking status), sex and socioeconomic level exhibited no effect on TTR and TTR efficiency. The frequency of annual visits for INR control was 10.02±3.80 and was lower than that in other studies.[17-19] A weak relationship was found between TTR and the frequency of INR visits per year.

Since the prevalence of CAD, hypertension, and CHF increased with age, the rate of these diseases and the mean age of the NVAF group were higher than those in the other 2 groups. The mean age of NVAF patients in our study was significantly lower

than that in other similar studies. Owing to the low socioeconomic level and poor living conditions of the elderly population in our study, medication might not have been initiated for patients with advanced age in the NVAF group. In the atrial fibrillation in Turkey: epidemiologic registry (AFTER) study conducted in Turkey, the ratio of physicians who refrained from warfarin therapy in elderly patients was 30.6%.[20] Both the physicians and patients avoid the use of warfarin at an advanced age owing to decreased cognitive capacity with aging, increased risk of bleeding, and difficulty in follow-up. Advanced age is an important predictor of warfarin dose.[21,22] In our study, the total weekly warfarin dose was lower in the NVAF group than in the other two groups. This may be associated with decreasing vitamin K stores and the slowing of warfarin metabolism with advanced age.

In many studies, it has been demonstrated that average TTR increases with age.[21,23-25] On the contrary, in this study, no difference was observed in TTR efficiency and mean TTR between decades of age because the elderly patient group contributed only a small part of the included patients and warfarin indications in our study were not limited to NVAF, unlike in other studies.[24]

The mean TTR of patients who were admitted to our hospital's outpatient clinic was 55.92±27.84%. Although this value was lower than that in many studies,[26] it was found to be similar to that in some studies.[27] Most studies consisted only of NVAF patients with advanced age.[21,23] Since these patients have a more stable warfarin metabolism, they have a lower target INR value and lower weekly warfarin dose requirements. Our study included the prosthetic valve group with younger patients, higher target INR values, and higher weekly warfarin dose requirements. As a result, our mean TTR value might have been lower than that in other studies.[21,23] However, the mean TTR value of this study was higher than that in the WARFARIN-TR study (49.52±22.93%) that analyzed the TTR value of patients from across Turkey with various indications such as valvular AF, NVAF, deep vein thrombosis, and prosthetic heart valves.[6] The mean TTR value of patients with AF (valvular AF [61.48±25.90] and NVAF [54.59±27.01]) in our study was higher than that in the WATER (Warfarin in Therapeutic Range) registry (42.3±18.4) from our country.[4] The ratio of patients with efficient TTR was higher in our study (48%) than that in the WARFARIN-TR study (24.6%)[6] and the AFTER study (37%) from Turkey.[20] In these 2 nationwide studies, the participants were included from all geographical regions of Turkey. Furthermore, various factors such as ethnicity, genetic variants, and different geographical locations of the participants could affect the results. In another single-center study conducted in Turkey that included 155 patients with AF, NVAF, prosthetic heart valves, and deep vein thrombosis, the mean TTR value (57.2±22.5%) and the ratio of the patients with efficient TTR (TTR ≥60% in 45.8% of the study group) were found to be similar to those in this study.[28]

In the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) registry, TTR of patients followed at anticoagulation clinics was found to be higher than that of patients not followed at anticoagulation clinics (69% versus 66%, respectively, p<0.0001).[29] In specialized INR clinics with experienced pharmacists, nurses, and physicians, the mean TTR value was found to be higher than that in other outpatient clinics.[19,30] Kilic et al.[19] studied the effects of specialized INR clinics and general outpatient cardiology clinics on the efficacy and safety of warfarin in a single center from the Aegean region of Turkey. They found that the mean TTR value of all patients was 62.10±20.73% and was better in specialized INR clinics than that in general outpatient cardiology clinics (68.80±15.88 versus 51.60±23.04 respectively), and the patients visited for INR control more frequently than they did in our study (14.1±3.67 versus 10.2±3.8, respectively). In the subgroup analysis of WARFARİN-TR study that analyzed the mean TTR value in patients from different geographic regions of Turkey, it was found that patients from the Aegean region had the second highest TTR (54.65±24.21) (patients from the Marmara region had the highest TTR of 54.99±20.91%), whereas the mean TTR value of patients from Central Anatolia, Turkey, was 45.47±19.97%.[25] Our study was conducted at a single tertiary center in Central Anatolia; however, the mean TTR value of our study was higher than that of the WARFARİN-TR subgroup. Participants of studies that analyze TTR exhibit different characteristics, ethnicity, drug usage, nutritional habitus, warfarin indications, warfarin monitoring technique, and frequencies of INR control. Therefore, when comparing the TTR value of

studies, we should consider whole characteristics of the study population. To overcome poor anticoagulation, specialized INR clinics should be widely organized to monitor more patients closely. Additionally, knowledge and awareness assessment of the patients should be integrated into INR visits, and dietary vitamin K intake, drug-drug interactions, and warfarin compliance should be queried at each visit.

Young age, female sex, low income, Black race, frequent hospitalization, multi-drug usage, decompensated heart failure, dementia, and CHF were associated with low TTR.[21,24,29] In our study, no sex difference was observed in terms of mean TTR and TTR efficiency. However, other studies showed that the male sex exhibited a positive effect on TTR efficiency and TTR value.[21,31,32] The reason for this might be that there were 3 groups of patients and the characteristics of the patients included in the study were non-homogeneous; therefore, a sex bias was not observed.

No difference was found between the smoking status and TTR efficiency and mean TTR. However, studies have shown that smoking has increased warfarin metabolism.[33,34] Smoking increases warfarin clearance by inducing CYP1A2, shortens the half-life, and decreases the volume of distribution of warfarin. The amount of daily cigarette consumption, the density of tobacco in cigarettes, and the passive smoking status of nonsmokers were not queried. Therefore, there was no significant relationship between the mean TTR value, TTR efficiency, and smoking.

In this study, a relationship between TTR and the frequency of INR visits per year was observed. The linear regression showed that patients should make at least 14 INR visits per year to have efficient TTR (TTR ≥60%). Frequent visitors (40 patients, >13/year) were further analyzed for evaluating TTR efficiency. Factors such as age, socioeconomic level, smoking, and the presence of comorbid conditions exerted no effect on TTR efficiency. This can be attributed to numerous factors, including genetic factors, drug–drug interactions, changes in diet, and the small sample size of our study. In a study that investigated the factors that affect INR variability, no cause was found in the majority of cases (52.8%); of all the known factors, noncompliance was most commonly noted (19.8%) along with food (13.2%), drugs (10.0%), alcoholic beverages (3.1%), and herbal supplements (1.1%).[35]

Awareness of the target INR value was higher in the prosthetic valve group. The duration of warfarin use was found to be longer in patients with prosthetic heart valves. Our study showed that as the duration of drug use increased, the awareness of the INR target value increased. The awareness in the prosthetic heart valve group being higher than that in the other groups could be attributed to the duration of warfarin use being longer than that in the other groups. The patients in the prosthetic valve group had undergone major surgery earlier or had a history of warfarin-associated complications; these important experiences might have increased their awareness. The mean TTR value of the patients who were aware of the target INR value was higher than that of the patients who were unaware of the value (60.31±28.11% versus 54.02±27.58%, respectively). The difference could have been statistically significant if the study population were greater.

DOACs are favorable options for patients with NVAF without effective INR control. Current guidelines recommend preferring any DOAC to warfarin with a Class Ia recommendation. Warfarin is the sole drug recommended for patients with valvular AF and prosthetic heart valves. Therefore, close monitoring and patient awareness and knowledge are crucial for this group.

Limitations

The study findings should be interpreted in the light of some limitations. The main limitations include the observational design with a small sample size. Since the study was conducted at a single center, its results may not be generalizable. The linear interpolation method is not the right choice for TTR measurement when INR measurement intervals are more than 56 days. In our study, some intervals of INR controls exceeded this duration. The study population is non-homogeneous in terms of warfarin indication (prosthetic heart valve patients constitute the majority of the participants) and other clinical characteristics.

Conclusion

In this study, anticoagulation control was found to be below the targeted TTR. The relationship between socioeconomic level, clinical–demographical characteristics, and warfarin efficacy could not be demon-

strated. The poor awareness of the patients regarding the target INR values and poor anticoagulation control showed that warfarin follow-up itself was complex and required close monitoring. Particularly, DOACs should be preferred in patients who do not have an effective TTR value with suitable indications. Moreover, in the remaining patient group, the factors that may affect TTR should be reviewed, and necessary arrangements should be made.

Ethics Committee Approval: Ethics committee approval for this study was obtained from the Ethics Committee of Turkey Yüksek İhtisas Hospital (Approval Date: January 7, 2013; Approval Number: EPKK-619-00370).

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REFERENCES

1. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349:1019-26. [Crossref]
2. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 2008;118:2029-37. [Crossref]
3. Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. Circulation 2012;125:2298-307. [Crossref]
4. Turk UO, Tuncer E, Alioglu E, Yuksel K, Pekel N, Ozpelit E, et al. Evaluation of the impact of warfarin time in therapeutic range on outcomes of patients with atrial fibrillation in Turkey: perspectives from the observational, prospective WATER Registry. Cardiol J 2015;22:567-75. [Crossref]
5. Ertaş F, Kaya H, Kaya Z, Bulur S, Köse N, Gül M, et al. Epidemiology of atrial fibrillation in Turkey: preliminary results of the multicenter AFTER study. Turk Kardiyol Dern Ars 2013;41:99-104. [Crossref]
6. Çelik A, İzci S, Kobat MA, Ateş AH, Çakmak A, Çakıllı Y, et al. The awareness, efficacy, safety, and time in therapeutic range of warfarin in the Turkish population: WARFARIN-TR. Anatol J Cardiol 2016;16:595-600. [Crossref]
7. Costa GL, Lamego RM, Colosimo EA, Valacio RA, Moreira Mda C. Identifying potential predictors of high-quality oral anticoagulation assessed by time in therapeutic international normalized ratio range: a prospective, long-term, single-center, observational study. Clin Ther 2012;34:1511-20. [Crossref]
8. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7:79-108. [Crossref]
9. Mansia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 ESH-ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Blood Press 2007;16:135-232. [Crossref]
10. Daskalopoulou SS, Khan NA, Quinn RR, Ruzicka M, McKay DW, Hackam DG, et al. The 2012 Canadian hypertension education program recommendations for the management of hypertension: blood pressure measurement, diagnosis, assessment of risk, and therapy. Can J Cardiol 2012;28:270-87. [Crossref]
11. Association AD. Standards of medical care in diabetes-2011. Diabetes Care 2011;34:S11-61. [Crossref]
12. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70. [Crossref]
13. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012;42:S1-44.
14. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69:236-9. [Crossref]
15. INR Desk 2.0 2010. [cited 2010; Available from: http://www.softpedia.com/get/Others/Home-Education/INR-Desk.shtml.
16. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4. [Crossref]
17. Han SY, Palmeri ST, Broderick SH, Hasselblad V, Rendall D, Stevens S, et al. Quality of anticoagulation with warfarin in patients with nonvalvular atrial fibrillation in the community setting. J Electrocardiol 2013;46:45-50. [Crossref]
18. Shalev V, Rogowski O, Shimron O, Sheinberg B, Shapira I, Seligsohn U, et al. The interval between prothrombin time tests and the quality of oral anticoagulants treatment in patients with chronic atrial fibrillation. Thromb Res 2007;120:201-6. [Crossref]
19. Kilic S, Soner Kemal H, Yuce EI, Simsek E, Yagmur B, Memisoglu Akgul N, et al. Comparison of Warfarin use in terms of efficacy and safety in two different polyclinics. Anatol J Cardiol 2017;18:328-33. [Crossref]
20. Kaya H, Ertaş F, Kaya Z, Kahya Eren N, Yüksel M, Köroğlu B, et al. Epidemiology, anticoagulant treatment and risk of thromboembolism in patients with valvular atrial fibrillation:

results from Atrial Fibrillation in Turkey: Epidemiologic Registry (AFTER). Cardiol J 2014;21:158-62. [Crossref]
21. Hylek EM. Vitamin K antagonists and time in the therapeutic range: implications, challenges, and strategies for improvement. J Thromb Thrombolysis 2013;2:2. [Crossref]
22. Garcia D, Regan S, Crowther M, Hughes RA, Hylek EM. Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. Chest 2005;127:2049-56. [Crossref]
23. Okumura K, Komatsu T, Yamashita T, Okuyama Y, Harada M, Konta Y, et al. Time in the therapeutic range during warfarin therapy in Japanese patients with non-valvular atrial fibrillation. - A multicenter study of its status and infuential factors. Circ J 2011;75:2087-94. [Crossref]
24. Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT_2R_2 score. Chest 2013;144:1555-63. [Crossref]
25. Kılıç S, Çelik A, Çakmak HA, Afşin A, Tekkeşin A, Açıksarı G, et al. The time in therapeutic range and bleeding complications of warfarin in different geographic regions of Turkey: A subgroup analysis of WARFARIN-TR study. Balkan Med J 2017;34(4):349-55. [Crossref]
26. Macedo AF, Bell J, McCarron C, Conroy R, Richardson J, Scowcroft A, et al. Determinants of oral anticoagulation control in new warfarin patients: analysis using data from Clinical Practice Research Datalink. Thrombosis Research 2015;136:250-60. [Crossref]
27. Singer DE, Hellkamp AS, Piccini JP, Mahaffey KW, Lokhnygina Y, Pan G, et al. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: data from the ROCKET AF clinical trial. J Am Heart Assoc 2013;2:e000067. [Crossref]
28. Erdemoğlu E, Uzunlulu M, Oğuz A, Köstek O, Telci Çaklılı Ö. Frequency of coagulation test results being in the therapeutic range in patients using warfarin treatment. 2015;30:105-9. [Crossref]
29. Pokorney SD, Simon DN, Thomas L, Fonarow GC, Kowey PR, Chang P, et al. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry. Am Heart J 2015;170:141-8, 8 e1. [Crossref]
30. Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. J Manag Care Pharm 2009;15:244-52. [Crossref]
31. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Patient characteristics associated with oral anticoagulation control: results of the Veterans AffaiRs Study to Improve Anticoagulation (VARIA). J Thromb Haemost 2010;8:2182-91. [Crossref]
32. Gurwitz JH, Avorn J, Ross-Degnan D, Choodnovskiy I, Ansell J. Aging and the anticoagulant response to warfarin therapy. Ann Intern Med 1992;116:901-4. [Crossref]
33. Bachmann K, Shapiro R, Fulton R, Carroll FT, Sullivan TJ. Smoking and warfarin disposition. Clin Pharmacol Ther 1979;25:309-15. [Crossref]
34. Evans M, Lewis GM. Increase in international normalized ratio after smoking cessation in a patient receiving warfarin. Pharmacotherapy 2005;25:1656-9. [Crossref]
35. Kim JH, Song YB, Shin DH, Kim JS, Choi JO, On YK, et al. How well does the target INR level maintain in warfarin-treated patients with non-valvular atrial fibrillation? Yonsei Med J 2009;50:83-8. [Crossref]

Keywords: Atrial fibrillation; international normalized ratio; socioeconomic factors; thromboembolism; warfarin

Anahtar Kelimeler: Atriyal fibrilasyon; uluslararası normalleştirilmiş oran; sosyoekonomik faktörler; tromboembolizm; varfarin

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Editöryal Yorum / Editorial

Kardiyoloji kliniklerinde kullanılan bilgilendirilmiş onam belgelerinin etik değerlendirmesi ve kurumsal standart yaklaşımın önemi

Ethical evaluation of informed consent forms used in the cardiology clinics and the importance of institutional standardized approach

Dr. Ufuk İyigün

Hatay Eğitim ve Araştırma Hastanesi Kardiyoloji Kliniği, Hatay, Türkiye

Hekimlere açılan hukuk ve ceza davalarının gün geçtikçe arttığı aşikar. En sık gördüklerimizden birisi de 'aydınlatılmış onam' kavramı üzerinden açılan davalar. Diğer adıyla bilgilendirilmiş rıza. Hekimlik müdahalelerinde hasta üzerinde tatbik edilen tıbbi müdahalelerin hukuka uygun olabilmesi açısından bir takım şartların olması gerekir. Bunlar müdahaleyi yapan kişinin hekim olması, yapılan işlemin tıp standartlarına uygun olması, endikasyonun diğer deyişle tıbbi gerekçenin olması ve hastanın rızasının olmasıdır.[1] Bu koşulların sağlanmadığı durumlarda hastaya yapılan uygulama hukuka uygunluğunu kaybedecek ve uygulamayı yapan kişi -hekim bile olsa- yaralama hatta olaya göre öldürme suçundan yargılanabilecektir.

Anayasamızın 17/2. maddesi 'Tıbbi zorunluklar ve kanunda yazılı haller dışında, kişinin vücut bütünlüğüne dokunulamaz; rızası olmadan bilimsel ve tıbbi deneylere tabi tutulamaz' ifadesi ile rızanın gerekliliğine gönderme yaparken, kısaltılmış adıyla 'Biyotıp Sözleşmesi' olarak adlandırılan uluslararası sözleşmenin birçok maddesinde hasta özerkliği kavramının üzerinde durulmaktadır. Bunların dışında 1219 sayılı Tababet ve Şuabatı San'atlarının Tarzı İcrasına Dair Kanun'un 70. maddesi, Tıbbi Deontoloji Tüzüğünün 14. maddesi, Hasta Hakları Yönetmeliği'nin 5. maddesi, Hekimlik Meslek Etiği Kuralları'nın 26. maddesi gibi mevzuatımızın birçok yerinde bu konuya yer verilmiştir.

Eski dönemlerde yapılan hekimlik uygulamalarına baktığımızda bilgilendirme ve hastanın rızasını alma durumunun nispeten yeni olduğu kolaylıkla fark edilir. Eski dönemlerde hakim olan paternalist yaklaşımın, süreç içerisinde 'hastanın özerkliği' yaklaşımına evrildiğini görürüz. Günümüzde 'Hasta için en iyisini hekim bilir ve gerekeni yapar' anlayışından 'Hasta, kendi vücudu ile ilgili kararları, kendisi almalıdır' anlayışına doğru bir değişim söz konusudur. Bu bağlamda, mevcut hastalığı ile ilgili yeterli düzeyde bilgilendirilmesi sonrasında, hasta tarafından rıza gösterilecek ve ardından tıbbi müdahale yapılabilecektir. Aldığı karar kendisi için zararlı bile olacak olsa hastanın kararına öncelik verilecektir.

Farklı değerleri, inanışları, beklentileri olan insanların kendileri için yararlı gördükleri birtakım durumları ya da işlemleri, hekimlerin aynı şekilde değerlendirebilmesi çoğu zaman mümkün değildir. Etik değerlendirme bu nedenle paternalist yaklaşımı sorunlu bulur.[2]

Otonomi ya da hasta özerkliği de denilen kavram dünyada ve ülkemizde uzun süredir üzerinde titizlikle durulan bir kavramdır. Temelinde hastanın kendi vücudu ile ilgili kararları yine kendi özgür iradesiyle almasını anlatır. Burada önemli olan konu, hastanın; hastalığı, bu hastalığın tedavisi, yapılacak müdahalenin olası komplikasyonları, alternatif tedavi yöntemleri gibi hemen her konuda yeterince aydınlatılmasıdır. Hukuk düzenimiz bu bilgilere sahip olmayan

Correspondence: Dr. Ufuk İyigün. Hatay Eğitim ve Araştırma Hastanesi Kardiyoloji Kliniği, Hatay, Türkiye
Tel: +90 505 904 06 48 e-mail: druiyigun@hotmail.com

hastanın aldığı kararın özgür olmayacağı ve aslında esas iradesinin ortaya çıkmayacağı görüşündedir.

Özellikle son dönemlerde hekimlere karşı açılan ceza ve tazminat davalarında üzerinde en çok durulan ve söz konusu edilen konu aydınlatılmış onamdır.[3] Son zamanlarda tıbbi malpraktis iddialarıyla açılan davalarda, davacı tarafın avukatları, özellikle de adli tıp ya da bilirkişi raporlarıyla hekime atfedilecek açık bir tıbbi uygulama kusuru olmadığı durumlarda, iddialarını hastanın aydınlatılmasının ve rızasının yeterli bir şekilde yapılmadığı savına dayandırabilmektedir. Bu gibi durumlarda özellikle hastaya göre kişiselleştirilmemiş, en azından ana noktalar konusunda hekimin hastayı bilgilendirdiğini açık bir şekilde ispat edemediği durumlarda, matbu onam formlarına imza attırmak olası hukuki süreçlerde hekimi korumayacaktır. Hukuk düzenimize göre hekim-hasta ilişkilerinde edimler eşit değildir. Hekim bu ilişkinin güçlü tarafıdır. Gerek bilgi olarak, gerekse hastanın hastalığının getirdiği fiziksel ve psikolojik etki altında karar aldığından, hekimden daha güçsüz taraf olduğu açıktır. Bu nedenle güçsüz tarafı korumak adına hukuk sistemimiz hastanın aydınlatıldığının ispat yükünü hekimlere yüklemiştir. Yargıya taşınan herhangi bir hukuki süreçte hasta bilgilendirilmediğini söylediğinde bunun aksini ispat etme külfeti hekimdedir. Ülkemiz özelinde, kamuda çalışan hekimlerin iş yükü göz önüne alındığında uzun uzadıya bilgilendirme yapmanın çok da mümkün olmadığı sıklıkla hekimler tarafından dile getirilen ve bilinen bir gerçektir. Ama ne yazık ki hekimlerin, işlerini yaparken göstermeleri gereken dikkat ve özen yükümlülüğü ve hafif farklı aydınlatılmış onam formları ile birlikte kaotik bir ortam yaratmaktadır. Tıp alanından oldukça kusurlarından bile sorumlu olacağı şeklindeki yargı kararları bu söylemin hukukta bir karşılığı olmadığını göstermektedir. Olsa olsa 'organizasyon kusuru' adı altında idarelerce sorumluluğun bölüşülmesine yol açabilecek bu durum başlı başına ayrı bir konudur ve mevcut çalışma dahilinde konumuz dışındadır.

Sağlık kurumlarında standart bilgilendirme prosedürlerinin olmaması, çoğu zaman hekimlerin, kendi değerlendirmeleri ve insiyatiflerine göre oluşturdukları onam formları, uygulamada birbirinden uzak hukukçuların ve temel hukuk bilgisinden yoksun hekimlerin bu alandaki düzenlemeleri sistematikten uzak, standardize olmayan rıza prosedürleri yaratmıştır.[4]

Bilgilendirmeden bahsettiğimizde bunun sınırı nasıl belirlenecektir? Esas soru işaretlerinin bulunduğu alanlardan biri de budur. En az ihtimalin bile anlatılması mı gereklidir? Böyle bir durumun çoğu zaman imkan dahilinde olmadığı açıktır. En sık görülebilecek komplikasyonlar mı anlatılmalıdır? Bu durumda nispeten seyrek görülen komplikasyonların geliştiği hastaların durumu ne olacaktır? Dava durumunda hakimin yaklaşımı ne olacaktır? Bu durumları değerlendirebilmek açısından 'Meslektaş ölçütü' 'Makul Kişi ölçütü' ve 'Öznel ölçüt' gibi bir takım öneriler sunulmuştur. Ama tek başına hiç biri yeterli değildir.[2] Bunların ulusal bazda sınırlarının netleştirilmesi; uzmanlık dernekleri, bakanlık temsilcileri, sağlık hukuku bilim uzmanları, akademisyenler vb. tüm paydaşları içeren bir komisyon içerisinde bir konsensüs oluşturulması ile çözülebilir.

Aydınlatılmış rıza ne zaman alınmalıdır? Bu konuda mevzuatımızda açık bir hüküm yoktur. Fakat bilgilendirme ile işlem arasındaki süre; hastanın düşünmesine ve değerlendirmesine yetecek düzeyde 'makul bir süre' olmalıdır.[5] Bu süre nispeten riski az lokal girişimlerde daha kısa olabilecekken, risk ve komplikasyonları yüksek cerrahi işlemlerde daha uzun tutulmalıdır.

Bu genel bilgiler ışığında özellikle aydınlatılmış onam konusunda hukuk düzenimizin hekimlerden beklediği işlemler açısından farkındalık yaratabilmek adına yapılan çalışma dikkat çekicidir. Her uzmanlık derneğinin kendi uygulama alanlarında detaylı bilgilendirme formlarını oluşturması ve bu formları oluştururken tıbbi uygulayıcılar yanında hukuki danışmanlarla çalışması, hatta ekibe etikçilerin katılması, özellikle periferde çalışan hekimlerin işleyişini kolaylaştırması ve formların etkililiği açısından önem taşımaktadır. Kardiyoloji özelinde işlemlerle alakalı radyasyon riski ve anestezi gerekliliği konusunda önceden riskler konusunda aydınlatma, hekimleri olası hukuki durumlarda koruyucu olacaktır. Bu açıdan çalışmada sunulan gerekçe yerinde ve önemlidir. Detaylı oluşturulan formların standardizasyonunun ve ülke genelinde uygulanmasının sağlanması ise bilgilendirme çalışmaları ile sağlanabilir. Bu konuda Türk Kardiyoloji Derneği'nin çalışmaları ve alınacak sorumluluk çok değerlidir.

Sonuç olarak hekimlere; bilgilendirilmiş rıza kavramının gittikçe artan oranda, tıbbi malpraktis iddiasıyla açılan davalarda yer bulduğu anlatılmalıdır.

Hekimlerin; gerek tıp eğitiminin içinde, gerekse mezuniyet sonrası eğitim sürecinde konu hakkında bilgilendirilmesi ve soru işaretlerinin çözülmesi önem arzetmektedir. Bilgilendirmenin içeriği, rızanın zamanı, metnin hukuki olarak ispat yükümlülüğünü sağlayacak şekilde düzenlenmesi, özellikle uzmanlık derneklerinin kendi alanlarıyla ilgili işlemlerde kullanılacak matbu onam formlarının detaylıca düzenlenmesinin sağlaması ve bunu standardize ederek, ülke genelindeki hastanelerde kullanımı konusunda çalışmalar yapılması önemlidir. Matbu olan onam formlarının altına, hastanın el yazısı ile yazılacak, en azından bilgilendirildiğini ve aydınlatıldığını ispatta kolaylık sağlayacak bir boşluk bulunması ve bu kısmın özellikle doldurulmasının talep edilmesi yönünde hekimlerin bilgilendirilmesi, olası dava süreçlerinde hekimi koruyacaktır. Hatta bir adım daha ileri gidilerek, ülkemiz koşullarında özellikle kamuda çalışan hekimler başta olmak üzere, iş yüklerini azaltıcı, görev paylaşımı sağlayıcı, bu konuda eğitim verilmiş bilgilendirme ekiplerinin kurulması, sağlıkta yapay zeka uygulamalarından faydalanılarak bilgilendirmenin sağlanması ve bunun kişisel verilerin korunması ve hastanın mahremiyet hakkı gibi temel ilkelere uyularak kayıt edilmesi, hem hekim iş yükünü azaltacak hem de ispat yükünü kolaylaştıracaktır. Böylelikle kafalarında soru işaretleri olan hastalar, hekimlerden yüz yüze bilgi alabilmek için ek zamana sahip olabileceklerdir. Tazminat davaları ve ceza davalarının günden güne arttığı günümüzde, hekimlerin kendi çalışma alanları dahilinde, hukuki konularda bilinçlendirilmesi özellikle uzmanlık dernekleri bünyesinde desteklenmelidir. Tazminat ve ceza korkusu nedeniyle hekimlerin defansif tıbba yönelimlerinin arttığı günümüzde, uzun vadede toplum sağlığını tehdit eden bu durumun gelişiminin engellenmesi açısından, hekimlerin hukuki endişelerini giderici eğitici çalışmalar yapılmalıdır. Bu çalışmalar; özellikle defansif tıp uygulamaları neticesinde hastaların sağlık hizmetine ulaşmada güçlük çekmesi, sağlık alanına ayrılan ulusal kaynakların gereksiz tetkik ve işlemlerle yararsız kullanımı gibi birtakım olumsuzlukların da önüne geçilmesini sağlayabilecektir.

REFERENCES

1. Hakeri H. Tıp hukuku. 20. Baskı. Ankara, Seçkin; 2020. p. 269-70.
2. Veatch RM. Bioetiğin temelleri. 1. Baskı. Prentice Hall; 2010. p.78-9.
3. Koç S. Adli tıbbi açıdan malpraktis ve hekim sorumluluğu. Toraks Cerrahisi Bülteni 2014;1:17.
4. Aktaş EÖ. Hak ve yüküm olarak bilgilendirilmiş rıza. In: Yılmaz EN, Özcengiz D, eds. Bilgilendirilmiş rıza. Ankara, Yetkin; 2020. p. 190.
5. Yılmaz B. Hekimin hukuki sorumluluğu. 2. Baskı. Ankara, Adalet; 2010. p. 48.

ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Ethical evaluation of informed consent forms used in cardiology clinics and the importance of institutional standardized approach

Kardiyoloji kliniklerinde kullanılan bilgilendirilmiş olur formlarının etik değerlendirmesi ve kurumsal standart yaklaşımın önemi

Aksüyek Savaş Çelebi, M.D.[1], Perihan Elif Ekmekçi, M.D.[2], Müberra Devrim Güner, M.D.[3]

[1]Department of Cardiology, TOBB Economy and Technology University School of Medicine, Ankara, Turkey
[2]Department of History of Medicine and Ethics, TOBB Economy and Technology University School of Medicine, Ankara, Turkey
[3]Department of Medical Pharmacology, TOBB Economy and Technology University School of Medicine, Ankara, Turkey

ABSTRACT

Objective: This study aimed to evaluate the content of informed consent forms (ICFs) used during cardiology interventions by the university, research and training (R&T), and private hospitals with regard to ethical standards and compare them with the Turkish Society of Cardiology (TSC) templates and among various institutions.

Methods: A total of 185 forms from the university, R&T, and private hospitals and 19 TSC templates were selected and analyzed for 26 criteria. Compliance with TSC templates was also evaluated. Data were presented as the percentage of ICFs satisfying the criteria and compared using the Fisher exact test, and 95% confidence intervals were calculated.

Results: TSC templates were more compatible and included more information to comply with ethical standards than ICFs of all 3 types of healthcare institutions. The areas of improvement for these templates were prospects of treatment and alternative treatments, quality of life, explanation for third-party consent, duration of hospitalization, and time to return to normal life. Among the 3 types of hospitals, R&T-ICFs were more compatible with templates. Private hospital ICFs had the poorest compliance with TSC templates. Separate anesthesia ICFs and detailed information about exposure to radioactivity were lacking.

Conclusion: The current ICFs for cardiology interventions have major ethical deficiencies and need urgent improvement. Professional societies such as TSC are essential institutions to develop and provide guidance and templates for ICFs to meet the ethical standards during the informed consent process and standardization of the process among various institutions.

ÖZET

Amaç: Bu çalışmanın amacı, üniversite, araştırma ve eğitim ve özel hastanelerin kardiyoloji girişimleri sırasında kullanılan bilgilendirilmiş olur formlarının (BOF) içeriğini etik standartlar açısından değerlendirmek ve Türk Kardiyoloji Derneği (TKD) taslak formları ile karşılaştırmak ve kurumlar arasındaki farkları belirlemektir.

Yöntemler: Üniversite, araştırma ve eğitim ve özel hastanelerde kullanılan 185 form ve 19 TKD şablon formu seçildi ve 26 kritere göre analiz edildi. Hastanelerde kullanılan formların TKD şablonlarına uyumları da değerlendirildi. Veriler, kriterleri karşılayan BOF'ların yüzdesi olarak sunuldu ve Fisher'in kesin testi kullanılarak karşılaştırıldı, %95 güven aralıkları hesaplandı.

Bulgular: TKD şablonları etik standartlarla daha uyumluydu ve her üç tür sağlık hizmeti kurumuna kıyasla etik standartlara uygun daha fazla bilgi içeriyordu. Bu şablonlarda tedavi ve alternatif tedavilere ilişkin beklentiler, yaşam kalitesi, üçüncü taraf onayının açıklaması, hastanede kalış süresi ve normal hayata dönme süresi kriterlerinde bazı eksikler saptandı. Üç hastane türü arasında araştırma ve eğitim hastanelerinde kullanılan BOF'lar TKD şablonlarına daha uyumluydu. Özel hastane BOF'ları TKD şablonlarıyla en zayıf uyuma sahipti. Ayrıca anestezi BOF'u ve radyoaktiviteye maruz kalma hakkında ayrıntılı bilgi sunumu genel olarak eksikti.

Sonuç: Kardiyoloji müdahalelerinde kullanılan mevcut BOF'ların büyük etik eksiklikleri vardır ve iyileştirilmesi gerekir. TKD gibi uzmanlık örgütleri, bilgilendirilmiş olur süreci ve çeşitli kurumlar arasında sürecin standardizasyonu ve etik standartlara uyumları için rehberlik sunmak ve BOF şablonları geliştirmek ve sağlamak için önemli ve temel kurumlardır.

The informed consent (IC) process is a fundamental ethical step in healthcare, especially for invasive procedures. The ethical basis for IC depends on the respect for autonomy principle. According to this principle, all competent individuals have the right to know and understand their disease, diagnostic and therapeutic means, alternatives, and risks and advantages of both the intended intervention and alternatives.[1] Moreover, they should come to a decision without undue influence. Beauchamp and Childress[2]

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Correspondence: Müberra Devrim Güner, M.D., Department of Medical Pharmacology, TOBB Economy and Technology University, School of Medicine, Ankara, Turkey
Tel: +90 532 698 48 88 e-mail: devrimguner@etu.edu.tr