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

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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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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.

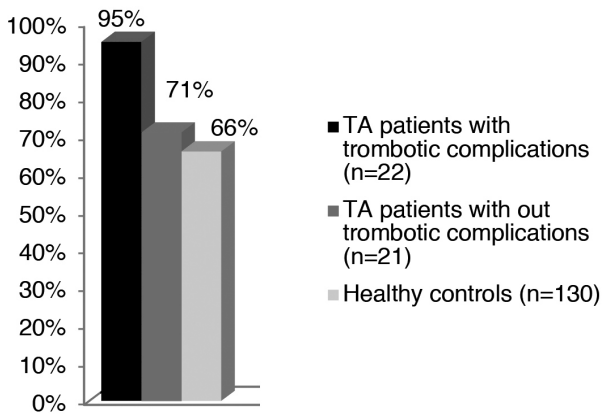

Figure 1. Plasminogen activator inhibitor-1 PAI-I (5G4G+4G4G) [A1] genotype distribution in patients with Takayasu arteritis with and without a history of thrombosis and in healthy [A2] controls.
TA: Takayasu arteritis.

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.

Peer-review: Externally peer-reviewed.

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