Frequency of Hereditary Prothrombotic Risk Factors in Patients with Down Syndrome

ABSTRACT

Objective: Down Syndrome (DS) is defined as chromosome 21 trisomy and associated with cardiovascular system diseases. We aimed to study inherited thrombophilia genes (MTHFR A1298C, MTHFR C677T, Factor II G20210A, Factor V Leiden G1691A, Factor V Cambridge G1091C, Factor XIII, APOB, ITGB3, FVHR2, FGB, PAI-1 and ACE) in patients with DS.

Methods: A total of 53 patients with DS (32 male and 21 female) were included in the study. Demographical, laboratory and clinical features of cases were recorded. 12-lead Electrocardiogram (ECG), transthoracic echocardiography and the inherited thrombophilia genes were evaluated.

Results: The clinical and developmental defect findings of the patients were high. The 39.6% of patients had both heterozygous MTHFR C677T and heterozygous MTHFR A1298C carriers, the 18.9% of patients had homozygous MTHFR A1298C carriers, the 17% of patients had heterozygous Factor V Leiden G1691A carriers, the 43.4% of patients had 4G/4G carriers, the 34% of patients had 4G/5G variant carriers for PAI, the 22.7% of patients had heterozygous Factor XIII carriers, the 49.1% of patients had ins/del carriers and the 37.7% of patients had del/del variation carriers for ACE. All patients had at least one of the homozygous and/or compound heterozygous variation for the inherited thrombophilia.

Conclusions: The patients with DS have a high risk for thrombosis-related cardiovascular system diseases. It may be said that the average life expectancy of individuals with DS may be increased by precautions (related to medical, social, lifestyle, etc.) to reduce complications associated with hereditary thrombophilia.

Keywords: Down Syndrome, Inherited Thrombophilia, Prothrombotic Risk Factors, Cardiovascular Diseases

Down Sendromlu Hastalarda Kalıtsal Protrombotik Risk Faktörlerinin Sıklığı

ÖZET

Amaç: Down Sendromu (DS), kromozom 21 trizomisi olarak tanınan ve kardiyovasiküler sistem hastalıkları ile ilişkilidir. Biz DS'li hastalarda kalıtsal trombofili genlerini (MTHFR A1298C, MTHFR C677T, Factor II G20210A, Factor V Leiden G1691A, Factor V Cambridge G1091C, Factor XIII, APOB, ITGB3, FVHR2, FGB, PAI-1 ve ACE) incelemedik amacladık.

Gereç ve Yöntem: Çalışmaya toplam 53 DS'li hasta (32 erkek ve 21 kadın) dahil edildi. Olguların demografik, laboratuvar ve klinik özellikleri kaydedildi. 12 derivasyonlu Elektrokardiogram (EKG), transtoralı ekokardiografi ve kalıtsal trombofili genleri değerlendirildi.

Bulgular: Hastaların klinik ve gelişimsel kusurları yüksekti. Hastaların %39,6’sı hem heterozigot MTHFR C677T hem de heterozigot MTHFR A1298C taşıyıcısı, hastaların %18,9’u homozigot MTHFR A1298C taşıyıcısı, hastaların %17’i heterozigot Faktör V Leiden G1691A taşıyıcısı, hastaların %43,4’ü 4G / 4G taşıyıcısı, hastaların %34’ü PAI için 4G / 5G varyasyon taşıyıcısı, hastaların %22,7’si heterozigot Faktör XIII taşıyıcısı, hastaların %49,1’i ins / del taşıyıcısı ve hastaların %37,7’si ACE için del / del varyasyon taşıyıcısı idi. Tüm hastalarda, kalıtsal trombofili için homozigot ve / veya bileşik heterozigot varyasyonlardan en az biri vardı.

Sonuç: DS’li hastalar tromboz ilişkili kardiyovasiküler sistem hastalıkları açısından yüksek risk tashmakta. Kalıtsal trombofili ile ilişkili komplikasyonları azaltmak için alnacak önlemlerle (tibbi, sosyal, yaşam tarz vb. ile ilgili) DS’li bireylerin ortalamaya yaşam beklentisinin arttırlabileceği söylenebilir.

Anahtar Kelimeler: Down Sendromu, Kalıtsal Trombofili, Protrombotik Risk Faktörleri, Kardiyovasiküler Hastalıklar
INTRODUCTION
Down Syndrome (DS) is defined as chromosome 21 trisomy and occurs when the chromosome 21 does not separate during egg or sperm development. The incidence is approximately 1 in 700 live births. Although the ratio varies according to the mother’s age, it is more common especially in births over 45 years of age.

Since many organs and systems are affected simultaneously in DS patients, phenotypic features are variable. DS phenotype often consists of dysmorphic facial features (flat nasal bridge, small chin, slanted eye, smallmouth and large tongue), muscle hypotonia, short stature, congenital heart diseases and cognitive disorders.

The average life expectancy of individuals with DS, thanks to advanced modern medical facilities and social support, in developed countries is 55 years. Congenital heart diseases occur in 40 to 60% of individuals with DS and this situation is the main reason for morbidity and mortality, particularly in the first 2 years. Among congenital heart diseases, ventricular septal defect (VSD), atrioventricular septal defects (AVSD), atrial septal defect (ASD), and patent ductus arteriosus (PDA) are frequently reported in DS (1,2). In a large study comparing the DS group with the non-DS group, the prevalence of cardiac arrhythmia, pulmonary hypertension, diabetes, congenital heart disease and the frequency of cerebrovascular events were reported to be higher in the DS group (3). Also in other studies, vascular disorders such as artery occlusion, cerebral venous sinus thrombosis (CVST) have been associated with DS (4-7). Cardiovascular system diseases and thromboembolic events developing on this basis suggest that there may be a tendency for hypercoagulation or thromboembolism simultaneously. Therefore, we aimed to study a number of genes that have the potential to increase the tendency to thrombosis in individuals with DS. These genes (MTHFR A1298C, MTHFR C677T, Factor II G20210A, Factor V Leiden G1691A, Factor V Cambridge G1091C, Factor XIII(V34L), APOB, ITGB3, FVHR2, FGB, PAI-1 and ACE) were included in the study.

Table 1. Clinical and developmental defects findings of patients with DS

| Clinical and Developmental Defects | Mean ± SD / n;% |
|-----------------------------------|-----------------|
| Mean age                          | 5.16±4.428      |
| Mean length                       | 96.95±29.293    |
| Mean weight                       | 22.05±21.482    |
| Mean birth weight                 | 2955.28±397.122 |
| Delay in holding their head       | 22 (79.2%)      |
| Delay in unsupported sitting      | 43 (81.1%)      |
| Delay in walking                  | 41 (77.4%)      |
| Hypotonia                         | 28 (52.8%)      |
| Mild developmental delay          | 20 (37.7%)      |
| Moderate developmental delay      | 23 (43.4%)      |
| Severe developmental delay        | 7 (13.2%)       |
| System anomalies                  | 44 (64.1%)      |
| Hypothyroidism                    | 27 (51%)        |
| Hyperthyroidism                   | 3 (5.7)         |
| Hearing problem                   | 12 (22.6%)      |
| Vision problem                    | 7 (13.2%)       |
| Convulsion history                | 2 (3.8%)        |
| Cardiac operation history         | 8 (15.1%)       |

Table 1: Number of patients SD: Standard deviation

12-lead Electrocardiogram (ECG) was done for each cases at rest. Also, all of the patients in the study were evaluated with transthoracic echocardiography (Siemens Acuson SC 2000). Transthoracic two dimensional (2D) guided, color Doppler echocardiogram, and continuous wave Doppler were performed with suitable probes according to age. Cardiac anatomy, ventricular function and valve competence were assessed using standardized projections and measurements were performed according to the recommendations of the American Society of Echocardiography (16). Additionally, inherited thrombophilia factors including MTHFR A1298C, MTHFR C677T, Factor II G20210A, Factor V Leiden G1691A, Factor V Cambridge G1091C, Factor XIII(V34L), APOB, ITGB3, FVHR2, FGB, PAI-1 and ACE genes were evaluated. The study protocol was certified by the local Ethics Committee (2018/220).

Statistical Analysis: Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, New York, USA). Quantitative variables are expressed as mean±standard deviation, numbers and percentages. The descriptive statistic was carried out.

RESULTS
The clinical and developmental defect findings of the patients were given in Table 1. Echocardiographic and electrocardiographic findings of patients were given in Table 2. When we analyzed hereditary thrombophilic factors in patients included in the study, we found a remarkably high rate especially in some parameters.
Table 2. Echocardiographic and electrocardiographic findings

| Condition                        | (n; %)          |
|----------------------------------|-----------------|
| Atrial septal defect (ASD)       | 13 (24.5%)      |
| Ventricular septal defect (VSD)  | 9 (17%)         |
| Patent foramen ovale (PFO)       | 5 (9.4%)        |
| Patent ductus arteriosus (PDA)   | 3 (5.7%)        |
| Aortic regurgitation (AR)        | 3 (5.7%) / 2 of them had mild AR and 1 of them had moderate AR |
| Mitral regurgitation (MR)        | 6 (11.4%) / 4 of them had mild MR, 1 of them had moderate MR, and 1 of them had severe MR |
| Tricuspid regurgitation (TR)     | 16 (30.3%) / 11 of them had mild TR, 5 of them had moderate TR |
| Pulmonary regurgitation (PR)     | 2 (3.8%) (Mild) |
| Pulmonary hypertension (PH)      | 14 (26.4%) / 2 of them had stage I (PAP between 25 and 40mmHg), 11 of them had stage II (PAP between 41 and 55mmHg) and 1 of them had stage III (PAP >55mmHg). |
| Electrocardiography              | 14 of cases (26.4%) had incomplete right bundle branch block |

Twenty one patients (39.6%) had heterozygous MTHFR C677T carriers, twenty one patients (39.6%) had heterozygous MTHFR A1298C carriers, nine patients (17%) had heterozygous Factor V Leiden G1691A carriers, twenty-three patients (43.4%) had 4G/4G carriers, eighteen patients (34%) had 4G/5G variation carriers for PAI, twelve patients (22.7%) had heterozygous Factor XIII(V34L) carriers, twenty-six patients (49.1%) had ins/del carriers and twenty patients (37.7%) had del/del variation carriers for ACE. All patients had at least one of the homozygous and/or compound heterozygous variations for the inherited thrombophilia. The frequency of inherited thrombophilia factors was given in Table 3.

Table 3. Frequency of inherited thrombophilia factors

| Gene                     | Homozygous (n; %) | Heterozygous (n; %) |
|--------------------------|-------------------|---------------------|
| MTHFR A1298C            | 10 (18.9%)        | 21 (39.6%)          |
| Factor II G20210A       | -                 | 1 (1.9%)            |
| Factor V Leiden G1691A  | -                 | 9 (17%)             |
| Factor V Cambridge G1091C | -              | 3 (5.7%)            |
| MTHFR C677T             | 1 (1.9%)          | 21 (39.6%)          |
| Factor XIII(V34L)       | 1 (1.9%)          | 12 (22.7%)          |
| ITGB                    | -                 | 6 (11.3%)           |
| FGB                     | -                 | 2 (3.8%)            |
| APOB                    | -                 | -                   |
| FVHR2                   | -                 | -                   |
| PAI                     | 23 (43.4%) for 4G/4G | 18 (34%) for 4G/5G |
| ACE                     | 20 (37.7%) for del/del | 26 (49.1%) for ins/del |

n: Number of patients
MTHFR: methylenetetrahydrofolate reductase
ITGB: Integrin beta-1
FGB: β-fibrinogen gene
APOB: Apolipoprotein B
FVHR2: Factor V HR2
ACEI: Angiotensin Converting Enzyme Inhibitors
PAI: Plasminogen Activator Inhibitor-1

DISCUSSION

To the best of our knowledge, there are no studies evaluating the risk of cardiovascular system disease in DS patients by studying a large number of genes. In this study, we examined patients with DS in terms of genes related to cardiovascular system diseases.

According to our results, considering all patients included in the study, the carrier rate for ins/del and del/del variation for ACE, heterozygous MTHFR A1298C, homozygous MTHFR A1298C, heterozygous MTHFR C677T, 4G/4G and 4G/5G variation for PAI, heterozygous Factor XIII, heterozygous Factor V Leiden G1691A attract attention. In the literature, ACE I/D genotype (del/del), homozygous MTHFR (A1298C) polymorphism and factor V Leiden (G1691A) heterozygous were detected in a hereditary thrombophilia evaluation due to diffuse bilateral lower extremity vein thrombosis in a patient with down syndrome in the pediatric age group (17). In a study with non-DS patients, 144 patients with ischemic stroke and 62 myocardial infarction (MI) or peripheral arterial occlusive disease (PAOD) were compared for the prevalence of prothrombotic gene polymorphism. In particular, we to be taken into consideration the polymorphism prevalence of ACE, MTHFR, PAI-1, Factor V Leiden genes in patients with DS by
In addition to the relationship between \textit{ITGB3} polymorphism and acute coronary syndrome and atherosclerosis, the relationship between \textit{FXIIIB} and cardioembolic ischemic stroke has been demonstrated by different studies (25,26). Both mutations were seen significantly higher in our study. Also, we could not detect \textit{APOB} or \textit{FVHR2} gene mutation in DS patients.

The main limitation of the study was lower number of patients with DS (53 individuals) and the comparison was performed with control groups of the previous studies. But it is important that the current study was first study in the literature.

Compared to the literature (27), the incidence of congenital heart disease was lower since the average age of the patients included in our study was higher during the evaluation. This situation may be caused by a significant part of congenital heart diseases can recover spontaneously in early childhood.

**CONCLUSION**

To the best of our knowledge our current study is the first that performed a broad number of inherited thrombophilia including \textit{MTHFR A1298C}, \textit{MTHFR C677T}, \textit{Factor II G20210A}, \textit{Factor V Leiden G1691A}, \textit{Factor V Cambridge G1091C}, \textit{Factor XIII(V34I)}, \textit{APOB}, \textit{ITGB3}, \textit{FVHR2}, \textit{FGB}, \textit{PAI-1} and \textit{ACE} genes in patients with DS. According to our results, the patients with DS have increased cardiovascular system diseases related with thrombosis. May the short life expectancy of patients with DS may be caused by increased inherited thrombophilia risk although the advanced modern medical facilities and social support? When the precautions (related with medical, social, lifestyle etc.) to be developed that decrease the inherited thrombophilia risks, the average life expectancy of individuals with DS may be increased? To obtain more certain knowledge about the current topic, additional studies should be performed.

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