Prothrombin Gene Mutation as a Risk Factor in Young Ischemic Stroke: A Case Report

Dilcan Kotan[1], Lütfi Özel [2], Hızır Ulvi[2], Recep Aygül[2]

[1]*Sakarya Üniversitesi Tıp Fakültesi, Nöroloji, Sakarya, Türkiye*
[2]*Atatürk Üniversitesi Tıp Fakültesi, Nöroloji, Erzurum, Türkiye*

ABSTRACT

Stroke at young age is the stroke seen under the age of 45 years with the incidence range between 2.5 and 40/100.000. Stroke at young age is account for 4-10% of overall stroke cases. The majority of strokes in young adults are of ischemic origin. The causes of young ischemic strokes are different than those of advanced age and many analyses may be required to find out the underlying reason. These analyses include cerebral angiography, transesophageal echocardiography, tests to detect coagulation disorders, and investigation of collagen vascular diseases. Studies have most frequently focused on FV Leiden, MTHFR C677T and Prothrombin G20210A, which are among prothrombotic gene mutations in thrombophilia panel. Herein, a young female case with young ischemic stroke, in which heterozygote polymorphism of prothrombotic gene has been detected, was presented.

Key words: young stroke, prothrombin gene mutation, pregnancy

GENÇ İSKEMIK İNMEDE RİSK FAKTÖRÜ OLARAK PROTROMBİN GEN MUTASYONU: BİR OLGU SUNUMU

ÖZET

Genç inme, kırkbeş yaşın altında görülen inmelerdir ve inme insidansı 2,5 -40/100.000 arasında değişmektedir. Bütün inmelerin %4+-10 kadarı gençlerde görülür. Genç erişkindeki inmelerin çoğu iskemik orjinlidir. Genç iskemik inme nedenleri ileri yaşa oranla daha farklıdır ve altta yatan nedeni bulmaya yönelik pekçok araştırma yapmak gerekebilir. Bu araştırmalar serebral anjiyografi, transözefageyal ekokardiyografi, koagulasyon bozukluklarını tespit için testler ve kollajen vasküler hastalıkların araştırılması gibi tetkikleri içermektedir. Trombofili panelindeki protrombotik mutasyonlardan FV Leiden, MTHFR C677T ve Protrombin G20210A üzerinde şimdiye kadar daha yoğun çalışılmıştır. Burada, protrombotik gen heterozigot polimorfizimi tespit edilen genç iskemik inmeli bir kadın olgu sunulmaktadır.

Anahtar sözcükler: genç inme, protrombin gen mutasyonu, gebelik

Ischemic stroke is a complex multifactorial disorder influenced by genetic and environmental factors, the incidence of which increases with age. Of overall stroke cases, 4-10% is encountered in young people. It is quite difficult to determine exact incidence of stroke in young people. In various studies, etiology of stroke shows great variety. Etiological factors are more heterogeneous in young ischemic patients as compared to older population with no etiological factor found in 15-40% of the cases (1). Recently, it has been stated that prothrombotic gene mutations might be a risk factor for stroke in young people. However, role of these mutations in both ischemic and hemorrhagic stroke remains as a debatable issue. Many studies have suggested significant link between prothrombotic gene mutation and stroke (2,3,4). Small sample size and variety of the methods used might have contributed to the differences in results.

Hematological disorders or coagulopathies account for 4-17% of young strokes and 1% of overall ischemic strokes. Prothrombin gene mutation is considered to be hereditary and is the second most prevalent genetic disorder after FVL in the patients with thrombosis (4). Prothrombin, which is the precursor of thrombin, is a single-chain glycoprotein synthesized from liver. It plays a role in critical events such as activation of factor V, factor VIII and thrombocyte and transformation of fibrinogen into fibrin. A baseline change from

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İletişim: Dilcan Kotan • **E-Posta:** dilcankotan@yahoo.com

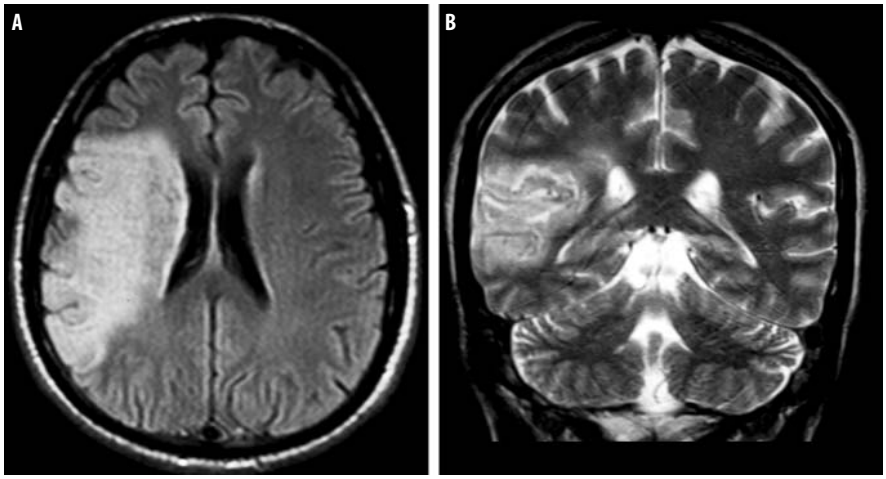

Figure 1. **A-B:** MRI scan demonstrating a hyperintense area of the right temporoparietal region.

guanine on the position 20210 of prothrombin gene, which is located on 11th chromosome, into adenine results in an increase in prothrombin concentrations. The prevalence of this mutation is 2-3% in the population and 6% in patients with thrombosis. However, it poses lower (approximately 3 times) risk of thrombosis as compared to FVL. Its concurrency with FVL poses a great risk (2,4). Moreover, it has been indicated as a serious risk factor for cerebral thrombosis. Measurement of plasma prothrombin concentrations is of no benefit as a screening test. Molecular genetic analysis must be performed for identification of mutated allele. Herein, we presented a female young stroke case with history of two thromboses, one of which was venous and the other was arterial, in which heterozygote gene mutation was detected.

Case report

A 44-year-old right-handed female patient presented to emergency room with loss of strength in her left side and inability to speak. It was found out from her personal history that she had had deep venous thrombosis in the right leg 8 years ago during the last trimester of her pregnancy and has been smoking a package of cigarette in a day for 20 years. Her neurological examination revealed somnolent level of consciousness, dysarthric speech, left-sided central facial paralysis, left hemiparesis, and unresponsive left Babinski reflex. Cranial tomography performed in the emergency room was considered to be isodense. Her cardiac evaluation, extracranial Doppler ultrasonography, transthoracic and transcardiac ECHO examinations were unremarkable. MRI was consistent with infarction a hyperintense area in the right temporoparietal region (Figure 1,2). was, and peripherally hyperintense and centrally isointense thrombosis in T1 sequence. Blood analyses included complete blood count, total biochemistry, serum lipids, PT, aPTT, thyroid function tests, fibrinogen, D-dimer, protein C, protein S, antithrombin III, homocysteine, activated protein C resistance, FVL mutation, prothrombin 20210A mutation and MTHFR. Results were unremarkable except for heterozygote carriage for prothrombin 20210A mutation. The patient was informed about the fact that smoking in the presence of prothrombin gene mutation enhances the risk of thrombosis by 2-to-5 times. She was suggested to quit smoking. Long-term anticoagulant therapy was recommended since she had more than one prothrombotic risk.

Discussion

The risk of venous thrombosis is enhanced approximately by 3 times in heterozygote carriers of prothrombin gene mutation. The risk of venous thrombosis is enhanced by up to 16 times if heterozygotes have been receiving oral contraceptive medications (5). Prophylaxis is recommended in the events that lead to venous thrombosis such as long-term immobility, long travel, hospitalization, surgery, and pregnancy. It has been demonstrated that risk for recurrent deep venous thrombosis is enhanced in heterozygote prothrombin G20210A carriers (6,7). The present case had had deep venous thrombosis of the lower extremity 8 years ago in the last trimester of her pregnancy but had no recurrence within that time.

In a study conducted in 72 patients, who had ischemic stroke before the age of 50 years and had no other risk factor, it was found out that the risk of stroke was increased by 4-to-5 times in the carriers of prothrombin G20210A mutation (8). The prevalence of heterozygote form of prothrombin mutation in the population is 1-2%. In the present case as well, the mutation was heterozygote. Although this mutation has been reported to enhance primarily the risk of venous thrombosis, avoiding smoking, hypertension, hyperlipidemia, hypercholesterolemia,

obesity and sedentary life style should be recommended for these cases to be protected from the risk of arterial thrombosis (2,4,8) (Table 1). We oriented the present case to the Smoking Cessation Policlinic for her to quit smoking since smoking would enhance the risk.

The patients must be evaluated in terms of congenital and acquired causes of coagulopathy if the reason for ischemic stroke is unclear, there is thrombosis in the family, the patient had had recurrent strokes, and the site of stroke is a rarely encountered localization. Considering the case presented here and the literature, probability of presence of specific gene mutations and the fact that smoking substantially enhances the risk of thrombosis should be kept in mind in case cerebral thrombosis is detected in young patients.

Table 1. Risk of thrombosis in the presence of gene mutations and risk factors

F V Leiden heterozygote	X 4-7
F V Leiden homozygote	X 80
P 20210A	X 2-5
P 20210A+ Smoking	X5-10
Hyperhomocysteinemia	X 2-6
Oral contraceptive (OC) use	X 4
F V L. + P 20210A	X 20
F V L. + OC	X 35
F V L. + SMOKING	X 30

References

1. Nedeltchev K, Maur TA, Georgiadis D, et al. Ischemic stroke in young adults: predictors of outcome and recurrence. J Neurol Neurosurg Psychiatry. 2005;76:191-195.
2. Lalouschek W, Schillinger M, Hsieh K, Endler G, Tentschert S, Lang W, Cheng S, Mannhalter C. Matched Case-Control Study on Factor V Leiden and the Prothrombin G20210A Mutation in Patients With Ischemic Stroke/Transient Ischemic Attack Up to the Age of 60 Years. Stroke. 2005;36:1405-9.
3. Belvis R, Santamaría A, Marti-Fàbregas J, Cocho D, Borrell M, Fontcuberta J, Martí-Vilalta JL. Diagnostic yield of prothrombotic state studies in cryptogenic stroke. Acta Neurol Scand. 2006;114:250-3.
4. Xin XY, Song YY, Ma JF, Fan CN, Ding JQ, Yang GY et al. Gene polymorphisms and risk of adult early-onset ischemic stroke: a meta-analysis. Tromb Res. 2009;124:619-24.
5. Martinelli I, Taioli E, Bucciarelli P, Akhavan S, Mannucci PM: Interaction between the G20210A mutation of the prothrombin gene and oral contraceptive use in deep vein thrombosis. Arterioscler Thromb Vasc Biol 1999;19:700–703.
6. Simioni P, Prandoni P, Lensing AW, Manfrin D, Tormene D, Gavasso S, et al. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood 2000;96:3329-33.
7. Miles JS, Miletich JP, Goldhaber SZ, Hennekens CH, Ridker PM. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol 2001;37:215-8.
8. De Stefano V, Chiusolo P, Paciaroni K, Casorelli I, Rossi E, Molinari M, et al.Prothrombin G20210A mutant genotype is a risk factor for cerebrovascular ischemic disease in young patients. Blood 1998;91:3562-5.