Central Asian Journal of Medicine

ETIOLOGICAL ASPECTS OF ISCHEMIC STROKE IN A YOUNG WOMAN: A CASE REPORT

Gulnara K. Rakhmattulaeva [1], Aziza Sh. Kadirova [2]

1 MD, Associate Professor, Department of Neurology and Medical Psychology, Tashkent Medical Academy, Tashkent, Uzbekistan

2 PhD student of Department of Neurology and Medical Psychology, Tashkent Medical Academy, Tashkent, Uzbekistan
E-mail: azizka_k@mail.ru

ABSTRACT

One of the possible causes of early development of ischemic stroke is the inherited thrombophilia – a condition in which there is an increased tendency to form blood clots due to hereditary disorders of the hemostatic system. Thrombophilia refers to a group of disorders characterized by an increased predisposition to thrombus formation in blood vessels. Inherited thrombophilia is caused by genetic mutations that can impair to the normal regulation of blood coagulation. This article discusses the role of inherited thrombophilia in the development of ischemic stroke in a young woman – a clinical case, with a detailed description of the clinical features, diagnosis, and treatment of the patient.

Key words: inherited thrombophilia, ischemic stroke, factor V Leiden gene mutation, protein C gene mutation (MTHFR gene), gene polymorphism (PAI-I (SERPINE1)), F2 gene polymorphism, obstetric history, recurrent miscarriage.

INTRODUCTION

Ischemic stroke (IS) is one of the leading causes of disability and mortality worldwide. While ischemic stroke is more commonly observed in older adults, there has been a rising trend in the incidence of stroke among younger individuals in recent decades [1, 6]. One of the potential causes for the early onset of ischemic stroke is congenital thrombophilia, a condition characterized by an increased tendency to form blood clots due to inherited abnormalities in the hemostatic system [4, 13, 15].

Thrombophilia refers to a group of disorders that enhance the predisposition to thrombus formation in blood vessels. Congenital thrombophilia is caused by genetic

mutations that disrupt the normal regulation of blood clotting [2, 6, 9]. Various types of congenital thrombophilia exist, with the most common being:

1. **Factor V Leiden mutation (FV)** — the most common genetic cause of increased blood clotting, associated with a mutation in the factor V gene, which contributes to thrombus formation.

2. **Antithrombin III deficiency** — Antithrombin III is a natural inhibitor of blood clotting, and its deficiency can result in excessive clot formation.

3. **Protein C and S deficiency** — Two natural anticoagulants that help regulate the clotting process. Their deficiency increases the risk of thrombosis.

4. **Protein C gene mutation (MTHFR gene)** — Increases the risk of thrombus formation due to abnormalities in folate metabolism, which may lead to elevated homocysteine levels in the blood.

5. **PAI-1 gene polymorphism (SERPINE1) – 675 5G>4G** — The PAI-1 protein inhibits the activity of tissue plasminogen activator and urokinase, which activate the conversion of plasminogen to plasmin, responsible for fibrin breakdown in clots. Thus, SERPINE1 negatively affects fibrinolysis and prevents clot dissolution, increasing the risk of vascular complications and thromboembolic events.

6. **F2 gene polymorphism (FII 20210 G>A)** — The F2 gene encodes the amino acid sequence of the prothrombin protein. Excessive prothrombin production is a risk factor for myocardial infarction and various thromboembolic events, including pulmonary embolism, which often leads to fatal outcomes [3, 5, 8, 10, 12].

Congenital thrombophilia can increase the risk of ischemic stroke in younger individuals through several mechanisms:

1. **Increased blood viscosity**: Disorders in the blood coagulation system can lead to the formation of microthrombi, which block small blood vessels in the brain, potentially causing ischemic stroke [2, 7, 11].

2. **Vascular wall pathology**: Congenital thrombophilias may be associated with changes in the vessel walls, increasing the likelihood of damage and thrombus formation [1, 6, 14].

3. **Systemic inflammation**: Some forms of thrombophilia may be accompanied by elevated levels of inflammation in the body, which also promotes clot formation [11, 15].

This article discusses the role of congenital thrombophilia in the development of ischemic stroke in a young woman, presenting a clinical case with detailed descriptions of the clinical features, diagnosis, and treatment of the patient.

Description of the Clinical Case

We present our own observation. The patient, K.A.E., a 36-year-old woman, was admitted to the 7th City Clinical Hospital in the neurology department with complaints of weakness and limited movement in the right half of her body, speech disturbances, difficulty articulating words, slurred speech, headache (which began acutely, of moderate intensity), dizziness, and general weakness.

History of the Disease

The patient had experienced several episodes over the last two years, characterized by weakness in the right upper and lower limbs, accompanied by brief speech disturbances. These symptoms resolved spontaneously within a few hours without residual effects. However, in the last month, such episodes became more frequent, and the symptoms became more pronounced.

In the past few days, the symptoms worsened, with the patient noticing persistent weakness in her right arm and leg, as well as difficulty speaking, which did not resolve. Upon hospitalization, the patient exhibited severe weakness on the right side of her body, particularly in the right arm and leg, along with speech impairment (aphasia), which had started approximately 4 hours before admission. This condition persisted at the time of hospitalization.

Life History

The patient grew and developed normally according to her age. She had a history of childhood infections (chickenpox, rubella). She is married but has no children. Her professional activity involves office work.

In her obstetric history, the patient had several miscarriages at early stages of pregnancy, occurring in the first 10–12 weeks, typically accompanied by prior signs of threatened miscarriage.

Family History

The patient's family history is notable. Her mother, at the age of 48, was diagnosed with myocardial infarction and pulmonary artery thromboembolism.

The patient has no history of surgical interventions and no chronic heart or endocrine diseases. She denies any drug or food allergies.

Comorbidities

The patient has no history of diabetes, cardiovascular diseases, or endocrine disorders. She reports occasional increases in blood pressure (the highest recorded was 160/100 mm Hg).

Habits

The patient does not have a history of chronic alcohol abuse or drug addiction. Among her harmful habits, she notes smoking.

Objective Status upon Admission

General condition: satisfactory, body temperature: 36.7°C, heart rate: 78 beats/min, regular blood pressure: 120/80 mm hg, respiratory rate: 16 breaths/min, even, without disturbances, weight: 68 kg, height: 162 cm, body Mass Index (BMI): 25.9 (normal range: 18.5–24.9)

The skin appears fair and is free of pathological changes. There is no edema or cyanosis. Skin tone is normal, elastic, and firm. The abdomen is painless on palpation. Bowel movements are regular without signs of constipation or diarrhea.

The patient does not report any pain during urination. Urination is painless and regular. The menstrual cycle is regular, with no abnormalities, and there are no complaints of painful menstruation or amenorrhea.

Neurological Status upon Admission

The patient is conscious, alert, and oriented to time, place, and person. The Danzing-Kunakov sign is positive. Headache intensity increases with skull percussion.

Cranial Nerves

- I Cranial Nerve (olfactory): intact
- II Cranial Nerve (optic nerve): vision preserved, no complaints of diplopia, visual fields are within normal limits
- III, IV, VI Cranial Nerves (oculomotor nerves): symmetry of the eyeballs preserved, motor functions intact, no signs of ptosis or convergence disturbances
- V Cranial Nerve (trigeminal nerve): Valle's points are painless on palpation. Sensitivity on both sides of the face is preserved
- VII Cranial Nerve (facial nerve): Right-sided central paresis (CP), mild facial asymmetry, significant weakness of facial muscles on the right (hemifacial paralysis), positive Bell's sign
- VIII Cranial Nerve (vestibulocochlear nerve): no complaints of hearing loss or balance disturbances, no signs of vertigo or nystagmus
- IX, X Cranial Nerves (glossopharyngeal and vagus nerves): normal voice, no swallowing difficulties, no dysphagia, pharyngeal reflex preserved
- XI Cranial Nerve (accessory nerve): normal neck movements, no asymmetry in head or shoulder movements
- XII Cranial Nerve (hypoglossal nerve): right-sided central paresis (CP), impaired motor function of the tongue on the right side

Motor Function. Right-sided hemiparesis: active movements on the right side are limited, passive movements are normal on both sides, severe weakness in the right upper limb (3/5 in distal parts, 4/5 in proximal parts) and in the right lower limb (4/5), hypotonia in the right limbs, trophic status preserved in both limbs, hyperreflexia on the right side (br, tr, pr, ar d>s), expansion of reflexogenic zones on the right side, positive babinski reflex on the right side, positive Jakobson-Lask's sign on the right side.

Sensory Function. Right-sided hemihypesthesia: decreased sensitivity on the right side of the body, especially in the fingers and palms, with mild disturbances in tactile and temperature sensation.

Coordination. Impaired coordination on the right side of the body. The patient is unable to perform the finger-to-nose and heel-to-knee tests on the right side. When attempting to walk along a straight line, balance is impaired on the right leg.

Higher Mental Functions. Emotional state: stable, with the patient focused on treatment. Motor aphasia elements are present, with speech impairment and difficulty forming phrases. The patient controls her pelvic functions.

Laboratory and Instrumental Examination. Laboratory test results are provided in Table 1.

Table 1

Routine laboratory tests

		Test result
Complete Blood Count (CBC)	Hemoglobin	130 g/L
	Erythrocytes	4.6 × 10^12/L
	Leukocytes	7.2 × 10^9/L
	Platelets	250 × 10^9/L
	Hematocrit	0.40
	ESR	22 mm/h
Biochemical Blood Test	Glucose	5.2 mmol/L
	Total protein	70 g/L
	Creatinine	85 µmol/L
	Urea	6.0 mmol/L
	Total bilirubin	14 µmol/L
	Triglycerides	1.2 mmol/L
	Total cholesterol	5.5 mmol/L
	AST (aspartate aminotransferase)	25 U/L
	ALT (alanine aminotransferase	22 U/L
	LDH (lactate dehydrogenase	240 U/L
Coagulogram	INR	1.05
	PT	11.2 sec
	APTT	30 sec
	Fibrinogen	3.2 g/L

Urinalysis	Color	light, straw yellow, transparent
	Relative density	1.018
	Protein	negative
	Glucose	negative
	Ketones	negative
	Erythrocytes	1-2 in the field of view
	Leukocytes	2-3 in the field of view
	Bacteria	absent

ECG: Sinus rhythm, heart rate 57 bpm, normal axis.

Doppler of Brachiocephalic Vessels: Atherosclerotic changes in the walls of the brachiocephalic arteries. Hemodynamically insignificant stenosis of the right vertebral artery and left common carotid artery, up to 35%.

MRI: Diffuse ischemic changes in the left hemisphere, involving the cortical and white matter regions of the parietal-temporal lobe. Hyperintense foci on T2-weighted images and hypointense areas on T1-weighted images. Signs of acute ischemic stroke in the territory of the left middle cerebral artery (MCA).

A molecular genetic study was conducted to assess polymorphisms of genes related to blood coagulation factors and the folate cycle (see Table 2).

Table 2

Molecular genetic study on the polymorphisms of genes related to blood coagulation factors and the folate cycle

Gene	**Polymorphism**	**Research Result: Detected Genotype**	**Primary Interpretation of the Result**
F2	G20210A	A/A	**Homozygous mutant type**, increased risk of venous thrombosis and stroke
F5	G1691A	G/G	Normal genotype
MTHFR	C677T	T/T	**Homozygous mutation**, increased risk of hyperhomocysteinemia, thrombosis, and ischemic stroke
PAI-1	4G/5G	4G/4G	**Homozygous mutant type**, increased risk of thrombosis due to impaired fibrinolysis

Below, in Figure 1, as an example, are the PCR curves with threshold values for the patient with polymorphisms of these genes:

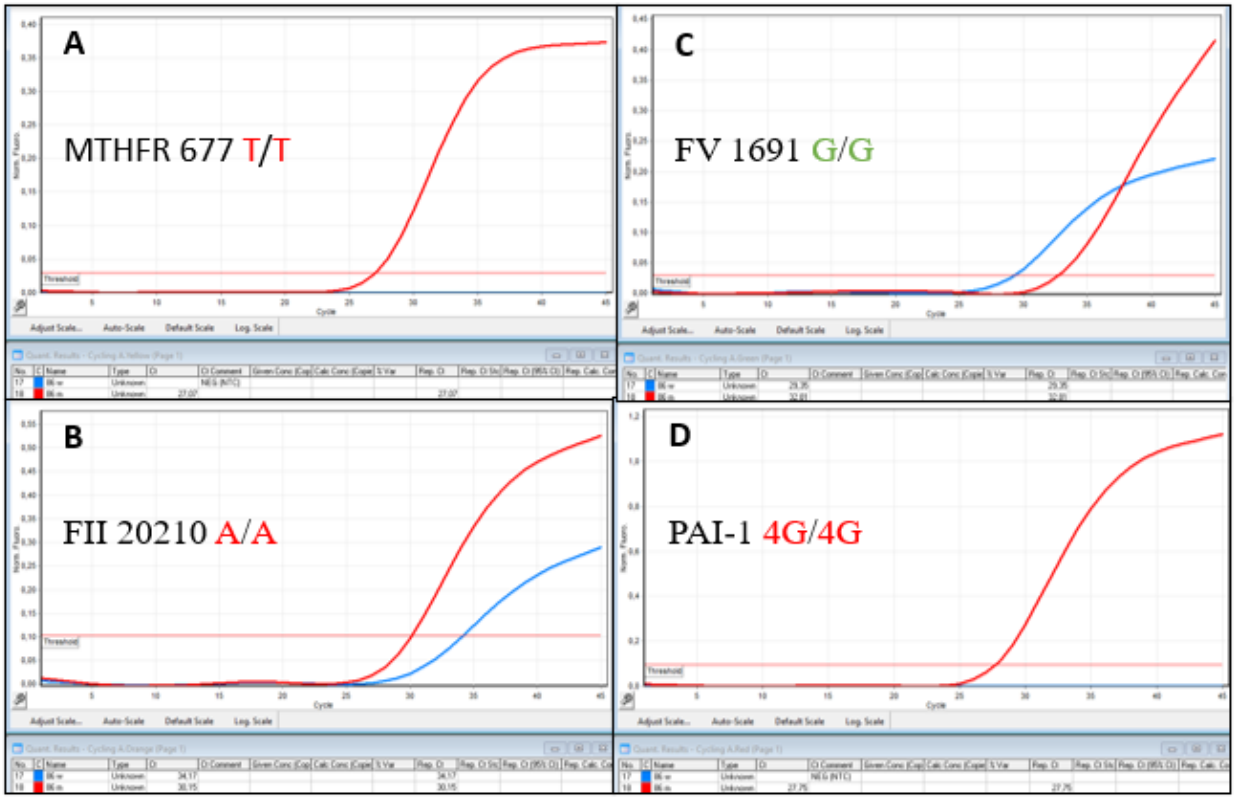

Figure 1. PCR curves with threshold values for the patient with polymorphisms MTHFR 677 T/T (Fig. 1A), FII 20210 A/A (Fig. 1B), FV 1691 G/G (Fig. 1C), PAI-1 4G/4G (Fig. 1D).

Conclusion Based on Laboratory and Instrumental Data:

Based on the results of laboratory tests, the patient exhibits signs of thrombophilia, which is confirmed by mutations in the FII, MTHFR, and PAI-1 genes. Given the combination of mutations in three genes responsible for blood coagulation, it can be hypothesized that these genetic factors contributed to the development of ischemic stroke at such a young age.

Diagnosis:

Primary diagnosis: Cerebrovascular disease, acute ischemic stroke in the territory of the left middle cerebral artery (MCA) with right-sided hemiparesis and elements of motor aphasia. (ICD-10: I63.5)

Secondary diagnosis: Hereditary thrombophilia. (ICD-10: D68.0)

Treatment Received in the Hospital:

The patient was hospitalized in the neurology department with the following therapeutic regimen:

Edaravone solution 30 mg (20.0 ml) with 100 ml saline, intravenously, twice a day for 7 days.

Cyticoline solution 1000 mg (4.0 ml) with 100 ml saline, intravenously, twice a day for 10 days.

Heparin 5000 units subcutaneously around the navel.

Aspirin tablets 125 mg after meals in the evening, long-term.

Home Recommendations:

1. **Continue antiplatelet therapy** (considering genetic predisposition to thrombosis, dual antiplatelet therapy is recommended):

Aspirin tablets 125 mg at night after meals, long-term.
Clopidogrel tablets 75 mg, 1 tablet once a day together with aspirin.

2. **For improving neuroconductivity**:

Nivalin tablets 5 mg, 1 tablet twice a day after meals for 5 days; if well tolerated, increase to 1 tablet three times a day for 1 month.

3. **For neuroprotection**:

Citioks tablets 500/800 mg, 1 tablet twice a day for 1 month, in the morning and afternoon after meals.

4. **To maintain homocysteine levels**:

Methylfolate capsules 100 mg, 1 capsule once a day, long-term, with monitoring of homocysteine levels.

Additionally, the patient will undergo physiotherapy, speech therapy sessions, and psychological rehabilitation.

Post-Hospitalization Progress. After treatment in the hospital, the patient's overall condition and well-being significantly improved. Strength in the right limbs increased, allowing her to walk independently, climb and descend stairs. Speech became clearer, cognitive impairments improved, and headaches and dizziness no longer troubled her. Hemodynamics remained stable.

Conclusion. The patient has several genetic risk factors, the combination of which likely contributed to the development of ischemic stroke at a young age. Specifically, she carries homozygous mutations in the PAI-1, F5, and MTHFR genes. Additionally, smoking was identified as a secondary risk factor. It is well-established that carrying homozygous mutations in these genes is a marker of hereditary thrombophilia, and their combination was likely the primary cause of her early stroke.

Therefore, early diagnosis and timely treatment of congenital thrombophilia can significantly reduce the risk of ischemic strokes, decrease the likelihood of recurrent strokes, and improve patient prognosis. Given the variety of clinical manifestations and individual characteristics of the disease course, interdisciplinary coordination between neurologists, cardiologists, and hematologists is essential for the effective management of such patients. It is important to note that standard coagulation tests may not reveal clear abnormalities; however, these patients have a high risk of venous thrombosis, making molecular genetic testing essential to confirm the diagnosis.

REFERENCES

1. Choi H, Kim SK, Lee H. A review of thrombophilic conditions and their relationship to cerebrovascular diseases. *J Clin Neurol*. 2017;13(3):255-263. doi:10.3988/jcn.2017.13.3.255.

2. Deryugina EI, Khasanova A, Kolomiets SS. Hereditary thrombophilia and ischemic stroke: a case report. *J Stroke Cerebrovasc Dis*. 2022;31(7):105998. doi:10.1016/j.jstrokecerebrovasdis.2022.105998.

3. Golubeva O.M., Sharkova L.S., Belova M.I. Congenital thrombophilias: diagnosis and management of patients with stroke. Clinical Laboratory Diagnostics. 2018;63(8):491-496. doi:10.24279/CLD.2018.8.491-496.

4. Goudie A, Figueroa L, Bhatt D. Genetic mutations in stroke patients with thrombotic risk: a case series and review. *Thromb Haemost*. 2019;119(1):26-31. doi:10.1055/s-0038-1678984.

5. Ivanova A.V., Sidorova I.P., Logvinova E.N. Features of the coagulation mechanism in patients with ischemic stroke at a young age. Russian Cardiological Journal. 2018;23(2):103-110. doi:10.26454/rcj.2018.2.103-110.

6. Kavakli K, Erbay AR, Gültekin M. The role of hereditary thrombophilia in young adults with ischemic stroke. *J Clin Neurol*. 2018;14(2):219-223. doi:10.3988/jcn.2018.14.2.219.

7. Martinelli I, De Stefano V, Mannucci PM. Inherited thrombophilia and ischemic stroke. *Cerebrovasc Dis*. 2015;40(5):284-290. doi:10.1159/000438121.

8. Morozova N.G., Petrova I.V. The role of genetic factors in the development of ischemic stroke in young women. Medical Journal of Tatarstan. 2019;34(3):79-83. doi:10.18821/medtatarstan.2019.34.3.79-83.

9. Nazarova E.N., Kudryavtsev V.P., Artemyeva V.A. Factor V Leiden gene mutation and the risk of stroke in young individuals. Hypertension and Stroke. 2019;26(1):44-50. doi:10.31498/AGI.2019.26.1.44-50.

10. Rousan TA, Alqallaf A, Fadly A. Role of protein C and S deficiencies in young adult ischemic stroke. *Neurol Sci*. 2016;37(6):935-939. doi:10.1007/s10072-016-2632-z.

11. Schmidt S.Y., Zakharova I.A., Gorkova L.V. Congenital thrombophilias and their impact on stroke development in young individuals. Thrombophilia and Vascular Diseases. 2017;7(4):49-53. doi:10.2478/tfsd-2017-0049.

12. Semyonova T.N., Kameneva O.P. The role of thrombophilias in ischemic stroke in young patients. Modern Problems of Neurology. 2020;28(6):97-103. doi:10.22448/spn.2020.6.97-103.

13. Tikhonova I.V., Safonova T.A., Pavlova N.I. Hereditary thrombophilias and their role in the development of ischemic stroke. Journal of Neurology and Psychiatry. 2020;120(5):47-52. doi:10.14531/jnp.2020.5.47-52.

14. Van Cott EM, Sheth S, DiNicolantonio J. Coagulation disorders and stroke: pathophysiology and clinical management. *Stroke*. 2020;51(6):1703-1711. doi:10.1161/STROKEAHA.120.030826.

15. Ziegler K, Evers S, Kornhuber J. Genetic aspects of ischemic stroke in young patients: the role of thrombophilia. *Eur J Neurol*. 2019;26(3):452-457. doi:10.1111/ene.13923.