# A young female adult patient with an ischaemic stroke and patent foramen ovale: a case report and literature review

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## Abstract:

Strokes in young adults are relatively rare. We present a 36-year old female patient, who came to the urgent neurological outpatient office of the Clinic for neurology due to symptoms presented two hours prior to the examination. The symptoms consisted of inability to move the left arm, partial motor weakness of the left leg, slurred speech and difficulty swallowing. The urgent CT scan result was normal. Despite the fulfilled conditions, thrombolysis was not possible. Brain MRI results revealed a small hypersignal lesion in FLAIR with diffusion restriction on the right, cortically to subcortically, in gyrus praecentralis. The genetic testing for cardiovascular diseases showed that the patient is a homozygote for the mutation C677T (OMIM® 607093.0003) in the gene for methylenetetrahydrofolate reductase (MTHFR) and heterozygote for the mutations eNOS G894T and LTA. The following gene polymorphisms were typed: PAI 5G/4G, HPA1 1b/1a, ACE deletion/insertion, EPCR A4600G A/A, EPCR G4678C C/G and APOE E3/E4. Trans-esophageal echocardiography discovered an aneurysm of the interatrial septum, with a present PFO channel, with a diameter of 6.8 mm. The bubble test was positive, and there were no visible thrombi in the left auricle. The cardiologist recommended closing of the PFO with a device and therapy with acetylsalicylic acid. The cause of the stroke was found and measures for secondary prevention were taken. The patient has returned to her work and private obligations. She upholds neurological consultations regularly and her recovery is closely observed.

Keywords: ischaemic stroke, young adult, patent foramen ovale, MTHFR, C677T homozygote

## Sažetak:

Mlada ženska odrasla osoba s ishemijskim moždanim udarom i otvorenim foramen ovale: prikaz slučaja i pregled literature

Moždani udar u mladih osoba je relativno rijedak. Predstavljamo 36-godišnju pacijenticu, koja je došla u urgentnu neurološku ambulantu Klinike za neurologiju zbog simptoma koji su se prezentirali dva sata prije pregleda. Simptomi su se sastojali od nemogućnsti pokretanja lijeve ruke, djelomične motorne slabosti lijeve noge, nerazgovjetnog govora i nemogućnosti gutanja. Rezultat hitne kompjuterske tomografije bio je normalan. Unatoč ispunjenim uvjetima, tromboliza nije bila moguća. Pacijentica je bila postavljena na konzervativnu terapiju za moždani udar. Rezultati magnetske rezonancije mozga su otkrili malu hipersignalnu leziju u FLAIR s restrikcijom difuzije desno, kortiko-subkortikalno, u precentralnom girusu. Genetsko testiranje za kardiovaskularne bolesti je pokazalo da je pacijentica homozigot za mutaciju C677T (OMIM® 607093.0003) u genu za metilentetrahidrofolat reduktazu (MTHFR) i heterozigot za mutacije eNOS G894T i LTA. Slijedeći genski polimorfizmi su bili tipizirani: PAI 5G/4G, HPA1 1b/1a, ACE delecija/insercija, EPCR A4600G A/A, EPCR G4678C C/G i

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APOE E3/E4. Transezofagealna ehokardiografija je otkrila aneurizmu interatrijskog septum, s prisutnim PFO kanalom, s promjerom od 6,8 mm. Test mjehurićima bio je pozitivan, i nije bilo vidljivih ugrušaka u lijevoj aurikuli. Kardiolog je preporučio zatvaranje PFO uređajem i terapiju acetilsalicilnom kiselinom. Razlog za moždani udar je pronađen i poduzete su mjere za sekundarnu prevenciju. Pacijentica se vratila svojim radnim i privatnim obvezama. Redovno dolazi na neurološke konzultacije i neprekidno pratimo njen oporavak.

Ključne riječi: ishemijski moždani udar, mlada odrasla osoba, otvoreni foramen ovale, MTHFR, C677T homozigot

## Introduction

Strokes in young adults are relatively rare. Although the incidence of ischaemic stroke increases with age, an estimated 10% to 20% of these events occur in young people aged 18 to 50 years (1). Incidence of any stroke in the young increases with age in patients over 35, is higher in women than men aged 18 – 44 years, and has increased by 23% in one decade, through an increase in ischemic stroke (2). While there is a large and increasing amount of evidence that ischemic stroke incidence is on the rise in young adults, the reasons for this trend are probably multiple (3). This disorder is a major cause of long-term disability and has profound effect on quality of life of patients and caregivers (4).

## Case description

We present a 36-year old female patient, who came to the urgent neurological outpatient office of the Clinic for neurology in March 2022 due to symptoms presented two hours prior to the examination. The symptoms consisted of inability to move the left arm, partial motor weakness of the left leg, slurred speech and difficulty swallowing.

The patient is married, mother of two children, works as a nurse, light smoker (8 – 9 cigarettes a day), with very limited alcohol consumption on particular special occasions. She is of normal build and her body mass index is within normal range (BMI = 22.6). The patient's medical history included slight dyspnea post-COVID-19 for a short time, which she had in September 2021. Sometimes she had mild dyspepsia and was slightly anaemic. Her blood pressure was usually low, around 100/60 mm Hg.

## Clinical course of the disease

Upon examination slight weakness of the left arm, slightly slurred speech, left facial droop, left palatal weakness, hemihypesthesia on the left side of the body, predominantly on the face, were noted, and the Babinski sign was found to be positive bilaterally. NIHSS score was 4. The blood pressure was 120/80 mm Hg and glycaemia was 5.3 mmol/L, both within normal range. The heart rhythm was normal. An urgent CT scan was ordered and blood was drawn for laboratory testing. The CT scan result was normal (Figure 1). As stroke was suspected, upon examination and anamnesis the conditions for thrombolysis were fulfilled, whereas no contraindications were detected. For mild disabling stroke symptoms, IV thrombolysis may be reasonable for patients who can be treated within 3 h – 4.5 h of ischemic stroke onset or patients last time known well (5).

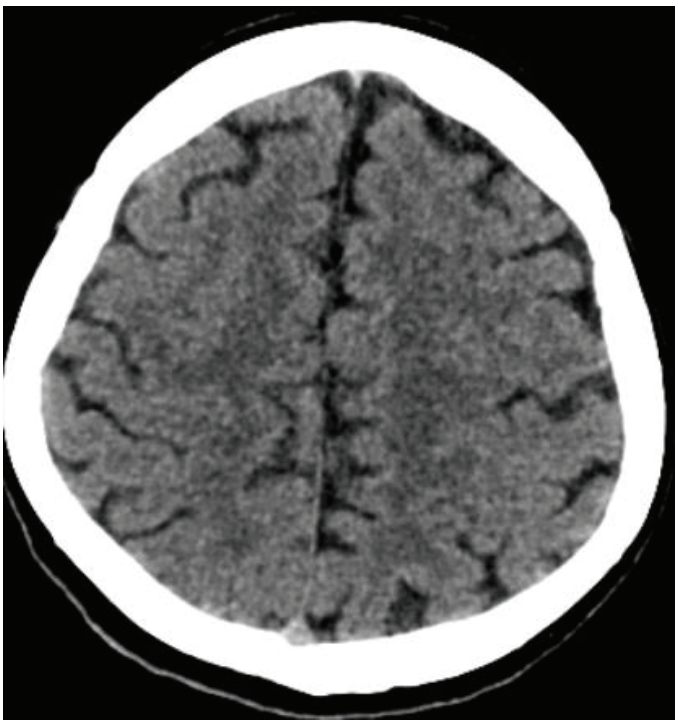

*Figure 1. Initial brain CT scan, showing a normal finding.*

Due to the patient's occupation, the neurological symptoms were strongly disabling for her. Yet, the University clinic for neurology was a COVID-centre at the time, and thrombolysis at the outpatient office was not possible, for the reason that the office is without monitoring possibility and there is not an option for the patient or staff to stay there beyond regular working hours. The patient was given the choice of being referred to another hospital, which included the very probable circumstance of the thrombolysis time window passing. The patient opted out for

conservative treatment for stroke through the service for medical home visits. A sick leave was recommended.
The treatment through the service for medical home visits consisted of vitamin, anti-edematous and anticoagulant therapy for five consecutive days, and the regular therapy to be applied from the very day of examination on were antiplatelet (acetylsalicylic acid 100 mg once daily), gastroprotective, supplement and amantadine at a starting dose of 100 mg once daily for two weeks and then increased to twice daily. The patient stopped smoking from the first day of the stroke and has not relapsed since then.
A control was recommended immediately after the laboratory results were obtained and a second control with a second imaging five days afterwards, as well as earlier if needed. The lipid values were within range: total cholesterol 4.7 mmol/L, HDL cholesterol 1.6 mmol/L, LDL cholesterol 2.6 mmol/L, triglycerides 0.96 mmol/L. The electrolyte status, HbA1C, C reactive protein, erythrocyte sedimentation rate and creatine kinase were within range. AST was 11 U/L, and ALT was on the low side: 9 U/L. Albumins were slightly elevated: 52 g/L, and globulins were marginally low: 26 g/L. The thyroid status was normal.
The patient was referred to the University clinic for cardiology for an examination, which turned out normal. ECG showed sinus rhythm at 71 BPM, normal axis (Figure 2). The neurologist referred the patient to genetic testing for cardiovascular diseases. At the next control, five days after the initial examination, the patient was also referred to a haematologist because of slightly decreased MCV (76 fL), haemoglobin (117 g/L) and hematocrit (33%), while iron, vitamin B12 and folic acid were within range. The haematologist prescribed ferrous fumarate, vitamin C and a multivitamin supplement.

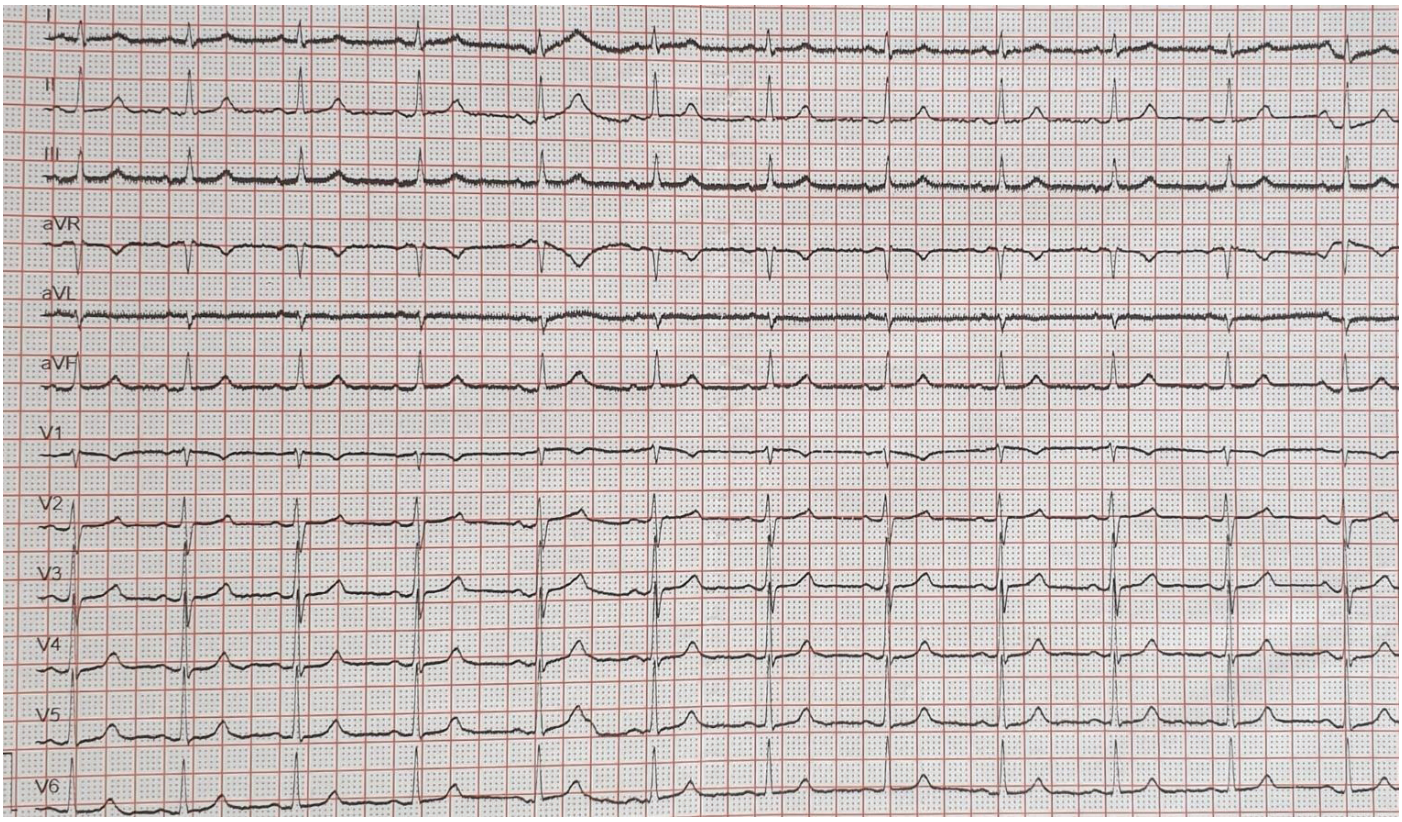


*Figure 2. The ECG of the patient, showing sinus rhythm*

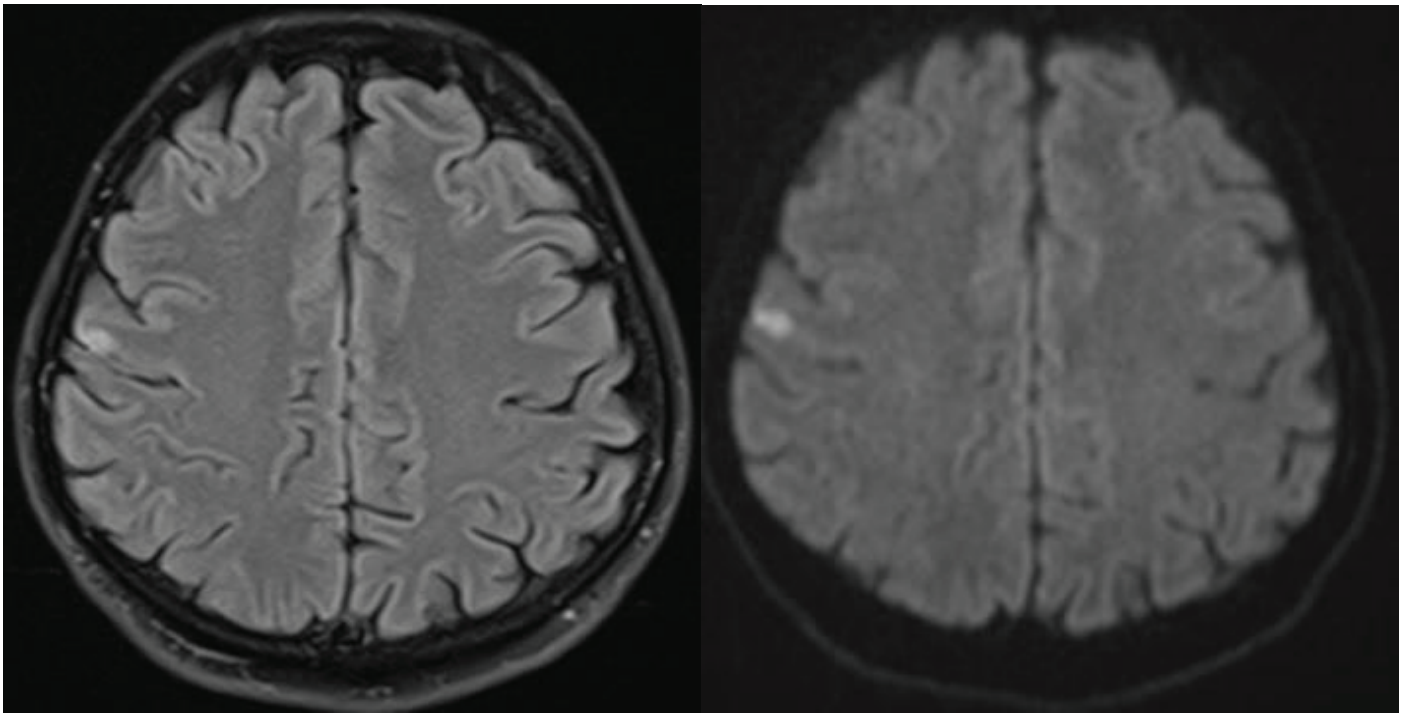

*Figure 3. Initial MRI of the brain, showing an infarction in the right precentral gyrus.*

In the meantime, results were obtained from the University clinic for transfusiology: Thrombocytes 372*$10^9$/L; Hct 33.3%; PT 11.3 sec; aPTT 30.7 sec; TT 20.1 sec; D-dimer 223.6 ng/mL; WBC 10.2*$10^9$/L; Lym 1.3*$10^9$/L; Mid 0.4*$10^9$/L; Gran 82.7*$10^9$/L;Hgb 117 g/L; MCV 76.3 fL; MCH 27 pg; MCHC 354 g/L; RDW 14.5%; RDWa 59.4 fL; MPV 7.7 fL; PCT 0.28%; PDW 10.5 fL; LPCR 11.8%. An antibiotic was prescribed from the primary health care physician.

The patient requested that all the examinations and controls be done with the same neurologist, and her wish was respected. A sick leave for one month, brain MRI and a control afterwards were recommended. The neurological everyday therapy recommendations were: antiplatelet (acetylsalicylic acid 100 mg once daily), gastroprotective, supplement and amantadine.

Brain MRI results quoted: On the right, cortically to subcortically, in gyrus praecentralis, there is a small hypersignal lesion in FLAIR with diffusion restriction, and it can be considered an ischaemic infarction (Figure 3). MRI control in 2 – 3 weeks. The rest of the parenchyma of the cerebrum, brainstem and cerebellum are without focal lesions. The ventricle system is of normal width, free. On the MRA with TOF, the visualized intracerebral arteries with the major branches are without pathologic lesions (Figure 4).

The genetic testing for cardiovascular diseases revealed that the patient is a homozygote for the mutation C677T (OMIM® 607093.0003) in the gene for methylenetetrahydrofolate reductase (MTHFR) and heterozygote for the mutations eNOS G894T and LTA. The following gene polymorphisms were typed: PAI 5G/4G, HPA1 1b/1a, ACE deletion/insertion, EPCR A4600G A/A, EPCR G4678C C/G and APOE E3/E4.

26 days after the stroke, at the control, the patient's condition was stable and significantly improved. There was discrete, almost non-detectable left facial droop. Swallowing, limb movements, strength and speech were normal.

Control brain MRI was performed, with the result: The previously described change on the right frontally, cortically to subcortically, in the precentral gyrus, is with reduced diameter and does not show diffusion restriction. There is not a mass effect, nor an oedema surrounding it (Figure 5). MRI control in 3 – 6 months.

Laboratory blood results were improved, with lower hematocrit of 36.6%, and all the other measured parameters within range.

In pursuit of a clear cause for the stroke, the patient was referred to a cardiologist for scheduling an ECG Holter monitor and echocardiography. Further treatment and examinations were conducted in continued consultation between the authors.

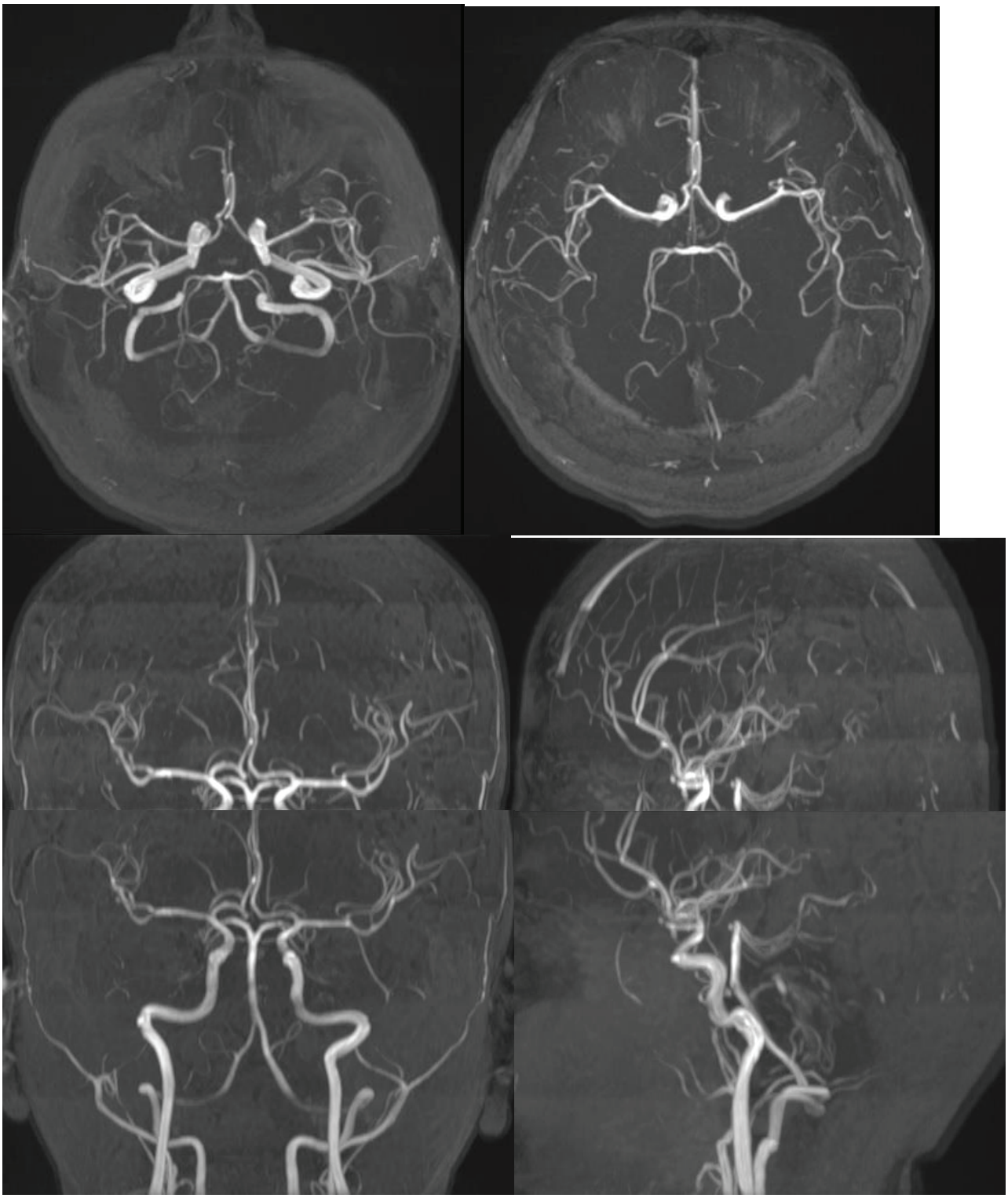

*Figure 4. On the MRA with TOF, the visualized intracerebral arteries with the major branches are without pathologic lesions.*

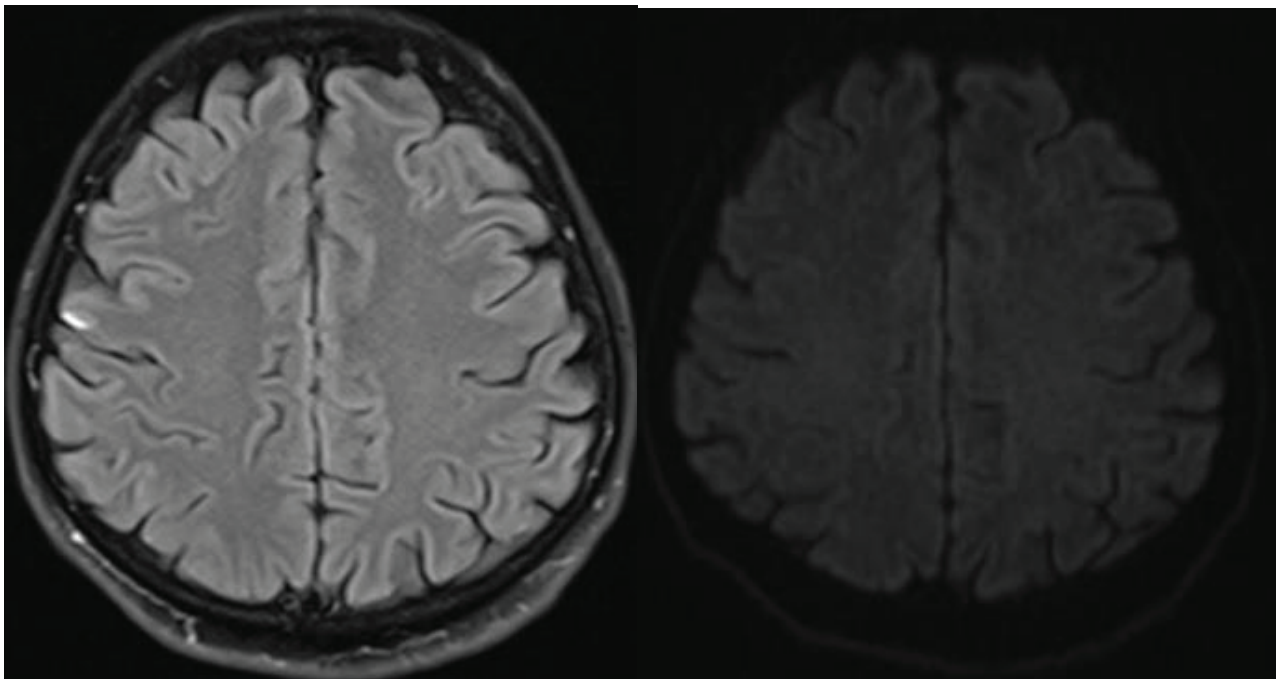

*Figure 5. The previously described change on the right frontally, cortically to subcortically, in the precentral gyrus, is with reduced diameter and does not show diffusion restriction.*

In the meantime, the cardiologist suggested to replace the recommended antiplatelet therapy from the neurologist (Aspirin 100 mg once daily) with a direct anticoagulant (Apixaban 2.5 mg twice daily). After consultation with the neurologist, given a choice, the patient decided not to switch to Apixaban.
While awaiting the results of the cardiological examinations, the neurologist decided to replace the antiplatelet therapy (Aspirin 100 mg once daily) by Nattokinase (NSK-SD® 20000 FU/g and calcium-L-methylfolate 200 mcg) – two tablets of 100 mg per day A probiotic (Lactobacillus rhamnosus LGG) was added. A Vitamin D3 deficit was discovered and supplementation with Vitamin D3 1000 IE/day was added. Amantadine and the previous supplement therapy remained. The gastroprotective therapy was prescribed as needed.
Five weeks post-stroke, the patient's condition improved further. There was very slight dyspepsia, rarely.
The cardiologist interpreted the results of the ECG Holter monitor as: Sinus rhythm with an average frequency of 83 BPM and range from 61 to 153 BPM, no significant pauses nor regular VES, 12 single SVES detected. The conclusion was a normal finding (Figure 6).
The echocardiography result was: The left atrium is with normal dimensions; global systolic function is regular. Lower closing of the mitral cusps with mild mitral valve regurgitation. The aortic valve has three leaflets and regular function. The interatrial septum is thin, mobile at length of 22 mm. The colour does not register a significant shunt; nevertheless, PFO cannot be excluded. There is not a right heart overload, slight tricuspidal regurgitation. A transcranial Doppler and trans-esophageal echocardiography are needed.
Trans-esophageal echocardiography revealed an aneurysm of the interatrial septum, with a present PFO channel, diameter 6.8 mm. The bubble test was positive, and there were no visible thrombi in the left auricle. The valvules were normal. The conclusion was: foramen ovale persistens, maintained systole function, and normal valvular apparatus. The cardiologist recommended closing of the PFO with a device and therapy with acetylsalicylic acid 100 mg 0+1+0. The patient was switched back to acetylsalicylic acid.
The cause of the stroke was found and measures for secondary prevention were taken. The patient has returned to her work and private obligations. She upholds neurological consultations regularly and her recovery is closely observed.

## Discussion

The patient's genetic testing revealed her to be a homozygote for the mutation C677T (OMIM® 607093.0003) in the gene for methylenetetrahydrofolate reductase (MTHFR). The homozygote genetic model of the C677T polymorphism is associated with congenital heart disease risk, including septal defects (6).

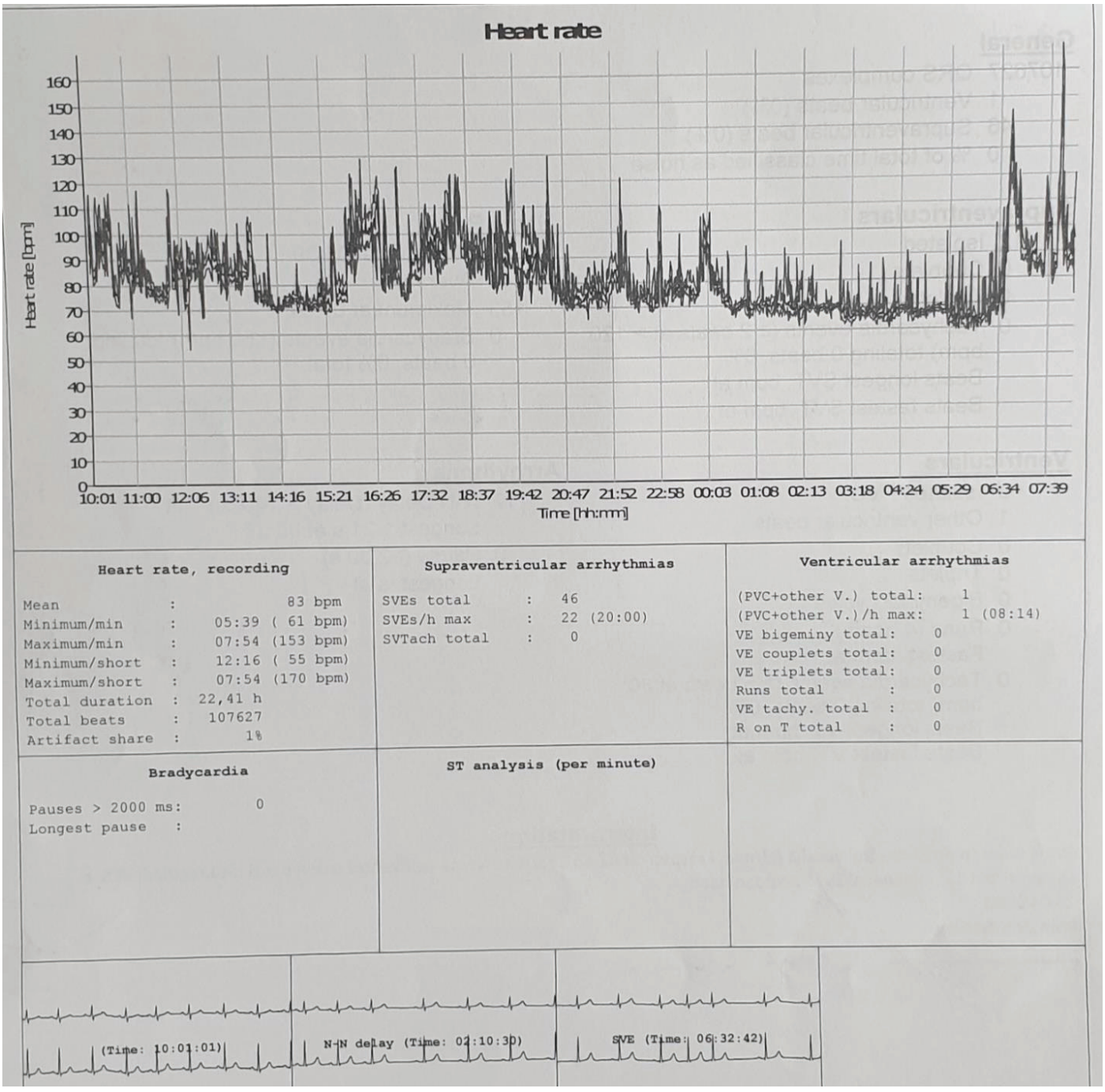


*Figure 6. ECG Holter monitor: Sinus rhythm with an average frequency of 83 BPM and range from 61 to 153 BPM, no significant pauses nor regular VES, normal finding.*

Our patient is also a heterozygote for the mutation eNOS G894T. The results of a meta-analysis by Wang et al. suggested that eNOS gene G894T polymorphism was associated with the increased risk of ischemic stroke (7).

Furthermore, our patient had lower vitamin D levels. Some women with MTHFR 677TT (homozygous mutation, TT) genotype have significantly lower vitamin D levels (8).

Regarding percutaneous closure of patent foramen ovale, there have been many studies in the past that contradicted each other. PFO closure seems to be associated with lower incidence of cryptogenic strokes among patients with inherited thrombophilias treated with anticoagulant or antiaggregant therapy (9). According to Turc et al., PFO closure is superior to antithrombotic therapy to prevent stroke recurrence after cryptogenic stroke. The annual absolute risk reduction of stroke is low, but it has to be tempered by a substantial time at risk (at least 5 years) in young and middle-aged patients. On the other hand, PFO closure is associated with an increased risk of atrial fibrillation (10). According to Mas et al., among patients who had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone. PFO closure was associated with an increased risk of atrial fibrillation (11).

The data outlined in Linnebank et al. suggest that MTHFR alleles with at least one of the mutant variants C677T and A1298C are associated with smoking (12), which further exacerbates the risk in patients who have already had vascular events or are at risk. Our patient was a light smoker previously and she stopped immediately after the stroke.
The Risk of Paradoxical Embolism (RoPE) Score (13) identifies stroke-related PFO in patients with cryptogenic stroke. It is used in patients with cryptogenic stroke found to have PFO and no other compelling cause for stroke. Our patient had a RoPE Score of 8 points, which, according to the authors, translates to 84% chance that the stroke is due to PFO. Futhermore, there seems to be 6% risk of 2-year recurrence of stroke/TIA. Closing of the PFO, putting the patient on antiplatelet therapy and smoking cessation (14) significantly decreases the risks of repetitive strokes in this individual.

## Conclusion

Thorough search for the stroke causes and their early detection in young individuals is of utmost importance in order to offer the patients the best possible care and well-informed secondary prevention.

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