Bilateral Superficial Femoral Artery Thrombosis in a 15-Year-Old Caucasian Male with Homozygous Prothrombin G20210A Genotype and Associated Antiphospholipid Syndrome

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Abstract

Prothrombin mutation was usually associated with other well-established predisposing factors for venous thrombosis such as antiphospholipid antibodies. Recently, even isolated prothrombin gene mutation G20210A has been reported to present severe or unusual vein thrombosis. Less clear is the role of prothrombin mutation in the formation of arterial thrombosis. We present a case of a 15-year-old healthy White male with acute bilateral femoral artery thrombosis. The patient presented with increasing left leg pain for about 1 week. He was a physically very active teenager with a new onset of leg pain aggravated by exercise. Physical examination revealed a pale and cold left foot with dorsal foot necrosis (2 × 2 cm) that started 2 days ago. In addition, he complained of moderate rest pain. No symptoms were noticed on the right lower extremity. The ankle brachial index was 0.3 on the left and 0.6 on the right. Duplex sonography showed bilateral superficial femoral artery thrombosis, which was confirmed by angiography. Subsequently, he undergoes left superficial femoral and popliteal artery lysis with rt-PA (Actilyse boehringer ingelheim, Ingelheim am Rhein, Germany) and full heparinization. Treatment was discontinued after 24 hours with no significant improvement of symptoms. Full anticoagulation with Coumadin (Bristol-Myers Squibb Company, New York, NY) and alprostadil (Prostvasin UCB, Brussels, Belgium) infusion for 2 weeks was initiated and eventually patient's symptoms improved. Laboratory testing revealed a homozygous prothrombin G20210A mutation and antiphospholipid syndrome. Homozygous prothrombin G20210A mutation in conjunction with antiphospholipid syndrome is a rare combination of coagulation disorder. Early intervention with full anticoagulation and subsequent lifelong anticoagulation should be considered in treatment strategy.

Keywords

- ▶ homozygous prothrombin mutation
- ▶ G20210A
- ▶ antiphospholipid syndrome
- ▶ femoral artery thrombosis

A 15-year-old healthy Caucasian male (body mass index: 21 kg/m², height: 171 cm, and weight: 60 kg) with no medical or surgical history presented with increasing left leg pain for

about 1 week. He was physically very active and the leg pain was aggravated by exercise. Physical examination revealed a pale and cold left foot with new onset of dorsal foot necrosis

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that started 2 days ago. In addition, he complains of moderate rest pain. He did not notice any symptoms at the right lower extremity.

Transcutaneous oxygen measurement (TcPo₂) of the foot in a horizontal state showed 17 mm Hg on the left and 52 mm Hg on the right. Dropping the left foot down the TcPo₂ increased to 52 mm Hg. The ankle brachial index (ABI) was 0.3 on the left and 0.6 on the right.

A color-coded duplex sonography was performed that showed an occlusion of the entire left superficial femoral artery. There was no blood flow in the peroneal bifurcation, posterior tibial artery, and anterior tibial artery. The peroneal artery showed minimal monophasic flow. In addition, the right superficial femoral artery showed an occlusion of approximately 6 to 10 cm. Reconstitution occurred from a collateral of the deep femoral artery. Anterior tibial artery, posterior tibial artery, and the peroneal artery showed monophasic signals. Interventional angiography confirmed these findings.

Further evaluation with an MRI-angiography to rule out involvement of larger vessel was negative. The aorta and carotid arteries were within normal limits and no other occlusion was identified. Echocardiography showed no abnormalities of the heart.

The patient subsequently underwent left superficial femoral and popliteal artery lysis. An ultrasound-assisted local lysis technique was used with infusion of the rt-PA (Actilyse) 1 mg/h and full heparinization. The catheter passed smoothly through the occlusion which confirms the acute event. The 24-hour reevaluation showed no improvement and the lysis therapy was stopped (► Fig. 1a, b). At this time, patient's lower extremity physical examination was unchanged compared with the baseline admission examination. There was no deterioration of skin necrosis, no new muscle paralysis, sensory loss, inaudible venous Doppler signal, or absent capillary return.

The case was discussed at the interdisciplinary vascular conference (Vascular Surgery, Angiology, Interventional Radiology) and based on the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) guideline,¹ the decision was made to continue with full anticoagulation and no surgical intervention. An infusion with alprostadil (Prostvasin) and full anticoagulation with Coumadin was started.

Initial laboratory studies including coagulation parameters were within normal limits. Circumstantial evaluation for thrombophilia were performed and revealed a homozygous prothrombin G20210A mutation and elevated lupus-like anticoagulant (73.9 second, Cardiolipin antibodies (96 U/mL) and β_2 glycoprotein IgG antibodies (9.5 U/mL). All the other thrombophilic parameters analyzed, antithrombin, protein C, protein S, heparin cofactor II, plasminogen, fibrinogen, antibodies, homocysteine, and activated protein C resistance, were in the normal range. Antithrombin III, activated protein C resistance, VIII, lipoprotein, homocysteine, partial thromboplastin time were normal.

After 2 weeks of treatment with alprostadil and Coumadin therapy, rest pain nearly disappeared, the TcPo₂ increased to 25 mm Hg and the ABI to 0.5 on the left lower extremity. Dorsal foot necrosis was replaced by new viable tissue and the left lower extremity did not show any new signs of limb ischemia. On discharge (hospital day 14), the patient was put on lifelong anticoagulation with Coumadin and a target international normalized ratio (INR) of 2.5 to 3.0.

Discussion

To our knowledge, this is the first case reporting of peripheral artery thrombosis with a homozygous prothrombin G20210A mutation and associated antiphospholipid syndrome.

Fig. 1 (a) Angiography of the left superficial femoral artery after 24-hour treatment of ultrasound assisted lysis with rt-PA (Actilyse). (b) Angiography of the left superficial femoral and popliteal artery after 24-hour treatment of ultrasound-assisted lysis with rt-PA (Actilyse).

Genetic and Epidemiology

Prothrombin is the precursor of thrombin. This protein is a vitamin K dependent and produced by the liver. It has a role in the conversion of fibrinogen into fibrin, limiting the hemostatic process and initiating platelet aggregation. In 1996, Poort et al² described a single substitution of adenine for guanine at position 20210 in the three introns of the prothrombin gene. Heterozygote prothrombin G20210A mutation is found mostly in Caucasians, with prevalence between 2 and 3%.³ Only a few homozygous individuals have been described thus far. Assuming that the prevalence of heterozygotes in the general population is 2 to 3%, the expected number of homozygous individuals in the normal population is 1.3 per 10,000 according to the Hardy-Weinberg equilibrium.⁴

Mutation and Thrombosis Risk

Prothrombin gene mutation G20210A is likely a risk factor for venous thromboembolism.⁵ Studies showed that circulating levels of microparticles (MP) may contribute to their thrombogenic profile. Higher levels of circulating MP found in prothrombin gene mutation carriers may play a role in the development of venous thromboembolism possibly by increasing thrombin generation.⁶

Less clear is the role of prothrombin mutation in the formation of arterial thrombosis. Especially, the relationship between these mutations and arterial thrombotic syndromes (coronary heart disease, myocardial infarction, and stroke) has not been established and is controversial.

Prothrombin mutation was usually associated with other well-established predisposing factors for thrombosis such as antiphospholipid antibodies,⁷ thrombocytosis,⁸ protein C deficiency, and heterozygosity for factor V Leiden.⁹

It has been published before that the majority of homozygous carriers of the prothrombin polymorphism G20210A remain asymptomatic even in the presence of several prothrombotic risk situations suggesting that the prothrombotic role played by this polymorphism is minor.¹⁰⁻¹²

But recently, several homozygous carriers have been reported to present severe or unusual vein thrombosis.¹³⁻¹⁶ In addition, cerebral venous sinus thrombosis in a neonate,¹⁷ 18-year-old woman with thrombosis during pregnancy,¹⁸ recurrent pulmonary embolism in a 13-year-old patient,¹⁹ and bilateral iliac vein thrombosis in an 19-year-old patient²⁰ were described. Arterial thrombosis in homozygous prothrombin G20210A mutation was reported in a 3-year-old patient with arterial stroke,²¹ and a 44-year-old patient with retinal artery thrombosis.²²

A femoral artery thrombosis is a very uncommon disorder in a 15-year-old male patient and it is important to perform a complete thrombophilia laboratory work-up. In addition, a genetic counseling and testing of family members should be considered.

A thrombotic event is most likely multifactorial and in this case the prothrombin mutation combined with antiphospholipid syndrome might have contributed to the femoral artery occlusion. Even in a physically very active young patient, an arterial thrombosis has to be considered with claudication and rest pain.

This case indicates that the homozygous prothrombin G20210A mutation might increase the arterial thrombotic risk in patients carrying further prothrombotic risk factors, such as, antiphospholipid syndromes. More data are needed to support the role of homozygote prothrombin mutation and arterial thrombosis.

Percutaneous Catheter-Directed Thrombolysis versus Surgical Thrombectomy

Percutaneous catheter-directed thrombolysis and open surgical revascularization are current options for the treatment of acute limb ischemia. Despite several systematic reviews and randomized controlled trials comparing the two options, no single treatment can yet be recommended as a universal initial management of acute limb ischemia. There is no overall difference in limb salvage or death at 1 year between initial surgery and initial thrombolysis.^{23,24} The higher risk and benefit of each treatment option must be balanced in each person.

The decision for percutaneous catheter-directed thrombolysis in this case was based on the patient's physical examination, age, medical history, and TASC II guideline¹ and quality improvement guidelines for percutaneous catheter-directed intra-arterial thrombolysis and mechanical thrombectomy for acute lower limb ischemia algorithm (►Fig. 2).²⁵

Salvageable limbs with audible venous Doppler signal and incomplete motor and sensory loss are eligible for percutaneous catheter-directed thrombolysis (Rutherford classification I and IIa-IIb, ►Table 1). Patients presenting with profound limb muscle paralysis (muscle rigor) and sensory loss, inaudible venous Doppler signal, and absent capillary return should be considered for an attempt at surgical revascularization (Rutherford classification III).

In our patient, the reevaluation after failed thrombolytic therapy showed an unchanged stable limb condition (class 2: marginally threatened). There was no deterioration of skin necrosis, no new muscle paralysis, sensory loss, inaudible venous Doppler signal, or absent capillary return. In addition, considering his young age and low risk of thrombolytic complication (hemorrhage and stroke), we decided to continue with alprostadil (Prostasin) infusion and full anticoagulation with Coumadin and no surgical intervention.

Ultrasound-Accelerated Thrombolysis Catheters versus Standard Catheter Thrombolysis

New generation ultrasound-accelerated thrombolysis catheters showed in experimental studies that high-intensity ultrasound may induce thrombolysis, with and without the addition of plasminogen activators, mainly by acoustic cavitation and mechanical disruption. Low intensity, high frequency ultrasound waves may actually enhance plasmin-mediated thrombolysis. A systematic review in 2011 by Doomernik et al showed that catheter-directed ultrasound accelerated thrombolysis was related to rapid revascularization and a reduction in treatment time, drug dosage, hospitalization time, and possibly major bleeding complications compared with standard thrombolysis.²⁶

Fig. 2 Treatment algorithm regarding acute limb ischemia.²³

Table 1 Rutherford classification for acute limb ischemia

Class	Category	Prognosis	Sensory loss	Muscle weakness	Arterial Doppler	Venous Doppler
I	Viable	No immediate limb threat	None	None	Audible	Audible
IIA	Threatened: marginal	Salvageable if treated promptly	Minimal none	None	± Audible	Audible
IIB	Threatened: Immediate	Salvageable if treated immediately	More than just toes	Mild moderate	Rare audible	Audible
III	Irreversible	Limb loss or permanent damage	Profound	Profound	None	None

Note: Society of Vascular Surgery/International Society of Cardiovascular Surgery (Rutherford et al 1997).²⁷

The DUET study (Dutch randomized trial comparing standard catheter-directed thrombolysis versus ultrasound-accelerated thrombolysis for thrombo-embolic infra-inguinal disease) reported preliminary result of earlier thrombolysis with ultrasound catheter than with standard catheter.²⁸ End report from the DUET study as well meta-analysis studies are warranted and should be awaited before considering catheter-directed ultrasound-accelerated thrombolysis as a new standard treatment.

Anticoagulation

Thrombophilia is a multifactorial disorder, involving both genetic and acquired risk factors that lead to an increased tendency to thrombosis. Therefore, the management of acute thrombosis in the setting of the G20210A mutation does not differ substantially from that of other conditions of inherited thrombophilia.

There are no studies or data that have evaluated the efficacy of different anticoagulation strategies (warfarin vs. aspirin vs. clopidogrel) in prothrombin mutation. The duration and combining antiplatelet drugs to warfarin should be assessed on an individual's risk of thrombosis such as the onset of symptoms, age, recurrence, and severity.

In general, warfarin is the standard of care for the chronic management of patients with antiphospholipid syndrome-associated thrombophilia. High-intensity warfarin was not superior to moderate intensity warfarin for thromboprophylaxis in patients with antiphospholipid antibodies and previous thrombosis. The low rate of recurrent thrombosis among patients in whom the target INR was 2.0 to 3.0 suggests that moderate intensity warfarin is appropriate for patients with the antiphospholipid antibody syndrome.²⁹

Antiplatelet agents such as aspirin and clopidogrel have been considered for the management of patients with antiphospholipid syndrome. In retrospective series, aspirin alone has been of minimal or no benefit for the prevention of thrombotic antiphospholipid syndrome manifestations in patients who have experienced previous events.³⁰ There is no data about clopidogrel efficacy and safety for patients with antiphospholipid syndrome.

In addition, no trial has been found that evaluated the role of aspirin or clopidogrel in prothrombin mutation.

Conclusion

We conclude that it emphasizes the need to consider the possibility of homozygous prothrombin mutation also in young children and adolescents presenting with occlusive or thrombotic events. However, the significance of the homozygous prothrombin G20210A mutation as an isolated risk cannot be concluded from our case. The importance of the isolated homozygous prothrombin G20210A mutation remains to be clarified by further studies.

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Conflict of Interest
None.

Contributions

Uzung Yoon contributed to patient care and writing the article. LaiLai Kwok contributed to literature research and writing the article. Ingo Flessenkaemper contributed to supervision of patient care and article.

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