

HYPERFIBRINOGENEMIA IN PERIPHERAL ARTERIAL DISEASE: COEXISTENT AND INDEPENDENT RISK FACTOR (A REPORT OF TWO CASES AND REVIEW OF LITERATURE)

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ABSTRACT

These case reports aim to show that hyperfibrinogenemia is a risk factor for the progression and prognosis of peripheral arterial disease (PAD), in patients with and without diabetes mellitus type 2.

We present a patient with PAD who has type 2 diabetes mellitus, who has previously been repeatedly treated for lower limb ischemia with multiple vascular surgeries performed. A few weeks before admission the patient developed critical lower limb ischemia, which was treated with an iliaco-popliteal and femorofemoral bypass. The patient had elevated serum fibrinogen values. In the current admission, renewed left limb ischemia was diagnosed, and surgically evaluated with a recommendation for amputation of the left limb as a surgical recommendation. Our second patient had a stable intermittent claudication, dyslipidemia and hyperfibrinogenemia. He was successfully treated for those risk factors. Regular monitoring of the patient showed improved claudication distance and quality of life

Our case reports, supported by a literature review, demonstrate that hyperfibrinogenemia is a possible risk factor for progression and the prognosis of PAD.

Key words: hyperfibrinogenemia, risk factor, prognosis, peripheral arterial disease

INTRODUCTION

Fibrinogen is a glycoprotein that is the most important in the final steps of the coagulation cascade. Fibrinogen plasma concentration normally circulates at 2-4 g/L. Prothrombogenic states rooted in abnormalities of individual coagulation factors have been well researched, as opposed to the less documented hyperfibrinogenemia. [1]

This condition occurred mostly in patients with diabetes, but was also recognized in those without diabetes. Current treatment of hyperfibrinogenemia is pharmacological, with the use of the fenofibrate and gemfibrozil.

These case reports tend to show that hyperfibrinogenemia is a risk factor for the progression and prognosis of peripheral arterial disease (PAD).

Case 1 summary

First patient, B.M., was a 58 year old male, with a negative family history for relevant diseases. He had a medical history of having been surgically treated for limb ischemia with multiple surgeries, including an aortofemoral bypass surgery and graft embolectomy surgery. He has had diabetes type 2 for 5 years with mean glycemia 6.8 mmol/L. He had a pericardiocentesis in two occasions with evacuation of a bloody effusion weeks prior to admission, as well as diabetes type 2. Weeks before admission, the patient was surgically evaluated for limb ischemia, and a CT angiography of the arteries of the legs, showed as seen in picture 1, an occlusion in both the left iliac artery and the aortofemoral bypass of the left leg. Consequently, femorofemoral and iliaco-popliteal bypass surgery on the left limb were performed. The patient was then transferred to our vascular wing with complaints of dyspnea and chest pain. At admission, he was slightly dyspneic, with blood pressure of 110/80 mmHg and heart rate



Picture 1. A CT angiography of the lower limbs shows a general calcification of the iliac arteries, with an occluded left iliac artery as well as an occluded aortofemoral bypass of the left leg

of 104 bpm. Physical examination revealed surgical scars from previous procedures as well as gangrenous changes of the left foot. ECG showed reduced amplitudes of the R wave in all leads. A TTE showed a small pericardial effusion, and a repeat TTE showed no evolution. Initial laboratory workup showed a borderline anemia, as well as reduced values of serum proteins, which were

slightly ameliorated with two units of fresh-frozen plasma. Blood cultures taken before admission came back positive, and parenteral vancomycin was started and given for the duration of the hospital stay. Repeat blood cultures also ultimately came back positive. During the hospital stay, vascular surgeons were consulted regarding surgical treatment options, and recommended a left lower leg amputation. Blood results showed borderline anemia, normal bleeding times, slightly elevated levels of serum fibrinogen (5.76 g/L). During the last days of the hospital stay, the patient received opioid analgesia due to the extreme pain in the left leg. Although the lower leg amputation was planned, the patient went into cardiac arrest and was not successfully resuscitated.

Case 2 summary

Second patient admitted to Vascular centre with symptoms of intermittent claudication on 500 meters. Lab analyses showed dyslipidemia (LDL = Cholesterol 3.7, HDL Cholesterol 0.8 mmol/L), and hyperfibrinogenemia (= 5.3 g/L). PAD was diagnosed with Echo Color Doppler sonography (obstruction of tibial arteries on both sides with measured indexes 0.7 on the right and 0.68 on the left). He was treated for those risk factors with Atorvastatin a 40 mg and Phenofibrate 175 mg. Cilostazol 200 mg/daily and Acetyl salicylic acid 100 mg /daily was also prescribed. Three months follow up showed improvement of claudication distance and quality of life. We measured value of indexes 0.78 on the right and 0.75 on the left leg. Control lab analyses showed value of LDL = Cholesterol 2.7 and HDL Cholesterol 0.9 mmol/L, fibrinogen level 3.1 g/L). Patient continued with prescribed therapy with advice for next control after 6 months.

DISCUSSION

The role of elevated fibrinogen serum levels and the related mortality has been well documented in recent years. Altes et al. explored the outcome of patients with stable PAD and raised fibrinogen levels in the outpatient setting. [2] Their findings showed that during 18 months of follow up these patients with raised fibrinogen had a two-fold increase in the rate of ischemic stroke, limb amputation and death. Establishing fibrinogen as an independent risk factor for prognosis of patients with PAD has been a topic of interest.

[3] Diabetic patients with PAD represent an important subgroup. Bak et al. concluded that along with age, BMI, LDL cholesterol and sex, fibrinogen joins the diverse list of independent factors that affect the ankle-brachial index. [4] Concededly, a study evaluated the correlation between endothelial dysfunction and metabolic parameters (low HDL, hypertriglyceridemia, obesity, systolic blood pressure) and CRP and fibrinogen in patients with CAD and diabetes type 2. [5] Association between a pro-thrombotic plasma fibrin clot phenotype and the pathogenesis and progression of PAD and thromboangiitis obliterans (TAO) was evaluated by Undas. [6] Fibrinogen molecule characteristics and fibrin clot morphology become increasingly diagnostically and therapeutically relevant. Casini discussed the highly heterogeneous clinical phenotypes of congenital dysfibrinogenemia (qualitative disorder of fibrinogen with normal antigen levels) [7] and the associated difficulty in determining the severity and prognosis in individual cases. Various studies (table 1) have tackled the elusive nature of hyperfibrinogenemia, through prognosticating its role in PAD, defining its specific characteristics in patients with diabetes type 2 and PAD, and even analysis of the fibrinogen molecule and the patterns of clot formation.

Table 1. *Studies of Fibrinogen and PAD [8]*

Study name	Value in the development of PAD	Value in the outcome of PAD
Nortwick	✓	
Speadwel	✓	
APSIS	✓	
Wilhelmsen	✓	
Stone	✓	
Banerje		✓
Violi		✓
ADEP		✓
Bosevski		✓
Altes		✓

CONCLUSION

Our case demonstrated that unrecognized hyperfibrinogenemia might be a risk factor for the progression and the prognosis of PAD. This condition is often coexistent with diabetes or dyslipidemia, but should be treated as a sepa-

rate one. It is clear that further exploration is required to elucidate and define in detail the role of hyperfibrinogenemia in peripheral arterial disease.

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Резиме**ХИПЕРФИБРИНОГЕНЕМИЈА КАЈ ПЕРИФЕРНА АРТЕРИСКА БОЛЕСТ:
КОЕГЗИСТИРАЧКИ И НЕЗАВИСЕН ФАКТОР НА РИЗИК
(ПРИКАЗ НА ДВА СЛУЧАИ И ПРЕГЛЕД НА ЛИТЕРАТУРА)**

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Овие прикази на случаи имаат цел да покажат дека хиперфибриногенемијата претставува ризик-фактор за прогресијата и за прогнозата на периферната артериска болест (ПАД) кај пациенти со и без дијабетес мелитус тип 2.

Ние прикажуваме пациент со ПАД, кој има тип 2 дијабетес мелитус, кој е претходно третиран во повеќе наврати за исхемија на долните екстремитети со направени мултипни васкуларни оперативни зафати. Неколку недели пред приемот пациентот разви критична исхемија на долен екстремитет, која беше третирана со илијако-поплитеален и феморо-феморален бајпас. Пациентот имаше зголемени вредности на серумски фибриноген. Во тековниот прием, дијагностицирана беше повторена исхемија на левата нога, хируршки евалуирана со препорака за ампутација на левата потколеница како хируршка препорака. Вториот наш пациент имаше стабилна интермитентна клаудикација, дислипидемија и хиперфибриногенемија. Тој беше успешно лекуван за тие ризик-фактори. Редовното следење на пациентот покажа подобрена клаудикациска дистанца и квалитет на живот.

Нашите прикази на случаи, поддржани со преглед на литература, демонстрираат дека хиперфибриногенемијата е можен ризик-фактор за прогресијата и прогнозата на ПАД.

Клучни зборови: хиперфибриногенемија, ризик-фактор, прогноза, периферна артериска болест