Fulminant arterial thrombosis leading to amputation of forearm in a 16-year-old girl – Disastrous combination of diabetes mellitus, factor V Leiden mutation and oral contraception

Christine Happle*; Carolin Hartmann*; Thomas Jack; Martin Boehne; Harald Bertram; Armin Wessel; Stephan Schoof
Department of Pediatrics and Adolescent Medicine, Pediatric Cardiology and Intensive Care Medicine, Hannover Medical School, Hannover, Germany

Dear Sir,
A 16.7-year-old girl presented to our pediatric emergency room with increasing pain in her right hand without history of a trauma. Physical examination showed livid discoloration, pressure pain and dysaesthesia of digits IV and V. Pulses of the right ulnar and radial arteries were reduced but palpable. Her past medical history included interventional closure of an atrial septal defect (23 mm STARFlex® occluder) at seven years of age, with uneventful cardiologic follow-up. Since adolescence, her body mass index (BMI) was 25 kg/m² (between P 90 and P 97). A combined oral contraceptives (OC) (0.02 mg ethinylestradiol plus 3 mg drospirenone/day) had been prescribed for eight months. Her mother and aunt both experienced deep venous thromboses and tested heterozygous for factor V Leiden (FVL) mutation (Q506). Her father suffered from diabetes mellitus (DM).

Reduced blood flow in right ulnar and radial arteries was detected by duplex sonography. The patient was immediately started on heparin (400 U heparin/kg/day). Transesophageal echocardiography showed complete closure of the atrial septal defect and excluded intracardiac thrombi. Initial blood tests revealed a state of chronic hyperglycaemia (repeated blood glucose levels > 20 mM, C-peptide serum level 0.59 ng/ml, glycosylated haemoglobin (HbA1c) 12.4 g/dl, glycated protein 557 µM) without ketoacidosis and slightly elevated D-dimers (940 μg/l).

Sixteen hours after admission digital subtraction angiography (DSA) showed a pronounced thrombosis of her proximal right brachial artery with absence of collateral supply to the forearm (Fig. 1a and b). Immediate local angioplasty failed and both local bolus (10 mg rt-PA plus 10,000 U heparin) as well as continuous intra-arterial catheter lysis (200 U heparin/kg/day plus 1 mg rt-PA/hour [h]) were administered for another 16 h. Progression of thrombosis and missing blood supply to the forearm necessitated an instant surgical fasciotomy of her right arm 36 h after admission, and an extensive thrombus was removed by Fogarty catheter. Post-operatively, she suffered from a severe systemic inflammatory response syndrome with increasing demand of catecholamines and ventilation. Persistent absence of arterial flow required a second surgical thrombectomy after another 24 h. An immediate intra-operative re-thrombosis and her life-threatening clinical condition necessitated amputation of her right forearm.

Pathology reports noted necrosis of muscles without evidence for malignancy or vasculitis. DSA after 14 days showed multiple residual, wall-adherent microthrombi of her proximal radial and ulnar artery and a slow but effective vascularisation of the stump. Anticoagulation included intravenous heparin (400 U/kg/day) plus oral clopidogrel (2 mg/kg/day), replaced by phenprocoumon (international normalised ratio [INR] 3.0–4.0) after final surgical revision.

Polymerase chain reaction (PCR) confirmed heterozygosity for Q506. Protein C (1996) and von Willebrand factor activities (173%) were elevated. Protein S, factor II, factor V and antithrombin III activities were within normal limits. Testing for lupus anticoagulant, antcardiolipin and anti-β2 glycoprotein I antibodies (IgM and IgG), rheumatoid factor, perinuclear antineutrophil cytoplasmic antibody, cytoplasmic antineutrophil cytoplasmic antibody, Scl-70 antibody, smooth muscle antibody, C3 and C4 complement levels, as well as PCR for prothrombin 20210 mutation were normal.

Inulin auto-antibodies, glutamate dehydrogenase antibodies and anti-IgA-antibodies were absent. Detailed genetic testing, especially for different types of maturity onset diabetes of the young (MODY) to further classify her type of DM, has yet to be performed. However, persistent high blood-glucose levels necessitated subcutaneous insulin therapy. Serology confirmed a hyperlipoproteinemia type IIA. The patient received a detailed diet consultancy and was discharged on life-long oral anticoagulation with phenprocoumon.

Monagle et al. found an incidence of arterial thromboembolism as high as 8.5/10,000 paediatric hospital admissions (1). Major causes included infections, cardiac surgery and inherited thrombophilia. FVL is characterised by a resistance of coagulation factor V to degradation by activated protein C with a frequency of 5 % among Caucasians. Heterozygosity for FVL Q506 mutation implies a seven-fold increased risk of thromboembolism. Young FVL patients are prone to venous and, less often, arterial thrombosis (2).

The hypercoagulative condition aggravates when metabolic disorders such as DM or hyperlipidaemia coincide. Haller et al. described a 12-year-old girl with type 1 DM and FVL heterozygosity, leading to a massive arterial thrombosis and amputation of a limb (3). Moreover, an 11-year-old diabetic FVL patient died from multiple cerebral infarctions, which underscores the significance of these combined risk factors in childhood (4). In contrast to our case, both of these patients had been diagnosed with DM more than two years prior to thrombosis, and thrombosis occurred during ke-

* These authors contributed equally to the work.
to acidosis. None of them was on any pro-
thrombotic medication. Both type 1 and 
type 2 DM are known to induce a hyper-
coagulable state by persistent activation of the 
haemostatic system with platelet acti-
vation and decreased fibrinolytic potential (5).
On admission, our patient showed chronic hyperglycaemia without ketoaci-
dosis, and laboratory analysis revealed an 
elevated level of lipoprotein(a). The latter has been reported as risk factor of venous and 
arterial thrombosis in the paediatric 
population (6).

Our patient had a family history of 
thrombosis in the presence of FVL het-
erozygosity. Although current guidelines 
recommend testing for hereditary throm-
bophilia in these adolescents prior to OC 
administration (7), she received a com-
bined OC for eight months. Despite on-
going controversies, there is growing evi-
dence for an increased risk of arterial is-
chaemic stroke in FVL patients during 
childhood and adolescence. OCs them-
selves raise this risk ~3-fold, whereas a 
combination of both hereditary throm-
bophilia and intake of OCs leads to a ~
11-fold increased risk of ischaemic stroke in young women (8). Obese women (BMI >25) taking OCs have a 10-fold risk of deep 
venous thrombosis as compared to normal 
weight women not taking OCs (9).

Since no guidelines for the treatment of 
arterial thrombosis in childhood and 
adolescence were available, our patient received 
treatment according to the guidelines for 
adults. Three therapeutic options exist: ca-
thereter-based thrombolysis, mechanical 
thrombectomy, and open surgical interven-
tion. In acute limb ischaemia of less than 14 
days duration, immediate catheter-based 
thrombolysis resulted in a reduction in the 
need for open procedures and a comparable 
long-term outcome compared to surgery (10). However, combined early surgical and 
thrombolytic intervention led to limb sal-
vage in a 24 year-old woman with upper 
limb ischaemia due to FVL (2). Whether or 
not early Surgical thrombectomy might 
have saved the limb in our patient remains 
questionable in consideration of the im-
mediate re-thrombosis under surgery. In-
stead, after failure of angioplasty due to the 
extent of thrombosis we started catheter-
based thrombolysis with a combination of 
unfractionated heparin and rt-PA, the latter 
being the thrombolytic agent of choice in 
children and adolescents (11). Awaiting 
other surgical interventions we avoided 
the use of low-molecular-weight heparin 
due to its inferior controllability by a 
prolonged half-life and lack of sufficient anti-
dotes. Nevertheless, institutions that are 
more familiar with the use of low-molecu-
lar-weight heparin in adolescents might 
consider this as an alternative option.

In this teenage girl, an unfortunate com-
bination of risk factors led to a disastrous 
arterial thrombosis. Our case report 
exemplifies the strong association of 
thrombophilia and FVL heterozygosity 
plus intake of OCs. Prior to prescribing 
OCs, a thorough case history regarding 
thrombophilia should be taken, and testing 
for thrombophilia should be performed as 
needed.

To our knowledge, open surgery shows 
no general advantage over catheter-based 
thrombolysis in acute arterial thrombosis. 
For selected patients, however, surgery 
might be the method of choice. More im-
portantly, we consider immediate and 
through diagnostic as well as a rapid 
decision making regarding the individual 
treatment, to be crucial for limb salvage in 
acute arterial thrombosis in adolescents. 
Further clinical research should address the 
development of guidelines for diagnostics 
and treatment of arterial thromboses in 
children and adolescents.

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