Arterial thrombosis in homozygous antithrombin deficiency

M. Olivieri1; C. Bidlingmaier1; S. Schetzeck2; I. Borggrave3; C. Geisen4; K. Kurnik1

1Department of Paediatric Haemostaseology, Paediatric Haemophilia Center, Dr. von Hauner’s Childrens Hospital, University of Munich, Germany; 2Department of Neonatology, Dr. von Hauner’s Childrens Hospital, University of Munich; 3Department of Neuropaediatrics, Dr. von Hauner’s Childrens Hospital, University of Munich; 4Department of Transfusion Medicine, DRK Blutspendedienst, Frankfurt am Main, Germany

Case report: We report a newborn with uncomplicated birth in the 40+5 week of gestation and postnatal appearance of a reticular, livide haematoma on the right upper arm and a tonic clonic epileptic seizure. Clinical examination revealed weak pulses in the A. radialis and ulnaris. MRI scan showed a large thrombus in the A. carotis interna and externa with large cerebral infarction and a thrombus in the A. subclavia. Laboratory work up showed elevated D-dimers and antithrombin levels <20% (lowest 15%), age-related values for protein C, protein S, plasminogen, and no other inherited thrombophilia. Therapy: We started anticoagulation with unfractionated heparin intravenously (aPTT: 50–60 s) and under suspicion of an AD the substitution of AT (70 U/kg body weight). In course of time we changed anticoagulation to low molecular weight heparin (Anti Xa 0.6–0.8 U/ml) and substitution of 250 E/kg AT every second day. In the molecular work up we found a homozygous missense mutation in exon 2 of SERPINC1 gene (type „Budapest 3”). Molecular analysis showed also heterozygous mutations in both parents and a homozygous mutation in the asymptomatic brother aged three years. At age of six months we changed the anticoagulation to coumadin (INR 2.5–3.5). Anticoagulation with coumadin was also started in the brother.

Discussion: Hereditary AD is associated with an increased risk of thrombosis. The homozygous status mainly leads to intrauterine fetal loss or the occurrence of peri- and postnatal thrombosis. Therapy consists in the substitution of AT and a lifelong anticoagulation with vitamin K antagonists also in asymptomatic patients.

Schlüsselwörter
Arterielle Thrombose, Antithrombinmangel, angeborene Thrombophilie, Antikoagulation

Zusammenfassung

Keywords
Arterial thrombosis, antithrombin deficiency, inherited thrombophilia, anticoagulation

Summary
Antithrombin (AT), a serin protease inhibitor (serpin) produced in the liver, inhibits mainly thrombin and factor Xa. Antithrombin deficiency (AD) is associated with a higher incidence of thrombosis. Case report: We report a newborn with uncomplicated birth in the 40+5 week of gestation and postnatal appearance of a reticular, livide haematoma on the right upper arm and a tonic clonic epileptic seizure. Clinical examination revealed weak pulses in the A. radialis and ulnaris. MRI scan showed a large thrombus in the A. carotis interna and externa with large cerebral infarction and a thrombus in the A. subclavia. Laboratory work up showed elevated D-dimers and antithrombin levels <20% (lowest 15%), age-related values for protein C, protein S, plasminogen, and no other inherited thrombophilia. Therapy: We started anticoagulation with unfractionated heparin intravenously (aPTT: 50–60 s) and under suspicion of an AD the substitution of AT (70 U/kg body weight). In course of time we changed anticoagulation to low molecular weight heparin (Anti Xa 0.6–0.8 U/ml) and substitution of 250 E/kg AT every second day. In the molecular work up we found a homozygous missense mutation in exon 2 of SERPINC1 gene (type „Budapest 3”). Molecular analysis showed also heterozygous mutations in both parents and a homozygous mutation in the asymptomatic brother aged three years. At age of six months we changed the anticoagulation to coumadin (INR 2.5–3.5). Anticoagulation with coumadin was also started in the brother.

Discussion: Hereditary AD is associated with an increased risk of thrombosis. The homozygous status mainly leads to intrauterine fetal loss or the occurrence of peri- and postnatal thrombosis. Therapy consists in the substitution of AT and a lifelong anticoagulation with vitamin K antagonists also in asymptomatic patients.
Antithrombin (AT) – a serine protease inhibitor produced in the liver – plays a critical role in the regulation of coagulation (1). As the most important anticoagulant AT inhibits with its cofactor heparin
• mainly factor Xa and thrombin
• but also the factors IXa, Xla, and XIIa (2).

Additionally, AT has an important anti-inflammatory effect by its binding to thrombin and factor Xa with consequent reduced release of interleukin 6 and interleukin 8 and by its binding to endothelial heparin sulfate with consequent increased production of anti-inflammatory prostacyclin (3).

Normal AT levels range between 80% and 120%, but are lower in neonates and infants. AT levels reach adult values at about six months of age.

Antithrombin deficiency (AD) is an autosomal dominant inherited disorder and was first described in 1965 by Egeberg in a Scandinavian family with venous thromboembolism (3, 4). There can be differentiated two types of AD:
• type I mutations with complete lack of AT proteins and neonatal thrombosis with often fatal course in utero in homozygous states and
• type II mutations that result in an altered AT protein with either impaired stability or impaired activity or the loss of affinity to heparin (5).

The reported prevalence of AD lies between 1:500 and 1:5000 in the overall population. In patients with venous thromboembolism is reported a prevalence of 1:20 to 1:200 (3, 6, 7). AD like other inherited hypercoagulable syndromes is associated primarily with venous thromboembolism and only in rare cases with arterial thrombosis. Venous thromboembolism occurs as
• deep vein thrombosis in the extremities,
• pulmonary embolism and
• in rare cases as cerebral, sinus, mesenteric or renal vein thrombosis.

For arterial thrombosis Moster et al. reported a frequency up to 5% in AD. All patients suffered a cerebral strokes in A. carotid territory (8).

Therapy of thromboembolism in AD consists of
• anticoagulation with unfractionated or low molecular weight heparin and
• substitution of antithrombin concentrate.

In homzygous deficiency or recurrent thromboembolism a long term anticoagulation with oral vitamin K antagonists is necessary.

Case report

We report a newborn with uncomplicated birth in the 40+5 week of gestation (G2P2) (Fig.). Parents are not related. After unproblematic cardiorespiratory adaptation there appeared a livide reticular haematoma on the right upper arm and a livide discoloration of the right forearm. Clinical examination revealed a prolonged capillary refill time and weak pulses in the A. radialis and A. ulnaris of the right arm. Additionally, a primary focal and secondary generalized tonic-clonic epileptic seizure occurred.

Doppler ultrasound showed an absent arterial signal in the A. brachialis and radialis and MRI scan showed a large thrombus in the bifurcation of the A. carotis interna and externa with large cerebral infarction distal to the A. cerebria media and a thrombus in the A. subclavia. Laboratory work up showed elevated D-dimers and repeated AT levels of < 20% (lowest 15%), age-related values for protein C, protein S, plasminogen, and no evidence of a factor V Leiden (G1691A)-, and prothrombin mutation (G20210A) or a MTHFR polymorphism (C677T). Antibiotic therapy was started with ampicillin, cefotaxim and aliclovir because of elevated inflammation parameters.

We started anticoagulation with unfractionated heparin and aPTT goal of 50–60 s in fear of secondary intracerebral bleeding and substituted AT to reach normal plasma levels (> 80%). We changed anticoagulation to enoxaparin in due course. We considered the incidence of recurrent thrombosis of about 10%/year. We decided to start a long term anticoagulation with oral coumadin after reaching six months of age and a stable clinical situation (2, 10).

Actually, there exist no data concerning the best treatment of artery thrombosis in AD, i. e. with antiplatelet drugs. But in consideration of the physiological role of AT in the coagulation cascade it is reasonable that

Discussion

AT is the most important anticoagulant in the human coagulation system and inhibits with the cofactor heparin mainly factor Xa and thrombin.

Homzygous deficiency is rare and associated with often fatal neonatal thrombosis. AD is mainly associated with venous thromboembolism and only in rare cases with arterial thrombosis.

In neonates most seizures are secondary to hypoxic ischemic injury and always need further diagnostic clarification by ultrasound and MRI (9). Recurrent low AT levels, the revealed arterial thrombosis and the genetic testing in course of leads us to the diagnosis AD and necessitated an anticoagulant treatment. We started treatment with unfractionated heparin and aPTT goal of 50–60 s in fear of secondary intracerebral bleeding and substituted AT to reach normal plasma levels (> 80%). We changed anticoagulation to enoxaparin in due course. We considered the incidence of recurrent thrombosis of about 10%/year. We decided to start a long term anticoagulation with oral coumadin after reaching six months of age and a stable clinical situation (2, 10).

Actually, there exist no data concerning the best treatment of artery thrombosis in AD, i. e. with antiplatelet drugs. But in consideration of the physiological role of AT in the coagulation cascade it is reasonable that...
an anticoagulant therapy is more effective than the antiplatelet therapy. Patnaik et al. also considered that in young patients with absent arteriosclerosis and AD as main cause of thrombotic events a long term anticoagulation may be appropriate (3).

Molecular workup revealed a familial mutation in the exon 2 of SERPINC1 gene described as type “Budapest 3”. The AT Budapest was the first described type II variant and is associated with a high incidence of thrombosis in affected relatives (11). The homozygous missense mutation causes a conformational change of AT with reduced affinity to heparin and lower plasma levels (12, 13). In heterozygous states the incidence of thrombosis is lower.

We found a homozygous mutation also in the brother aged three years, while both parents were heterozygous. Although different studies (2, 14, 15) do not recommend anticoagulation therapy in asymptomatic AD because of a high risk of bleeding, we started a long term anticoagulation also in the brother. We did so because according to Patnaik et al. individual thrombotic risk depends on

- family history,
- the presence of other thrombophilias,
- the subtype of AD with high incidence of thrombosis in relatives affected with a type “Budapest 3” mutation (11).

Our decision to anticoagulate also the asymptomatic brother was fortified by the early, perinatal appearance of thrombosis in the younger brother. For the parents we suggested an anticoagulation therapy in risk situations.

**Fig.**
Diagnosis of antithrombin deficiency in a newborn boy

- **a)** EEG on the 2nd day of life during focal epileptic seizure of the left arm with origin on the right site (C4).
- **b)** cranial ultrasound examination with cerebral infarction in the A. cerebri media territory
- **c)** Images described from the right: cranial MRI, diffusion sequence and T2w sequence with the cerebral infarction in the A. cerebri media territory. MR-angiography with thrombosis in the A. subclavia and the carotid bifurcation on the right site. Ultrasound examination of the right A. subclavia showing the thrombotic occlusion.
Conclusion

Antithrombin deficiency is a rare hereditary thrombophilia with a high risk of thrombosis. Thrombosis affects mainly veins and only in rare cases arterial territories. Therapy consists of primary and secondary anticoagulation and substitution of antithrombin concentrate.

Despite the absence of clinical symptoms in homozygous patients prophylactic long term anticoagulation must be discussed depending on familial history, additional and individual risk factors considering also the risk of bleeding.

Conflict of interest

MO, CB, and KK received financial support by several pharmaceutical companies producing coagulation factor concentrates, including Baxter, Bayer Health Care, Biotest, CSL Behring, Novo Nordisk, Octapharma and Plizer.

References