Stage 3:

Depending on the patient's history, the clinic and the results of the stages completed up to this point, further tests may be indicated, such as the following:

- Plasminogen activator inhibitor (PAI) activity per 1 citrate
- α2 antiplasmin activity
- Protein Z

Genetic analyses (declaration of consent) 1 EDTA

- PAI-1 gene polymorphism
- Factor V HR2 mutation (A4070G)
- Prothrombin mutation (A19911G)
- ACE (intron 16 deletion/insertion)
- tPA (intron h deletion/insertion)
- Factor VII activating protease (G511E)

Special cases:

1. In the case of an acute thromboembolic event, such as hepatic vein thrombosis in combination with haemolytic anaemia, thrombocytopenia and leukopenia, **paroxysmal nocturnal hemoglobinuria (PNH)** should be considered.

Mechanism: A somatic mutation in the hematopoietic stem cells in the phosphatidylinositol-glycan-A gene causes functional loss in GPI anchor. GPI anchor normally attaches regulator proteins to the blood cell membrane that inhibit the complement cascade. The mutation causes haemolysis via unregulated complement function and thrombophilia by activating the coagulation system.

Clinical suspicion of PNH: Haptoglobin ↓, bilirubin ↑, EDTA, serum flow cytometry: Absence of surface molecules, CD59, CD55 on erythrocytes, neutrophils, monocytes, thrombocytes

2. In the case of **thrombotic thrombocytopenic purpura (TTP)**, platelet-rich clots block the capillaries in the brain and kidneys and cause headache and mild damage to the kidneys. Other characteristics are fever, thrombocytopenia, and haemolytic anaemia with schistocytes in the blood count.

Mechanism: The ADAMTS13 protease splits off from the von Willebrand factor, which helps the blood platelets adhere to the damaged arterial wall. Inherited or acquiredADAMTS13 deficiency causes thrombophilia due to the impaired splitting of the von Willebrand factor.

Clinical suspicion of TTP: Full blood count with reticulocytes EDTA, serum, 2 citrate
Schistocytes +, haptoglobin ↓, bilirubin ↑, negative Coombs test, ADAMTS13 act., ADAMTS13 antigen and auto-act. against ADAMTS13

Contact:

Dr. med. Klaus-G. Heinze 030 - 77001 120

PATIENT INFORMATION

Handed out by:

Practice stamp

Please note that information regarding reimbursement is only valid for patients who are either members of German statutory or private health insurance.

For patients insured by the public health system:

Statutory insurance schemes may not cover some medical treatments at all, or not in certain cases (for example, if they are elective). Patients must therefore pay for them on their own.

For current prices, please see the request form for individual medical treatments.

For patients insured privately:

Costs will be covered by private health insurance according to a valid medical fee schedule, provided there has been no prior exclusion of benefits. Your physician will be happy to answer any questions you may have about this matter.

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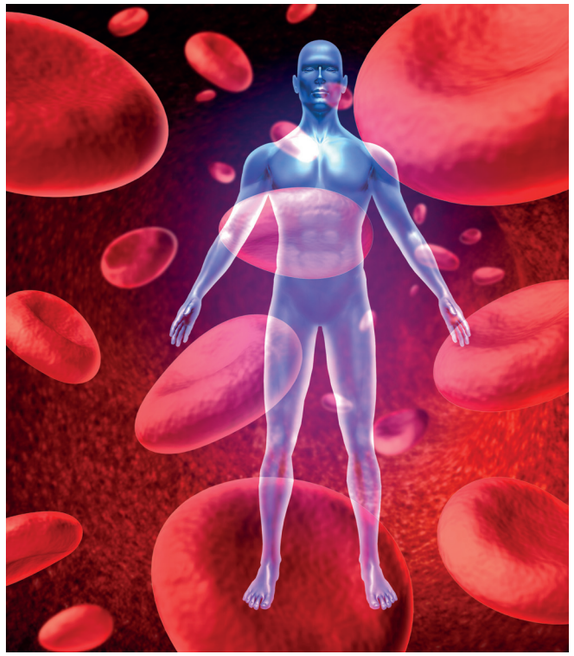
PATIENT INFORMATION

Thrombophilia

IMD Labor Berlin



The tendency toward increased blood clotting is called thrombophilia. It can be inherited or acquired; often, the two forms occur in combination (are „multifactorial"). After heart attacks, venous blood clots are one of the most common disorders of the cardiovascular system. In addition to the acute, often very painful closure of deep veins, injuries that are referred to collectively as „post-thrombotic syndrome" result. Common secondary diseases include everything from dysesthesias, pain and bleeding disorders to venous ulcers. Pulmonary artery occlusion is another serious and much-feared complication. Every year, some 40,000 people in Germany die from a pulmonary embolism.

Principles: Hemostasiology is „the study of how blood flow stops and becomes stuck". That was the way one of the forefathers of blood clot research, Rudolf Marx, described the processes of blood coagulation. The arrest of bleeding (hemostasis) is a complex system comprising not only vascular factors, blood platelets (thrombocytes) and plasmatic clotting factors but also antithrombotic and fibrinolytic (anticoagulant) factors that must be kept in balance. In the event of an injury, the arterioles contract, the platelets adhere to the endothelial defect, aggregate and cover the defect. They release procoagulant factors, and the activated plasmatic clotting factors form a clot that cushions the injury.

In what could be called a snowball effect, a composite of biochemical reactions occurs, passing from the formation of the prothrombin complex to thrombin, which splits fibrinogen into fibrin monomers. The fibrin monomers polymerise into fibrin and then form a stable complex amongst themselves, becoming a solid clot that occludes the defective site. At the same time, anti-thrombotic and fibrolytic factors that limit coagulation are activated, thus preventing thrombosis. If the balance between these two contrary processes is disturbed, the result is either haemorrhage or thrombophilia.

While patients may perceive heavy bleeding as a highly alarming symptom, they frequently view blood clots themselves as „nothing very dangerous". Often it is not until pain/limited movement increases that a „swollen leg" will motivate a patient to seek medical advice. However, early diagnosis with appropriate treatment can help to prevent complications that are sometimes life-threatening (a pulmonary embolism) or are chronic and severe (post-thrombotic syndrome, see above). Ideally, of course, the most desirable course of action against blood clotting is prevention (prophylaxis). In addition to the factors over which patients themselves have control (lack of exercise, body weight, smoking, medication use), other factors described below can also influence the assessment of embolism risk. These can be identified at our laboratory.

What are the risk factors for the formation of blood clots?

The following are the most common risk factors, either acquired or occurring in daily life:

- prolonged lying or sitting (e.g. at work, during a long flight or bus trip)
- Lack of movement following major operation
- Taking oral contraceptives („the pill") or undergoing hormone replacement therapy (oestrogens) during menopause and pregnancy
- Obesity, smoking
- Advanced age, poor general condition and malignant tumours.

There are also individual risk factors (acquired and hereditary changes in clotting and anticoagulant factors) that can be measured or identified in the blood.
An important consideration is that concomitant risk factors can reinforce one another and at times multiply their effect.
A variety of special laboratory tests of blood samples can investigate whether an elevated risk of thrombosis exists. Because the range of tests that may be applicable is very broad, we recommend employing staged diagnostics.

D-dimer 1 citrat

D-dimer is a key parameter to rule out an acute deep-vein thrombosis of the leg or pelvis or pulmonary embolism. The fact that it can be detected approximately four weeks after the end of a course of treatment with anticoagulants means that it can also be used to assess the risk of rethrombosis.

Stage 1:

Full blood count with reticulocytes, CRP, Quick, aPTT, fibrinogen, Lp(a), antithrombin activity (AT III), protein C activity, free protein S antigen, factor VIII activity, APC resistance, prothrombin mutation*, Phospholipid antibodies (lupus anticoagulant, cardiolipin antibodies, ß2 glycoprotein antibodies), homocysteine.

Materials: 1 serum, 2 EDTA and 3 citrate monovettes, 1 acidic citrate monovette (homocysteine), *patient's declaration of consent in accordance with the Genetic Diagnosis Act

Stage 2:

Result from Stage 1	Parameters	Material
In the event of pathological **APC resistance**	Faktor-V-Leiden-mutation	1 EDTA, Einwilligungserklärung
Primarily in cases of congenital **antithrombin deficiency**	Antithrombin concentration	1 Citrat
Primarily in cases of congenital **protein C deficiency**	Protein C-concentration	1 Citrat
Primarily in cases of congenital **protein S deficiency**	Combined Protein S-AG, Protein S-act.	2 Citrat
In case of antiphospholipid antibodies	Rheumatoid factors, anti-CCP- and -MCV-Ak, ANA, ENA-blot, ds-DNA, circulating immune complexes, C3c, C4	1 Serum
In case of **hyperhomocysteinemia**	Vitamin B12, holotranscobalamin, folic acid, Vitamin B6	1 Serum 2 EDTA
In case of **erythrocytosis,thrombocytosis**("polycythaemia")	JAK-2-mutation, erythropoetin	1 EDTA, 1Serum