Thrombophilia - cases

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Patient 1

Mr. J is a **20**-year-old college student who has been bothered by a sore leg for three days. Physical examination suggests venous thrombosis (VT); a Doppler study confirms the diagnosis. The resident who saw the patient reports that the patient is **healthy** and physically active; he plays soccer three to four times a week. He has no known medical problems. The patient is not aware of any family history of blood clots**. The resident was unable to identify any risk factors for VT**.

Is thrombophilia – testing indicated?

1. YES
2. NO

Which issues are important in thrombophilia-testing?

1. Severeness of the event
2. Age of the patiënt
3. Family history
4. Additional risk factors
5. Recurrent VTE
6. Male/Female

1. 2, 3 and 6
2. 1, 2, 3, 4, 5 and 6
3. 3, 5, 6
4. 1, 4, 5, 6

What is the reason to do thrombophilia investigation?

1. Different initial management
2. Different long-term management
3. Different treatment during pregnancy
4. Family screening

Answer:

C Pregnancy

B Long-term treatment (antithrombin deficiency/ antiphosholipid antibodies)

Table 1. Gene Variants Contributing to Venous Thrombosis Susceptibility (Thrombophilia)

Gene Variant	Prevalence (%)	Relative Risk (RR)
Factor V Leiden (FVL)	1-5	2-7
Prothrombin G20210A	1-4	3
Protein C deficiency	0.4	8
FVL and PT	0.1	20
Protein S deficiency	0.13	20
Antithrombin deficiency	0.2	50
FVL homozygote	0.02	22-80

Although the common gene variants FVL and PT increase risk for VT, they do not appear to increase the rate of **recurrent VT** significantly when they are present in the **heterozygous** state.

Back to the patient

Mr. J developed a VT at a **young age** and in the **absence of any known nongenetic risk factors**. From an epidemiological perspective, this presentation increases the likelihood of a significant genetic risk that, if found, would result in a recommendation for long-term anticoagulation — for example, an antithrombin deficiency or homozygous FVL?

→ **heterozygous FVL**

Guideline (1)

- Initiation and intensity of anticoagulant therapy following a diagnosis of acute venous thrombosis should be the same in patients with and without heritable thrombophilia (1B).
- Indiscriminate testing for heritable thrombophilias in unselected patients presenting with a first episode of venous thrombosis is not indicated (1B).

Guideline (2)

- Decisions regarding duration of anticoagulation (lifelong or not) in unselected patients should be made with reference to whether or not a first episode of venous thrombosis was provoked or not, other risk factors, and risk of anticoagulant therapy-related bleeding, **regardless of whether a heritable thrombophilia is known** (1B).

Guideline (3)

- Testing for heritable thrombophilias in selected patients, such as those with a strong family history of unprovoked recurrent thrombosis, may influence decisions regarding duration of anticoagulation (C). It is not possible to give a validated recommendation as to how such patients should be selected.

Patient 2 ♂ 1950

Recurrent venous thrombosis
(4 times):
FVL heterozygous
Life-long anticoagulation

Question:
Should my daughter (18) be tested for FVL?
Yes/ No?

UMC St Radboud

Should my daughter (18) be tested for FVL?

1. YES
2. NO

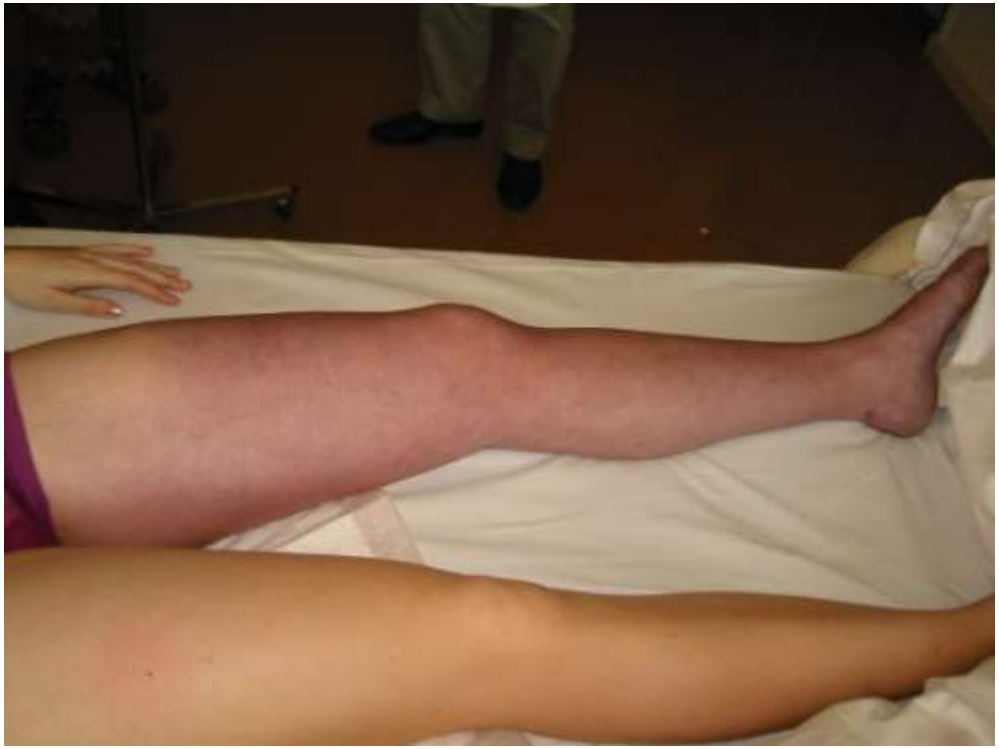
But can she use birth-control pills?

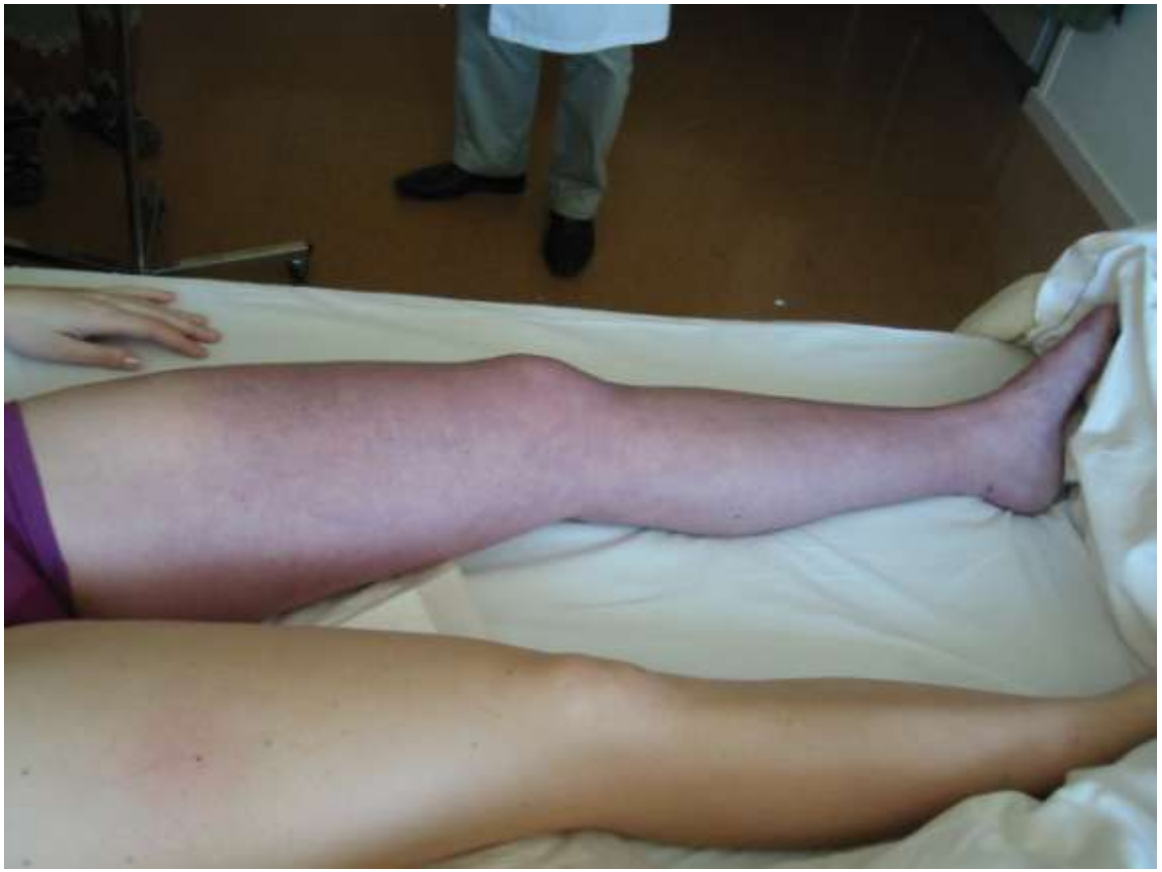
1. YES
2. NO

Daughter, 21 years

Painful red swollen leg – progressive

Phlegmasia cerulea dolens!





Daughter

Severe post-thrombotic syndrome

Uses elastic stockings (life-long)

FVL positive

Patient 3 ♀ 1974

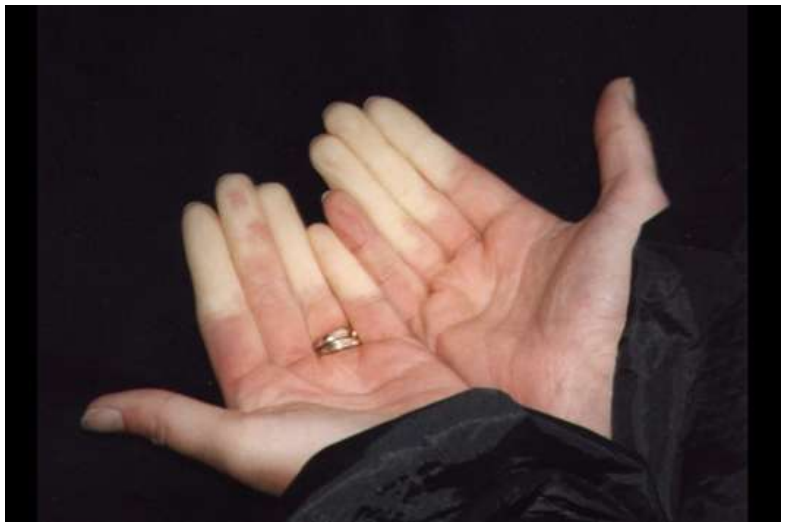
2009

Arthralgia

Raynauds- phenomenon

Rheumatologist:

No abnormalities



2010

Deep venous thrombosis after pregnancy

Family history –

Is thrombophilia research indicated?

1. YES
2. NO

Why?

Which thrombophilia-investigations would you ask for?

1. All, including homocystein
2. Only FVL
3. Only protein C/S, antithrombin deficiency
4. Antiphospholipid antibodies

DVT after risk factor (=pregnancy):
no indication for thrombophilia investigation.

But: Miscarriage in history/ Arthralgia / Raynaud:

Antiphospholipid antibodies

Results:

Anticardiolipin IgM en IgG positive

Lupus anticoagulans positive

Anti β 2 glycoprotein positive

:

Primary Antiphospholipid syndrome

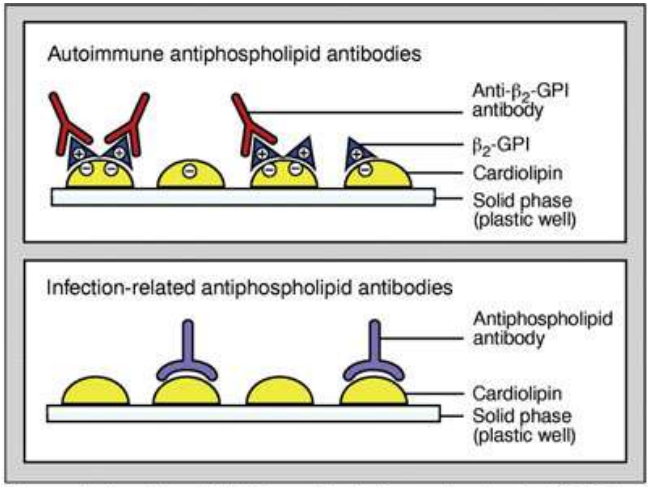


Figure 1. Antiphospholipid antibody determination by ELISA. Reprinted with permission from Reference 1.

Antiphospholipid syndrome:

Primary

Secondary (SLE)

Definition:

Positive antiphopholipid antibodies 2 times with an interval of 12 weeks.

A venous or arterial thrombotic event

Or

Pregnancy complications

Treatment:

After 1 event at least one year -

Life-long anticoagulation

Patient 3:

Recent 2nd pregnancy:

Succesfull treatment with low molecular weight heparin in therapeutic dose.

Patient 4 ♂ 1969

On holiday in Germany:

Fever

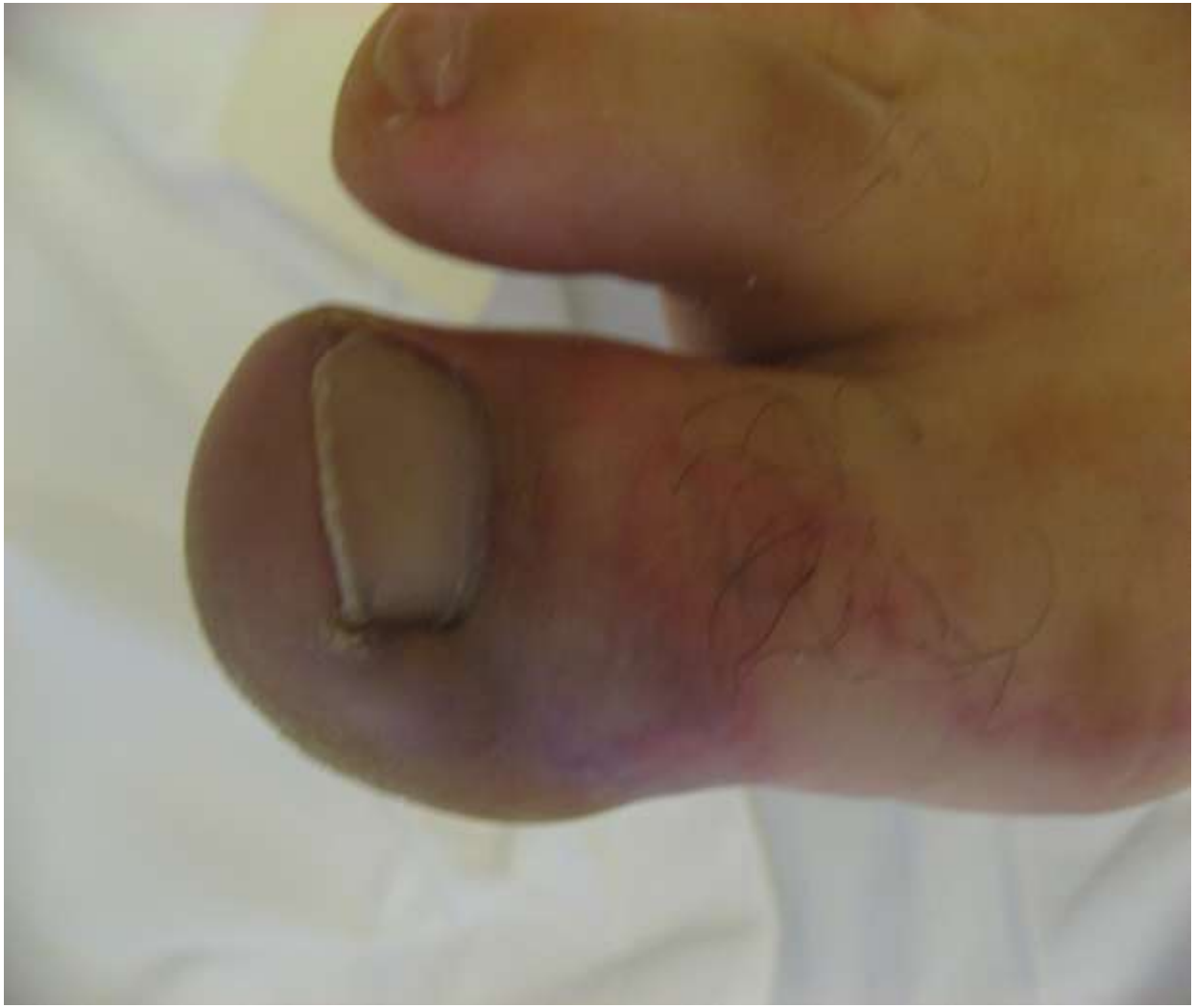
Blue toe

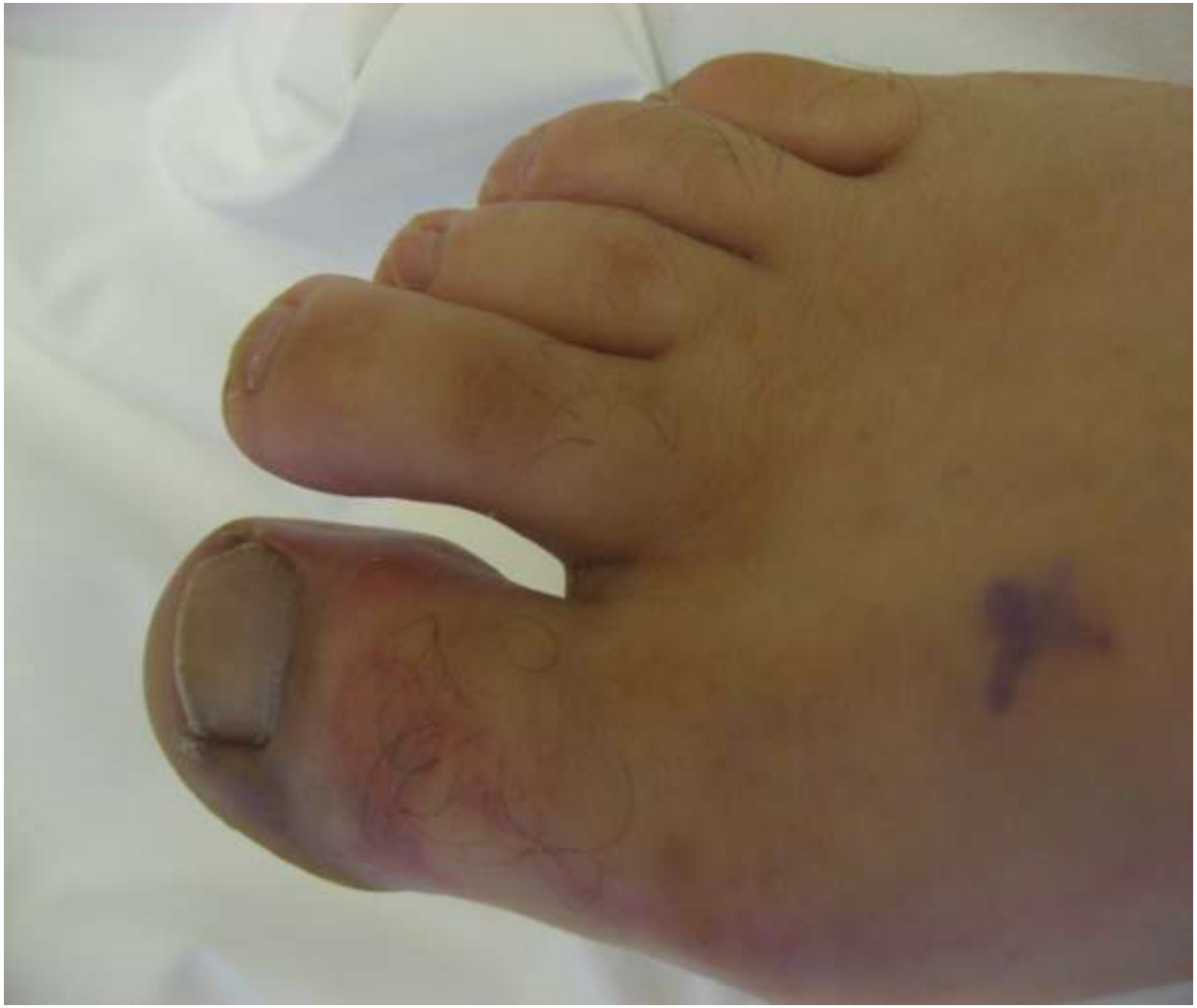
More pain

Loss of sensibility of the legs

Lab:

Anemia, Thomb 40, CK 1000





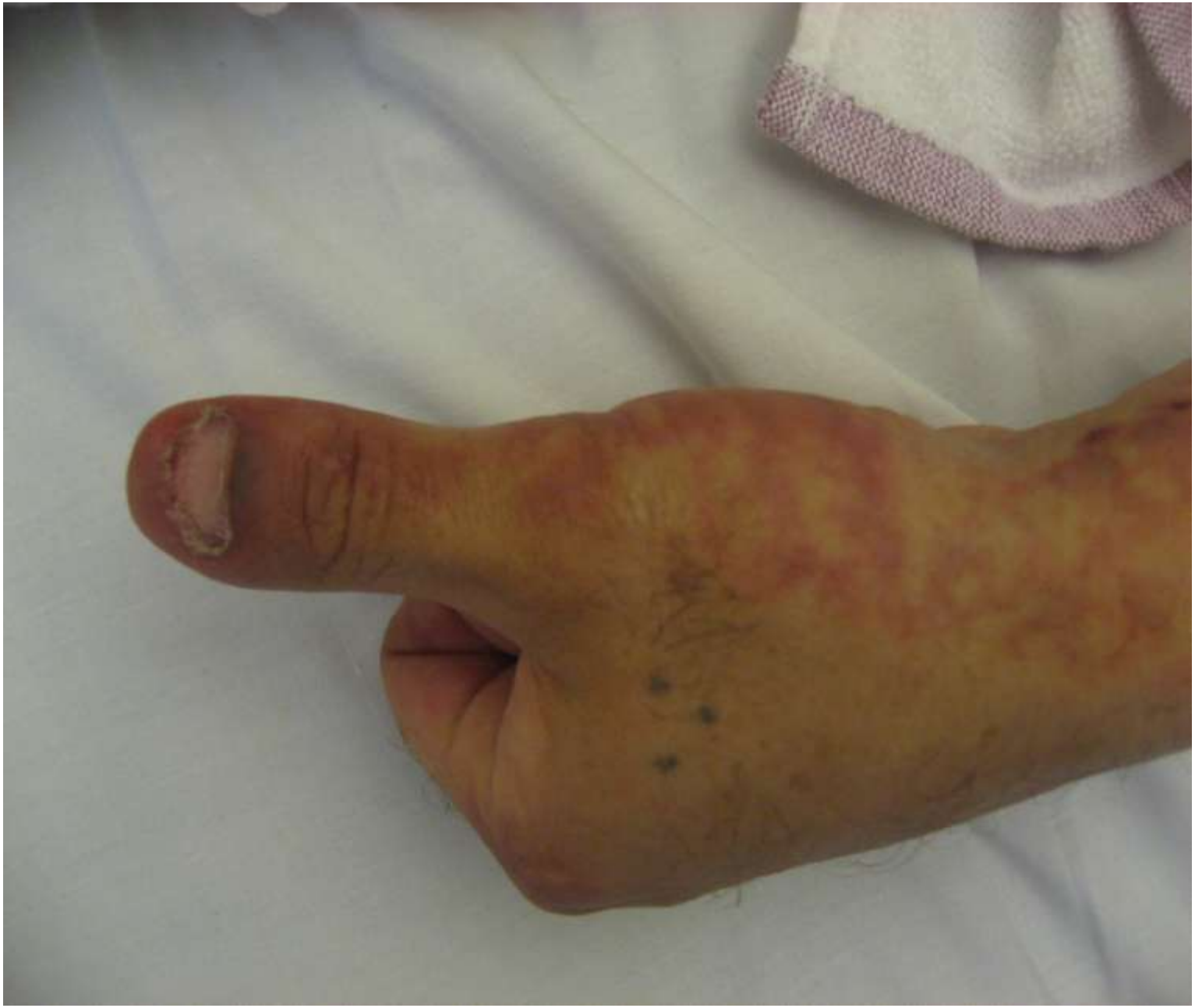
Arterial thombosis of the leg:

Heparin
Thrombolysis
Thrombectomy

Amputation of the lower leg

After that:

Pain in both hands and purple coloring of the fingers.



Angiography:

Massive thrombosis aortic arch- distal aorta !

What is your differential diagnosis?

Differential diagnosis:

(Cholesterol)- emboli

Tromboangiitis obliterans (M Buerger)

Vasculitis

Cryoglobulinemia

Antifosfolipid-syndrome

HUS / TTP

Infectious?

Diagnosis:

Catastrophic antiphopholipid syndrome

Treatment:

Plasmapheresis

Prednisone

Patient 5 ♀ 1974

2005 miscarriage

2006 pre-eclampsia

2006 spontaneous delivery

2 months after delivery:

Acute arterial occlusion of the right leg:

Embolectomy/ heparin/ vitamin K antagonist

Indication for thrombophilia-testing?

Young

Female

Miscarriage

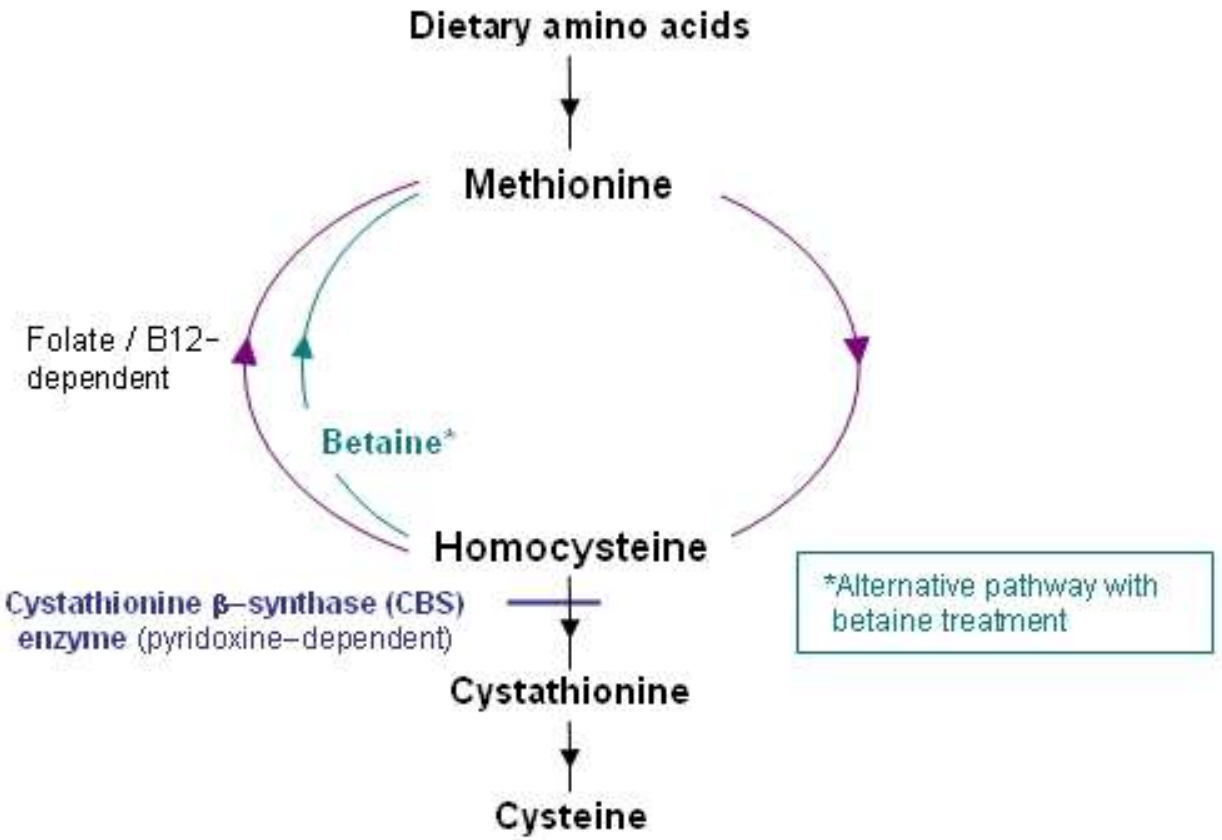
Arterial thrombosis

(after risk factor = delivery)

We performed complete thrombophilia-testing:

Homocysteine 300 µmol/L!

Classical Homocystinuria!



Classical Homocystinuria

Scoliosis

Myopia: lensluxations!

Treatment:

Vitamin B 6

Folic Acid

Acetylsalicyc acid

Homocystein levels ± 20 µmol/L

Patient 6 ♂ 30 years old

Cerebral infarction

Young stroke protocol:

Bloodpressure OK
Lipids OK
No overweight
No smoking

Indication for thrombophilia – testing ?

??????

Homozygous prothrombin-mutation!

Patient 6

Echocardiogram + contrast:

Normal

2 younger brothers. Should they be tested?

1. YES
2. NO

General Practitionar:

Both also homozygous!

What's your advice?

Literature (case-reports):

1 review of case reports:

N=36

10 asymptomatic

12 symptoms in cominbinations with another risk factor

14 thrombotic event

Another study:

OR **208** voor ischemic stroke!

Advice?

No preventive anticoagulation

Control and treatment of classical risk factors if necessary