Hypercoagulable states

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Phlebology Course, 2007

Venous thromboembolism

- Incidence 1-2:1000
  age dependent
  - 20s 1:10,000
  - 50s 1:1000
  - 80s >1:100
- Mean age 1st VTE event 62 years

Venous thromboembolic disease

- Presentations
  - Superficial thrombophlebitis
  - Deep venous thrombosis
  - Pulmonary embolism, sudden death
  - Post-thrombotic syndrome
  - Pulmonary hypertension

VTE Aetiology

- Acquired
- Hereditary
- Multifactorial
  Interplay of genetic & environmental influences

Acquired – risk factors

General

- Age
- Immobilisation >3days
- Pregnancy and postpartum
- Major surgery previous 4 wks
- Long plane or car trips(<4h) in prev 4wks

risk factors

Medical

- Cancer
- Previous DVT
- Stroke
- AMI
- CHF
- Sepsis, nephrotic syn, ulcerative colitis

Trauma

- Multiple trauma
- CNS/spinal injury
- Burns
- Lower extremity fractures

Vasculitis

- SLE and lupus anticoagulant
- Behcet syndrome
- homocystinuria

Haematologic

- Polycythaemia rubra vera
- Thrombocytosis
- Inherited disorders of coagulation
- Antithrombin III, protein C, S deficiency
- Dysfibrinogenaemias and disorders of plasminogen activation

Drugs/medications

- IV drug abuse
- Oral contraceptives
- Oestrogens
- tamoxifen
- Heparin-induced thrombocytopenia

Oral Contraceptives and VTE

- Low dose *(30-40microg ethinylestradiol)* assoc with increase risk 3-6x
- Risk highest if 1st year of use
- Absolute risk 3-4 per 10,000 person years cf 1 per 10,000 in nonusers
- HRT assoc with 2-4x increased risk, probably not significant after 1 year

Influence of Progestins

- Higher risk with 3rd generation progestins *desogestrel, gestodene* cf 2nd generation *levonorgestrel, norgestrel*
- Progestin only OC have lower risk than combined OC

Inherited thrombophilia

Common

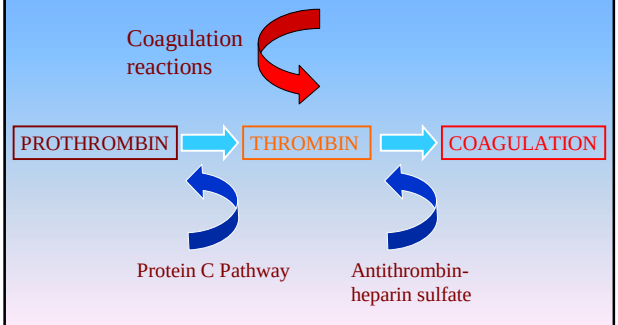
1. Mutation in factor V gene (factor V Leiden)
2. Mutation in prothrombin (FII) gene
3. Homozygous methyltetrahydrofolate reductase (MTHFR) gene mutation

Frequency of Inherited Thrombophilias

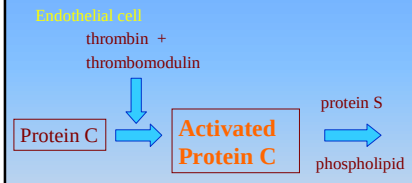
Risk factor	Prevalence in general population %	Prevalence in DVT pts %	Relative risk of DVT
Factor V Leiden	5*	20	7
Prothrombin G20210A	2*	6	3
Protein C deficiency	0.2-0.4	3	7
Protein S deficiency	0.7	2	10
Antithrombin deficiency	0.02	1	5
homocystinuria	1:335,000	<0.1	2.5

*very rare in Asians and Africans

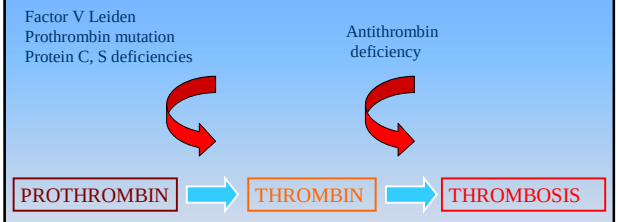
Normal control of coagulation



Protein C Pathway



Mechanisms of Thrombosis



Factor V Leiden

- Factor V protein resistant to inactivation by APC
- Single base substitution – adenine for guanine at position 1691 in the factor V gene
- Translated protein has AA glutamine instead of arginine at residue 506
- 506 is the 1st of 3 sites of cleavage by APC
- *In vitro* - Failure of activated protein C to prolong the aPTT (APC resistance)

Factor V Leiden

- Accounts for 95% genetic abnormalities in APC resistance
- Found in 20% VTE pts, 5% general population
- VTE risk in carriers variable, prevalence of 13-25%, RR 5-10X (much higher if coinherit other thrombophilias)
- 2/3s VTE associated with an environmental precipitant

- **Acquired APC resistance**
  - Pregnancy
  - OCP
  - Elevated factor VIII
  - APL syndrome
  - Oral anticoagulants
  - Anti-protein C antibodies
  - stroke

Prothrombin G20210A

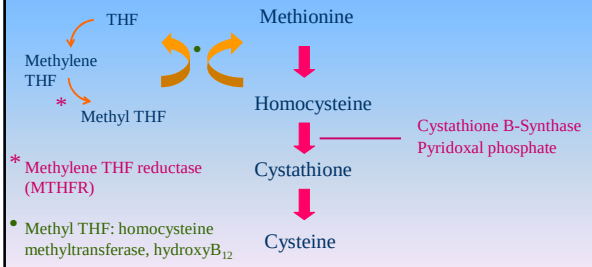
- Adenine substitution for guanine at nucleotide position 20210
- Increased prothombin levels
- ?altered processing of mRNA
- Found in 6% pts with VTE, 2% healthy subjects

Hyperhomocysteinaemia

- Genetic and acquired forms
- Arterial & venous thrombosis
- Increases VTE risk in pts with the common inherited thrombophilias

Transsulfuration Pathway

- Transfer of sulfur atom from methionine to cysteine



Hyperhomocysteinaemia

- Acquired causes
  - Folate, B12, B6 deficiency
  - Renal failure
  - Hypothyroidism
  - Increasing age
  - Smoking
  - Tx: folic acid supplement, plus B6 and B12 if normal homocysteine levels not achieved

C677T MTHFR gene mutation

- Thermolabile variant of MTHFR with reduced activity
- 5-15% of caucasians, East Asians
- Mild hyperhomocysteinaemia in persons with folate deficient diet
- ?risk factor for VTE

Thrombophilia - hereditary

Consider when:

- No acquired risk factors for VTE*
- Unusual site – cerebral, visceral, axillary+
- Family history VTE
- <45-50yo
- Female with multiple miscarriages, stillbirths

*>50% associated with known acquired risk factor

+Most present with DVT of legs and/or PE

Thrombophilia Panel

- Antithrombin activity
- Protein C, S activity
- Activated protein C resistance or factor V Leiden
- Prothrombin gene mutation
- Homocysteine levels
- Anticardiolipin Ab, lupus anticoagulant
- Factor VIII activity

Thrombophilia screen

First line tests *Seligsohn, NEJM 2001*

- Activated protein C resistance
- Factor V mutation
- G20210A prothrombin mutation
- Homocysteine level
- Factor VIII level
- Lupus anticoagulant

Intermediate priority

- Protein C activity, protein S Ag
- Antithrombin activity
- Anticardiolipin antibody titres

Low priority

- Dysfibrinogenaemia (normal-low fibrinogen level and prolonged thrombin time)
- Increased fibrinogen
- Increased factor IX, XI activity
- MTHFR C677T mutation

False positives

- Thrombosis – low antithrombin levels, elevated factor VIII
- Heparin – low antithrombin levels
- Warfarin – low protein C, S
- Increased factor VIII – acute phase response, stress, pregnancy, oral contraceptive, older age

Decreased protein C, S levels

- Vit K deficiency
- Liver disease
- warfarin
- DIC
- Acute phase response (protein S)
- Factor V Leiden interferes with coagulation assays of C and S