Factor V Leiden

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Introduction

Venous thromboembolism is a major cause of morbidity and mortality with an incidence of about 1 per 1000 per year [1]. Predisposing factors can be either genetic or acquired. Acquired risk factors are surgery, immobilisation, malignancy, oral contraceptives, pregnancy and puerperium [2].

Until 1993, a specific genetic defect could be identified in only 10–15% of affected subjects [3]. These defects included deficiencies of protein C, protein S and antithrombin [4]. Protein C is an important inhibitor of the clotting system, which inactivates cofactors Va and VIIIa [5, 6]. Both these cofactors accelerate the production of thrombin which converts soluble fibrinogen into insoluble fibrin.

Inherited resistance to activated protein C (APC resistance), first described in 1993 by Dahlbäck [7] (see article by A. Hillarp and B. Dahlbäck, ***Vessels***, this issue), is the result of an abnormal factor V molecule, (FV^{R506Q}, FV Leiden) which turned out to be the most common known cause of inherited thrombophilia [8–12].

Molecular genetics of Factor V Leiden

APC resistance is strongly associated with a single point mutation (1,691 G→A transition) in exon 10 of the factor V gene (mapped to chromosome 1 (1q21–25)). This mutation predicts the replacement of Arg-506 (CGA) by Gln (CAA) in the factor V molecule which results in FV^{R506Q} or FV Leiden (Fig 1). Normally, Arg-506–Gly-507 is one of the cleavage sites for APC, so replacement of Arg-506 results in an inadequate inactivation by APC (APC resistance) of the mutated Factor V molecule which causes an increased tendency to develop thrombosis [12]. This explains APC resistance in vitro, for the activated thromboplastin time (APTT) is affected by factor Va and the rate of its inactivation by APC. When APC is added to plasma, it leads to a prolongation of the APTT. In the presence of mutated factor V, this prolongation of the APTT after administration of APC is much reduced [7]. This is expressed as the APC sensitivity ratio, i.e. the ratio of the APTTs before and after APC being added to the plasma.

Inherited APC resistance is an autosomal dominant trait [9, 10]. This implies that on average, 50% of the

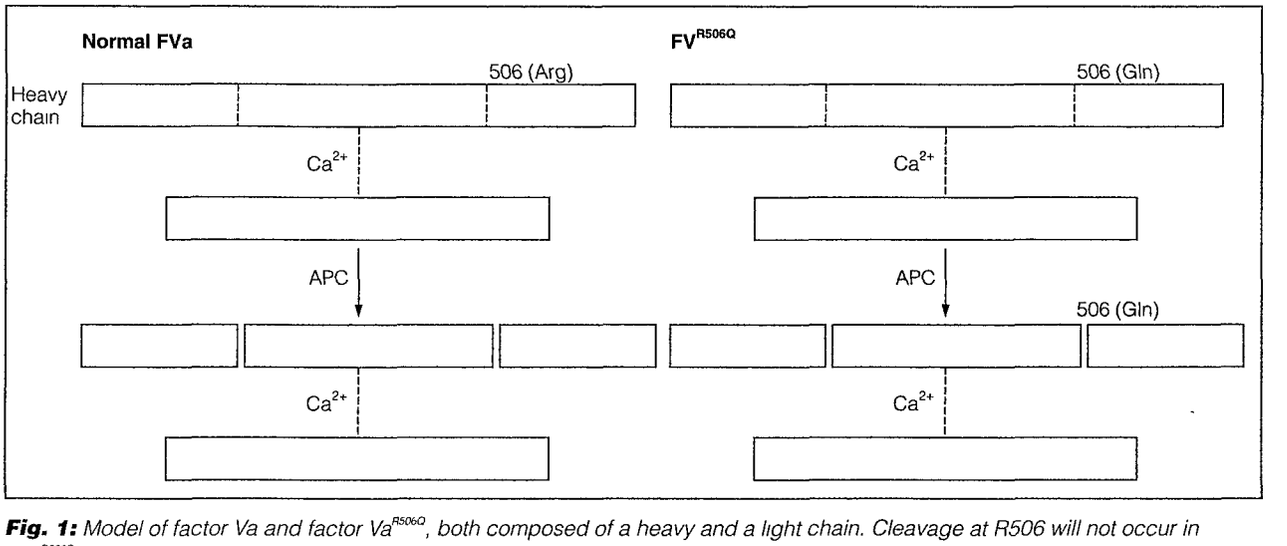

Fig. 1: *Model of factor Va and factor Va^{R506Q}, both composed of a heavy and a light chain. Cleavage at R506 will not occur in FVa^{R506Q} which results in a reduced inactivation of the molecule APC = activated protein C.*

siblings, children and parents of a heterozygous carrier of FV Leiden also carry the mutation, and will be APC resistant.

Epidemiology of Factor V Leiden

In a case–control study of 474 unselected consecutive patients with a first deep venous thrombosis (Leiden Thrombophilia Study, LETS), 14 of the 474 healthy controls (3%) were heterozygous carriers of the FV Leiden mutation. This is about ten times the prevalence of protein C deficiency, protein S deficiency and antithrombin deficiency combined. Others have reported prevalences among healthy individuals ranging between 0 and 15%. This wide range can be explained to some extent by the mode of selection, but there can be little doubt that there are true racial and probably regional differences. The highest prevalence has been found in Caucasians in Europe and Northern America and the lowest in Asia and Africa [13]. Within Europe, higher prevalences have been reported in Northern Europe than in Southern Europe with the exception of some clusters of FV Leiden in Greek Cypriots and Alsatians [14] (13.3% and 9.6%, respectively, of healthy controls) (Table I)

Among patients with venous thrombosis, the estimated prevalence of FV Leiden ranges from 20% of unselected patients from the LETS study to 50% of selected symptomatic individuals from families referred because of unexplained familial thrombophilia [9, 10]. Again, this far exceeds the prevalence of the other forms of inherited thrombophilia in patients with venous thrombosis. The prevalence of (heterozygous) deficiencies of protein C, protein S and antithrombin is about 3% in unselected consecutive patients and 10–15% in selected symptomatic individuals from thrombophilia families [15–17]

Risk of venous thrombosis

The LETS case–control study, and other studies have demonstrated that, as for protein C deficiency, heterozygous carriers of FV Leiden mutation have a seven- to 10-fold increased risk of venous thrombosis. The risk of thrombosis for homozygous carriers is increased by about 100-fold compared with non-carriers (Table II) [18]. Ridker et al. performed a cohort study and found an overall risk ratio of 2.7, which, after restriction to individuals of 60 years and older, increased to 7.0 [19].

Several studies demonstrate that the probability of being free of venous thrombosis in thrombophilia-families with FV Leiden was significantly reduced in carriers. At the age of 50 years, about 25% of the carriers had experienced at least one thrombotic event (compared with about 5% for 50-year-old non-carriers (Fig. 2)) [10, 20]. Higher risks were found in thrombophilia families with protein C deficiency; these families however, were included by more selective inclusion criteria [21].

This variation in prevalence and risk demonstrates the role of the selection of individuals. Many studies have been performed using different inclusion criteria (e.g. patients with a young age of onset, with experience of recurrences, with thrombotic events in the absence of main risk factors, with a positive family history, unselected consecutive patients etc.) yielding different kinds of information. We recently compared the

Table I: *Prevalence of FV^{R506Q} among healthy individuals.*

Region	Prevalence of FV^{R506Q} among healthy individuals (%)
Africa	0
Asia	0–1.1
Brazil	2.0
Northern Europe	3.4–7 9
Southern Europe	0.6–2.9
USA	6.0–7.6

Table II: *FV^{R506Q} and protein C deficiency in unselected patients and controls [16,18, 22, 35].*

	Protein C deficiency	FV^{R506Q}
Relative risk	>7.0	>7.0
Prevalence in controls	0.4%	5%
Prevalence in patients	3%	20%
Age of onset (years)	47	43

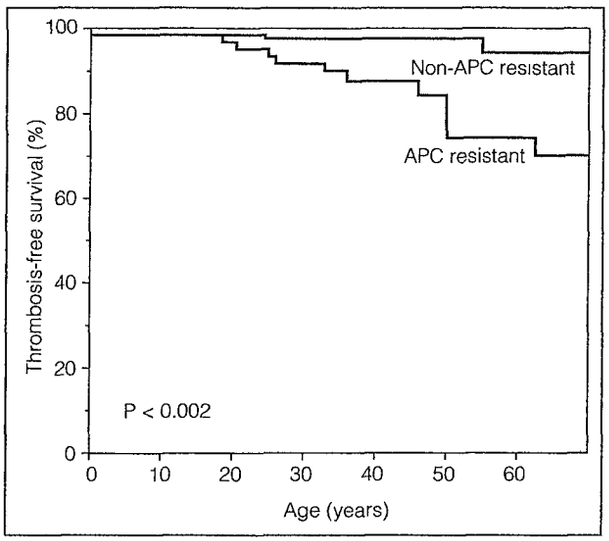

Fig. 2: *Thrombosis-free survival in people with activated protein C (APC) resistance and normal relatives. Differences between affected and non-affected individuals were highly significant. (Reprinted with permission; NEJM 1994, 330: 517–22.).*

thrombotic tendency of FV Leiden and protein C deficiency – defined as the median age of the first thrombotic event – in unselected patients from the LETS study and in selected family members of patients who were referred for thrombophilia work-up (Fig. 3). The median age at the first thrombosis in the unselected symptomatic carriers of FV Leiden from the LETS study was 43 years (range 16–69 years) and for unselected protein C deficient patients 47 years (range 19–63 years). In thrombophilia families the median age of onset for selected symptomatic relatives (no probandi) with FV Leiden was 29 years (range 15–74 years), and for selected symptomatic relatives with protein C deficiency 35 years (range 17–67 years) [22]. This suggests that the overall thrombotic risk is similar in carriers of FV Leiden and carriers of protein C deficiency and that the median age of onset mainly depends on the way patients are identified.

Combinations of gene defects, such as FV Leiden and protein C deficiency, FV Leiden and protein S deficiency or FV Leiden and antithrombin deficiency, each result in a higher risk than for the single defect. In families in which protein C deficiency and FV Leiden cosegregated, the lifetime risk of thrombosis was 31% for carriers of only protein C deficiency, 13% for carriers of only FV Leiden and 73% for those with the combined defect [23]. In families with cosegregation of protein S deficiency and FV Leiden, the lifetime risk of thrombosis was 19% for carriers of only protein S deficiency, 19% for carriers of only FV Leiden and 72% for those with both defects [24]. Another study confirmed the high risk for this combined defect [25]. In families in which antithrombin deficiency cosegregated with FV Leiden, lifetime risk of thrombosis was 50% for carriers of only antithrombin deficiency, 20% for carriers of only FV Leiden and 92% for those with both defects [26].

A synergistic gene–environmental effect has been demonstrated for carrying FV Leiden and the use of oral contraceptives. Within the LETS study, 155 premenopausal female cases and 169 premenopausal female controls were investigated. The risk of venous thrombosis for users of oral contraceptives was increased four-fold while this risk among carriers of FV Leiden was increased eight-fold. Compared with non-affected non-users, the relative risk of venous thrombosis in carriers of FV Leiden who used oral contraceptives was increased 30-fold (relative risk: 34.7; 95% C.I., 7.8–154) [27]. This synergistic effect stood out

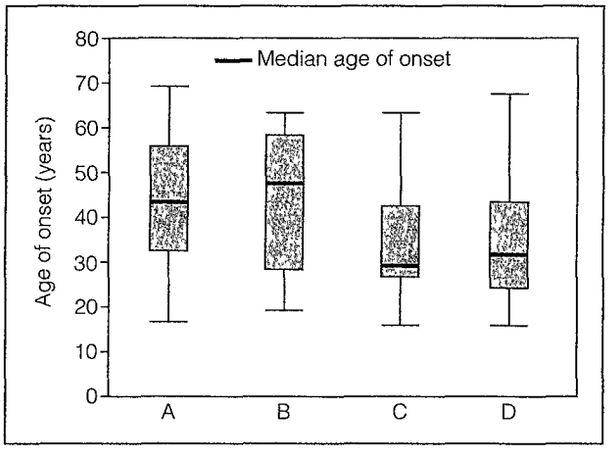

Fig. 3: *Boxplot of age at the first venous thrombotic event according to genetic defect in the four main groups. It shows the range (horizontal lines at the end of the boxes) and median age of onset (horizontal lines inside the boxes). The upper and lower boundaries are the 25th and 75th percentiles. Individuals with combined defects were excluded*

A: unselected patients from the LETS case–control study with FV^{R506Q}.

B: unselected patients from the LETS case–control study with protein C deficiency.

C: selected patients from thrombophilia families with FV^{R506Q}.

D: selected patients from thrombophilia families with protein C deficiency

most clearly for so-called third generation oral contraceptives – those containing the progestogens desogestrel and gestodene [28]

Arterial thrombosis

Some studies have demonstrated an association between the presence of FV Leiden and coronary heart disease [29], though others have failed to show this [30] This inconsistency may be the result of different modes of selection of patients Regarding the high prevalence of the FV Leiden mutation and the high prevalence of arterial thrombosis, it is important to assess a possible association between the two In 1994, Holm et al showed an association of myocardial infarction and homozygosity of FV Leiden in two young women [31] In a population-based case–control study in Seattle, 472 women (84 cases with a first myocardial infarction and 388 controls) were tested for the presence of FV Leiden When adjusted for major myocardial risk factors FV Leiden lead to a four-fold increased risk of myocardial infarction (95% C I , 1 2–12 1) [32] This suggests that FV Leiden is a risk factor for arterial disease in young women but not in (older) men

Pregnancy and foetal loss

FV Leiden strongly increases the risk of venous thrombosis in pregnancy In one study, 60% of women with thrombosis in pregnancy carried the FV Leiden mutation [33] Carriers of FV Leiden have an increased risk of foetal loss (miscarriage or stillbirth) Preston et al demonstrated that the risk for stillbirth in pregnant carriers of FV Leiden was increased two-fold (95% C I , 0 5–7 7) (the odds ratio for miscarriages in carriers was 0 9, 95% C I , 0 5 –1 5) [34]

Conclusion

Given the high prevalence of FV Leiden among healthy individuals (~5%) it is unlikely that APC resistance in itself is sufficient to cause thrombosis [35] Important to clinicians is the question of which prophylactic and diagnostic measures are advisable for patients with FV Leiden and their relatives, especially when they are exposed to other major risk factors such as surgery, immobilisation, pregnancy or use of oral contraceptives Unfortunately very few data are available on which to base such guidelines [17] Most centres will avoid lifelong treatment with oral anticoagulants for asymptomatic carriers Treatment with anticoagulants after a first venous thrombosis will usually be temporary but duration of this treatment may also depend on the severity of the thrombotic event, positive family history and other individual factors In general, recurrence of a thrombotic event will result in lifelong therapy with anticoagulants Surgery and immobilisation will, of course require adequate anticoagulant prophylaxis

Before APC resistance was described by Dahlback in 1993, few patients were diagnosed with hereditary thrombophilia Considering the fact that the prevalence of FV Leiden is at least 10-fold higher than the prevalence of other known genetic deficiencies together, this affects many patients and new studies are needed to arrive at a rational clinical management policy for these patients

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