Apparent different thrombotic tendency in patients with factor V Leiden and protein C deficiency due to selection of patients

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Apparent Different Thrombotic Tendency in Patients With Factor V Leiden and Protein C Deficiency Due to Selection of Patients

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Both activated protein C (APC) resistance and protein C deficiency are associated with an increased risk for venous thrombosis. To assess their tendencies to venous thrombosis, we compared the median age of first venous thromboembolism in patients with factor V Leiden or protein C deficiency, who were identified either within unselected consecutive cases with a first deep venous thrombosis derived from a population-based case-control study, or identified by selection of patients with a deep venous thrombosis, who were referred for thrombophilia work-up. The median age of onset for 92 unselected APC resistant cases was 43 years and for 13 unselected protein C–deficient cases 47 years. The median age at the first thrombotic event for 28 APC-resistant members of thrombophilia families was 29 years and for 50 protein C–deficient members of thrombophilia families 31.5 years. The median age of onset for all unselected patients (n = 105) was 45 years of age (range, 16 to 69 years) and the median age of onset for all selected patients from the thrombophilia families (n = 78) was 30.5 years (range, 16 to 67 years) These results show that within the case-control study and the family studies, the median age of onset is very similar in patients with APC resistance and patients with protein C deficiency This suggests that APC resistance is not less severe with respect to risk of thrombosis than (heterozygous) protein C deficiency. In conclusion, the median age at which the first thrombosis occurs mainly depends on the way the patients are identified and not on the type of thrombophilia

PROTEIN C is an important inhibitor of the clotting system that inactivates the coagulation cofactors Va and VIIIa [1] In familial resistance to activated protein C (APC resistance) and in protein C deficiency, factor Va is not properly inactivated by APC APC resistance is associated with a mutation in the factor V gene, which predicts the synthesis of an abnormal factor V molecule (FV Leiden) [2,4] In protein C deficiency, the occurrence of thrombosis is directly related to the reduced level of functional protein C Heterozygotes of factor V Leiden or protein C deficiency have a 5- to 10-fold increased risk of venous thrombosis [5,6]

APC resistance has the highest prevalence of the thrombophilia disorders (20% of unselected thromboembolic patients, 50% of individuals with thrombophilia, and 3% to 5% of healthy individuals) [2,5] Therefore, the clinical management (ie, treatment and prophylactic measures for patients with protein C deficiency or factor V Leiden and their relatives) will affect many individuals Even though specific studies into the management of APC resistance are presently unavailable, clinicians seek optimal care for their patients A first approach might be to adopt a similar policy as for protein C deficiency This may be valid, unless APC resistance has a different clinical presentation, for instance a less pronounced thrombotic risk, as has been suggested [7]

To obtain a first assessment of the thrombotic tendency in APC-resistant individuals, we compared protein C–deficient patients and APC-resistant patients with regard to the age at which the first thrombotic event occurred We hypothesized that selection of patients will play an important role To assess this role of selection in the presentation of the first thrombotic event (ie, deep venous thrombosis), we compared a series of unselected consecutive patients from a population-based case-control study with a group of selected patients who had been referred for hitherto unexplained familial thrombophilia

MATERIALS AND METHODS

The first group of patients (unselected patients) was derived from a population based case control study on venous thrombosis, the Leiden Thrombophilia Study (LETS) [5,6] These cases were 471 consecutive patients younger than 70 years, with a first, objectively confirmed episode of deep vein thrombosis and free of underlying malignancy APC resistance was detected (presence of factor V Leiden) in 92 cases (84 heterozygotes and eight homozygotes) Protein C deficiency, confirmed by the identification of a protein C gene mutation, was detected in 13 cases (all heterozygotes) None of the cases carried both gene defects, so there were 366 noncarriers

The second group of patients (selected patients) originates from two large panels of patients with a first deep venous thrombosis, recruited from patients who were referred to our center for diagnostic work up for venous thrombophilia These were patients with a positive family history of thrombosis and patients who had experienced a thrombotic event before the age of 40 years in the absence of precipitating conditions The first panel, collected by Engesser et al,[8] consisted of 113 probandi In several of these probandi, mutations leading to protein C deficiency (and protein S deficiency, antithrombin deficiency) and later APC resistance were identified From this panel, 12 APC resistant probandi were randomly selected, and of these probandi, we tested 88 family members for the presence of factor V Leiden [9] The second panel, collected by Allaart et al,[9] consisted of 80 protein C–deficient probandi From this panel, 24 protein C–deficient probandi were randomly selected, and of these probandi, we tested 153 family members for the presence of the protein C gene mutation private to a particular family [9] In the families of these 36 APC-resistant or protein C–deficient probandi, we investigated siblings, children, and parents of the proband plus sib lings of the affected parent of the proband Family members over 70 years of age and family members with underlying malignancy were excluded for practical purposes

For the two groups unselected, consecutive patients with factor V Leiden or protein C deficiency from a population-based case

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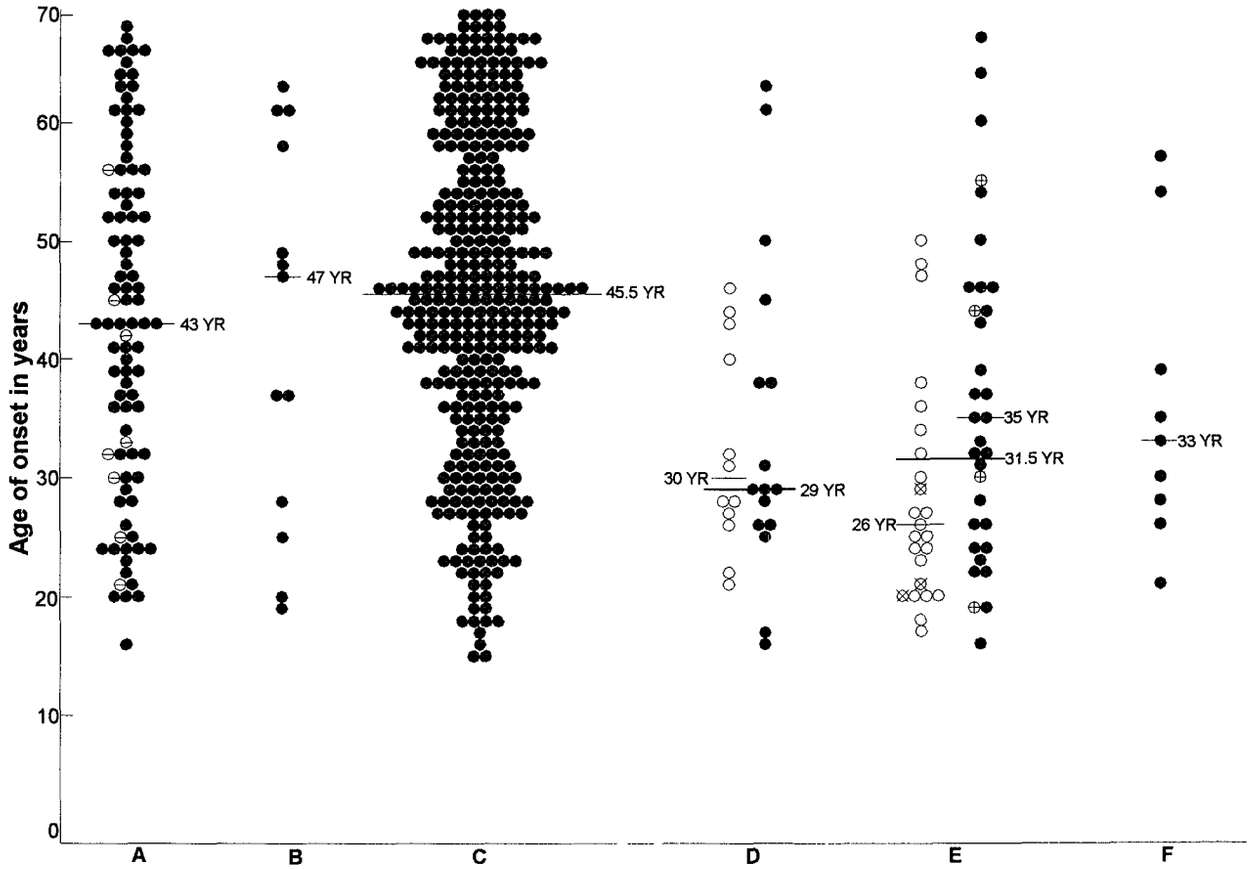

Fig 1. Age at first venous thrombotic event of all unselected (LETS) cases and of patients from 36 selected thrombophilia families. The horizontal lines represent the median ages of onset. The bold horizontal lines represent the median ages of onset of the probandi and their relatives together in families with APC resistance or protein C deficiency. For the protein C deficiency families, the median age of onset was calculated without the seven probandi and relatives who carried both defects. (A) LETS cases, APC-resistant (n = 92). (⊖), homozygous; (●), heterozygous. (B) LETS cases, Protein C (PC)–deficient (n = 13). (C) LETS cases, noncarriers (n = 366). (D) APC-resistant families, APC resistant relatives (n = 28). (○), proband. (E) PC–deficient families, PC–deficient relatives (n = 57). (○), proband; (⊗), APC-resistant and PC-deficient proband; (●), PC-deficient relative; (⊕), APC-resistant and PC-deficient relative. (F) APC resistance and PC deficiency families, noncarriers (n = 9).

control study, and selected patients from thrombophilia families with hereditary APC resistance or protein C deficiency, we calculated the median age at the first venous thrombotic event. The median ages in the different groups were compared by the Mann-Whitney U test.

With the terms unselected and selected, we wish to emphasize the difference in identification mechanisms. In the first group (unselected consecutive cases, not referred for thrombophilia work-up), the including criteria were not so stringent as in the thrombophilia group (the selected group including probandi who were referred for thrombophilia work-up and their family members who experienced a first deep venous thrombosis) and specifically not aimed at detecting hereditary cases.

Our analysis did not concern pulmonary embolism or superficial thrombophlebitis. In the thrombophilia families, as well as in the case-control study, we included only the thrombotic events, which were diagnosed objectively.

RESULTS

The median age at the first thrombotic event for the 92 cases with factor V Leiden from the population-based case-control study was 43 years (range, 16 to 69 years; median age eight homozygotes: 32.5 years, range, 22 to 56 years) (Fig 1). For the 13 cases with protein C deficiency in this study, the median age at the first thrombotic event was 47 years (range, 19 to 63 years). For the 366 noncarriers, the median age at the first thrombosis was 45.5 years (range, 15 to 69 years).

In the 12 thrombophilia families with APC resistance, factor V Leiden was detected in 48 of the 88 relatives (all heterozygotes, probandi excluded). Venous thrombotic events had occurred in 16 carriers and in four of the 40 noncarriers. There were no carriers of both APC resistance and protein C deficiency.

For the 12 probandi in thrombophilia families with APC resistance, the median age at the first thrombosis was 29.5 years (range, 21 to 46 years). For their 16 APC-resistant relatives, the median age at the first thrombosis was 29 years (range, 16 to 63 years). The median age of onset of the probandi and their relatives together was 29 years (range, 16 to 63 years). The median age of onset for the four noncarriers was 33.5 years (range, 26 to 54 years).

In the 24 thrombophilia families with protein C deficiency, protein C deficiency alone was detected in 66 of the 153

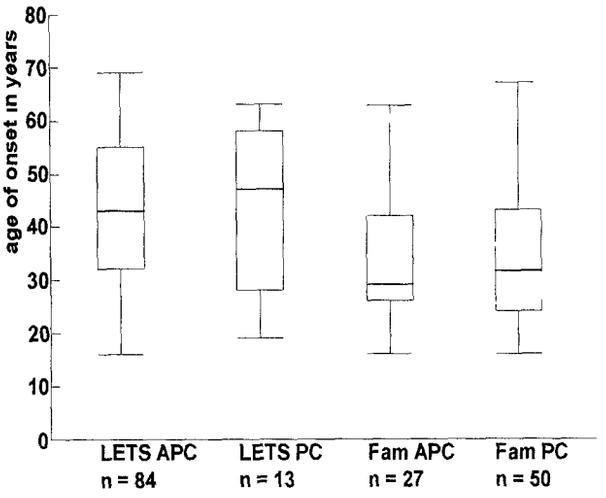

Fig 2 Box plot of age at first thrombosis according to defect in the four main groups It shows the eldest and youngest observed age of onset (horizontal lines at the end of the boxes), and the median age of onset (horizontal line inside the boxes) The lower and upper boundaries are the 25th and 75th percentiles, their difference corresponds to the interquartile range and the length of each box Fifty percent of the cases of each group have values within the box

relatives (all heterozygous, probandi excluded), and 29 of these carriers had experienced a venous thrombotic event Both APC resistance and protein C deficiency were detected in three probandi and nine relatives (four of them had experienced venous thrombosis) Factor V Leiden alone was detected in seven relatives, and two of them had experienced venous thrombosis Venous thrombosis did occur in five of the 71 noncarriers

The median age at first thrombosis for the 21 probandi in thrombophilia families with protein C deficiency was 26 years (range, 16 to 50 years) For their 29 protein C–deficient relatives, the median age at first thrombosis was 35 years (range, 17 to 67 years) The median age of onset of the probandi and their relatives together was 31 5 years (range, 16 to 67 years) For the three probandi who carried both defects, the median age of onset was 21 years (range 20 to 29 years), and the median age of onset of the four relatives who carried both defects was 30 years (range, 19 to 55 years) The age of onset of the two relatives with factor V Leiden alone was 25 years (range, 29 to 41 years, not mentioned in Fig 1) The median age of onset for the five noncarriers was 33 years (range, 21 to 57 years)

When we compare (Fig 2) all unselected APC resistant and protein C–deficient cases from the case-control study (n = 97) with all selected APC resistant and protein C–deficient patients from the thrombophilia families (n = 78, excluding homozygous patients and patients with both gene defects), the median age at the first thrombosis for all unselected patients was 45 years (range, 16 to 69 years) and the median age at the first thrombosis for all (selected) patients from the thrombophilia families was 30 5 years (range, 16 to 67 years, $P < 001$)

DISCUSSION

We compared patients with APC resistance and protein C deficiency, who were identified either from consecutive patients with a first deep venous thrombosis (unselected), or identified from patients with a first deep venous thrombosis who were referred for thrombophilia work-up and their family members who had experienced a deep venous thrombosis (selected)

We found that the median age at which the first thrombosis occurred only depended on the way the patients were identified and not on the type of gene defect The first thrombotic event occurred earlier in life in (selected) symptomatic relatives of APC-resistant or protein C–deficient probandi than in unselected APC-resistant or protein C–deficient cases from the case-control study ($P < 001$ for APC resistance and $P = 025$ for protein C deficiency)

Within each group (selected and unselected patients) the median age of onset in patients with APC resistance and patients with protein C deficiency was very similar (Fig 2) These findings do not support a difference in severity, with regard to thrombotic tendency, between APC resistance and heterozygous protein C deficiency The fact that the selection of the thrombophilia families shows a lower mean age of first thrombotic event than the group of unselected patients, may be based on coincidence, ie, selection of those in the lower range of the distribution of ages of onset As pointed out by Majerus,[10] it seems likely that these individuals also carry other genetic or environmental risk factors, which will determine individual risk [10] Because there is no reason to assume that these factors are more often present in combination with protein C deficiency than with APC resistance, or vice versa, we conclude that protein C deficiency and APC resistance contribute to about an equal extent to the risk of thrombosis This risk may be further enhanced by other factors, as has been shown previously (Koeleman et al,[11] Van denbroucke et al[12]), and those with the most unfavorable risk profile of known or unknown causes, will be identified through stringent selection [11 12]

In accordance with previous reports (Koeleman et al,[11] Gandrille et al,[13] and Zoller et al[14]) and according to the previous remark carriership of two defects does lead to an increased thrombotic tendency, as manifested in the striking young median age in the probandi of the protein C–deficient families who carried both defects (21 years, range, 20 to 29 years) [11 13 14] The fact that the median age at first thrombosis in referred thrombophilia families is lower than the median age at first thrombosis in unselected cases, appears to be the result of selection These results cannot rule out the possibility of differences in thrombotic tendency between types of thrombophilia We show here, however, that these differences will be only minor compared with the effect of differences in the mode of selection of patients The absence of much difference in thrombotic tendency in protein C deficiency and APC resistance is also in accordance with the results of the LETS-study, where uniform selection criteria were applied the relative risk for protein C deficiency (6 5) was very similar to that for APC resistance (6 6) [5 6]

The results in the group of thrombophilia families were obtained under stringent selection criteria APC resistance, has a much (about 10 fold) higher frequency than protein C deficiency Clinicians in actual practice will diagnose APC resistance easier than protein C deficiency, and the age of onset in these patients probably will approximate the median

age of onset in the group of unselected cases. Because protein C deficiency is so rare, most protein C–deficient patients will be identified in referred families, and the age of onset in these patients will approximate the median age of onset in the group of selected patients from the group of thrombophilia families.

We conclude that the overall thrombotic risk is similar in protein C deficiency and APC resistance. Major differences are found, however, between selected individuals, ie, those referred for thrombophilia work-up, and unselected individuals, ie, consecutive patients with venous thrombosis. Therefore, there is no reason to differentiate in clinical management by type of thrombophilia, whereas it may prove beneficial to take the way an individual was identified into account in customizing individualized care.

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