Trabajo número 3:

Patients with venous thromboembolism have a lower APC response than controls. Should this be regarded as a continuous risk factor for venous thrombosis?

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Patients with venous thromboembolism have a lower APC response than controls. Should this be regarded as a continuous risk factor for venous thrombosis?

Sir,

Activated protein C (APC) resistance is characterized by a poor anticoagulant response to APC.[1,2] In most cases it is caused by the factor V Leiden mutation (FVLm) (1,691G→A).[3] Inherited APC-resistance has been found in 15-40% of thrombotic patients.[4] We report the APC-response of a group of thrombotic patients, the prevalence of APC-resistance and its thrombotic risk.

We studied 186 thrombotic patients (104 female, 82 male), referred to our Unit from January 1994 to March 1997. The clinical characteristics of the thrombotic individuals are shown in Table 1. The control group comprised 103 healthy blood donors (57 male, 46 female). Blood was collected 3-6 months after the most recent thrombotic event without influence of oral anticoagulants. APC-resistance was measured using a kit from Chromogenix (Möndal, Sweden). Antithrombin, protein C, S and lupus anticoagulant (LA) were also analyzed. Detection of FVLm was performed as described elsewhere.[3] Sex differences and influence of age were assessed by the chi-square test and correlation analysis. APC-ratios were compared by ANOVA, including age and sex as covariants. A logistic regression model was employed to estimate the odds ratio (OR), and to evaluate the risk of thrombosis associated with APC-resistance. The normal range was defined as the 2.5 and 97.5 percentiles (2.08-3.95). Patients had lower APC-ratios than controls (Figure 1) (difference after exclusion of APC-resistant individuals: 0.15, 95% CI: 0.03-0.27, $p<0.05$). Females had lower APC-ratios (difference after exclusion of APC-resistant individuals 0.20, 95% CI: 0.092-0.30, $p<0.0001$). No age influence was observed.

Patients with APC-resistance showed more than a five-fold increase in risk of thrombosis (OR 5.4; 95% CI: 1.8-16.4, adjusted for age and sex). A tendency towards an inverse relationship between the risk of thrombosis and the degree of APC-response was found [APC-ratio <2.08, OR 6.25 (95% CI: 2.01-19.42); APC-ratio 2.08-2.50, OR 1.82 (95% CI: 0.92-3.59); APC-ratio >2.5 was the reference interval].

Table 1. Clinical characteristics of the 186 thrombotic patients.

	n (%)
Sex	
male	82 (44)
female	104 (56)
Family history of thrombosis	77 (41)
Age at first thrombosis (mean±SD)	42.8±15.6
Spontaneous	67 (36)
Secondary*	119 (64)
orthopedic surgery	18 (9.7)
abdominal surgery	20 (10.8)
gynecological surgery	8 (4.3)
immobilization	8 (20.4)
pregnancy°	17 (16.3)
oral contraceptives°	14 (13.5)
varicose veins	12 (6.5)
neoplasms	8 (4.3)
others	15 (8.1)
Site of thrombosis	
deep vein thrombosis	109 (58.6)
pulmonary embolism#	53 (28.5)
superficial thrombophlebitis	14 (7.5)
upper arm thrombosis	5 (2.7)
mesenteric thrombosis	4 (2.2)
intracranial vein thrombosis	1 (0.5)

**Some patients had more than one risk factor (percentage of all cases); °only women were considered; #deep vein thrombosis was diagnosed in 36 patients with pulmonary embolism.*

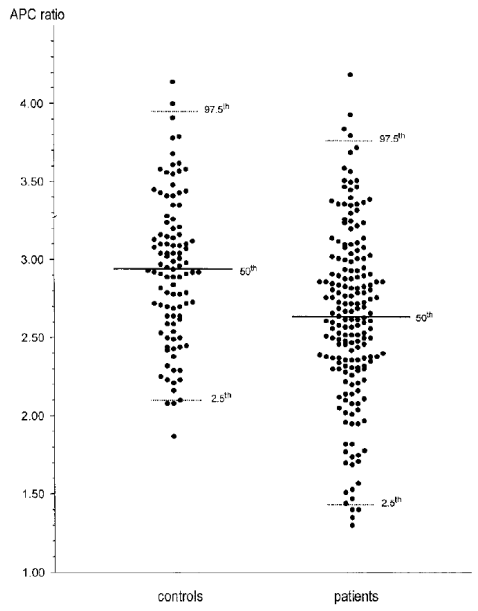

Figure 1. Anticoagulant response to APC in controls and patients with thrombosis. The response to APC was determined by the APC-resistance test, and the results were plotted as APC-ratios. Each person is represented by a full circle. The 2.5, 50 and 97.5 percentiles are indicated.

Activated partial thromboplastin time (APTT) was lower in patients and was inversely related to age, but we found that APTT-ratios and APC-ratios were independent.

Four controls and 29 patients had APC-resistance [prevalence 3.9% (95% CI: 1.1-9.6) and 15.6% (95% CI: 10.4-20.8) respectively]. When 6 patients with LA were excluded, the prevalence decreased to 12.8% (95% CI: 7.9-17.7). Other prothrombotic abnormalities were identified in 17 patients (2 antithrombin, 2 protein C and 13 protein S deficiencies). One patient with PS deficiency had APC-resistance and carried the FVLm. Two heterozygotes were identified in the control group (2/103, prevalence of 1.9%, 95% CI: 2.4-6.8). Seventeen out of 22 APC-resistant patients without LA were heterozygotes (77.3%; 95% CI: 54.6-92.2).

Although thrombosis is common, inherited deficiencies of anticoagulant proteins are unusual.[5,6] APC-resistance is probably the most frequent abnormality in patients with thrombophilia.[1] Despite the fact that the prevalence of APC-resistance in our region is lower than in other European areas,[2,4,7] it was the most common defect until we found that the prevalence of the prothrombin 20210A allele was 17.2%.[8] Unfortunately, we were not able to detect this variant retrospectively in our patients. Our patients had lower APC-ratios than controls even after the exclusion of APC-resistant subjects. An acute-phase response effect has been suggested[2,9,10] but this was not the case with our patients. Another possibility is the existence of genetic or acquired abnormalities that could contribute to APC-resistance. In agreement with other authors,[4] we found a tendency towards a relationship between thrombotic risk and APC-ratios. This suggests that APC-resistance should be regarded as a continuous variable that increases thrombotic risk. Further studies are required to ascertain whether a reduced response to APC is associated with an increased risk of thromboembolism, regardless of the presence of FVLm.

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