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Natural anticoagulants deficiency and the risk of venous thromboembolism: a meta-analysis of observational studies

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ABSTRACT

Introduction: Natural anticoagulants deficiency (antithrombin [AT], protein C [PC], protein S [PS]) is a rare, but potent risk factor for venous thromboembolism (VTE). We performed a meta-analysis of observational studies evaluating the impact of inherited natural anticoagulants deficiency on VTE risk.
Materials and Methods: Case–control and cohort studies evaluating the association of these abnormalities with VTE were systematically searched in the PubMed, Web of Science, Scopus and EMBASE databases.
Results: Twenty-one studies were included in the analysis. Thirteen studies (3,452 cases and 11,562 controls) showed an increased risk of first VTE in AT deficient subjects compared to controls (OR: 16.26, 95%CI:9.90-26.70; P < 0.00001). An increased risk of first VTE was also found in PC (11 studies, 2,554 cases and 9,355 controls; OR: 7.51, 95%CI:3.21-17.52; P < 0.00001) and PS deficient patients (14 studies, 4,955 cases and 9,267 controls; OR: 5.37; 95%CI:2.70-10.67; P < 0.00001) compared to controls. Evaluating the risk of VTE recurrence, we found a significant association with AT (4 studies, 142 cases and 1,927 controls; OR: 3.61; 95%CI:1.46-8.95; P = 0.006) and with PC (2 studies, 80 cases and 546 controls; OR: 2.94; 95%CI:1.43-6.04; P = 0.03), but not with PS deficiency (2 studies, 57 cases and 589 controls; OR: 2.52; 95%CI:0.89-7.16; P = 0.08). Sensitivity and subgroup analyses confirmed these results. The association among natural anticoagulants deficiency and VTE was maximal for patients with unprovoked events.
Conclusion: The VTE risk is increased in patients with natural anticoagulants deficiency, but additional studies are warranted to better assess the risk of VTE recurrence.

Introduction

With an incidence rate of 1–3 per 1,000 individuals/year, venous thromboembolism (VTE), and its main clinical features (deep-vein thrombosis [DVT] and pulmonary embolism [PE]), is the third cause of morbidity and mortality in Western countries [1].

VTE recognizes a multifactorial etiology in which the genetic predisposition related to one or more thrombophilic traits interacts with acquired conditions and circumstantial risk factors [2]. The leading causes of inherited thrombophilia in Caucasians are the activated protein C resistance - in most cases due to the Factor V Leiden polymorphism - and the prothrombin G20210A gene polymorphism [3,4]. Besides these two common thrombophilic conditions (prevalence in the general population of 3-7% and 0.7-4%, respectively) [2], reductions in plasma natural anticoagulants (antithrombin [AT], protein C [PC] or protein S [PS]) have long been recognized as rare, but potent risk factors for VTE [5–7].

Inherited AT deficiency, described in 1965, was the very first identified genetic cause of thrombophilia [8]. Prevalence of heterozygous AT deficiency ranges from 0.02% to 0.2% in the general population, with a 1-4% annual incidence of VTE [2]. Also PC and PS deficiencies are rare, with prevalence rates of approximately 0.2-0.4% and 0.03-0.5%, respectively [2,9]. The reported annual VTE incidence is 1-2% for PC deficient subjects and 0.7-2% for PS deficient subjects [2,10].

Although the association between inherited deficiency of endogenous anticoagulant proteins and VTE has been widely recognized, meta-analytical data providing an overall information about the risk of VTE in AT, PC and PS deficient subjects are currently lacking. As a consequence, whether the presence of natural anticoagulant deficiency could impact on the clinical management of patients is still widely discussed [11]. The aim of the present study is to perform a systematic review and meta-analysis of studies evaluating the impact of inherited deficiency of natural anticoagulants on first and recurrent VTE.

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Methods

A protocol for this review was developed a priori, detailing the specific objectives, the criteria for study selection, the approach to assess study quality, the outcomes, and the statistical methods.

Search Strategy

To identify all available studies, a detailed search pertaining to AT, PC or PS deficiency and VTE was conducted according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [12]. A systematic search was performed in the electronic databases (PubMed, Web of Science, Scopus, EMBASE), using the following search terms in all possible combinations: *antithrombin, protein C, protein S, natural anticoagulants, thrombophilia, thrombosis* and *thromboembolism*. The last search was performed on September 2014. The search strategy was developed without any language restriction.

In addition, abstract books from 2003–2013 congresses of the International Society on Thrombosis and Haemostasis (ISTH) and of the American Society of Hematology (ASH) and the reference lists of all retrieved articles were manually reviewed. In case of missing data, study Authors were contacted by e-mail to try to retrieve original data. Two independent Authors (MNDDM and PA) analyzed each article and performed the data extraction independently. In case of disagreement, a third investigator was consulted (FD). Discrepancies were resolved by consensus. Selection results have been reported according to PRISMA flowchart (Appendix 1).

Data Extraction and Quality Assessment

According to the pre-specified protocol, in this meta-analysis both retrospective and prospective studies on deficiency of natural anticoagulants and VTE occurrence were included. In addition, studies on AT, PC or PS deficiency and VTE recurrence were also taken into account. Case-reports, case-series without a control group, reviews and animal studies were excluded. The included studies were classified as having a case–control design or a cohort design. Only inherited deficiencies were considered in this meta-analysis. Criteria to define the presence of a deficiency were reported in each included study and were based on levels below normal laboratory cut-off.

Moreover, only data about lower limbs DVT and PE were taken into consideration, while data concerning thrombosis in other sites (e.g. upper extremity, splanchnic, retinal, and cerebral vein thrombosis) were excluded. Studies not reporting the row number or the percentage of patients with deficiency of natural anticoagulants and/or with VTE were excluded.

In each study, data regarding sample size, major clinical and demographic variables, presence of AT, PC or PS deficiency and history of VTE were extracted.

Given the characteristics of the included studies, the evaluation of methodological quality of each study was performed with the Newcastle-Ottawa Scale (NOS), which is specifically developed to assess quality of observational studies [13]. The scoring system encompasses three major domains (selection, comparability and exposure/outcome) and a resulting score range between 0 and 8, a higher score representing a better methodological quality. Results of the NOS quality assessment are reported in Appendix 2.

Statistical Analysis and Risk of Bias Assessment

Statistical analysis was carried out using Review Manager [Version 5.2, The Cochrane Collaboration, Copenhagen, Denmark] provided by The Cochrane Collaboration.

The evaluation of the risk of a first VTE related to AT, PC or PS deficiency was made considering together case–control and cohort studies. Separate analyses for case–control and cohort studies were performed thereafter. In addition, studies on VTE recurrence have been evaluated in a subsequent analysis.

In order to evaluate the strength of the association between AT, PC or PS deficiency and the risk of VTE, Odds Ratio (OR) and corresponding 95% confidence intervals (95%CI) were calculated. The overall effect was tested using Z scores and significance was set at $P < 0.05$. Statistical heterogeneity between studies was assessed with chi square Cochran's Q test and with I^2 statistic, which measures the inconsistency across study results and describes the proportion of total variation in study estimates, that is due to heterogeneity rather than sampling error. In detail, I^2 values of 0% indicates no heterogeneity, 25% low, 25-50% moderate, and 50% high heterogeneity [14]. In case of significant heterogeneity among the studies, potential sources of heterogeneity were searched. Results of sensitivity and subgroup analyses are provided. Finally, we removed one study at a time to assess potential source of the heterogeneity.

Risk of VTE recurrence attributable to the presence of AT, PC or PS deficiency was calculated as previously described.

Publication bias was represented graphically by funnel plots of the standard difference in means versus the standard error. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect [15].

The random-effect method was used to take into account the variability among included studies,.

Sensitivity Analyses

We repeated sensitivity analyses by including only studies judged as "high quality" according to NOS (i.e. NOS ≥ to the median value found among included studies).

Sub-group Analyses

In the frame of subgroup analyses, we planned 1) to include only studies reporting on first VTE episode; 2) to separately analyze data on unprovoked and provoked events and 3) to evaluate the overall VTE risk after excluding familial studies (i.e. on parents and relatives of patients with inherited thrombophilia).

Results

After excluding duplicate results, the search retrieved 8,901 articles. Of these studies, 8,410 were excluded because they were off the topic after scanning the title and/or the abstract, 31 because they were reviews/comments/case reports or they lacked data of interest. Other 434 studies were excluded after full-length paper evaluation. In addition, five studies [16–20], were excluded because evaluating the same population as other published studies [21–25].

Thus, 21 articles are included in the final analysis (Appendix 1), of which 10 case–control and 6 cohort studies on VTE; 3 cohort studies and 1 randomized prospective study on VTE recurrence. One further cohort study [26] reported separate data on both VTE and VTE recurrence.

Study Characteristics

Major characteristics of the 21 studies included in the meta-analysis are summarized in Tables 1–3.

Among the case–control studies, the number of VTE patients varied from 78 to 2,047, the mean age from 36.5 to 56 years, the prevalence of male gender from 35.6% to 83.3%. A concomitant presence of factor V Leiden was found in 13.8-27%, and of prothrombin G20210A polymorphism in 4.4-12.1% of patients.

Among the cohort studies, the number of patients with AT deficiency varied from 17 to 145, with PC deficiency from 53 to 188, and with PS deficiency from 41 to 287. As detailed in Table 2 (footnote), four cohort