Antithrombin Deficiency: Frequency in Patients with Thrombosis and Thrombophilic Families

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ABSTRACT

Purpose: Antithrombin (AT) deficiency is a well-known inherited risk factor for venous thromboembolism (VTE). However, F V Leiden and F II20210a mutations have drawn much more attention in the recent years. Therefore, we have decided to analyze the frequency of antithrombin deficiency in different cohorts of patients and tried to formulate indications for its testing.

Results: Antithrombin deficiency was found in 4% of patients with recurrent VTE ≤ 50 years of age with, in 1% of patients with splanchnic vein thrombosis and in 2% of cases associated with combined oral contraceptives (COC) use or pregnancy. In patients with central venous thrombosis, antithrombin deficiency was not found.

Recommendation: We consider antithrombin testing useful in patients with thrombosis occuring up to 45 years of age without any risk factors. Namely, females with VTE in pregnancy and puerperium should be tested as well as females with thrombosis on COC, if VTE occurred within the first year of their use.

Conclusion: In spite of degressive interest in thrombophilia work up, we still consider antithrombin testing useful in defined clinical situations.

KEYWORDS

thrombophilia; venous thromboembolism; antithrombin; pregnancy

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INTRODUCTION

Antithrombin (AT) is a natural anticoagulant that plays a pivotal role in coagulation homeostasis. The target proteases of AT are those of contact activation pathway (formerly known as the intrinsic pathway), namely the activated forms of Factor X (Xa), Factor IX (IXa), Factor XI (XIa), Factor XII (XIIa) and, to a greater extent, Factor II (thrombin) (IIa) (1). Factor VII (VIIa) from the tissue factor pathway and kallikrein are inactivated too.

Normal plasma activity levels are in the range of 80–120%, where 100% of AT corresponds to 1 unit of antithrombin in 1 mL of reference plasma. With congenital AT deficiency, functional AT levels are often reduced to 40–60% of normal. AT deficiency as an inherited risk factor for venous thromboembolism (VTE) was first described by Olav Egeberg in 1965 (2). The interest in inherited thrombophilia has dramatically accelerated after the discovery of APC resistence (3) and detection of F V Leiden (4) and F II202010a mutations (5). Over the next decade, thrombophilia work-up was widely available and excessively used in daily routine work. However, since the precise knowledge of its clinical implications became more clarified, the interest in testing somewhat fainted away and thrombophilia testing, including testing for AT deficiency, has undergone a critical reappraisal (6). Nevertheless, thrombophilia work-up should be done on individual basis with the focus on further benefit for certain group of patients (7). AT deficiency is a strong risk factor for venous thromboembolism, particularly its increased recurrence rate compared with patients with mild thrombophilia (8). The absolute risk of the first and recurrent VTE was summarized (9). Based on 19 studies, odds ration (OR) estimates for the first VTE is 14.0 (95% credible interval (CrI), 5.5 to 29.0). Based on 10 studies, meta-analysis showed that the annual VTE risk was significantly higher in AT deficient 1.2% (95% CrI, 0.8–1.7) than in non-AT deficient individuals 0.07% (95% CrI, 0.01–0.14). In prospective studies, the annual VTE risk in antithrombin deficient individuals was as high as 2.3% (95% CrI, 0.2–6.5). The OR for recurrent VTE based on 10 studies was 2.1 (95% CrI, 0.2 to 4.0). The annual recurrence risk without long-term anticoagulant therapy based on 4 studies was 8.8% (95% CrI, 4.6–14.1) for antithrombin-deficient and 4.3% (95% CrI, 1.5–7.9) for non-AT deficient VTE patients [9]. The incidence of inherited AT deficiency has been estimated between 1 : 2000 and 1 : 3000 in the normal population (10), but precise data from Czech Republic are not available.

THE AIM OF THE STUDY

Our goals were:

1. Finding out the frequency of AT deficiency in several subgroups of patients with VTE.
2. Formulation of the indications for AT testing in patients with VTE in our Centre.

Why have we decided to analyze AT deficiency?

1. It is assocciated with increased risk of recurrence of VTE.
2. Therapy can have some impact in specific clinical situations:
   a) AT concentrate use in high risk situations or in therapy of acute thrombosis,
   b) heparin therapy is not adequate in some subtypes of AT deficiency.
3. It is important for females in the management of subsequent pregnancies and deliveries.

MATERIALS AND METHODS

We analyzed frequency of AT deficiency in the following cohorts of patients:

1. with VTE – deep vein thrombosis (DVT) and pulmonary embolism (PE) according to our criteria until 2002 or with a strong positive family history of VTE (11),
2. with splanchnic vein thrombosis (SVT),
3. with thrombosis in central nervous system, i.e. central venous thrombosis (CVT), stroke and transitory ischemic attack (TIA),
4. with thrombosis in all areas in association with pregnancy or COC use.

Patients were recruited within the last 20 years (1998–2018) in our thrombosis Center.

TESTING OF ANTITHROMBIN

Blood samples were collected by venipuncture into plastic tubes containing 1/10 volume of 3.8% sodium citrate for coagulation assays. AT level was determined by chromogenic assay using the Stachrom AT kit (STAGO D; normal value 80–120%). The normal range for AT was obtained by examination of 100 healthy individuals (50 men, 50 women) from our region, and normal values were compared with the normal ranges recommended by the manufacturer.

The presence of AT deficiency was accepted only after multiple testing with elimination of bias. Decreased activity was found in acute thrombosis, on heparin therapy and was also slightly decreased in COCs users and pregnancy. On the contrary, level can be somewhat increased on coumadine therapy. DOACs also have an impact on measurements of AT (12). We did not have to measure antigen levels as it is recommended by Scientific Subcommittee of the International Society on Thrombosis and Haemostasis (13).

We have also tested other thrombophilias: F V Leiden and F II20210a mutations, protein S and C deficiencies. Antiphosholipid antibodies and lupus anticoagulant were tested as well.

RESULTS

1. PATIENTS WITH VTE – DEEP VEIN THROMBOSIS (DVT) AND PULMONARY EMBOLISM (PE)

Since 1998 till 2002 we performed complete thrombophilia work-up in 325 patients (the mean age of 1st VTE was 33.5 y.). Every patient had to fulfill at least one of the following criteria:

1. VTE ≤ 50 years of age.
2. Recurrent VTE.
3. VTE at an unusual site.

4. Patients with recurrent thrombophlebitis (without varicose veins) (≥ 3 events).
5. Individuals with a positive family history of VTE ≤ 50 y. of age.

The results are shown in table 1.

AT deficiency was found in 4% of patients. Females with VTE in association with COCs or pregnancy were calculated separetely (cohort 4).

Tab. 1 AT deficiency and other thrombophilias in VTE.

Thrombophilia	%
F V Leiden	40.3
F II20210a	5.8
AT deficiency	**4.0**
Proteinu C def.	6.2
Proteinu S def.	10.5
APS /LA, ACa/	6.0

2. PATIENTS WITH SPLANCHNIC THROMBOSIS

We have assessed AT deficiency in a cohort of 90 patients with thrombosis of portal, mesenteric, splenic veins and Budd-Chiari syndrome. The patients were recruited between 2012 and 2019 with the first event ≤ 50 years. Patients with tumor or liver cirrhosis were not included.

Results are summarized in table 2.

AT deficiency was found in 1%, in one male with spontaneous portal vein thrombosis.

Tab. 2 AT deficiency in SVT + other thrombophilia.

SVT	90	Male 35	Female 55
Mean age (range)	38 (16–76)	41 (19–52)	36 (16–76)
F V Leiden	10	5	5
F II20210a	5	3	2
Deficit PC	5	2	3
APS	5	3	2
JAK-2 kinase	25	10	15
AT deficiency	1	1	0
Deficit PS	0	0	0

3. PATIENTS WITH THROMBOSIS IN CENTRAL NERVOUS SYSTEM

Antitrombin deficiency was evaluated in group of 50 patients with thrombosis in CNS.

Results are shown in table 3.

AT, PC, PS deficiency were not detected in this cohort.

4. FEMALES WITH VTE AND CNS THROMBOSIS IN ALL LOCALISATIONS AND IN ASSOCIATION WITH PREGNANCY OR COC USE

The onset of all cases of AT deficiency during COCs use was during the first six months of use. Proximal DVT was found in all cases, 10 cases represented pulmonary embolism. DVT in pregnancy was manifested in the third trimester and it was always proximal or pelvic.

Tab. 3 AT deficiency in CVT + other thrombophilia.

CVT	50	Male 22	Female 28
Mean age	36 (17–78)	40 (17–73)	35 (17–78)
F V Leiden	5	3	2
F II20210	5	2	3
APS (LA, ACa)	4	2	2
JAK -2 kinasa	2	1	1
AT deficiency	0	0	0
Deficit PC	0	0	0
Deficit PS	0	0	0

Tab. 4 AT deficiency on COCs.

Number (N)	850	
Mean age (years) at the time of thrombophilia work-up (range)	32 (16–50)	
Mean age (years) at the time of the first VTE (range)	26 (16–50)	
Antitrombin deficiency (N, %)	17 (2)	
COCs + VTE (DVT + PE) (N) COCs + stroke, TIA, CVT Pregnancy	730 70 50	15 p. = 2.0% 1 p. = 1.4% 1 p. = 2.0%

If we summarize the entire cohort of 1315 patients with various forms of thrombosis, with the first thrombotic event ≤ 50 years of age in 95.5% (N = 1255 p.), AT deficiency was found in 2.3%.

DISCUSSION

Thrombophilia testing has been widely accessible in the new millenium. However, in most of the cases of thrombophilia testing, results have had no clinical consequences. Despite these findings, thrombophilia work-up is still done more frequently than necessary in the Czech Republic, mainly F V Leiden and F II20210a mutations. The awareness about other thrombophilias has fainted. Congenital AT deficiency is an infrequently encountered genetic risk factor for VTE and different subtypes vary with regard to their thrombotic risk (14). Therefore, we decided to analyze frequency of AT deficiency in different cohorts of patients and formulate the indication for AT testing.

Concerning CVT, we have not found significant AT deficiency, except in 1.4% subset of females in the 4th cohort. In the large international study CEVETIS, AT deficency was revealed in 2% (564 patients were tested) (15). In other similar studies, frequency of AT deficiency was around 2% (4/172 patients) as well. (16).

Frequency of AT deficiency was found in 1% in our cohort with splachnic thrombosis, which was lower in comparison with 4.5% found in a similar size of cohort (17).

In our first cohort of patients with complete thrombophilia-work up, AT deficiency was found in 4%, therefore more frequently than in other studies, where among 1165 of individuals with unprovoked VTE, AT deficiency was

detected only in 1% (18). However, we used different criteria for testing, mainly in the term of age limit.

In females of reproductive age, AT deficiency was found in 2% in association with COCs and 2% with pregnancy. In cases on COCs, the onset of VTE was in 90% of cases during the first 6 months of pill introduction and in 100% within one year. Regarding the severity of the event, thrombosis was always clinically significant. It means only proximal DVT, PE or CVT were diagnosed. According to a meta-analysis of 12 case–control and three cohort studies, severe thrombophilia increased the risk of VTE on COCs 7-fold (RR, 7.15; 95% CI, 2.93–17.45) (19). Seven case–control studies showed the incidence of antithrombin, protein C and protein S deficiency in COC-users in 4.3 (95% CI, 1.4– 9.7) to 4.62 (95% CI, 2.5–7.9) vs. 0.48 (95% CI, 0.1–1.4) to 0.7 (95% CI, 0.0–3.7) per 100 pill-years in non-deficient COC-users (20,21).

Regarding absolute risks of pregnancy associated VTE, high risk was found in AT deficiency (antepartum: 7.3%, 95% credible interval 1.8% to 15.6%; post partum: 11.1%, 3.7% to 21.0% (22). We found that diagnosis of AT deficiency is important, especially in reproductive age, because the risk of pregnancy related VTE and its obstetrical complications is significant (23–26).

Based on our results we have formulated the strategy of AT evaluation. We consider testing of AT useful in all males with unprovoked VTE up to 45 years of age, as well as for all females at this age category, who were not pregnant or did not take COC. Females with VTE in pregnancy and puerperium are tested as females with VTE in association with COC, when VTE is at least proximal and within the first year of use. We recommend long-term anticoagulation after idiopathic VTE and thromboprophylaxis in subsequent pregnancies. However, final management decisions in such cases ultimately hinge on individualized consideration of the benefits and risks of anticoagulation along with patient preference rather than on an algorithmic pathway (7).

We are avare of some shortcomings. There are several subtypes of congenital AT deficiency with different thrombophilic potential. We did not measure the antigen so that we cannot subclassify our patients. Gene mutation testing is available only in limited number of patients.

CONCLUSION

It is the 58th anniversary of the first description of AT deficiency. In the last 25 years the strategy for thrombophilia work up has changed and nowadays it is less recommended. We recommend thrombophilia work-up of idiopathic thrombosis based upon an individual assessment of each clinical scenario with particular emphasis on potential sequals for each patient separately. That is why we consider antithrombin testing useful in defined clinical situations.

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