

LABORATORIO E FATTORI PREDITTIVI

HYPERCOAGULABILITY IN WILD-TYPE TRANSTHYRETIN AMYLOIDOSIS: EVIDENCE FROM WHOLE BLOOD THROMBOELASTOMETRY.

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Background and Aims: Thromboembolic events are a well-recognized complication of wild-type transthyretin amyloidosis (ATTRwt), with reported prevalence ranging from 6% to 28%. Atrial fibrillation (AF), mechanical atrial dysfunction, and systemic myopathy have been identified as major contributing factors. However, thromboembolic events have also been reported in patients in sinus rhythm and in those receiving adequate anticoagulant therapy, suggesting intrinsic prothrombotic mechanisms may also be at play. This study aimed to compare conventional coagulation parameters and whole blood thromboelastometry (ROTEM) profiles between patients with ATTRwt and age- and sex-matched healthy controls, to identify potential hypercoagulable features independent of AF or anticoagulation therapy.

Methods: Twenty-five patients with confirmed ATTRwt (median age 81 years; 18 males, 7 females), all in sinus rhythm and not receiving anticoagulant therapy, were prospectively enrolled and compared with 50 healthy controls matched for age (± 3 years) and sex. Blood samples were collected and analyzed for routine coagulation tests, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and plasma levels of coagulation factors VIII, X, and XI. Natural anticoagulants such as antithrombin, protein C, and protein S were also measured, along with antiphospholipid antibodies, including lupus anticoagulant (LAC), anticardiolipin antibodies (aCL), and anti-beta-2-glycoprotein I antibodies

(anti- $\beta 2$ GP1). Additionally, thromboelastometry (ROTEM) parameters were assessed, specifically Clotting Time (CT) and Maximum Clot Firmness (MCF), using the INTEM, EXTEM, and FIBTEM assays. This research was funded by the PRINN 2022 Grant - PROT. 2022ZSA2JP.

Results: Standard coagulation tests were within normal limits in both groups, with the exception of factor VIII, which was significantly elevated in ATTRwt patients compared to controls (171% vs. 142%, $p = 0.02$). All patients tested negative for LAC, aCL, and anti- $\beta 2$ GP1 antibodies.

ROTEM analysis revealed a significantly hypercoagulable profile in ATTRwt patients. Clotting times were markedly shorter in INTEM and EXTEM assays ($p < 0.001$ for both), and MCF values were significantly higher across all three ROTEM assays ($p < 0.001$), indicating stronger clot formation and potentially enhanced thrombin generation and fibrin polymerization (Table 1).

Conclusions: While traditional coagulation assays did not differ significantly between ATTRwt patients and healthy controls—apart from elevated factor VIII levels—ROTEM revealed a consistent hypercoagulable state in the ATTRwt group. These findings suggest that whole blood thromboelastometry may uncover subclinical prothrombotic tendencies not detected by conventional tests. Further research is warranted to elucidate the molecular basis of this hypercoagulability and to determine whether ROTEM parameters are predictive of thromboembolic risk in patients with ATTRwt.

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	ATTRwt patients (n. 25)	Healthy Controls (n.50)	p-value
Sex (male/female)	18/7	36/14	-
Median age (years)	81 (\pm 16)	80 (\pm 14)	-
Traditional coagulation tests			
Prothrombin time (%)	94 (\pm 17)	98 (\pm 9)	0.36
Activated Partial Thromboplastin Time (sec)	27 (\pm 2.7)	27 (\pm 2.5)	0.79
FVIII (%)	171 (\pm 80)	142 (\pm 30)	0.02
FIX (%)	113 (\pm 34)	110 (\pm 22)	0.53
FX (%)	84 (\pm 21)	100 (\pm 13)	<0.001
Antithrombin (%)	87 (\pm 14)	98 (\pm 11)	<0.001
Protein C coagulometric activity (%)	99 (\pm 25)	99 (\pm 14)	0.82
Protein C chromogenic activity (%)	112 (\pm 29)	107 (\pm 15)	0.33
Protein C antigen (%)	112 (\pm 24)	108 (\pm 17)	0.38
Protein S coagulometric activity (%)	113 (\pm 22)	110 (\pm 19)	0.53
Protein S free antigen (%)	103 (\pm 16)	104 (\pm 16)	0.60
Protein S total antigen (%)	118 (\pm 17)	112 (\pm 19)	0.11
Rotational thromboelastometry (ROTEM®)			
EXTEM			
Clotting time (sec)	74 (\pm 11)	60 (\pm 12)	<0.001
Clot formation time (sec)	89 (\pm 14)	94 (\pm 28)	0.54
Maximum Clot Firmness (mm)	64 (\pm 3)	56 (\pm 5)	<0.001
INTEM			
Clotting time (sec)	225 (\pm 34)	176 (\pm 26)	<0.001
Clot formation time (sec)	86 (\pm 13)	85 (\pm 20)	0.81
Maximum Clot Firmness (mm)	62 (\pm 4)	57 (\pm 4)	<0.001
FIBTEM			
Maximum Clot Firmness (mm)	18 (\pm 3)	12 (\pm 4)	<0.001

Comparison of Traditional Coagulation Tests and Rotational Thromboelastometry (ROTEM®) Findings Between ATTRwt Patients and Healthy Individuals