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ABSTRACT N. PO47

HEMOPHILIA A AND ANTITHROMBIN DEFICIENCY: A CASE OF NATURAL HEMOSTATIC REBALANCING.

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Background: Hemostasis is governed by a dynamic balance between procoagulant and anticoagulant forces. While inherited bleeding and thrombotic disorders are typically studied as discrete entities, rare cases of co-inheritance may produce unique clinical phenotypes due to compensatory interactions. Among these, hemophilia A and antithrombin (AT) deficiency represent prototypical yet contrasting conditions: patients with severe hemophilia A often experience spontaneous joint and muscle bleeding, requiring lifelong prophylaxis or on-demand therapy with FVIII concentrates, whereas AT deficiency is associated with a markedly increased risk of venous thromboembolism (VTE), particularly in high-risk situations such as surgery, trauma, or prolonged immobilization. Understanding how opposing defects interact within the same individual may inform individualized management and therapeutic innovation.

Case Report: We describe the case of a 19-year-old male with severe hemophilia A (FVIII <1%, no inhibitors), carrying a mutation in exon 3 of the F8 gene (NM_000132.4:c.296A>G, resulting in p.His99Arg), co-inherited with congenital AT deficiency (~50% activity). At birth, neonatal screening was prompted by a maternal family history of hemophilia A and a paternal history of thrombophilia. The patient's father had been diagnosed with AT deficiency following a life-threatening episode of VTE involving extensive ilio-caval thrombosis and pulmonary embolism. Despite the severe FVIII deficiency, the patient has remained asymptomatic, with an annual bleeding rate (ABR) of zero and no history of spontaneous hemorrhage. He has only received perioperative FVIII prophylaxis and has remained free of thrombotic complications. Thrombin generation assay (TGA) showed delayed initiation and propagation, reduced peak and velocity index, but preserved endogenous thrombin potential (ETP), suggesting a compensatory procoagulant effect from AT deficiency (Figure 1). Although the patient demonstrated impaired thrombin amplification – consistent with FVIII deficiency – the preserved ETP suggests that decreased anticoagulant activity due to AT deficiency provides sufficient compensatory procoagulant effect to maintain clinical hemostasis. This dynamic interplay reflects a finely tuned compensatory mechanism that may alter the clinical expression of inherited bleeding disorders.

Conclusions: This case exemplifies a naturally rebalanced hemostatic state resulting from the dual inheritance of opposing coagulation traits, and aligns with previously reported cases. The preserved ETP despite FVIII deficiency supports the concept of compensatory interplay and provides a rationale for rebalancing therapies such as Fitusiran, a small interfering RNA (siRNA) agent that suppresses hepatic AT production. By mimicking this compensatory mechanism, Fitusiran enhances thrombin generation and may improve coagulation in hemophilia patients, including those with inhibitors. Recognition of such rare but informative genetic constellations not only improves diagnostic accuracy, but also has significant implications for therapeutic decision-making. Comprehensive coagulation profiling, including genetic and functional assays, is essential for characterizing atypical presentations and guiding personalized treatment strategies.

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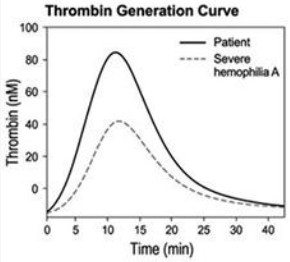
A



B

PARAMETER	PROBAND	SUBJECT WITH SEVERE HEMOPHILIA A	REFERENCE VALUES	UNITS
INR	1.06	0.95		
PTT ratio	1.77	2.58	0.9-1.2	
Antithrombin	57	111	80-120	%
Factor VIII	0.8	0.3	50-150	%
Lag time	2.67	3.67	~3.00	min
Time to peak	10.67	12.5	~7.92	min
Thrombin peak	87.18	28.75	153.48	nM
Velocity index	10.92	3.31	31.33	nM/min
Start tail	38.00	36.33	25.33	min
Endogenous thrombin potential	1310.84	400.72	1272.77	nM·min

Thrombin generation assay (A) and coagulation parameters (B) of the patient with co-inherited severe hemophilia A and congenital antithrombin deficiency compared with those of a subject with severe hemophilia A alone.