Afibrinogenemia: haemorrhagic and/or thrombotic disease?

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Introduction

- Afibrinogenemia is an "ultra-rare disease" estimated to 1:1'000'000.
- It is characterized by a complex physiopathology, involving both coagulant and fibrinolytic systems as well as platelets activities. Although hemorrhagic manifestations are the most frequent clinical presentation, severe thrombotic event can occur. Thombosis was described as symptoms at diagnosis in more than 20% of patient. *DeMoerloose et al. Semin Thromb Hem 2019;39:585; Santoro C et al. Semin Thromb Hem 2016 Epub*
  - ✓ There is an increased level of thrombin generation .*Dupuy et al.Thromb Res 2001*
  - ✓ There is an increased levels of prothrombin activation fragments, TAT. *Korte et al.Clin Invest 1994*
  - ✓ These markers are normalised by infusion of fibrinogen. *De Bosch Thromb Haemost 2002*
  - ✓ There is impaired plasmin generation in the plasma of afibrinogenemic patient *Santoro C et al. Semin Thromb Hem 2016 Epub*

Aims

Describe cumulative incidence of thrombotic events in a well-defined cohort of afibrinogenemic patients from Lebanon during a follow-up period of 12 years

Identify thrombotic risk factor correlated with thrombosis

Patients and Methods

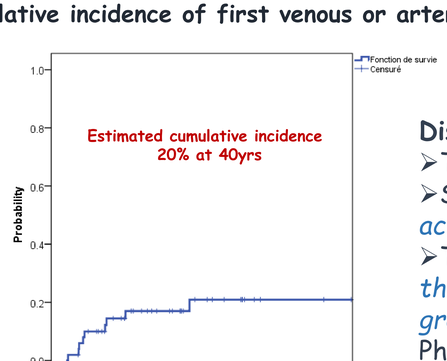
- Monocentric retrospective study with a median follow-up from diagnosis of 12 years . Fifty one patients were evaluated from January 2004 to January 2016.
- All thrombotic events were objectively documented.
- Venous thromboembolism (VTE) was stratified into provoked or unprovoked and correlated to venous thrombotic risk factors and fibrinogen replacement therapy.
- Kaplan-Meyer curves was done for cumulative incidence.
- Univariate analysis for bone pain, gender, splenectomy, and other venous thrombotic risk was performed

Result

Population demography

Patients, n=51	Total
Age end of follow-up, median	14 (13)
Gender Males, n (%) Females, n (%)	 29 (57) 22 (43)
Genotype Hom*FGG R134X*, n (%) Hom*FGA L212X*, n (%) Hom*FGA Y95X*, n(%)	 4 (8) 47 (90) 1 (2)
Life threatening bleeds, n (%)	47 (91)
Fibrinogen replacement On demand, n(%) On prophylaxis, n(%)	 44 (87) 7 (13)

Cumulative incidence of first venous or arterial thrombosis



Characteristic of patient thrombosis

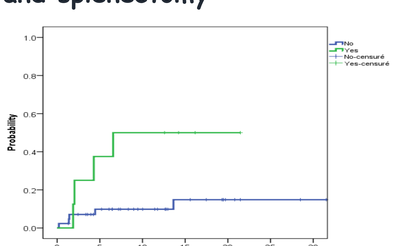
Patients,n=51	Total	Venous thrombosis	Arterial thrombosis
First thrombotic event, n	9	7 (77)	2 (23)
Thrombosis recurence, n	8	3 (38)	5 (62)
Tinzaparin, n(%)	6	5 (83)	1 (17)
Antiplatelets, n(%)	5	0 (0)	5 (100)
Deep Vein Thrombosis, n	**3 (27)**		
Splanchnic venous thronbosis, n	7 (45)		
Limb ischemia, n	6 (27)		
Aortic thrombosis, n	1 (9)		

Characteristics of thrombosis population

Patients, n=9	Total	Venous Thrombosis	Arterial Thrombosis
Age first event , Median (SD)	25 (13)	25(13)	25 (14)
Gender Males, n(%) Females, n(%)	 6 (63) 3 (37)	 5 (50) 2 (25)	 1 (12) 1 (12)
Splenectomy, n(%)	4 (44)	4 (100)	
Positive thrombophilia, n(%)	0 (100)	0 (0)	0 (0)
Oestrogen replacement, n(%)	3 (37)	2 (25)	1 (12)
Cardiovascular risk factor, n(%)	0 (100)	0 (0)	0 (0)

Univariate analysis to gender , bone pain and splenectomy

	Hazard ratio	p	95% CI
Female	0.53	0.373	0.13-2.13
Bone pain	1.8	0.924	0.22-5.21
Splenectomy	4.43	0.026	1.19-16.51



Discussion and conclusion

- There is a high incidence of thrombotic events in young with high prevalence of splanchnic thrombosis.
- Splenectomy could be a risk factor for venous thrombosis in afibrinogenemic patients . *Loss of "filtering" activities of the spleen? Spleen rupture due to thrombosis?*
- There is high rate of arterial recurrence despite accurate antiplatelet therapy. *Hemorrhage within vessel wall that induce thrombine generation ? The high level of thrombin may stimulate platelets to release several growth factors that induce vascular smooth muscle cell proliferation and intimal hyperplasia?* *Dupuy et al.Thromb Res 2001*

Phenotype of afibrinogenemic patient and their relatives had to be evaluated with Thrombin generation assay to compare the two population . In afibrinogenemia plasma before and after fibrinogen infusion must be evaluated by thrombine generation.

- Thrombophylaxis should be considered in all highly thrombotic risk situations.
- Time correlation and clinical improvement with fibrinogen replacement needs to be assessed by further studies.