ENDOGENOUS THROMBIN GENERATION POTENTIAL: AN ADDED VALUE PARAMETER TO INDIVIDUALIZE PROPHYLAXIS TREATMENT IN PEDIATRIC HAEMOPHILIAC PATIENTS?

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Introduction

Haemophilia is a genetic disorder caused by a deficient factor VIII (haemophilia A) or factor IX (haemophilia B). It's a rare X-linked recessive disease. The clinical features overall depend on the levels of residual factors. Nevertheless, significant **differences** have been noted **in patients having the same level of coagulation factors**, which is therefore **not reflecting the patient clinical phenotype.**

Goal

Use the Thrombin generation assay (TGA), a method of global evaluation of the coagulation process, to find a relationship between clinical phenotype and TGA parameters. It could be a very important tool in both the follow-up and treatment adaptation of patients with haemophilia.

Methods

- We analysed the computerized medical charts (starting from the diagnosis to January 2014) and some plasma samples (taken between July 2008 and January 2014) of 35 haemophiliac A and B patients. Following exclusions criteria only 18 patients were retained.
- 31 citrated blood samples of these 18 patients were analysed with TGA using Calibrated Automated Thrombinography ® (CAT) as described by Hemker et al (Thrombinoscope®, Maastricht, The Netherlands).
- We evaluated Endogenous thrombin potential (ETP) as it represents the whole quantity of thrombin generated during the all coagulation process.
- Individual analysis of each patient including the computation of a clinical score (number of bleeding episodes/ duration of treatment) was confronted to ETP.
- A ROC curve was made to define a threshold ETP value : - controls : samples> 4 months before or after haemorrhagic events
  - cases : samples in the 4 months preceding bleeding
- A contingency table was performed with the ETP treshold and the clincal score.

EXCLUSIONS CRITERIA :
- Patients in induction of immune tolerance
- Samples with level of FVIII/IX >3%
- Sample taken on the day of a bleeding event or 4 months following a bleeding event

Results

- ROC curve allowed the determination of the threshold ETP value at **144 nM.min** below which the bleeding frequency is increased.
- **Statistically significant relationship between ETP and clinical phenotype was** revealed : the majority of the patients with a low clinical score have an ETP value > 144 nM.min and patients with an important clinical score (> 0,1) have an ETP value < 144 nM.min.
  In addition the clinical score values which are borderline (= 0,1) were also associated with borderline values of the ETP **(**144 - 151,2**).**
- Individual analysis :

Patients which sample taken during on demand treatement

Haemophilia	N° patient	Age	Follow-up (month)	FVIII / FIX %	Clinical score (nbr bleeding episodes/duration of treatement in months) **on demand treatement**	ETP nM.min
	1	9y 11m	95	2,46	0,07	300
A moderate	2	16y 5m	173	2,87	0,1	145,5
	4	1y 9m	21	0,84	0,1	161
				0,43		278,5
	7	3y 3m	39	0,49	0,28	95
	8	18y 10m	226	1,3	0,18	140,5
				0,44		86
A severe	16	4y 3m	41	0,25	0,5	102

	: clinical score > 0,10 (frequent bleeding)
	: hypocoagulability value (ETP<144;F<1%) linked to clinical score (>0,10 or borderline)
	: borderline velue (ETP: from 144 to 144+5% (151,2) ; score : 0,10 +- 5% (0,095-0,105)
	: discordant values (ETP>144+5% or F>1% if score>0,10 ; ETP<144 or F<1% if score<0,10)

Samples of patients shifted on prophylaxis

Haemophilia	N° patient	Age	Duration of treatement	Traitement (dosis)	FVIII / FIX %	Clinical score (nbr bleeding episodes/duration of treatement in months) **on prophylaxis**	ETP nM.min
			02/10/01-06/2011) : 116 months	70U/kg/sem	0,95	0,08	267
					1,33		438
	3	21y 1m	(01/2012-20/02/14) : 25 months	55U/kg/sem	1,71	0,04	284,5
	5	9y 2m	(06/08/13-20/02/14) : 6 months	45U/kg/sem	1,61	0	197,5
			23/11/10-24/05/11) : 16 months	35U/kg/sem	0,37	0,17	169,5
	6	5y 11m	24/05/11-20/02/14) : 33 months	65 U/kg/sem	0,56	0	114,5
					2,93		196
	9	15y 3m	(01/2006-20/02/14) : 97 months	130U/kg/sem	2,94	0,01	226,5
					0,69		195,5
	10	31y 10m	02/2005-20/02/14) : 108 months	60Ukg/sem	2,32	0,04	253
			(10/2012-08/08/13) : 10 months	30U/kg/sem	0,68	0,1	142,5
	11	4y 6m	(08/08/13-20/02/14) : 6 months	60U/kg/sem	0,69	0,5	241
	12	5y	(08/2012-20/02/14) : 18 months	30U/kg/sem	0,92	0,05	261,5
	13	10y 2m	(16/04/09-2/02/14) : 58 months	85U/kg/sem	2,74	0,03	224
	14	29y 4m	15/05/12-20/02/14) : 21 months	75U/kg/sem	0,92	0	207,5
					1,25		203,5
	15	7y 6m	12/05/09-20/02/14) : 57 months	90U/kg/sem	0,38	0,03	322
			12/07/11-21/08/12) : 13 months	45U/kg/sem	0,33	0,31	150,5
A sévère	16	4y 3m	21/08/12-20/02/14) : 18 months	70U/kg/sem	0,82	0,17	93
	17	9y 6m	29/02/08-20/02/14) : 72 months	70U/kg/sem	2,14	0,03	150,5
					1,81		108
B sévère	18	7y 9m	(08/2008-20/02/14) : 66 months	90U/kg/sem	1,46	0	73,5

Conclusion

- Factor level is not always reflecting the clinical phenotype of haemophiliac patients. We observed **differences between clinical scores of patients with the same level of factor. This could be explain by multifactorial variability.**
- **Statistically significant relationship between ETP and clinical phenotype** : the majority of patients with an elevated clinical score (> 0,1) have an ETP < 144 nM.min.
- **The threshold ETP value brings out the patients with a high risk of bleeding** and could be use to insure a better follow up and prevent haemorrhagic event.

- To conclude, a relationship between ETP and the clinical features of haemophiliac patients was demonstrated. We suggested that TGA may be of added value in the follow-up and individualized prophylactic treatment of patients with haemophilia.

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