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Different clinical phenotype between Hemophilia B and Hemophilia A: results of global coagulation assays

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Background

- Some observations suggest that severe hemophilia B may exhibit a milder bleeding tendency than severe hemophilia A.
- Possible differences in the coagulation profile of severe hemophilia B and A that may account for such phenotypic variability have not been extensively investigated.

Hypothesis/Aim of the study

To compare the clinical and laboratory phenotype of patients with severe hemophilia B (***cases***) with patients with severe hemophilia A (***controls***) in order to ascertain potential determinants for a milder bleeding phenotype.

Study Design

- ✓ Patients with severe hemophilia B (FIX < 1IU/dL) and severe hemophilia A (FVIII < 1IU/dL) of any age, without current or previous inhibitor history, followed-up at a single center were asked to undergo blood sampling after a ***minimum wash-out period of 5 days*** from the last FIX or FVIII concentrate infusion
- ✓ Data on medical history, annual bleeding frequency, annual factor consumption, type of treatment regimen, orthopaedic status and FIX/FVIII gene mutations were collected from patients' files.

Materials and Methods

- Several coagulation tests including global testing by means of ***thrombin generation assay*** (TGA) and ***thromboelastography*** (TEG) were performed on blood samples.
- TGA was performed in platelet-rich plasma (PRP) with the addition of of corn trypsin inhibitor (CTI).
- Four parameters of the TGA curve were evaluated: lagtime, endogenous thrombin potential (ETP), peak and time-to-peak.
- TEG was performed in whole citrated blood by means of the 4 channel ROTEM Gamma equipment.
- FIX and FVIII clotting activity was measured by one-stage clotting assay as well as by chromogenic assay.

Results (1)

- ✓ Results are available for the first 33 consecutive eligible patients: 16 with severe hemophilia B and 17 with severe hemophilia A.
- ✓ A written informed consent was obtained from enrolled patients.

Table 1 – Characteristics of the 33 patients enrolled

	HB (n=16)	HA (n=17)	p value
Median age at enrolment, yrs (IQR)	41 (36-54)	41 (37-48)	ns
Median age at first bleed, yrs (IQR)	2.8 (1.7-5.0)	1.4 (1.0-2.8)	0.05
Null gene mutations, %	2 (13)	10 (59)	0.01
Pts with target joints, %	12 (75)	14 (82)	ns
Previous orthopaedic surgery, %	3 (19)	12 (71)	< 0.01
Pts on regular prophylaxis, %	3 (19)	7 (41)	ns

HB: hemophilia B; **HA**: hemophilia A; **yrs**: years; **IQR**: interquartile range; **Pts**: patients

Results (2)

- ✓ Only patients who were able to maintain the required wash-out period from the last factor infusions were considered eligible.
- ✓ Baseline levels of FIX and FVIII were confirmed <1 IU/dL in all patients by one-stage and chromogenic assays.

Table 2 – Characteristics of patients treated on demand

	HB (n=13)	HA (n=10)	p value
Median n of joint bleeds/yr, (IQR)	1.5 (0-11)	11 (6-17)	0.05
Median factor usage, IU/kg/yr (IQR)	320 (14-853)	1448 (724-2677)	0.01
Median HJHS score, (IQR)	5 (1-19)	31 (18-48)	<0.01

HB: hemophilia B; **HA**: hemophilia A; **yr**: year; **IQR**: interquartile range; **HJHS**: Hemophilia Joint Health Score

THROMBIN GENERATION ASSAY

- Among TGA parameters a significant difference between HB and HA was found with respect to ***Thrombin peak that was higher in HB than in HA patients*** (median thrombin peak 30.4 nM in HB versus 18.4 nM in HA; p=0.05).

Table 3 - Thromboelastography

Parameters	HB (n=16)	HA (n=17)	p value
Median CT, sec (IQR)	310 (272-406)	598 (509-671)	<0.01
Median CFT, sec (IQR)	93 (77-109)	133 (114-171)	<0.01
Median alfa Angle, degrees (IQR)	72 (68-75)	65 (59-68)	<0.01
Median MCF, mm (IQR)	59 (55-62)	57 (54-60)	ns

HB: hemophilia B; **HA**: hemophilia A; **CT**: clotting time; **CFT**: clotting formation time; **MCF**: maximum clot firmness; **sec**: seconds; **IQR**: interquartile range.

Conclusions

- ✓ Our results indicate that ***patients with severe hemophilia B may have a milder bleeding phenotype*** as compared with patients with severe hemophilia A.
- ✓ Global coagulation assays such as ***TGA and TEG have the potential to reveal different coagulation profiles*** and to investigate correlations between clinical and laboratory phenotype in patients with severe hemophilia.
- ✓ Further studies are warranted in order to explore the biological mechanisms that may enhance coagulation activation in hemophilia irrespective of FIX/FVIII activity in plasma..

Disclosures

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