Prevalence of Inhibitors in a prospective cohort of hemophilic children under 4 years of age from a single center

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Introduction: The development of alloantibodies in patients with congenital hemophilia is considered the most serious complication of replacement treatment. Inhibitors usually arise early in the patient's life after relatively few factor exposure days. Many genetic and environmental risk factors have been associated with their development.
Objective: To evaluate the prevalence of new inhibitors and analyze associated risk factors in patients under 4 years of age registered prospectively at the Buenos Aires Hemophilia Foundation.

Methods: All patients diagnosed with hemophilia at the Hemophilia Foundation of Buenos Aires from January 2008 to December 2011 were registered. Patients meeting the enrollment criteria were eligible to participate in the study. Inclusion criteria included age lower than 4 years and no previous history of inhibitor. Data collected for analysis were: diagnosis; mayor bleeding events; exposure days; type of factor; continuous infusion/bolus; prophylaxis/ on demand and genetic testing. Family history of inhibitor development was also evaluated. For the purpose of this analysis, two groups of subjects were chosen. The firs group consisted of subjects who developed an inhibitor (inhibitor detected >0,6 BU in two consecutive samples), the second, the control group, was composed of subjects with hemophilia exposed to factor concentrate who never developed an inhibitor >0,6 BU.
Statistical analysis: we used Chi-square test and Fisher exact test to compare dichotomous variables and Wilcoxon rank sum test to compare exposure days, the only continuous variable without normal distribution.

Results: From a total of 180 patients with hemophilia registered between January 2008 and December 2011, 56 were younger than 4 years old. Eight patients were lost to follow up. Of the 48 patients included in the analysis, 44 had hemophilia A (34 severe, 5 moderate and 5 mild) and 4 hemophilia B. Eleven patients developed inhibitors (22,9%), all with severe hemophilia A.
Although the median exposure days (ED) in the inhibitor group was 40 (7-150), 8 of the 11 patients had < 20 ED.
Considering risk factors (ED, type of factor –recombinant vs. plasma derived-, prophylaxis vs. on demand, continuous infusion vs. bolus, major events: surgery, trauma, intracranial hemorrhaged, or not, family history of inhibitors) there was no statistically significant difference between the two groups (inhibitor positive/negative) for any of these variables.
Mutation status was not available in all patients therefore it was not included in the analysis.

Table 1: Exposured patients with haemophilia.

Inhibitor	Positive (N=11)	Negative (N=30)	*P*
PDF	5	18	0.717
RF	5	12	
ED median	40.6	36.13	0.385
Continuous Infusion	2	0	0.067

Inhibitor	Positive (N=11)	Negative (N=30)	*P*
Prophylaxis	1	6	0.651
Mayor Event †	2	0	0.067
Family History of Inhibitor	2	0	0.067
Inv 22	5	3	

† Intracranial hemorrhage.

Conclusion: In our population of patients under 4 years of age with hemophilia, the prevalence of inhibitor was similar to that reported in the literature. We could not identify risk factors related to the inhibitor development, likely related to the fact that the sample size was too small to reveal any significant differences between the two groups.

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