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POSTER ABSTRACTS

311.DISORDERS OF PLATELET NUMBER OR FUNCTION: CLINICAL AND EPIDEMIOLOGICAL

Impact of Age on Hemostasis of Patients with Immune Thrombocytopenia

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Introduction

Incidence of primary immune thrombocytopenia (ITP) has two peaks: one in children and young adult and one in the elderly. Management of older patients represents a challenge, because older age is associated with increased frailty, comorbidities, polypharmacy, and worse outcome. Moreover, we cannot rule out the effect of old age on hemostasis of individuals without ITP.

Objectives

We aimed to compare characteristics of hemostasis in healthy controls and in patients with ITP stratified according to their age in ≤65 years old (yo) and >65 yo, in order to determine if old age modifies hemostasis and if there is an increased risk of bleeding in older patients with ITP.

Methods

This is a prospective project that was approved by the Ethics Committee from Hospital Universitario La Paz. Informed consent was signed before sampling. ITP patients (n=100≤65 yo and n=68>65 yo) and healthy controls (n=100≤65 yo and n=28>65 yo) were recruited.

Patients with ITP and participants with uncontrolled hypertension, artery disease, abnormal hepatic or renal function tests, a diagnosis of a bleeding disorder or thrombopathy, treatment with drugs that could affect hemostasis or a history of thrombotic episodes were excluded.

We evaluated platelet activation markers (TRAP and ADP-induced activation of fibrinogen receptor determined through PAC1-binding, and TRAP-induced P-selectin exposure with anti-P-selectin antibody); active caspase-3, -7, -8 and -9; surface loss of sialic acid determined by the binding of Ricinus Communis Agglutinin I (RCA) to galactose residues; and presence of GlcNAc residues on platelet's surface determined by the binding of Wheat Germ Agglutinin (WGA). Neuraminidase 1 (NEU1) associated to membrane of quiescent platelets were tested with anti-NEU1-Alexa ^{546} antibody. All samples were analyzed by flow cytometry.

Thrombin generation was measured in platelet-poor plasma by Calibrated automated thrombogram (CAT) and coagulation was triggered by proper recalcification and the addition (final concentrations) of 1 pmol/l of recombinant human tissue factor and 4 µmol/l of phospholipid mixture (PPP-Reagent LOW). The following parameters were measured: Lagtime (= time when 10 nmol/l thrombin is formed); peak height (PH = maximum thrombin concentration reached); and endogenous thrombin potential (ETP = area under the thrombin-concentration-vs-time curve) were calculated with the Thrombinoscope software package (Thrombinoscope BV).

Statistical analyses were performed with GraphPrism 6.0. Comparisons between controls vs ITP patients with similar range of age; controls ≤65 vs >65 yo; and ITP patients ≤65 vs >65 yo were performed with 2 way ANOVA and $p<0.05$ were considered as significant.

Results

Table 1 shows results obtained. There was no difference in age between controls and ITP groups with the same age range. Platelets from patients with ITP had a low ability to be activated when compared to their corresponding control group, and impairment in activation of fibrinogen receptor was even more evident for the older group of ITP patients.This fact was not due to a reduction in the number of fibrinogen receptors. Caspases 3, 8 and 9 were higher in ITP patients than their age-matched controls. Moreover, caspase 3 was higher in older ITP than in patients ≤65 yo.

Regarding analyses of glycoside residues, platelets from patients with ITP had less sialic acid and more GlcNAc residues on their surface when compared with the corresponding controls. Surprisingly, sialic content in platelets from controls > 65yo was higher than in the controls ≤65 yo, and this fact is in accordance to the lowest content of NEU1 associated to their membrane.

Plasma from ITP patients had a higher capacity to generate thrombin when compared with their age-matched control group. Nevertheless, both groups (control and ITP)> 65 yo generated less thrombin than the groups ≤65 yo. No differences were observed in other CAT parameters.

Conclusion

Platelets from patients with ITP are less functional than those from control groups. This impairment seemed to be more pronounced in platelets from patients >65 yo, putting forward the possibility of an increased risk of bleeding in older patients with ITP. This study also demonstrates that old age might modify hemostasis even in individuals without ITP.

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		CONTROL (Mean±SD)		ITP (Mean±SD)	
AGE (yo)	≤65	42.4±11.9	a	42.6±17.4	b
	>65	77.0±9.2		75.1±6.1	
TRAP-PAC1 (% positive)	≤65	71.3±16.9		52.1±25.4#	b
	>65	61.8±20.7		41.7±29.9#	
ADP-PAC1 (% positive)	≤65	69.2±17.0		61.2±22.0#	b
	>65	68.9±13.7		51.8±25.6#	
TRAP-Psel (% positive)	≤65	82.5±11.5		72.2±20.6#	
	>65	80.3±7.9		66.9±20.9#	
CASPASE 3 (% positive)	≤65	56.2±11.0		60.2.±9.8#	b
	>65	53.4±9.6		67.8±9.9#	
CASPASE 8 (% positive)	≤65	56.4±12.0		62.3±11.0#	
	>65	54.2±7.7		68.0±10.8#	
CASPASE 9 (% positive)	≤65	58.7±9.8		66.2±13.4#	
	>65	60.2±4.4		69.7±9.3#	
WGA (MF)	≤65	204.3±210.0		546±87.6#	
	>65	131.0±116.4		512.8±20.7#	
RCA (MF)	≤65	672.2±50.4	a	928.1±83.9#	b
	>65	217.5±24.7		1061.6±106.9#	
NEU1 (MF)	≤65	597.0±197	a	782.9±201.9#	
	>65	378.8±238.7		862.4±111.0#	
Lagtime (min)	≤65	4.7±1.1		5.5±2.9	
	>65	6.5±3.8		6.9±4.0	
ETP (nMxmin)	≤65	1482±377		1369±385	
	>65	1330±382		1240±531	
PEAK (nM)	≤65	246.9±77.0	a	290.4±65.9#	b
	>65	185.8±88.8		254.7±93.6#	

TABLE 1- yo: years old; % positive: % positive cells; MF: mean fluorescence; WGA: Wheat Germ Agglutinin; RCA: Ricinus Communis Agglutinin I; NEU1: neuraminidase 1; PEAK: maximum thrombin concentration reached; ETP = area under the thrombin-concentration-vs-time curve
Significant differences (p<0.05): #: PTI vs age-matched control group: a: controls ≤65 vs controls >65 yo; b: ITP ≤65 vs ITP >65 yo

Figure 1

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