

Piastrine: Alterazioni qualitative o quantitative

CHARACTERIZATION OF PLATELET DYSFUNCTION IN NOONAN SYNDROME PATIENTS

S. Sorrentino[1], I. Lazzareschi[2], A. Ferretti[1], R. Onesimo[2], A. Romano[3], G. Zampino[2], C. Leoni[2], E. De Candia[1]

[1]UOS Piastrinopenie Congenite e Piastrinopatie, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy; [2]UOC Pediatria, Fondazione Policlinico Universitario Agostino Gemelli IRCSS, Roma, Italy; [3]UOC Oncologia Pediatrica, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy

Background and aims. Noonan syndrome (NS) is a RASopathy characterized by dysregulation of the Ras/MAPK pathway and frequently associated with bleeding diathesis. Although hemostatic abnormalities are reported in the majority of patients, the underlying mechanisms remain incompletely defined, particularly with regard to platelet function. Preliminary evidence suggests a high prevalence of platelet defects, but their functional characterization and pathway involvement are still poorly delineated. This study aimed to refine the platelet dysfunction phenotype in NS by integrating aggregation and secretion data.

Methods. In this case–control monocentric study, 29 NS patients were compared with 20 age-matched healthy controls at a single center. Bleeding tendency was assessed using the ISTH-BAT score. Standard coagulation parameters (PT, aPTT, fibrinogen, platelet count) were evaluated. Platelet function was investigated by light transmission aggregometry (LTA) using adenosine diphosphate (ADP), collagen, epinephrine, arachidonic acid (AA), and PAR1-activating peptide (PAR1-AP). Maximal aggregation (MA, %) and collagen lag phase (LP, sec) were recorded. Platelet secretion was assessed by flow cytometry through CD63 and CD62p expression after stimulation. Platelet Function Analyzer (PFA-100) closure times were available in a subset of patients.

Results. An abnormal ISTH-BAT score (>3) was observed in 24% of NS patients. PT, fibrinogen levels, and platelet count were comparable between groups, whereas prolonged aPTT was detected in 30% of patients. LTA revealed a consistent and pathway-specific impairment of platelet aggregation. ADP-induced responses were markedly reduced, with MA <60% in 91.6% and 79% of patients at 2 µM and 4 µM, respectively. Collagen-induced aggregation was also impaired, with MA <75% in 42% and prolonged LP (>50 sec) in 87% of patients. Impaired responses were also observed with epinephrine (MA <60% at 180 sec in 87% NS) and PAR1-AP (MA <75% in 45.8% NS). In contrast, AA-induced aggregation was largely preserved, suggesting selective pathway involvement rather than a global defect. Flow cytometry confirmed a secretion defect, with reduced CD63 and CD62p expression after PAR1-AP stimulation. Prolonged PFA-CEPI and PFA-ADP closure times were observed in 82% and 47% of tested patients, respectively.

Conclusions. This study demonstrates that the majority of patients with NS exhibit platelet dysfunction, characterized by impaired aggregation responses to ADP, collagen, and thrombin receptor stimulation, and associated with defective granule secretion. Platelet dysfunction may be detected by prolonged PFA-CEPI closure time. These findings underscore the importance of identifying and characterizing platelet abnormalities in NS patients to optimize the management of bleeding symptoms and to guide hemostatic support during surgical or invasive procedures.

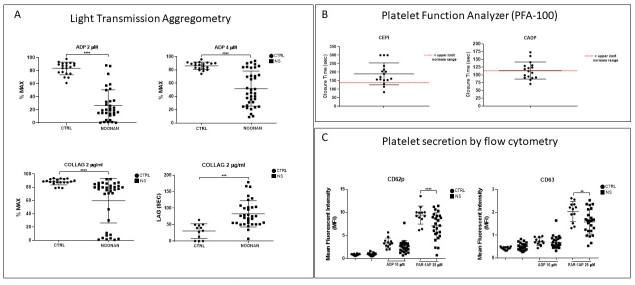


Figure 1: Platelet function was evaluated in Noonan syndrome (NS) patients and age-matched healthy controls using multiple complementary approaches. **A):** Light transmission aggregometry (LTA) showing maximal aggregation (MA, %) in response to ADP (2 and 4 µM) and collagen (2 µg/mL), and collagen-induced lag phase (LP, sec). **B):** Platelet Function Analyzer (PFA-100) closure times for collagen/epinephrine (CEPI) and collagen/ADP (CADP) cartridges; dashed lines indicate upper normal limits. **C):** Platelet secretion assessed by flow cytometry, reported as mean fluorescence intensity (MFI) of CD62p and CD63 expression following stimulation with ADP and PAR1-activating peptide (PAR1-AP). Each dot represents an individual subject; horizontal lines indicate mean ± SD. CTRL: healthy controls; NS: Noonan syndrome patients. Statistical significance is indicated as follows: *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.