

BRIDGING THE CLINICAL CHASM: GENETIC ANALYSIS AS A CONFIRMATORY TOOL IN MISMATCHED GLANZMANN THROMBASTHENIA

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Background and Aims. Glanzmann thrombasthenia (GT) is a rare inherited recessive platelet function disorder caused by quantitative or qualitative defects of the glycoprotein IIb/IIIa (GPIIb/IIIa), encoded by the ITGA2B/ITGB3 genes (chromosome 17), resulting in impaired platelet aggregation. Several pathogenic variants have been described, mainly in ITGA2B gene because of its larger size compared with ITGB3; however the associated clinical phenotypes are indistinguishable. We report the case of a 55-year-old woman referred to our centre for recently developed haemorrhagic diathesis: epistaxis, prolonged wound or gum bleeding and easy bruising, but negative bleeding history even in trigger conditions (surgery, pregnancy, delivery), no comorbidities at diagnosis and no family history. This atypical clinical presentation, including late-onset bleeding, raised suspicion for an acquired form. In this way genetic test helped. The aim of this study is to show the usefulness of genetic analysis as a confirmatory step in the diagnostic work-up, particularly when a mismatch exists between laboratory results and medical history.

Materials and Methods. Platelet function was assessed by Platelet Function Analyser (PFA-100), Total Thrombus-Formation Analysis System (T-TAS®01) and aggregometry.

Absence of GPIIb/IIIa and presence of platelet autoantibodies/alloantibodies were tested by flow cytometry (Beckman Coulter Epics, High Wycombe, UK). Platelet antibody specificity was determined by Enzyme-Linked Immunosorbent Assay (ELISA). Owing to the discrepancy between the medical history and laboratory findings suggestive of congenital GT, molecular genetic analysis was performed.

Results. PFA-100 and T-TAS were elongated. Aggregometry showed a profile consistent with GT. Flow cytometric analysis showed a GPIIb/IIIa expression profile comparable to that observed in a patient with a confirmed diagnosis of GT. No antibodies or associated disease were detected. Genetic testing identified two heterozygous mutations c.1947-1_1947ins in ITGA2B gene, never reported in ClinVar, that represents a novel mutation, and another one c.260G>A reported only once in the GnomAD database.

Conclusions. Because this disorder is rare and its diagnostic work-up complicated, its management remains challenging, particularly when discrepancies arise between laboratory findings and the patient's medical history. For this reason, it may be important to include molecular genetic analysis not as an exclusive test for specific cases, but as a fundamental tool in the diagnostic process.