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ABSTRACT N. PO61

ACTN1-RELATED THROMBOCYTOPENIA AND SEVERE HYPERHOMOCYSTEINEMIA: A CASE REPORT.

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Background

ACTN1-related thrombocytopenia (ACTN1-RT) is a recently identified form of inherited thrombocytopenia (IT), estimated to be the fourth most common worldwide. It features mild thrombocytopenia and platelet macrocytosis, with a negligible bleeding risk, thus considered a benign form of IT. Hyperhomocysteinemia (HHcy) due to cystathionine β-synthase (CβS) deficiency is an autosomal recessive disorder presenting with skeletal, ocular, neurological, and thrombotic features. Its major complication is early-onset arterial and venous thromboembolism, even with moderate homocysteine (Hcy) elevation.

Case Report

We report a 35-year-old man with a personal and familial history of ACTN1-RT (heterozygous ACTN1 exon 10, 1019 C>T mutation) and no bleeding history, referred to our clinic in January 2024 for severe HHcy. He had mild thrombocytopenia (platelets: 75–80,000/µL), elevated serum Hcy (209 µmol/L), and underwent bilateral eye surgery for ectopia lentis. He had no thromboembolic events. Imaging excluded vascular/connective tissue involvement. NGS revealed two heterozygous CβS mutations (exon 10: 833T>C and exon 14: 1224G>A), inherited from father and mother respectively. Neither parents nor sister exhibited HHcy-related complications. Pyridoxine supplementation normalized Hcy levels. As of February 2025, the patient remains asymptomatic without thrombotic or bleeding events. The CβS variants were classified as pyridoxine-sensitive pathogenic and likely pathogenic. These may explain the phenotype. Remarkably, despite severe HHcy, no thrombotic events occurred. Although CβS deficiency displays clinical variability, we hypothesize that coexisting ACTN1-RT may have mitigated vascular complications. The ACTN1 mutation is classified as likely pathogenic. While ACTN1's role in platelet function is unclear, it encodes a non-muscle α-actinin isoform involved in cytoskeletal organization. Human cases rarely bleed, but α-actinin-1 knockout mice show impaired platelet function and reduced thrombosis. HHcy contributes to atherosclerosis via mechanisms including endothelial damage, prothrombotic changes, and increased platelet thromboxane A2 production.

Conclusion

We propose that platelet dysfunction related to ACTN1-RT may have counteracted prothrombotic mechanisms of HHcy, preventing vascular events. This observation suggests a possible protective role and underscores the need to further investigate ACTN1’s function. Understanding its influence on platelet biology could inform antiplatelet drug development and offer novel therapeutic strategies for HHcy and related disorders.

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