



COMPLEX COAGULATION PROFILE IN ALG8-CDG: EXPANDING CLINICAL RECOGNITION OF A RARE DISORDER

R. Santacroce¹, M. Schiavulli², G. D'Andrea¹, G. Tiscia³, F. Cappucci³, M.L. Tramontano², E. Grandone^{3|4}, M. Margaglione¹

¹Genetica Medica - Dip.to di Medicina Clinica e Sperimentale, Università di Foggia, Italy; ²Haemophilia and Congenital Bleeding Disorders, Treatment Center Santobono-Pausilipon Children Hospital, AORN, Napoli, Italy; ³Unità di Emostasi e Trombosi, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo (FG), Italy; ⁴Ostericia e Ginecologia, Dip.to di Scienze Mediche e Chirurgiche, Università di Foggia, Italy

Congenital disorders of glycosylation (CDG) comprise a rapidly expanding group of metabolic diseases caused by genetic defects affecting glycoprotein synthesis. CDGs are clinically and genetically heterogeneous, and to date, approximately 100 types have been identified, with over 700 patients reported worldwide. ALG8-CDG (OMIM #608104) is one of the rarer CDG subtypes that is caused by variants in the ALG8 gene which encodes glucosyltransferase 2 (dolyl-yl-phosphateglucose 1-mannose 9-N acetylglucosamine glucosyltransferase). Fewer than 30 patients have been reported in the literature. It affects an early step in protein glycosylation and is generally associated with a poor prognosis. Patients with ALG8-CDG typically present with highly consistent clinical features, including neonatal onset, and a fatal outcome within the first year of life may occur. Early distinguishing features include multisystem involvement, dysmorphic features, neurological symptoms, and cataracts in approximately 50% of cases. Currently, no curative treatment is available for ALG8-CDG; however, establishing a molecular diagnosis is essential for family counseling and prenatal

diagnosis. We report the case of a 2-year-old girl who presented with delayed psychomotor development, language delay, and febrile seizures. She exhibited axial hypotonia at birth. Laboratory investigations repeatedly demonstrated a complex deficiency of hemostatic factors (aPTT ratio: 1.44; antithrombin: 40%; protein C: 28%; factor IX: 14%; factor XI: 45.4%). In addition, she carried the FII A20210G variant in the heterozygous state. Her parents were asymptomatic and showed no abnormalities of hemostatic factors. Whole-exome sequencing revealed compound heterozygosity in the ALG8 gene: c.685C>T (p.Arg229*) and c.206C>T (p.Pro69Leu). In silico tools predicted these variants to be deleterious; the former is classified as pathogenic (ACMG criteria: PVS1, PM2, PP5), while the latter is considered likely pathogenic (ACMG criteria: PM3, PP3, PP5). We describe a new case of ALG8-CDG that further expands current knowledge of this very rare autosomal recessive disorder and confirms the presence of a complex coagulation profile, likely related to hepatic involvement. These features represent a significant challenge for the clinical management of ALG8-CDG.