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Clinical, genetic and immunological analysis of patients with ataxia telangiectasia - of one center experience

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Ataxia telangiectasia is a very rare primary immunodeficiency with a circle of chromosomal instability occurring around the world with a known genetic defect in the gene ATM.

These patients have a number of progressive abnormalities, neurological (ataxia, intention tremor) and the variable irregularities in the immune system (progressive decrease in the number of T cells, the deficit of the major classes of immunoglobulins and IgG subclasses, inability to repair DNA strands), hypersensitivity to ionizing radiation and the huge trend the occurrence of neoplastic diseases.

Analysis covered 11 patients (aged 2 to 22 years old, 7 women and 3 men) who are under the care of the Department of Clinical Immunology and Pediatrics who have been identified for the treatment of intravenous immunoglobulins because of recurrent infections and deficit of IgG or IgG subclasses.

Analyzed: Clinical course (the first neurological symptoms, the first clinical signs of immunodeficiency) selected immunological tests (the concentration of the major classes of immunoglobulins, IgG subclasses, haemolytic activity of complement, properties of neutrophils phagocytosis, a panel of T cells, B cells and NK cells, and the concentration of AFP) depending on the performance of the individual mutations in the ATM gene.

Among the changes detected mutations: c.6754_6754delAfs5X c.434T> G c.6145T> G were not previously reported in the literature. Mutations c.6095G> A c.7630-2A> C are the most commonly detected mutations among patients with ataxia telangiectasia in Poland. Mutations detected in the study group were generally localized in the domain of N-Terminal domain protein and FAT domain.

At the two boys in whom the disease manifested itself very early we observed specific mutation and rapid and extremely aggressive course of the disease. These two brothers both carry a novel mutations: c.434T>G, p.L145R, c.6145T>G p.Y2049D. First mutation replaces non-polar, hydrophobic leucine with basic amino arginine at position 145. Second mutation is a substitution of aromatic tyrosine for acidic amino aspartic acid at position 2049 in the protein sequence. To predict the biological effect of two missense changes, in silico analysis was performed using the Protein Variation Effect Analyzer (PROVEAN, J. Craig Venter Institute). The algorithm of analysis predicted c.434T>G (score 3.403) and c.6145T>G (score 6.956) to be pathogenic.

Biography

Gerard Pasternak was graduated from the Medical University Wroclaw in 2008. Since 2015, he has been the Assistant at the Department and Clinic of Pediatrics, Immunology and Rheumatology of Developmental Age MU Wroclaw and the Department of Immunology and Pediatrics, Provincial Hospital J. Gromkowski, Wrocław (since 2010). He serves as a didactic Assistant Professor in the Department. He participates in conducting activities in the field of primary immunodeficiency for students of III-VI of the year and takes part in the preparation and conducting of workshops for patients with PID and their families. His professional interests and research are concentrated on the diagnosis and treatment of primary and secondary immunodeficiencies with particular emphasis on deficit of the IgG subclasses.