Significant prevalence of severe monogenic immune defects among children with Type 1 diabetes and low T1D-genetic risk score

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Introduction and objectives:
Monogenic Type 1 diabetes (T1D) is a rare disease caused by pathogenic variant in a single gene leading to dysregulation of immune system. T1D is combined with other autoimmunity like immune cytopenias, inflammatory bowel disease, rheumatoid arthritis, atopic eczema, autoimmune thyroid disease etc in these patients. Pathogenic variants in the AIRE, FOXP3, LRBA, IL2RA, CTLA4, STAT3 and STAT1 genes have been described as causal for monogenic T1D.

Patients and methods: Out of 519 paediatric patients with T1D from single tertiary center, 18 patients had at least two additional autoimmune conditions or a combination of T1D and autoimmune hepatitis, cytopenia or rheumatoid arthritis. In four patients with specific phenotype were analyzed by direct Sanger sequencing of the FOXP3, STAT3 and CTLA4 genes. DNA from the additional 14 patients was investigated using whole exome sequencing (WES). In addition, the T1D-genetic risk score (T1D-GRS) was used to discriminate monogenic autoimmunity from polygenic T1D.

Results: All four clinically highly suspected patients carried the causal variants in selected genes: One patient was diagnosed with IPEX syndrome with variant in the FOXP3 gene (p.Ser241Pro). Second patient manifested with recurrent episodes of immune thrombocytopenic purpura (ITP), autoimmune haemolytic anaemia (AIHA) and T1D. He presented total alopecia and optic nerve neuritis. His younger brother manifested with T1D at age 1 year and 10 months. Later on, he also developed ITP and AIHA. They carried a heterozygous variant in the STAT3 gene (p.Tyr60Asn). The fourth patient was diagnosed with multiple early-onset autoimmune conditions due to the activation mutation in the STAT3 gene (p.Pro715Leu). No other causal variant in selected genes was found in remaining 14 highly suspicious patients. These four children have the T1D-GRS below 40th centile.

In conclusion, we found four of the 18 patients with genetically confirmed monogenic form of T1D representing 22% in our specific cohort with severe T1D associated multiple autoimmunity. The T1D-GRS is a novel tool that can be helpful for discrimination between monogenic and polygenic forms of diabetes and combined with analysis by WES will be useful for searching genes causing monogenic T1D.

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