A Syndrome of Permanent Neonatal Diabetes Mellitus and Neurological Abnormalities Due To a Novel Homozygous Missense c.449T>A (p.I150N) Mutation in NEUROD1 Gene

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Neonatal diabetes mellitus (NDM) is a rare form of monogenic diabetes presenting in the first 6 months of life. NEUROD1 is a transcriptional factor involved in the development of endocrine pancreas. A few patients with maturity onset diabetes of the young (MODY) due to heterozygous NEUROD1 mutations and only two cases with permanent NDM (PNDM) associated to neurological disorders and cerebellar hypoplasia due to homozygous mutations in the NEUROD1 gene have been reported.

Case:

A 13 years-old female was referred to our endocrine department due to hyperglycemia. She was on insulin therapy due to diagnosis of NDM whilst missed her regular follow-up visits. Parents were third cousins. Father and one aunt had a diagnosis of Type 2 DM. Auxological measurements were within normal ranges. In the laboratory examination HbA1c was 8.9% and fasting c-peptide was undetectable (<0.1ng/ml). She had developed difficulty in walking at the age of 4 years which had worsen over time. In the further evaluation the diagnosis of visual impairment, mental retardation, ataxic gait, retinitis pigmentosa and sensori-neural deafness was considered. Cranial magnetic resonance imaging (MRI) revealed cerebellar hypoplasia. Molecular genetics analysis using targeted next generation sequencing detected a novel homozygous missense p.I150N (c.449T>A) mutation in exon 2 of NEUROD1. This mutation affects a highly conserved residue within the DNA-binding domain of NEUROD1 and current evidence suggests that the mutation is likely to be pathogenic. Both parents and two siblings were heterozygous for the mutation.

Conclusion:

Homozygous NEUROD1 mutations cause a rare syndrome of PNDM associated to neurological abnormalities. Heterozygous mutations, however, may present with MODY phenotype with extremely variable penetrance among individuals who carry identical mutation, even within same family.