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.

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