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Abstract Topic:- Molecular effects of genetic variation

Abstract Title:- Mitochondrial complex I deficiency, nuclear type 5: Analysis of NDUFS1 gene to explore its genetic variants and related phenotype

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Aims:-Mitochondrial complex 1 deficiency (MC1D) is a group of rare, often fatal mitochondrial illnesses that primarily affect the cell's energy-producing organelles, the mitochondria. This condition, which primarily affects the brain and neurological system, is typically hereditary in origin and autosomal recessive in type. This project aims to investigate the genetic, clinical, and neuroimaging aspects of mitochondrial complex 1 deficiency nuclear type 5 (MC1DN5), a hereditary disorder caused by mutations in the NADH-Ubiquinone Oxidoreductase Fe-S protein 1 (NDUFS1) gene.

Methods:- This investigation was carried out in the Pediatric Neurology department of a tertiary care centre by the department of Pediatrics. Investigations and records were made of the clinical and demographic information pertaining to pediatric MC1D patients. Next generation sequencing was used to find the genetic variant. To record the neuroimaging results, the neuroradiologist assessed magnetic resonance imaging (MRI) scans of the brain.

Results:- Seven pediatric patients with MCIDN5 are reported in the study; one had the late infantile form and the other six had infantile onset. The clinical profile included neuro-regression (28.57%), regression of motor milestones (57.14%), seizures (71.42%), global developmental delay (42.85%), hypertonia (28.57%), hypotonia (28.57%), dystonia (28.57%), spasticity (85.71%), fever (42.85%), vomiting (28.57%), and microcephaly (14.28%). Compared to male paediatric patients (42.85%), more female paediatric patients (57.14%) were observed. T2/FLAIR hyperintensities in periventricular white matter and corpus callosum involvement were indicative of the MRI changes. Seven children had a total of three NDUFS1 gene variations identified, with the c.2102G>A mutation predominating in four cases (42.8%). In our investigation, 6/7 cases (85.71%) showed a predominant further substitution of asparagine for serine in the amino acid sequence.

Conclusions:- A genetic validation is essential given the wide range of clinical and neuroimaging results in children. Compared to the wild type residue serine, the mutant residue asparagine is larger and more hydrophobic. This difference could disrupt protein interactions and the passage of signals from the binding domain to the activity domain. Thus, the extremely prevalent p.Ser701/715Asn mutation in the NDUFS1 gene should be the focus of future research on diagnostic and therapeutic approaches in MCID.

Keywords:- Mitochondrial complex I deficiency, MCIDN5, NDUFS1, Genetic variation