MITOCHONDRIAL COMPLEX I DEFICIENCY: CLINICAL MANIFESTATION, NEUROIMAGING AND GENETIC PROFILING IN PEDIATRIC PATIENTS

Arushi Gahlot Saini[1], Sanjhi Paliwal[1],, Yashu Sharma[1], Vikas Bhatia[2], Prateek Bhatia[1], Savita Verma Attri[1], Priyanka Shrivastatava[1], Naveen Sankhyan[1]

[1]Department of Pediatrics, and [2]**Ra**diodiagnosis, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh

18TH ICNC 2024 Footprints to the future
INTERNATIONAL CHILD NEUROLOGY CONGRESS
Cape Town, South Africa I May 6-10, 2024

MITOCHONDRIAL RESPIRATORY CHAIN DEFECTS

- Disorders of electron transport chain and oxidative phosphorylation
- Nuclear-encoded disorders are autosomal-recessive
- Complex I: largest and most commonly affected
- NADH-Ubiquinone Oxidoreductase Fe-S protein 1 (*NDUFS1*) gene codes for its core subunit
- *Clinical:* Leigh syndrome most common presentation

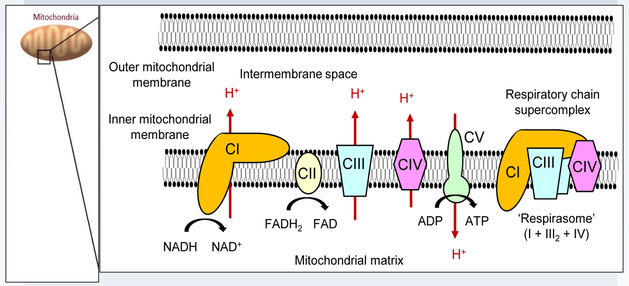


Fig 1: Mitochondrial respiratory chain and complex I-V assembly

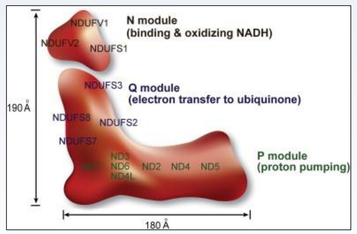


Fig 2: Position of NDUFS1 in mito respiratory chain complex I

AIM

To explore clinical, neuroimaging and genetic framework of mitochondrial complex I deficiency related to *NDUFS1* gene

Study design
- Crosse-sectional study
- 149 children with suspected mitochondrial leukoencephalopathy screened in Paediatric Neurology Clinic.

Neuroimaging
- MRI of brain on 3T machine
- Evaluated by team of radiologist and neurologist

WES
- NGS (illumina), bioinformatics analysis (BWA-MEM, GATK), variant filtering, in-silico characterization
- Pathogenicity as per ACMG criteria and 3D protein structure prediction using HOPE software

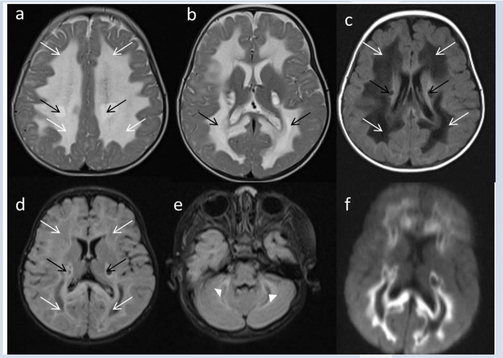
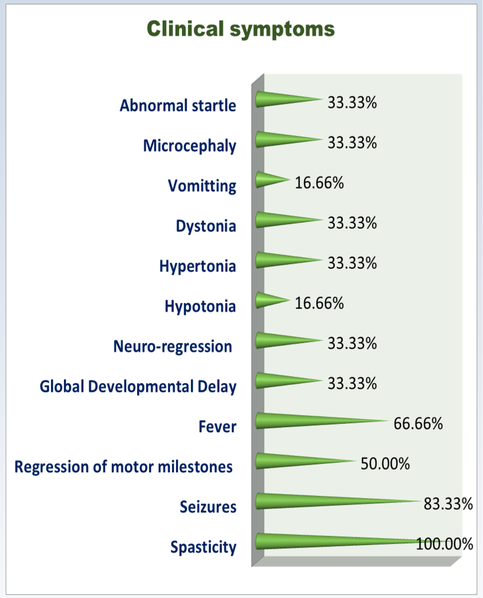


Fig 6: Axial T2w (a, b) diffuse hyper intensities in bilateral cerebral hemispheres (white arrows), (c) hypointense on T1 (d) mildly hyperintense on FLAIR images. Multiple cystic changes in periventricular WM, basal ganglia and corpus collasum (black arrows) and bilateral cerebellar hemispheres (e). DWI (f) shows diffusion restriction with sparing in cystic areas

Cases: Out of 149 paediatric patients screened, 6 cases had pathogenic **p.Ser701Asn** mutation in *NDUFS1* gene (Insilico prediction: MetaRNN score 0.5997536 and CADD score 25.9)

Onset: Infantile onset



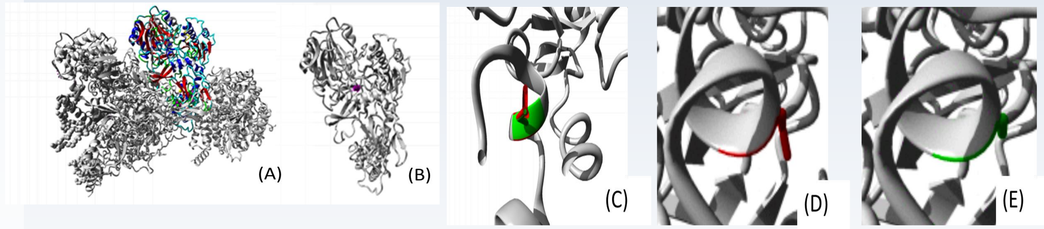
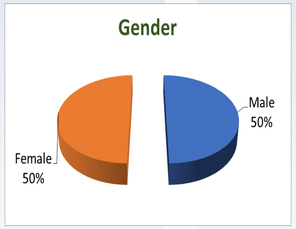
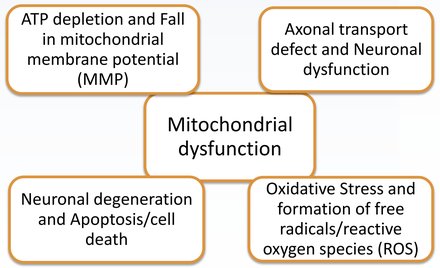


Fig. 2: A ribbon form of the **NDUFS1** protein as predicted with HOPE program. (A): α-helix **blue**, β-strand **red**, turn **green**, 3/10 helix **yellow**, random coil **cyan**, complex molecules **grey**; (B): the small balls of mutated residue [Asp] is **magenta**. (C)-(E): Close-up of the mutation **p.Ser701Asn**; protein **grey**, mutant side chain **red** and wild type side chain **green**



Discussion and Conclusion

- The larger and more hydrophobic mutant Asparagine causes loss of hydrogen bonding with Aspartic acid at position 698, disrupting protein interactions and passage of signals from binding domain to activity domain
- **p.Ser701Asn** previously reported in 4 other affected individual with Leigh presentation and cystic leukoencephalopathy.[3,4,5]
- Future potential: To study the underlying mechanisms in p.Ser701Asn mutation of *NDUFS1* gene in-vitro or in-vivo and creating viable treatments for them



This research was supported by funding from DST-SERB, India and the study was approved by the Institutional Ethics Committee. We declare no conflict of interest.

1. Gorman GS, et al. Suomalainen A, Thorburn DR, Zeviani M, Turnbull DM. Mitochondrial diseases. Nat Rev Dis Primers. 2016 Oct 20;2:16080. doi: 10.1038/nrdp.2016.80. 2. Lemarie, A., Grimm, S. Mitochondrial respiratory chain complexes: apoptosis sensors mutated in cancer?. Oncogene 30, 3985–4003 (2011). https://doi.org/10.1038/onc.2011.167 3. Björkman K, Sofou K, Darin N, Holme E, Kollberg G, Asin-Cayuela J, Holmberg Dahle KM, Oldfors A, Moslemi AR, Tulinius M. Broad phenotypic variability in patients with complex I deficiency due to mutations in NDUFS1 and NDUFV1. Mitochondrion. 2015 Mar;21:33-40. doi: 10.1016/j.mito.2015.01.003 4. Lim AZ, Ng YS, Blain A, Jiminez-Moreno C, Alston CL, Nesbitt V, Simmons L, Santra S, Wassmer E, Blakely EL, Turnbull DM, Taylor RW, Gorman GS, McFarland R. Natural History of Leigh Syndrome: A Study of Disease Burden and Progression. Ann Neurol. 2022 Jan;91(1):117-130. doi: 10.1002/ana.26260 5. Schlüter A, Rodríguez-Palmero A, Verdura E, Vélez-Santamaría V, Ruiz M, Fourcade S, Planas-Serra L, Martínez JJ, Guilera C, Girós M, Artuch R et al., Diagnosis of Genetic White Matter Disorders by Singleton Whole-Exome and Genome Sequencing Using Interactome-Driven Prioritization. Neurology. 2022 Mar 1;98(9):e912-e923. doi: 10.1212/WNL.0000000000013278