NDUFV1 Related Mitochondrial Complex-1 Disorders – A Retrospective Case Series and Literature Review

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INTRODUCTION

- *NDUFV1* gene is a vital component of the mitochondrial complex-1 [1]
- Pathogenic variants in this *NDUFV1* gene have broad clinico-radiological spectrum, of which Leigh syndrome and cavitating leukodystrophy pattern are most common[2]
- The onset may mimic a demyelinating disorder in form of acute deterioration after a stress and disease course maybe static to rapidly progressive[3]
- Pyramidal weakness, seizures, and encephalopathy are the most common presenting features

OBJECTIVES

- To describe a case series of seven cases from our centre, which constitutes the largest cohort of pathogenic variants in the NDUFV1 gene. We aim to provide detailed descriptions of the clinical, radiological, and genetic variants of our cases, followed by a comparison with cases reported in existing literature

MATRIALS AND METHODS

- Details of DUFV1 cases with pathogenic variants from our center were collected
- A comprehensive search of PubMed, Scopus and Google Scholar databases was done to collect all the existing reported cases
- Clical, radiological, and genetic variant details were entered in a predesigned format
- Clinical features were described, and MRI pattern was classified as one of the following:
  - **Leigh pattern**: Putamen, thalamus, basal ganglia, and brainstem involvement
  - **Leukodystrophy pattern**: White matter involvement accompanied by cystic cavitations
  - **Mixed pattern**: Combined feature of above two pattern
- Clinical comparison of clinical features, radiological findings, genetic variants and final outcomes between our cohort and the combined cohort was conducted
- In the combined cohort, we conducted an analysis to examine the relationship between the age of disease onset, genetic variants, MRI phenotype, comorbidities, and factors associated with mortality

RESULTS

- A total of 37 cases from 23 studies were included from the literature for final analysis along with 7 cases of our cohort
- All cases in our cohort exhibited homozygous pathogenic variants, c.1156C>T (p.Arg386Cys), located in exon 8 of the *NDUFV1* gene. All cases in our cohort were alive at last available follow-up
- 5/7 children had leukodystrophy pattern (Figure-1) and 2/7 has mixed pattern on MRI (Figure-2)
- Hypertonia (7/7) and dystonia (3/7) were most common clinical features in our cohort and more common as compared to the overall cohort
- All 7 children from our cohort received mitochondrial cocktail therapy

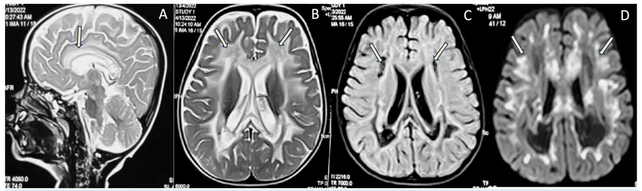

Figure-1: MRI brain T2 sagittal section shows hyperintensity in corpus callosum hyperintensity (arrow in A). T2 and FLAIR axial section show hyperintensity and cavitations in bilateral diffuse , periventricular and subcortical white matter (arrows in B and D). DWI shows diffusion restriction in corresponding white matter(arrows in D). (Mitochondrial Leukodystrophy pattern)

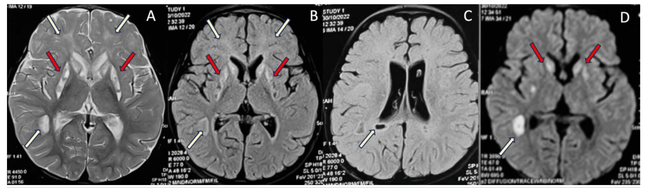

Figure-2: MRI brain T2 axial section and T2 FLAIR axial sections show hyperintensity and cavitation in bilateral frontal dominant periventricular and subcortical white matter, right parietal white matter(arrows in A,B & C) and basal ganglia(arrows in red in A & B). DWI shows diffusion restriction in bilateral basal ganglia(red arrows in D) and parietal cortical white matter(arrow in D) (Mixed pattern)

COMBINED COHORT

- Median age of onset of symptoms was 9 months and majority (66%) cases presenting before 12 months
- Common clinical presenting symptoms were hypertonia with psychomotor regression (61.3%), oculomotor dysfunction (56.8%), feeding difficulty (38.6%) and hypotonia at onset (34.1%)
- MRI brain details were available for 42 cases, with 22 showing a leukodystrophy pattern, 14 Leigh pattern, and 6 had mixed pattern
- No correlation between the age of symptom onset or MRI patterns with death or treatment response
- Cases with the variant c.1156C>T p.Arg386Cys had significant irritability (44.4% vs. 7.7%, *p*-0.008) and dystonia (27.8% vs. 3.8%, *p*-0.03)
- Genetic variant had no correlation with death or treatment response
- Cases with Leigh type MRI pattern had more respiratory complications (42.8%, *p*-0.009) and higher number of deaths (Leigh-54.5%, leukodystrophy-16.7% and mixed-0, *p*-0.021)
- All children who received mitochondrial cocktail therapy survived (100%), while only 4/7 that did not receive mitochondrial therapy survived (57.1%) (*p*- 0.013)

CONCLUSION

- c.1156C>T (p.Arg386Cys is most variant from Asia
- c.1156C>T variants show lesser seizures, higher irritability and dystonia, and a higher probability of leukodystrophy or mixed MRI pattern
- MRI pattern correlates with clinical presentation and outcome
- Treatment with a mitochondrial cocktail may reduce mortality and improve outcomes, irrespective genetic variant and age of onset

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