Multiple Mitochondrial Dysfunctions Syndrome-5 caused by Iron Sulphur Cluster Assembly 1 (ISCA 1) – Case report

Dr Ashwin Sardesai [1], Dr Mahesh Kamate [1], Dr Thanuja B [1]

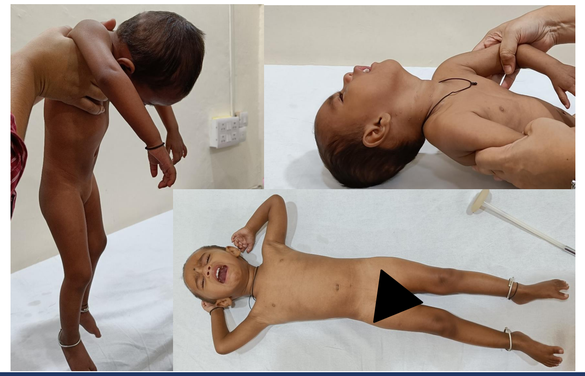
[1] Department of Paediatric Neurology, Jawaharlal Nehru Medical College, Belagavi, Karnataka, India

INTRODUCTION

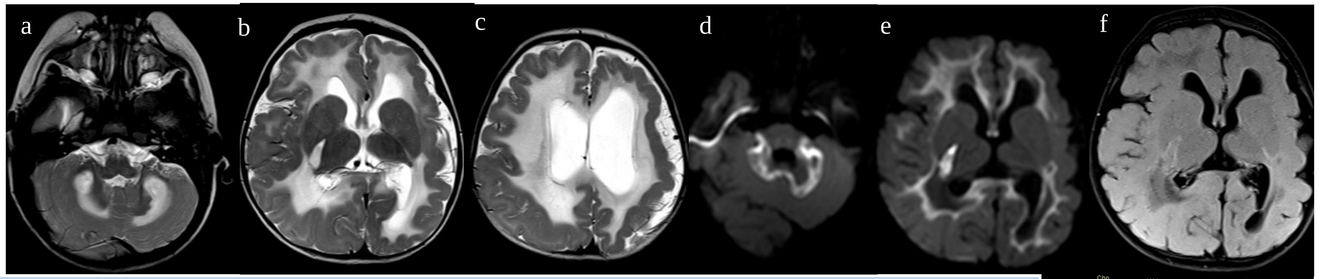
- ISCA1-MMDS a severe neurodegenerative condition with either no attainment of developmental milestones or very early loss of achieved milestones, seizures in early infancy, spasticity with exaggerated DTRs, nystagmus, and risk for sensorineural hearing loss.
- Two presentations: (i) severe early encephalopathy with major psychomotor retardation and few or no achieved milestones leading to early death (Indian Genotype) (ii) moderate encephalopathy (Egypt,Italy).
- Here we present a case report from India with unique combination of neuroimaging findings of vacuolating Leukodystrophy with pachygyria and restricted diffusion

CASE REPORT

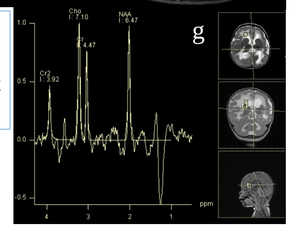
- 1 year and 9 months old female child born of third degree consanguineous marriage
- Birth history: Term, LSCS, Cried at birth, 2.5 kg birth weight, No neonatal encephalopathy
- Presented with global developmental delay, failure to thrive and difficulty in feeding. No h/o seizures.
- Dystonia noticed since last 3 months.
- Microcephaly, plagiocephaly, nystagmus,
- Truncal hypotonia, limb spasticity with brisk deep tendon reflexes and dystonic tremors.



INVESTIGATIONS



Images a,b,c (MRI Brain T2W axial) show bilateral symmetrical white matter involvement with cystic changes. Posterior limb of internal capsule and cerebellar white matter involvement. Restricted diffusion in noted in the same areas (Images d,e). Pachygyria is seen in the left frontoparietal region. Basal ganglia are normal(Image f) Involvement of the lateral and dorsal aspect of cervical spinal cord. MR spectroscopy (Image g): Elevated Lactate peak



- Clinically, child was suspected to have spastic quadriparetic cerebral palsy
- Radiological D/D: Vanishing white matter disease, LBSL, Van der Knapp disease, MMDS
- Whole Exome Sequencing : ISCA 1 gene variant confirmed by Sanger sequencing of parents

Gene & Transcript	Variant	Location	Zygosity	Disorder (OMIM)	Inheritance	Classification
ISCA1 NM_030940.4	c.259G>A (p.Glu87Lys)	Exon 4	Homozygous	Multiple mitochondrial dysfunctions syndrome 5 (617613)	Autosomal Recessive	Likely Pathogenic

DISCUSSION

Previous Case reports	Age at Onset/ Age at Death	Metabolic Findings	Ophthalmic Findings	Clinical Feature	Brain MRI / Spectroscopy	Genotype (ISCA1:NM_030940.3)
Shukla et al 4 (2Families, India)	Neonate (2/4) 2–3 mo (2/4)/ 11 mo to 5 y	Elevated CPK (1/2)	Nystagmus (1/4) fundus pigmentation (1/2)	Major PMDD, SP, SZ, FD	Pachygyria (2/4), VMG, cerebral and cerebellar WM LD/lactate peak	c.[259G > A],p.[(Gln87Lys)] Homozygous
Torraco et al 1 (Italia)	3 mo/11 yr	High lactate (bl) and glycine (ur) levels	Nystagmus	Mild PMDD, SP, FD	Vacuolating LD, TCC	c.[29T > G],p.[(Val10Gly)] Homozygous
Shukla et al 1 (India)	3 mo/NA	NA	No	Major PMDD, SP, SZ	Pachygyria (n = 2/4), VMG, cerebral and cerebellar WM LD/lactate peak	c.[259G > A],p.[(Gln87Lys)] Homozygous
Lebigot et al 1 (Egypt)	20 m/alive at 7 yr	High lactate (bl) level	No	Mild PMDD, SP, hemiparesis	Vacuolating LD, TCC, VMG/lactate peak	c.[302A>G],p.[(Tyr101Cys)] Homozygous
1 (Belagavi) Our case	3 m / alive at 2 yr	NA	Nystagmus	PMDD, SP, FD	Vacuolating LD, VMG, cerebellar WM LD, Pachygyria, lactate peak	c.[259G > A],p.[(Gln87Lys)] Homozygous

FD- Feeding difficulty, LD –Leukodystrophy, PMDD –Psychomotor developmental delay, SZ –Seizure, SP –Spasticity, TCC –Thin Corpus callosum, VMG- Ventriculomegaly, WM – white matter, bl- blood, CPK- creatine phosphokinase, ur- urine, NA- Information not available

DISCUSSION (continued)

- Mitochondrial proteins carrying iron-sulfur (Fe-S) clusters are involved in essential cellular pathways such as oxidative phosphorylation, lipoic acid synthesis, and iron metabolism.
- NFU1, BOLA3, IBA57, ISCA2, and ISCA1 are involved in the last steps of the maturation of mitochondrial [4Fe-4S]-containing proteins and are responsible for Multiple Mitochondrial dysfunctions syndrome 1 to 5 respectively.
- ISCA 1 causes MMMDS 5
- The mutation in our case is the same as the founder mutation described in India by Shukla et al
- However the neuroimaging findings are a unique combination of findings described in cases of India and abroad

CONCLUSION

- This is the eighth reported case worldwide of MMDS 5 due to ISCA1 and has unique MRI brain findings
- In a child with CP where MRI shows the unusual combination of cortical malformation with cystic changes (suggestive of congenital/chronic etiology) along with restricted diffusion(which hints at an acute pathology), we must think of MMDS and consider genetic testing

REFERENCES

1. Lebigot E, Schiff M, Golinelli-Cohen MP. A Review of Multiple Mitochondrial Dysfunction Syndromes, Syndromes Associated with Defective Fe-S Protein Maturation. Biomedicines. 2021 Aug 10;9(8):989.
2. Shukla A, Narayanan DL, Kaur P, et al. ISCA1-Related Multiple Mitochondrial Dysfunctions Syndrome. 2019 Oct 3. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.
3. Shukla A, Hebbar M, Srivastava A, Kadavigere R, Upadhyai P et al, Homozygous p.(Glu87Lys) variant in ISCA1 is associated with a multiple mitochondrial dysfunction syndrome. J Hum Genet. 2017 Jul;62(7):723-727

CONTACT

drmaheshkamate@gmail.com
ashwin.sayzz@gmail.com