A SWEET DEGENENERATION

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CHIEF COMPLAINTS

- 16y/F
- Unsteady gait and slurring of speech since 6 yrs of age.
- H/O involuntary movments of bilateral upper limb x 3 yrs
- Currently came with C/O 2 episodes of seizures in 3 days.

HOPI

- 16 yr old girl
- Born to 2nd degree consanguinous marriage
- Developmentally normal till 6 yrs of age
- Suddenly developed difficulty in walking and slurring of speech - progressive.
- Currently able to walk without support but gait is unsteady - tiptoe walking (Left leg)
- contracture deformity of left ankle.

- Able to hold pen but unable to write.
- H/O involuntary movements of b/l upper limb x 3 yrs - in the form of choreiform movements
- Progressive
- In class 12 (scribe method)
- Had one episode of seizure at 13 yrs - Started on T.Eptoin.

- Currently has come with 2 episodes of seizure in 3 days - deviation of mouth, stiffening of limbs
- < 5 mins.
- Associated with vomiting.

PAST HISTORY

- H/O one episode of seizure at 3 months of age - admitted in hospital for 14 days.
- Started on AED
- continued till 5 yrs of age.

BIRTH HISTORY

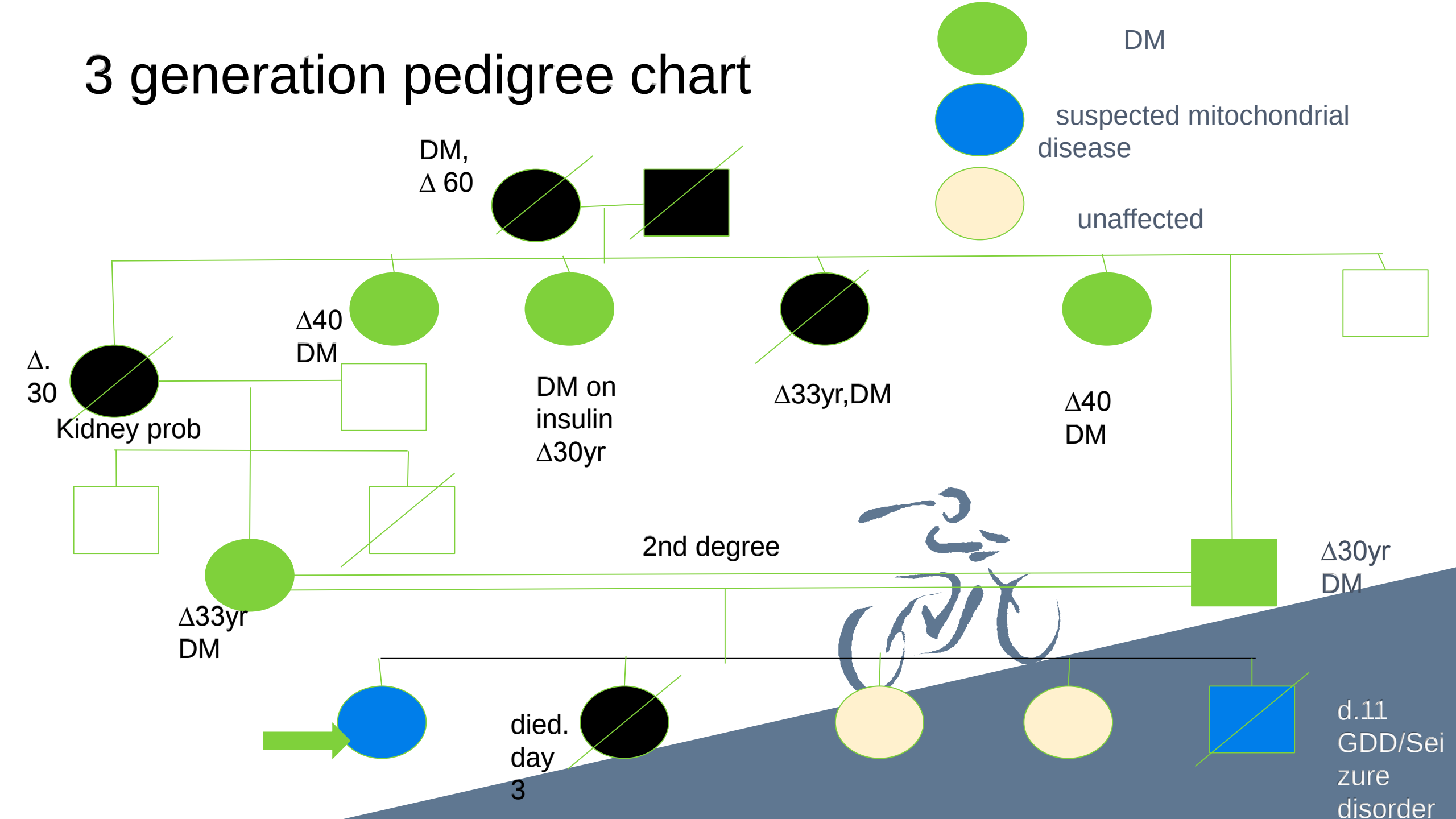
- Antenatal - Uneventful
- Natal - FTNVD, 2.7 Kg, cried at birth
- Post natal - No NICU admission

DEVELOPMENT

DOMAIN	BEST ATTAINED	CURRENT	DEVELOPMENTAL AGE
GROSS MOTOR	Hopping, Rides bicycle	Walking without support, unsteady gait.	1 YEAR
FINE MOTOR	Writes sentences	Turns pages of books, cannot hold pen and write.	1 YEAR
LANGUAGE	Narrated stories	short sentences,slow and Slurred speech present	3 YEAR
SOCIAL	Had many friends, was playing with peers.	Has many friends, is in class 12. Avereage scholastic performance.	

IMP - Neuroregression from 6yrs of age, mainly motor.

3 generation pedigree chart



Examination

- Head to toe - Normal, No neurocutaneous markers.
- Vitals

HR - 80/min

RR- 18/min

BP - 120/80 mm hg

Anthropometry

Wt for age - 65 kgs (90th to 97th centile)

Ht for age - 158cm (50th to 75th centile)

HC - 54cm

BMI - 27 (overweight)

CNS - Higher mental function - Conscious, oriented

Speech - dysarthric

Motor system - Tone,bulk - normal

Reflexes - not elicitable

Power - 4/5 in all 4 limbs around all joints

contracture + in left ankle

Cranial nerves- normal

Cerebellar - negative

Meningeal signs - negative

spine - normal

OTHER SYSTEMS - Normal

PROVISIONAL DIAGNOSIS -

Neuroregression/Seizures + GDD in younger sibling(expired),neonatal death,early onset DM among family members.

?Mitochondrial encephalopathies ?MELAS

DD

IEM/Leukodystrophies/Multiple sclerosis/Wilson's disease/

INVESTIGATIONS

CBC - Normal

LFT/RFT - Normal

Metabolic work up

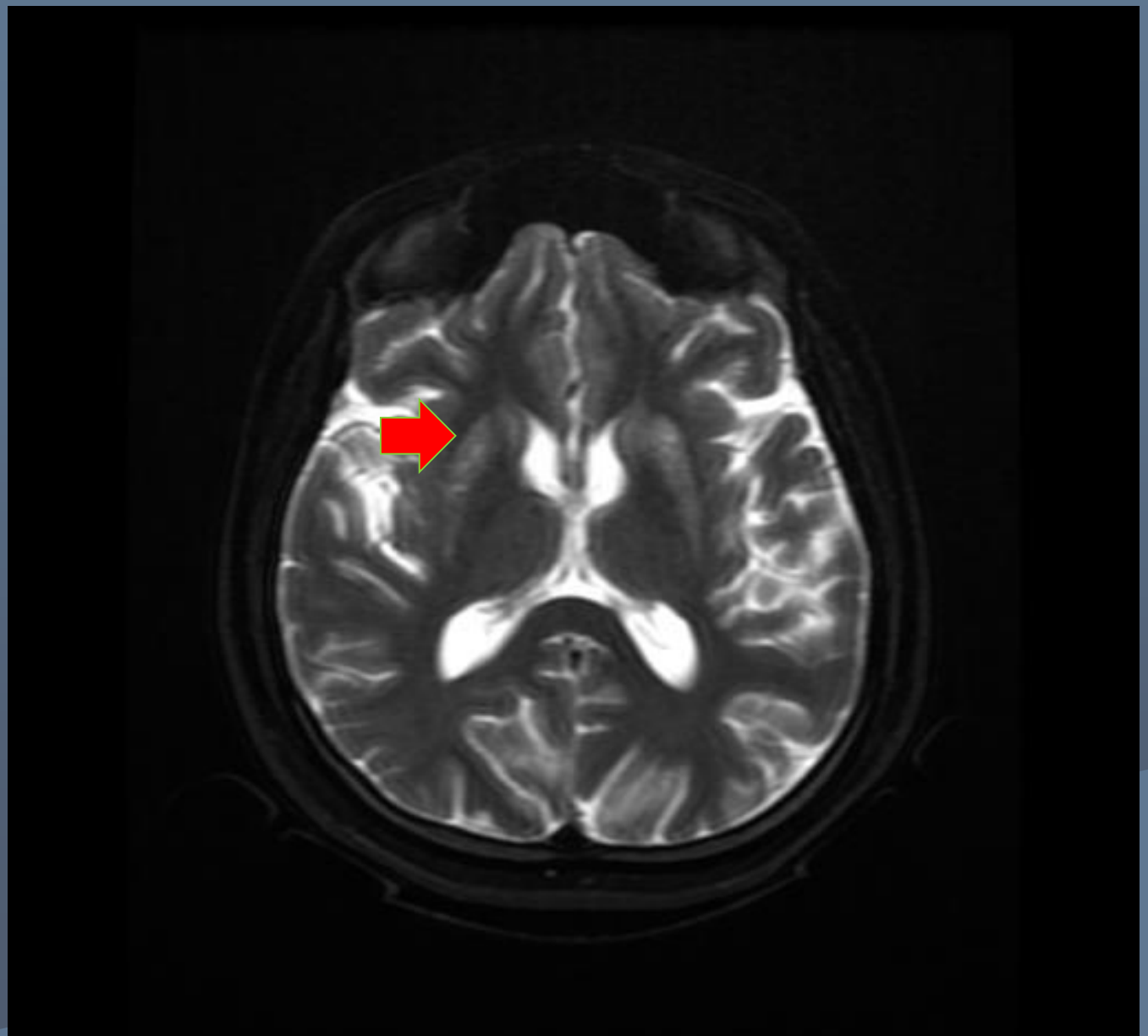
FBS - 320 mg/dl

Sr. Ammonia - normal

Lactate - 2.9

Urine ketone - Negative

MRI BRAIN

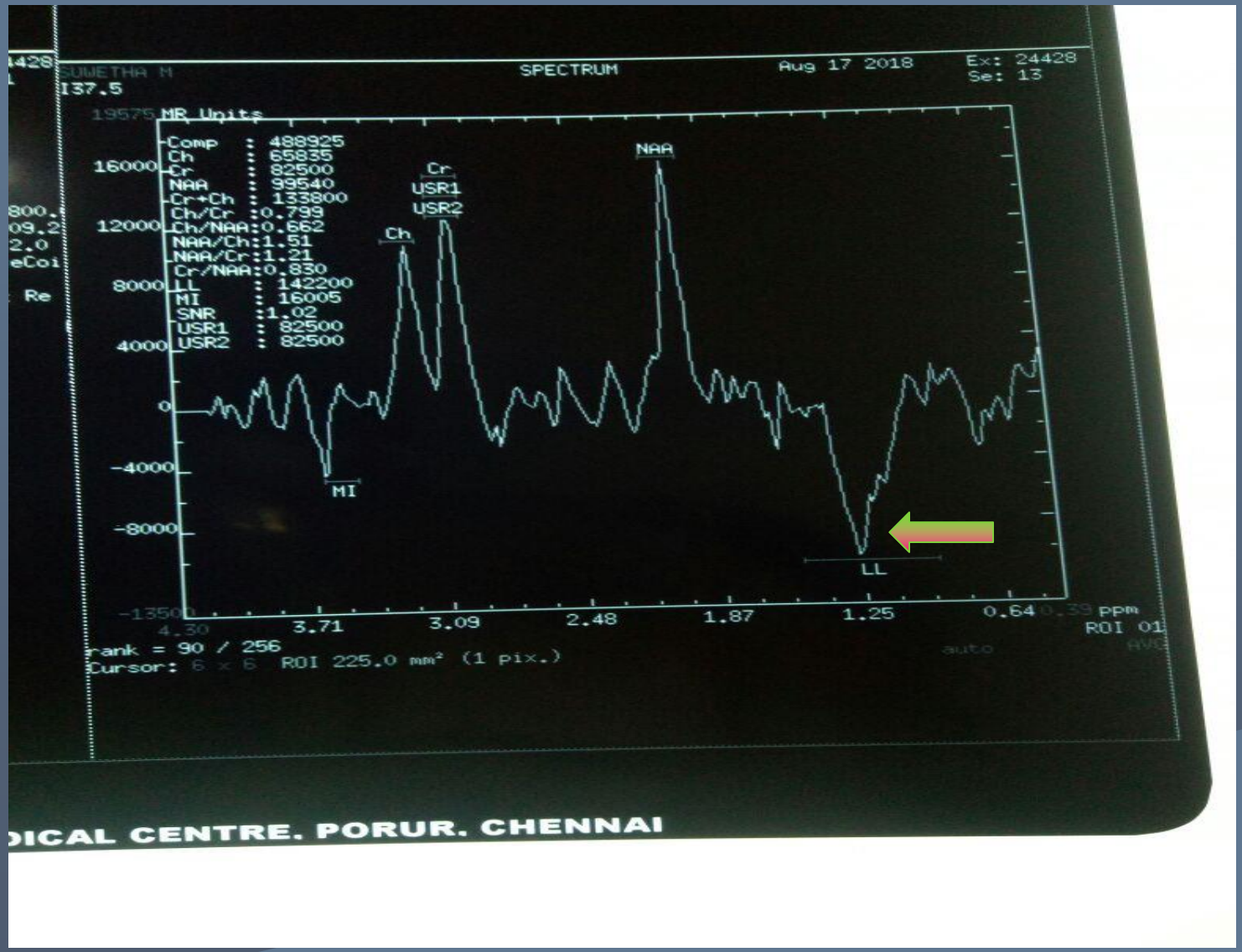


IMP-

- Extensive multiple scattered areas of T2 hyperintensities with areas of diffusion restriction (infarcts) involving B/L Parietal lobes, left tempero-occipital lobe, right occipital and B/L cerebellar hemispheres.
- T2 hyperintensities involving caudate and putamensparing the globus pallidus.

MR SPECTROSCOPY

IMP- DOUBLET LACTATE PEAK



HbA1c - 10.9

Sr. Insulin - 7.3 (0.78 - 5.19)

C peptide -2.46 (6 - 27)

Ophthal evaluation - Normal

ENT -

BERA - L minimal hearing loss +

GENETIC STUDIES

Mitochondrial gene sequencing for MELAS - NEGATIVE.

Clinical Exome sequencing of nuclear DNA for LEIGHS - planned.

Final Diagnosis

Mitochondrial encephalomyopathy - Most probably LEIGHS?mitochondrial diabetes.

MANAGEMENT

- AED- T. levitercetam 750 mg BD
- Inj. Regular insulin 14 U - 14U - 14U
- Inj. Glargine 0 - 0 - 12U

Mitochondrial enzyme cocktail

- T. Riboflavin C.EVION
- T. Leucovirin Syp. Carnitine
- Co enzyme Q T. Benalgis

CURRENT STATUS OF THE CHILD

After 4 months of treatment with mitochondrial cocktail

- Involuntary movements - reduced
- Seizures- under control
- Blood sugars - normal

Classification of neurodegenerative disorder

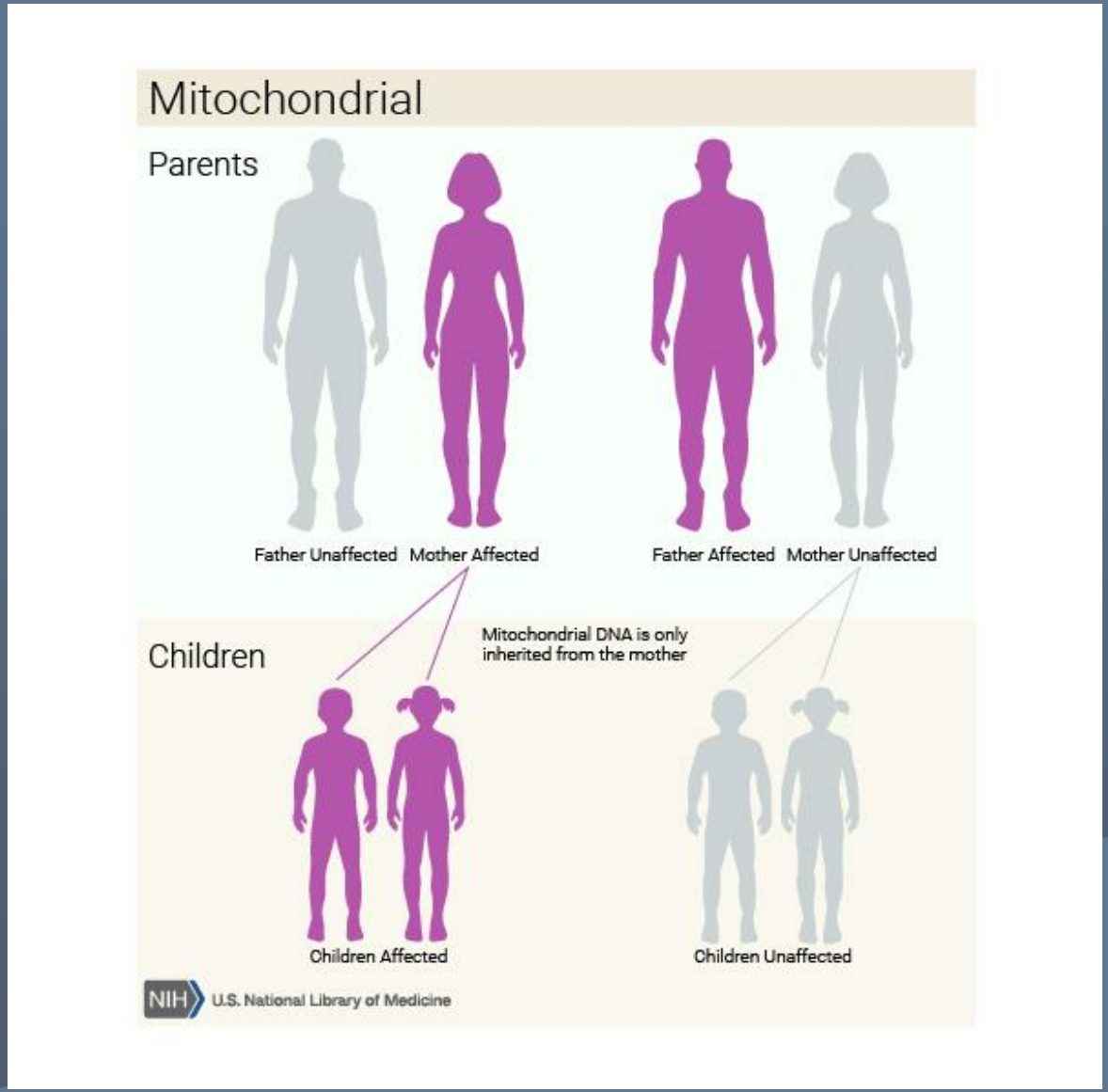
AGE AT ONSET	CONDITIONS
<2 YR WITH HEPATOMEGALY	Galactosemia
	LSD (Gaucher,Tay sachs, niemann- pick)
	MPS
< 2 YR WITHOUT HEPATOMEGALY	Rett syndrome
	MSUD
	Phenylketonuria
2 - 5 yrs	Wilson disease
	Mitochondrial encephalopathies (MELAS,MERRF)
5 - 15 YRS	Multiple sclerosis
	SSPE
	Adrenoleukodystrophy

Mitochondrial cytopathy

- Heterogenous group of clinical syndrome caused by genetic lesions that impair energy production through oxidative phophorylation.
- 3 groups

1. Defects of mt DNA
2. Defects of nDNA
3. Defects of communication between mitochondrial and nuclear genome.

Mitochondrial inheritance



MITOCHONDRIALMYOPATHY,ENCEPHALOPATHY,LACTIC ACIDOSIS, STROKE LIKE EPISODES (MELAS)

- MELAS A3243G mutation in mitochondrial DNA - muscle is the preferable tissue.
- Clinical manifestations

CNS - regression, seizures, ataxia, migraine, deafness, cortical blindness, movement disorder, peripheral neuropathy.

•Anemia, lactic acidosis, Diabetes mellitus, fanconi syndrome.

•Ophthalmoplegia, pigmented retinopathy, hypertrophic or dilated cardiomyopathy maybe present.

LEIGH'S DISEASE

- Mutation in nuclear DNA.
- CLINICAL SYMPTOMS

  CNS- Delayed motor and language milestones/Seizures/hypotonia/ataxia/nystagmus/tremor
- ophthal - Ptosis, decreased visual acquity, retinitis pigmentosa, optic atrophy may be seen.
- Others- Hypertrophic cardiomyopathy, hepatic failure, renal tubular dysfunction.

OTHERS

- Myoclonus epilepsy and ragged red fibres (MERRF)
- Neuropathy,ataxia and retinits pigmentosa syndrome(NARP)
- Leber hereditary optic neuropathy (LHON)
- Kearns - sayre syndrome (KSS)
- Reye syndrome
- Reversible infantile cytochrome C oxidase deficiency myopathy.

CONCLUSION

- Suspect mitochondrial encephalopathies in a child with neuroregression and positive family history of diabetes.
- Screening for associated co-morbidities (CVS,endocrinopathies,etc).
- Mitochondrial cocktail therapy has shown transient improvement in neurological condition.
- Comprehensive and multidisciplinary care needed.

- Nelson textbook of pediatrics, 20th edition.
- Hideki Onishi, ken Inoue,Hitoshi osaka, Seiji Kimura, Hideki nagatomo, Tokiji Hanihara et al, Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke like episodes (MELAS) and diabetes mellitus: molecular genetic analysis and family study, Journal of neurological sciences, 114 (1993) 205-208

THANK YOU