EPILEPTIC CLUES TO A METABOLIC MYSTERY: SEIZURE AS PRESENTATION OF MENKES DISEASE

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BACKCROUND

Seizures are one of the most common neurological symptoms that occur in infancy and childhood Copper deficiency as occurs in Menkes disease is a rare cause of infantile epilepsy.

Patients usually exhibit a severe clinical course with death in early childhood.

Early diagnosis of Menkes disease is clinically very challenging because of the subtle clinical features and nonspecific biochemical markers

AIM

To highlight **seizure as the first manifestation of Menkes disease** and emphasize the **importance of metabolic evaluation** in infants with unexplained seizures and relevant family history.

CLINICAL HISTORY

7 month old male child, 2nd born of NCM parentage ,normal vaginal delivery, with no history of NICU admissions, mild developmental delay in form of delayed head control, presented with incessant cry for 3 days with occasional jerky movements of limbs.

h/o previous seizure like episode 1 month back

History of seizures in elder brother since age of 3 months , who expired at age of 1 and 1/2 year due to seizures as per mother. No h/o seizures in any other family members

GENERAL PHYSICAL EXAMINATION

- Child was alert active, afebrile
- Hair- sparse curly brittle hairs with discolouration
- seborrheic dermatitis +
- No neurocutaneous markers
- No dysmorphic facies
- External genitalia normal
- b/l testes palpable

CNS:

- b/l pupils RTL; DEM present
- Follows light
- Turns head to sound
- tone- increased in all 4 limbs
- Head lag + on pulling to sit
- Moves all 4 limbs spontaneously
- DTR- 2+
- Plantar- b/l extensor

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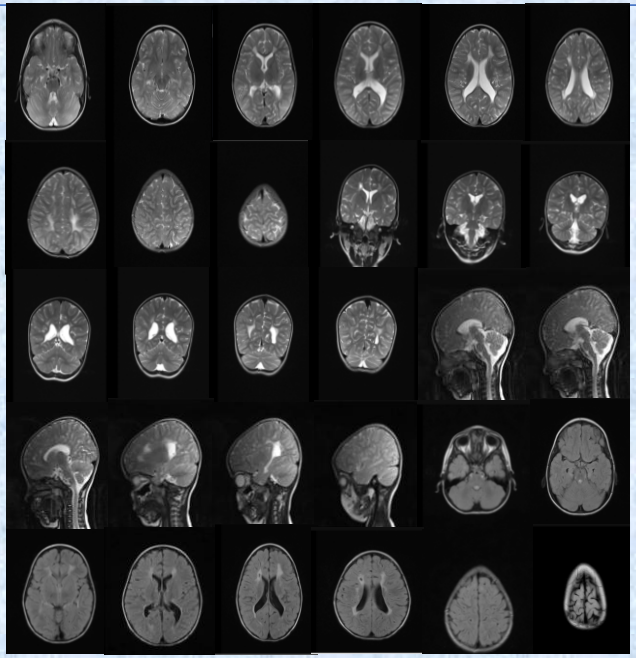
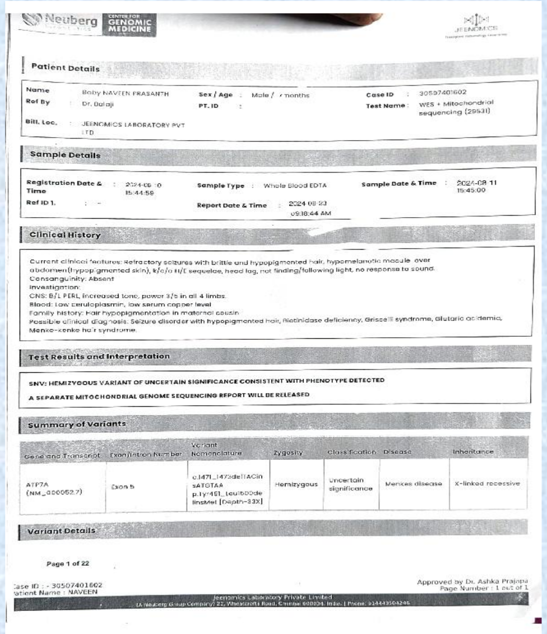
INVESTIGATIONS

Hb: 9.7g%
TC: 9000/uL
Plt: 5.3 L/uL
Creatinine: 0.5 mg/dL
LFT: WNL
Ca: 10.3 mg/dL
Na: 141mEq/L
K: 4.7mEq/L
TSH: 3.19 mIU/L
Ammonia: 97
Lactate: 58
UMS: negative
TMS: citrullin mildly elevated
S. biotidinase: 32.6nmol/ml/min
Serum copper: 22 mcg/dL
Serum ceruloplasmin: 5 mg/dL
P.smear: mild normocytic normochromic anaemia with thrombocytosis



MRI brain: paucity of white matter with T2/ FLAIR hyperintensity showing no diffusion restriction in bilateral periventricular,peritrigonal region- leucomalacia



Neuberg CENTER FOR GENOMIC MEDICINE — JEENOMICS

Patient Details

Name : Baby NAVEEN PRASANTH — Sex / Age : Male / ₍months — Case ID : 30507401602
Ref By : Dr. Balaji — PT. ID : — Test Name : WES + Mitochondrial sequencing (29531)
Bill. Loc. : JEENOMICS LABORATORY PVT LTD

Sample Details

Registration Date & Time : 2024-08-10 15:44:59 — Sample Type : Whole Blood EDTA — Sample Date & Time : 2024-08-11 15:45:00
Ref ID 1. : -- — Report Date & Time : 2024-08-23 09:18:44 AM

Clinical History

Current clinical features: Refractory seizures with brittle and hypopigmented hair, hypomelanotic macule over abdomen(hypopigmented skin), k/c/o H/E sequelae, head lag, not finding/following light, no response to sound.
Consanguinity: Absent
Investigation:
CNS: B/L PERL, increased tone, power 3/5 in all 4 limbs.
Blood: Low ceruloplasmin, low serum copper level
Family history: Hair hypopigmentation in maternal cousin
Possible clinical diagnosis: Seizure disorder with hypopigmented hair, Biotinidase deficiency, Griscelli syndrome, Glutaric acidemia, Menke-kenke hair syndrome.

Test Results and Interpretation

SNV: HEMIZYGOUS VARIANT OF UNCERTAIN SIGNIFICANCE CONSISTENT WITH PHENOTYPE DETECTED
A SEPARATE MITOCHONDRIAL GENOME SEQUENCING REPORT WILL BE RELEASED

Summary of Variants

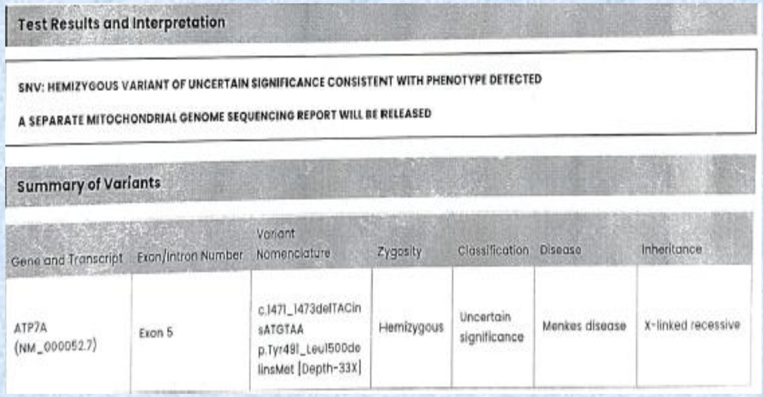
Gene and Transcript	Exon/Intron Number	Variant Nomenclature	Zygosity	Classification	Disease	Inheritance
ATP7A (NM_000052.7)	Exon 5	c.1471_1473delTACinsATGTAA p.Tyr491_Leu500delinsMet [Depth-33X]	Hemizygous	Uncertain significance	Menkes disease	X-linked recessive

Variant Details

Page 1 of 22

Case ID : - 30507401602 — Approved by Dr. Ashka Prajapa
Patient Name : NAVEEN — Page Number : 1 out of 1
Jeenomics Laboratory Private Limited
(A Neuberg Group Company) 22, Wheatcrofts Road, Chennai 600034, India. | Phone: 914443504246

Whole exon sequencing:
ATP 7A mutation
s/o MENKES KINKE HAIR DISEASE
hair shaft analysis: normal
electrophoresis: negative for hemoglobinopathies



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CXR- normal study
Skeletal survey- normal study
USG abdomen: Normal study
USG carotid doppler- no e/o significant stenosis
USG cranium: brain parenchyma appears to be reduced with surrounding increased csf space

EEG: delta slowing of background activity

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DISCUSSION

- **Menkes disease** (also called **kinky hair disease**) is a **rare X-linked recessive neurodegenerative disorder** of **copper metabolism**.
- **Incidence:** ~1 in 100,000 to 250,000 live births
- It results from **defective transport of copper** across cells, leading to **low copper levels in the brain and other tissues** and **accumulation in some organs (intestine, kidney)**.
- copper deficiency as occurs in Menkes disease is a rare cause of infantile epilepsy.
- Patients usually exhibit a severe clinical course with death in early childhood.

PATHOPHYSIOLOGY

•***ATP7A*** encodes a **copper-transporting ATPase** needed for copper absorption from the gut and delivery to copper-dependent enzymes.

Deficiency → ↓ activity of **copper-dependent enzymes** such as:

•Lysyl oxidase → connective tissue defect
•Cyt c oxidase → neurodegeneration
•Dopamine β-hydroxylase → autonomic dysfunction
•Tyrosinase → hypopigmentation

CLINICAL FEATURES

- Sparse kinky hair
- Loss of developmental milestones
- Truncal hypotonia
- Epilepsy
- Failure to thrive
- Pudgy, cherubic face
- Skeletal abnormalities (osteoporosis, metaphyseal widening)
- Arterial tortuosity and aneurysms
- Hypothermia (due to autonomic dysfunction)

TREATMENT

•**Early parenteral copper-histidine (CuHis)** therapy may improve survival and neurodevelopment *if started in the neonatal period (before neurological damage)*.
•Supportive therapy:

- Antiepileptic drugs for seizures
- Nutritional and physiotherapy support
- Management of temperature instability

CONCLUSION

•**Seizure can be the first clue** to an underlying **metabolic or genetic disorder** like Menkes disease.
•Thorough **metabolic and genetic work-up** is essential in **infants with unexplained seizures**.
•**Early diagnosis may improve outcome** with disease-specific therapy and family planning guidance.