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# Thiamine Pyrophosphokinase Deficiency in Indian origin Siblings
## Expanding the phenotype

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EN1 NEURO

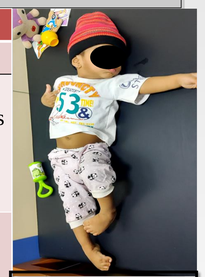
ICNC 2022 – 17th INTERNATIONAL CHILD NEUROLOGY CONGRESS – ANTALYA, TURKEY | OCTOBER 3-7, 2022

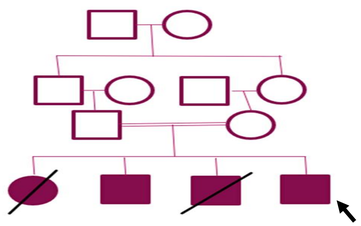
## CASE REPORT

| | |
|---|---|
| | Normal birth history, developed well till 1 yr. |
| 1 year | Episodic movements → dystonic posturing of the fingers and toes + stops activity. (Video 1)<br>Episodic reduced oral intake due to difficulty in swallowing (? dysphagia) + Irritability |
| 1.5 years | Developed axial dystonia and asymmetric appendicular dystonia<br>Increased severity + frequency of dystonia + ?<br>Decompensation episodes |
| 3 years | Complete regression of milestones<br>Persistent dystonia |

## FAMILY HISTORY

| Eldest Girl | Eldest Boy | 2nd Boy |
|---|---|---|
| Normal till 1 year | | |
| Abnormal movement ? Tonic posturing Seizures | Abnormal movements since 11/2 yrs, progressive Regression motor > cognitive, speech | Abnormal movements ? Tonic posturing Seizures |
| Expired at 2 years ? Cause | At present 6 years Bedridden , no speech,<br>No feeding issues<br>Dystonia<br>No episodic decompensation | Expired at 2 years ? cause |





## ON EXAMINATION

| | PROBAND | ELDER BROTER |
|---|---|---|
| Head circumference | Microcephaly<br>Failure to thrive | |
| Anthropometry | | |
| Cognition | Recognises parents, eye contact + | No |
| CNS examination | Spasticity , Dystonia (appendicular > axial)<br>Brisk Reflexes<br>No nystagmus | |
| | Severe dysphagia | No dysphagia |
| | Normal cerebellar signs and cranial nerves | |
| Other system examination | Normal | |

## CLINICAL SUSPICION

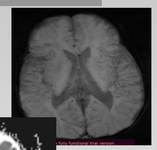
Significant Family history
Movement abnormality
Neuroregression
Episodic decompensation
Fast progressive

↓

Neurotransmitter disorders
Neurodegenerative disorders
Mitochondrial disorders

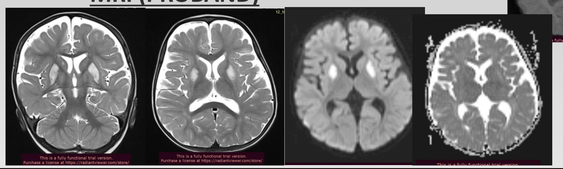
## INVESTIGATION

| | |
|---|---|
| **Basic blood, metabolic , ophthalmic evaluation in Proband** | **Normal** |
| NCV (In elder brother) | |



Bilaterally symmetrical T2 HI lesions involving Putamen & Globus pallidus externa.
Restricted diffusion
Similar HI in T1 also

### MRI (PROBAND)



WHOLE EXOMW SEQUENCING IN PROBAND + SANGER SEQUENCING IN OTHER

| | Detected variants | | |
|---|---|---|---|
| **Proband** | **TPK1**<br>Homozygous missense variant | **PMP22**<br>Heterozygous missense variant | **BRCA2**<br>Heterozygous nonsense variant |
| | Thiamine metabolism dysfunction syndrome 5 episodic encephalopathy type | Charcot-Marie-Tooth disease demyelinating type 1a | Breast cancer male susceptibility to |
| | **VARIANT OF UNCERTAIN SIGNIFICANCE** | **VARIANT OF UNCERTAIN SIGNIFICANCE** | **PATHOGENIC** |
| **Elder brother** | **Homozygous** | Not done | Not done |
| **Parents** | **Heterozygous** | Not done | Not done |

## MANAGEMENT GIVEN

Anti spasticity + Anti dystonia medication given + Oral thiamine (Poor compliance) was started in the proband → no improvement, clinical worsening

## DISCUSSION

### Thiamine Metabolism Dysfunction Syndrome 5 (TMDS5)

Childhood onset subacute progressive disorder
Initial development – can be Normal/ delayed
Episodes of decompensation during illness /stress with lactic acidosis
- Ataxia , dysarthria, dystonia, Psychomotor regression

Seizures ophthalmoplegia, nystagmus – less common
Biochemical feature: elevation of multiple organic acids especially 2-ketoglutaric acid.
- Plasma thiamine level can be normal or slightly reduced
- decrease in blood TPP

Neuroimaging : T2W Hyperintensity in basal ganglia + cerebellum (dentate)
Defects in TPK1 gene causing reduced / gain of activity of Thiamine phosphokinase 1
Early treatment with thiamine (100-500mg/day) + Biotin - improves psychomotor + movement disorder
Utility of ketogenic diet remains unclear
Late or no treatment → Poor prognosis

## OTHER THIAMINE METABOLISM DEFECTS

| | SLC19A2 Mutations - Rogers syndrome | SLC19A3 Mutation – Biotin Thiamine responsive basal ganglia disease | SLC25A19 Mutation- Defects of the mitochondrial thiamine pyrophosphate transporter | Nutritional deficits |
|---|---|---|---|---|
| Clinical criteria | Megaloblastic Anemia, thrombocytopenia, diabetes mellitus, and sensorineural deafness | Acute / Recurrent episodes of encephalopathy with dystonia, hypotonia, ataxia, bulbar dysfunction, seizures.<br>Rarely rigidity + quadriparesis | Severe encephalopathy with progressive peripheral neuropathy<br>OR<br>Severe congenital microcephaly with brain malformation. | Later onset Neurological symptoms mimic inborn pyruvate oxidation deficiencies. Significant systemic findings |
| Biochemical features | | Normal in blood but Low free thiamine in CSF/ fibroblast | Normal thiamine in blood | Low thiamine blood levels |
| | High excretion of alpha keto-glutaric acid in urine | | | |
| Neuroimaging | | Symmetrical T2W HI in caudate, putamen, thalamus + cortico/subcortical areas | Symmetrical T2W HI in caudate + putamen | Thalamus , periaqueductal region, mamillary body HI |
| Therapy | Thiamine responsive | | | |

## TAKE HOME MESSAGE

Rare but potentially treatable
Consider in patients with recurrent episodic encephalopathy and/or dystonia, increased blood lactate + basal ganglia and thalamic involvement on MRI
No specific biomarker hence molecular testing necessary
EARLY SUSPICION → EARLY DIAGNOSIS →EARLY TREATMENT = GOOD PROGNOSIS
Further studies required to understand the complete spectrum and optimize treatment.


## REFERENCES

1. Mayr JA, Freisinger P, Schlachter K, et al. Thiamine pyrophosphokinase deficiency in encephalopathic children with defects in the pyruvate oxidation pathway. Am J Hum Genet. 2011 Dec 9;89(6):806-12. 2. Ortigoza-Escobar JD, Alfadhel M, Molero-Luis M, et al. Thiamine Deficiency Study Group. Thiamine deficiency in childhood with attention to genetic causes: Survival and outcome predictors. Ann Neurol. 2017 Sep;82(3):317-330. 3. Ortigoza-Escobar JD, Molero-Luis M, Arias A, et al. Treatment of genetic defects of thiamine transport and metabolism. Expert Rev Neurother. 2016 Jul;16(7):755-63. 4. Eckenweiler M, Mayr JA, Grünert S, Abicht A, et al. Treatment and Favorable Outcome in an Infant with Biallelic TPK1 Variants. Neuropediatrics. 2021 Apr;52(2):123-125. 5. Rüsch CT, Wortmann SB, Kovacs-Nagy R, et al. Thiamine Pyrophosphokinase Deficiency due to Mutations in the TPK1 Gene: A Rare, Treatable Neurodegenerative Disorder. Neuropediatrics. 2021 Apr;52(2):126-132. 6. Marcé-Grau A, Martí-Sánchez L, Baide-Mairena H, et al. Genetic defects of thiamine transport and metabolism: A review of clinical phenotypes, genetics, and functional studies. J Inherit Metab Dis. 2019 Jul;42(4):581-597.



## ACKNOWLEDGEMENT

Thank the patient and her family for their permission to share the details of their family and to cooperate through this difficult medical journey