A Case of Thiamine Metabolism Dysfunction Syndrome-2 With Special Emphasis on Management and Prenatal Genetic Counseling

Dr. Prashant Utage , Dr. Aparna Prashant, Mr. Nadir Aman, Ms. Krishnendu Menon, Dr. Umesh Bhammarkar

Utage Child Development Centre, Hyderabad, India-500027

BACKGROUND

Thiamine metabolism dysfunction syndrome-2 (THMD-2) (OMIM #607483) is an autosomal recessive metabolic disorder characterized by episodic encephalopathy, often triggered by febrile illness, presenting as confusion, seizures, external ophthalmoplegia, dysphagia, and sometimes coma and death. An important gene associated with THMD-2 is SLC19A3. Affiliated tissues include brain, and related phenotypes are global developmental delay and ptosis. Early diagnosis and interventions improves quality of life and survival rate.

FAMILY HISTORY

A female child of age 1-year 9-months born to 3rd degree consanguineous parent presented with developmental delay, motor regression post fever at 15-months of age. Her antenatal and birth history was uneventful. There were no significant facial dysmorphism was observed. She was diagnosed with THMD-2.

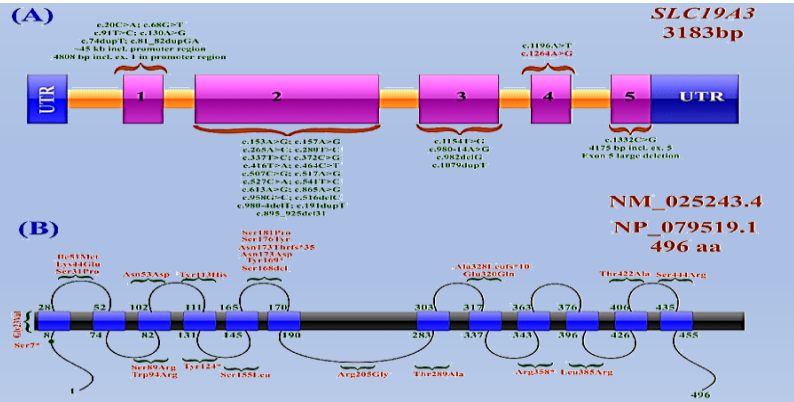
Proband under treatment and management

INVESTIGATIONS

Clinical examination was done which showed NBS for IEM was by TMS showed positive report. MRI brain showed multiple T2 FLAIR hyperintensities without diffusion restriction noted in bilateral frontal, parietal, occipital, temporal, basal ganglia and thalami. EEG report showed normal study. Genetic evaluation was done by Whole exome sequencing to confirm the diagnosis.

RESULTS

Whole exome sequencing report revealed Likely pathogenic variant of SLC19A3 gene mutation in homozygous condition causing Thiamine metabolism dysfunction syndrome-2



Schematic representation of SLC19A3 exons and protein domains representing the identified mutations reported to-date

GENETIC COUNSELING

THMD-2 is an autosomal recessive metabolic disorder caused due to the homozygous or compound heterozygous mutation in the SLC19A3 gene which encodes a thiamine transporter on chromosome 2q36. If both parents are known to be heterozygous for SLC19A3 pathogenic variant, each sib of an affected individual has at conception there would be a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected. Administration of high doses of biotin, and sometimes thiamine, during these crises results in partial or complete improvement within days. If untreated, encephalopathies can result in permanent dystonia. Carrier testing for at-risk family members and prenatal testing and preimplantation genetic testing for pregnancies at increased risk are possible if the SLC19A3 pathogenic variants in the family have been identified.