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Paediatrics

TBCK GENE RELATED ENCEPHALOPATHY : A UNKNOWN ORPHAN DISEASE

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ABSTRACT **Background :** TBCK-related encephalopathy is a very rare condition recently diagnosed effecting the paediatric age group. It was first discovered in 2015 by Saudi scientists who identified the role of TBCK gene mutation in a family of 13 members with ID. Mutations in this gene lends the children to have developmental delays, ID ranging from moderate to severe degree, hypotonia (low muscle tone) and seizures. Until this date only 35 cases have been reported worldwide. **Case report:** Our case describes a 3 year old female child hailing from Tadepalligudem, Andhra Pradesh, India. A first order child of 3rd degree consanguineous marriage presented to us with complaints of repeated generalized tonic clonic seizures and showing physical traits of coarse face , over arching of eyebrows, anteverted nares ,cupid bow, bitemporal shrinking , atypical rash on the thigh region, flat foot, hypotonia ,overall psychomotor delay and severe intellectual disability which resembled like storage disorder disease or chromosomal disorder . All the symptoms were taken into count and blood investigations were done which were inconclusive of any storage disorder that was known , upon more researching we read about TBCK disorder which was one of the causes of intellectual disorders, been recently diagnosed we gathered more information and an MRI, EEG and Genetic studies like Whole Exome Sequencing (on child and parents) were done . This came back confirmed case of TBCK gene defect, also known as TBCK gene syndrome **Conclusion:** This case is a very rare entity which causes intellectual disability , more awareness of this might bring more light into the exact pathogenesis of this disease. Currently there is research about treatment options for this disease through increasing leucine which acts through mTOR pathway. Similar to supplementation of phenylalanine for phenylketonuria which improves the disease process decreases the chance of intellectual disability.

KEYWORDS :

BACKGROUND

TBCK-related encephalopathy is a rare neurogenetic autosomal recessive disorder, meaning it is caused by genetic mutations usually carried by both parents. [1]

TBCK related encephalopathy is often accompanied by global developmental delay, distinctive facial features like deeply set eyes and tented upper lip vermilion, medication refractory epilepsy and chronic respiratory failure [2] . Typical brain imaging signs are brain atrophy and progressive leukoencephalopathy with a thinned corpus callosum. The disease has a generally short survival and only exceptional clinical courses up to two decades have been described. [3,4]

In all reported cases, the different TBCK mutations resulted in aberrant TBCK protein. The knowledge about the function of TBCK is still limited. The protein contains a Tre-2/Bub2/Cdc16 (TBC) domain, a rhodanase-like domain and a kinase domain, which has been proposed to be inactive due to a lack of essential catalytic subdomains.[5,6,7] .

The TBCK GENE has been shown to suppress cell proliferation [6] and to play a role in cell growth and actin organization by enhancing the signaling pathways of mammalian target of rapamycin (mTOR), presumably at a transcriptional or post-transcriptional level.

Abnormal mTOR signaling is already known to play a role in brain abnormalities, epilepsy, autism and Intellectual disability.

TBCK syndrome causes a wide range of symptoms. Most children with TBCK have developmental delays, ranging from moderate to severe and low muscle tone. Some children also have seizures and weakness.

The full list of potential symptoms includes

1. Coarse facial features,
2. Congenital hypotonia (low muscle tone)
3. Global developmental delay, ranging from moderate to severe
4. Dysphagia (difficulty swallowing)
5. Respiratory insufficiency due to weakness
6. Epilepsy
7. MRI features, including white matter changes, cerebellar atrophy and thin corpus callosum
8. Absent/severely delayed expressive language
9. Hyporeflexia/areflexia (below normal or absent reflexes)
10. Hypothyroidism (underactive thyroid gland)
11. Osteopenia (weak bones)
12. Hypercholesterolemia (high cholesterol)
13. Frequent urinary tract infections/nephrolithiasis (kidney stones)

Diagnosis: Done through whole exome sequencing, one of the most extensive genetic tests available, which compares the DNA of the parents and child. Targeted TBCK gene testing can also confirm the diagnosis in patients with known family history or high clinical suspicion of this disorder.

Treatment: symptomatic treatment is the current regimen, however new research implies the use of leucine amino acid that acts along mTOR pathway and increases the signaling of patients cell. Similar to patients with phenylketonuria a long-recognized genetic condition identified in routine newborn screening. In which case supplementation would prevent brain damage .

CASE PRESENTATION

A 3 year old female child named Moksha Sri a resident from Tadepalligudem, West Godavari, Andhra Pradesh, India. She is known case of infantile hyptonia and global developmental delay brought to our hospital with complaints of abnormal movements of both upper and lower limbs 2 episodes in past 5 days.

Past history shows similar seizure activity 5 days back and developmental delay along with hypotonia since birth.

Family history is significant for 3rd degree consanguineous marriage, she is the first born of the two children.

Her antenatal history is unremarkable, natal history is a institutional delivery, she was a term neonate, born through emergency cesarean section in view of fetal distress, a birth weight 3600 grams, vigorous at birth, APGAR score at 1 minute of 5 and at 5 minutes 8. She was admitted into NICU in view of respiratory distress. In NICU the

neonate had episodes of seizures on day 2 not owing to electrolyte and metabolic disturbances; she was taken home against medical advice on day 3.

Developmental History
The gross motor attained is stands with support, compared to her age which has to be riding a tricycle or walking up and downstairs with alternating feet. Developmental quotient for age is 33%.

The fine motor skills attained are mature pincer grasp, compared to her age which has to be copying a circle. Developmental quotient for age is 25%.

Social: claps compared to her age she has to know her full name and gender also she should be sharing her toys with other kids (DQ – 33%)

Language: Bi syllables compared to her age which has to be asks questions and she should know her complete name and gender (DQ – 25%)

Overall DQ – 29%

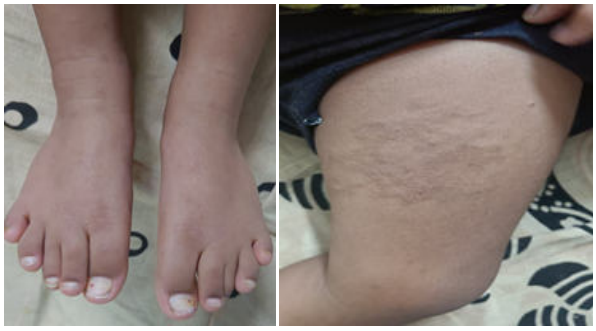
General Examination
Pallor is present and the head to toe examination showed macrocephaly, coarse faces, overarching of eyebrows, overlapping of 2nd and 3rd toes of lower limbs, flat foot, multiple ill defined skin coloured plaques with few overlying papules present over left thigh.

SYSTEMIC EXAMINATION
Central Nervous System examination
Higher mental functions recognises mother, cranial nerves are intact, bulk of the muscle is normal, hypotonia in both upper and lower limbs, power is 2/5 in all limbs, superficial reflexes such as corneal, conjunctival, abdominal are present and bilateral plantar is extensor.

Deep tendon reflexes are absent. The child responds to touch, pain and temperature.

Cardio-Vascular System: S1 S2 present, no murmur
Respiratory System: Bilateral air entry present, Normal vesicular breath sounds heard
Gastro-Intestinal Tract: Per abdomen soft, no organomegaly

1st image from right shows anteverted nares, bitemporal shrinking, the mouth shows cupid bow, over arching of eyebrows . 2nd picture shows child unable to stand on his own.



1st image from right shows over lapping of toes on the left foot. 2nd picture shows multiple ill defined skin coloured plaques with few overlying papules present over left thigh1

INVESTIGATIONS
Routine investigations of blood workup showed microcytic hypochromic anemia and rest of the hematological and biochemical study remained normal.

Extensive metabolic investigations were performed, including CSF amino acids and neurotransmitters, muscle biopsy with histology and respiratory chain enzymes, white cell enzymes, very long chain fatty acids, and transferrin isoelectric focusing, all of which were normal.

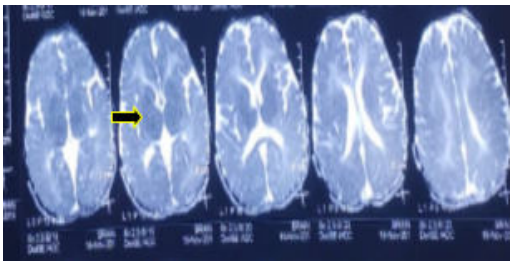
Spectroscopy showed normal peaks for N-acetylaspartate, creatine, and choline.

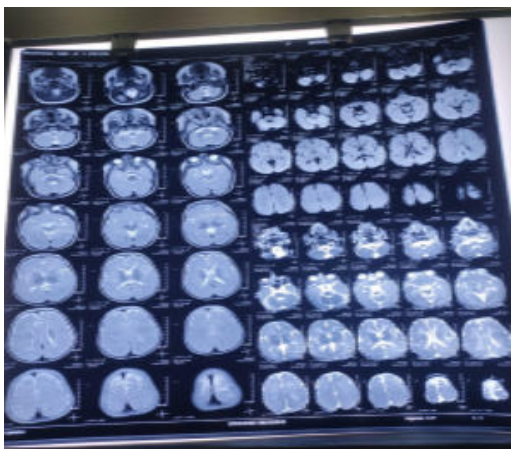
The electroencephalogram was suggestive of generalized seizure disorder

EMG was done which showed no peripheral muscle and peripheral nerve damage.

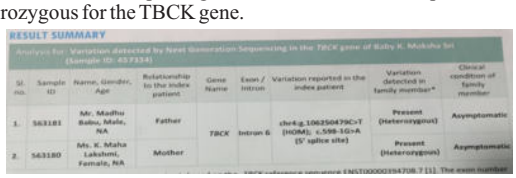
Genetic investigations included routine karyotyping, 250k single-nucleotide polymorphism arrays, subtelomeric fluorescent in situ hybridization, and mitochondrial gene analysis. Despite these investigations, the molecular defect underlying this disorder had remained unidentified.

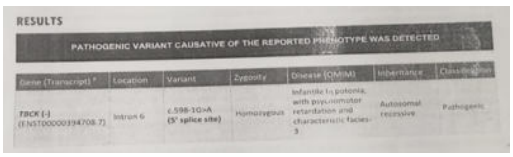
Radiology investigations
MRI in T2/ FLAIR sequence shows hyper intense areas seen involving white matter of bilateral cerebral hemispheres more predominantly in periventricular region and at level of Centrum semiovale with slight volume loss, leukomalacia changes were noted.





Whole exome sequencing was done and a variation was detected in our patient on chromosome 4, c.598-1G>A (5' splice site) variant classification was pathogenic variant with the parents been heterozygous for the TBCK gene.





Treatment
Child is discharged on supportive treatment. Leucine was started and longer duration of observation is required for noticing its positive

effects. The child is on regular follow up in our clinic.

CONCLUSION

TBCK gene encephalopathy is a recently discovered entity; only 35 cases are reported worldwide .Our findings are in line with previously reports of the association of mutations in the TBCK gene with poor psychomotor and speech development, and inability to walk independently along with coarse facial features, overarching of eyebrows, overlapping of toes. Alazami et al. [10] identified a homozygous splice site mutation in the TBCK gene in two sibs with infantile hypotonia, psychomotor retardation, and specific facial findings, born to consanguineous Saudi parents. The family was part of a large cohort of 143 multiplex consanguineous families with various neurodevelopment disorders who underwent exome sequencing. [10] Bhoj et al. and Chong et al. added another 18 affected individuals with TBCK deficiency to the reported families. [9,11] Guerreiro et al. characterized a family with three siblings affected by a severe, yet viable, congenital disorder. All affected siblings had epilepsy with onset between 9 months to 3 years, profound hypotonia, strabismus, and global delay. [12] TBCK is a putative GTPase-activating protein (GAP) for small GTPases of the Rab family and has been shown to control cell growth and proliferation, actin-cytoskeleton dynamics, and mTOR signaling. However, in contrast to other disorders caused by dysregulated mTOR signaling associated with focal or global brain overgrowth, impaired TBCK function results in progressive loss of brain volume. [9]Most reported individuals had convulsions, frequently resistant to medication as in our case report too. Some of the patients had poor or no visual function. Brain MRI showed thin or incomplete corpus callosum , widening of brain ventricles without excessive pressure (ex vacuo), PVL, and a range of changes of the white matter (from non-specific changes to leukodystrophy).[9,11]Our case had leukomalacia changes along with volume loss and periventricular dilation. Although the condition is called “infantile hypotonia with psychomotor retardation and characteristic facies” (OMIM 616900), it seems that a true, consistent, distinctive typical gestalt does not really exist. Various dysmorphic features were reported in patients, including high-arched eyebrows, deep-set eyes, high nasal bridge and anteverted nares, [9,11] a phenotype that was totally exhibited by our patient. As described by Bhoj et al., the clinical picture is complicated by significant variability even within sibling pairs: a few affected individuals demonstrated facial features reminiscent of storage disorder, several showed other mild facial anomalies, but none appeared diagnostic. [11] Skeletal manifestation appears to be part of the clinical spectrum, as scoliosis and osteoporosis were described in previous publications but not to be found in our case.

In this study we describe a female child of 3 years showing psychomotor delay and various gross features of TBCK gene defect. Which was later confirmed by Whole exome sequence a mutant version on chromosome 4 , c.598-1G>A (5' splice site) variant .

REFERENCES

1. https://www.chop.edu/conditions-diseases/tbck-syndrome
2. Zapata-Aldana E, Kim DD, Remtulla S, Prasad C, Nguyen CT, Campbell C (2018) Further delineation of TBCK - infantile hypotonia with psychomotor retardation and characteristic facies type 3. Eur J Med Genet. https://doi.org/ 10.1016 /j.ejmg. 2018.08.004
3. Guerreiro RJ, Brown R, Dian D, de Goede C, Bras J, Mole SE (2016) Mutation of TBCK causes a rare recessive developmental disorder. Neurol Genet 2:e76. https://doi.org/10.1212/nxg.0000000000000076
4. Ortiz-Gonzalez XR, Tintos-Hernandez JA, Keller K, Li X, Foley AR, BharuchaGoebel DX, Kessler SK, Yum SW, Crino PB, He M, Wallace DC, Bonnemann CG (2018) Homozygous boricua TBCK mutation causes neurodegeneration and aberrant autophagy. Ann Neurol 83:153–165. https://doi.org/10.1002/ ana.25130
5. Boudeau J, Miranda-Saavedra D, Barton GJ, Alessi DR (2006) Emerging roles of pseudokinases. Trends Cell Biol 16:443–452. https://doi.org/10.1016/j.tcb. 2006.07.003
6. Liu Y, Yan X, Zhou T (2013) TBCK influences cell proliferation, cell size and mTOR signaling pathway. PLoS One 8:e71349. https://doi.org/10.1371/ journal.pone.0071349
7. Scheeff ED, Eswaran J, Bunkoczi G, Knapp S, Manning G (2009) Structure of the pseudokinase VRK3 reveals a degraded catalytic site, a highly conserved kinase fold, and a putative regulatory binding site. Structure 17:128–138. https:// doi.org/ 10.1016/ j.str.2008.10.018
8. Bockaert J, Marin P (2015) mTOR in brain physiology and pathologies. Physiol Rev 95:1157–1187. https://doi.org/10.1152/physrev.00038.2014
9. Chong JX, Caputo V, Phelps IG, Stella L, Worgan L, Dempsey JC, Nguyen A, Leuzzi V, Webster R, Pizzuti A, Marvin CT, Ishak GE, ArdernHolmes S, Richmond Z, Bamshad MJ, Ortiz-Gonzalez XR, Tartaglia M, Chopra M, Doherty D (2016) Recessive inactivating mutations in TBCK, encoding a Rab GTPase-activating protein, cause severe infantile syndromic encephalopathy. Am J Hum Genet 98:772–781. https://doi.org/10.1016/j.ajhg.2016.01.016
10. Alazami, A. M., Patel, N., Shamseldin, H. E., Anazi, S., Al-Dosari, M. S., Alzahrani, F., Hijazi, H., Alshammari, M., Aldahmesh, M. A., Salih, M. A., Faqeih, E., Alhashem, A., and 41 others. Accelerating novel candidate gene discovery in neurogenetic disorders via whole-exome sequencing of prescreened multiplex consanguineous families. Cell Rep. 10: 148-161, 2015.
11. Bhoj, E. J., Li, D., Harr, M., Edvardson, S., Elpeleg, O., Chisholm, E., Juusola, J., Douglas, G., Guillen Sacoto, M. J., Siquier-Pernet, K., Saadi, A., Bole-Feysot, C., and 12 others. Mutations in TBCK, encoding TBC1-domain-containing kinase, lead to a recognizable syndrome of intellectual disability and hypotonia. Am. J. Hum. Genet. 98: 782-788, 2016.
12. Guerreiro, Rita J.; Brown, Rachel; Dian, Donnai; de Goede, Christian; Bras, Jose; Mole, Sara E. (2016). Mutation of TBCK causes a rare recessive developmental disorder. Neurology Genetics, 2(3), e76–. doi:10.1212/nxg.0000000000000076