TBC1D24 gene related disorders: A unique cause of myoclonus and developmental encephalopathy

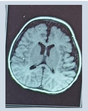
Dr Ashwin Sardesai [1], Dr Mahesh Kamate [1], Dr Bhavana Koppad [1]

[1] Department of Paediatric Neurology, Jawaharlal Nehru Medical College, Belagavi, Karnataka, India

INTRODUCTION

- TBC1D24 gene - regulation of synaptic vesicle trafficking, brain and somatic development.
- Tre2/Bub2/Cdc16 (TBC) domain, shared by Rab GTPase-activating proteins (Rab-GAPs).
- TBC1D24 - expressed in several tissues, highest in brain - all layers of cerebral cortex, hippocampus
- Continuum of features - seizures, developmental and epileptic encephalopathy, skeletal and dental abnormalities, myoclonus and hearing loss.
- Slowly progressive course with a refractory myoclonus that can go on for hours resembling focal status epilepticus.
- EEGs show mild diffuse slowing with few or no epileptic discharges
- Myoclonus -responds well to oral Triclofos.
- We present four confirmed cases of TBC1D24 gene related disorders

CASE DETAILS

	Case 1	Case 2	Case 3	Case 4
Age	9 years	10.5 years	4.5 years	1year 10 months
Sex	Male	Male	Female	Female
Consanguinity	3rd degree	Non consanguinous	Non consanguinous	2nd degree
Age of Onset	40 days	4 months	5 months	3 months
Type of Seizures	Myoclonic, focal clonic	Multifocal myoclonus , EPC	Generalised as well as focal onset seizures	Focal clonic, myoclonic
Myoclonus	Segmental, multifocal, abdomen	myoclonus of face, lips, limbs - fingers and toes	Multifocal myoclonus	Multifocal – face, perioral, hands, feet
Dyskinesia	Facial and oromotor	Oromotor dysfunction	No	No
Motor Examination	Asymmetric mixed dystonic and spastic quadriparesis with brisk reflexes and clonus	Asymmetric spastic quadriparesis (R>L) with ataxia, clonus	Developmental delay, feeding difficulties,.	Dystonic quadriparesis with brisk reflexes
Eye	Strabismus	Nystagmus	Normal	Strabismus
Phenotype	DEE	DEE	DEE	DEE
MRI Brain	Cerebral Atrophy	Cerebellar Atrophy	Initially normal, later cerebral and cerebellar atrophy periventricular WM signal changes	Mild Cerebral atrophy 
EEG	Normal	Normal	Normal- multiple EEG	Multifocal discharges
Treatment received	VPA,CLB, PER	TPM,BRV,LCM,CZP, PER, Steroids	PB,PHT,VPA,CLB	OXB,CLB. Started on PER, and VPA recently
Response to Triclofos	Partial	Yes	Yes	Not yet assessed

- Seizures were presenting complains in all four
- Whole exome sequencing: TBC1D24 gene- Homozygous missense variant in all four cases.

Case	Variant	Locus	Zygosity	Disorder		Classification
1	c.751T>G(p.Phe251Val)	Exon 2	Homo-zygous	Developmental and Epileptic Encephalopathy 16 (DEE 16)	AR	VUS (Parental sanger confirmed)
2	c.1499C>T(p.Ala500Val)	Exon 7	Homo-zygous	DEE16/DOORS syndrome/ Epilepsy Rolandic with paroxysmal exercise-induced dystonia and writer's cramp/ Myoclonic epilepsy, infantile, familial	AR	Likely Pathogenic
3	c.920A>C (p.N307T)	Exon 2	Homo-zygous	Myoclonic epilepsy infantile, familial, EIEE 16	AR	VOUS
4	c.545C>T(p.Thr182Met)	Exon 2	Homo-zygous	Developmental and Epileptic Encephalopathy 16 (DEE 16)	AR	VOUS

- GDD in all ; Microcephaly in all except Case 4
- Case 2 - neuroregression at 7 years of age following status epilepticus
- No hearing loss/facial dysmorphism in any of the cases

DISCUSSION

- TBC1D24 epilepsy syndromes occur with both compound heterozygous and homozygous recessive mutations.
- Marked phenotypic pleiotropy
- The types of seizures and epilepsies are diverse.
- Seizures : Infantile spasms and febrile convulsive, myoclonic, clonic, tonic, absence, tonic-clonic with or without apparent focal onset, and focal seizures.

DISCUSSION

- Myoclonic seizures - segmental or generalized, sometimes evolving into tonic-clonic seizures.
- Unilateral or bilateral, migrating, alternating, rhythmic, or pseudorhythmic, occurring both at rest and on maintaining posture. Variety of triggers
- Often in clusters, can be very prolonged, lasting several days
- Myoclonus is noticed to subside in sleep.
- 2 out of 4 cases had good seizure control upon adding Triclofos without sedative side effects. One case had partial response.
- EEG: Normal or slow background activity and multifocal paroxysmal abnormalities
- Seizures are commonly drug-resistant.
- Loss of function produces more severe disease. In our cases, missense variants were noted in which no specific pattern of severity or outcome has been documented
- Balestrini et al: 18/48 (38%) had myoclonic epilepsies. focal (25%), multifocal (2%), generalized (4%), and unclassified epilepsy (6%), and early-onset epileptic encephalopathy (25%). 30/48 patients had drug-resistant epilepsy
- Zhang et al 11 /19 patients -EPC responded to chloral hydrate
- Ngoh et al- used chloral hydrate in 2 cases- multifocal myoclonus

CONCLUSIONS

- First case series from India
- Resistant epilepsy. However, EEGs do not show a high burden of epileptic discharges
- Incessantly continuing myoclonus – often mislabelled as status epilepticus and overtreated.
- Multifocal myoclonus responds well to Triclofos

REFERENCES

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CONTACT

drmaheshkamate@gmail.com ; ashwin.sayzz@gmail.com