Letters to the Editor

Parkinsonism, Olivary Hypertrophy and Cerebellar Atrophy with TTC19 Gene Mutation

Dear Editor,

Mitochondrial respiratory chain (MRC) complex III is responsible for the transfer of electrons from reduced coenzyme Q to cytochrome C needed for the formation of electrochemical potential and adenosine triphosphate (ATP) generation. The mutations in the TTC19 gene have been identified to cause a deficiency of MRC complex III. MRC complex III deficiency nuclear type 2 due to the mutations in the TTC19 gene is inherited in an autosomal recessive pattern. The mutations in the TTC19 gene cause developmental delay and regression with failure to thrive, Leigh syndrome, progressive psychosis, and spinocerebellar ataxia. Hereby, we report an adolescent female who presented with Parkinsonism. Her Plasma lactate was high and muscle MRC enzyme assay showed complex III deficiency with clinical exome sequencing showing splice site homozygous mutation in TTC19 gene.

A 15-year-old girl with normal birth and developmental history born to consanguineous parentage presented with a history of slowness in daily activities, slowness in walking with imbalance and low volume speech of 5 years duration. She had a history of febrile illness 5 years back of 2 days duration followed by an altered level of consciousness lasting for 3-4 days and slowly recovered from the encephalopathy episode. There was no history of seizures, vomiting, diarrhea, pain abdomen. After returning to a normal level of consciousness, she was found to be slow in daily activities, slow in comprehension and expression, reduced volume of speech which was monotonous. She had reduced interest in daily activities. The speed of walking was reduced with imbalance and tendency to fall. Systemic examination was unremarkable. Speech was low volume and monotonous. Fundus examination was normal. Her vertical saccades were slow with normal range. She had rigidity of all limbs with brisk deep tendon reflexes. She had limb bradykinesia. Plantar responses were mute. Her gait was short stepped with imbalance while turning and had postural instability. She had terminal dysmetria of both upper limbs. Her first brain magnetic resonance imaging (MRI) at time of febrile illness showed symmetrical T2 hyperintensities in caudate, putamen. Repeat brain MRI showed T1 hypointense and T2 hyperintense patchy lesion in bilateral striatum with hyperintensity in ventral medulla involving inferior olivary nucleus suggesting hypertrophic olivary degeneration and cerebellar atrophy [Figure 1]. Complete hemogram, renal liver...
and thyroid function tests, serum electrolytes were normal. Serum electrolytes, copper, and ceruloplasmin were normal. Plasma lactate was high (42 mg/dl). Quadriceps muscle biopsy did not show mitochondrial pathology. Respiratory chain complex assay from muscle sample showed reduced complex III deficiency (<20%). Clinical exome sequencing showed novel consensus splice site variation in homozygous state in intron 8 of the TTC19 gene (c. 831 + 2 T > A). She was treated with carnitine, coenzyme Q10, riboflavin, thiamine, vitamin E, and biotin. There was no response of Parkinsonism to levodopa (600 mg) at 3 months follow-up.

Isolated deficiency of MRC complex III is a least commonly diagnosed mitochondrial disorder. Their diagnosis is difficult due to the lack of histological and biochemical hallmarks in skeletal muscle biopsies (no ragged red fibers or cytochrome oxidase negative fibers). The gene mutation associated with complex III deficiency is MT-CKB, BCORS, UQCRB, UQCRQ, UQRC2, CYC1, UQCC2, UQCC3, LYRM7, and TTC19.\[3\]

TTC19 gene located on the chromosome 17p12 encodes a TTC19 (tetratricopeptide repeat domain 19) protein embedded in the inner mitochondrial membrane needed for the assembly and activation of MRC complex III. TTC19 gene mutation causes early-onset neuroregression to cerebellar ataxia and psychosis in adults.\[1\] Ghezzi et al. (2011) first reported TTC19 gene mutations in 4 patients who presented with early-onset cognitive impairment and ataxia with pyramidal and extrapyramidal signs in three patients and late-onset (42 years) gait apraxia, dysarthria, dystonia, bradykinesia, and psychiatric symptoms in one patient. All patients had complex III deficiency in muscle. Brain MRI showed hyperintensities in the caudate, putamen, and inferior olivary nucleus in the medulla with ponto-cerebellar atrophy. The early-onset patients had c. 656T > C; p.Leu219 mutations with the synthesis of truncated TTC19 protein. Adult-onset patient had c. 517C > T; p.Gln173 nonsense mutation with the absence of protein in muscle.\[11\] Nogueira et al. (2013) reported four affected siblings who presented in adolescence/adulthood with rapidly progressive ataxia and psychiatric symptoms. They had frameshift mutations in the TTC19 gene.\[4\] Atwal PS. (2013) reported a patient with early-onset slowly progressive neurodevelopmental regression and MRI brain showing bilateral striatal and brainstem necrosis.\[9\] Morino et al. (2014) described a patient with late-onset rapidly progressive cerebellar ataxia and cognitive impairment with c. 829C > T homozygous nonsense mutation. Brain MRI showed cerebellar atrophy.\[6\] Kunii M, et al. (2015) reported an adult with cerebellar ataxia, spastic paraparesis, loss of deep sensation, mild frontal lobe dysfunction. Brain MRI showed cerebellar atrophy and bilateral high-intensity signals in the inferior olives. A novel homozygous frameshift mutation c. 157_158dup [p.Pro54Alafs*48] in the TTC19 gene was found.\[7\] Koch J, et al. (2015) reported 3 cases with early-onset developmental delay, ataxia, and neuroregression. They found novel missense mutations (c. 544 T > C/p.Leu185Pro; c. 917 T > C/p.Leu324Pro) and brain MRI showed hypertensive lesions in basal ganglia, brainstem with cerebellar atrophy and hypertrophic olivary degeneration.\[2\] Habibzadeh P, et al. (2019) reported an adolescent with cerebellar ataxia, psychiatric symptoms, spastic paraparesis and intestinal pseudoobstruction.\[8\]

Our patient had a normal birth and developmental history, developed symptomatic Parkinsonism following febrile illness with encephalopathy. Brain MRI showed bilateral striatal lesions with hypertrophic olivary degeneration and cerebellar atrophy. Muscle biopsy showed isolated reduced complex III deficiency with splice site homozygous mutation (c. 831 + 2T > A) in the TTC19 gene.

Isolated complex III deficiency due to TTC19 gene mutation is less common with varied clinical phenotypes. The parkinsonian phenotype in complex III deficiency due to TTC19 gene mutation has not been described.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Rohan R. Mahale, Gautham Arunachal, Jyothi Gautam, Debaran Dutta, Jennifer Kooor, Pooja Mailankody, Hanshahree Padmanabha, Mathuranaath PS
Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, Karnataka, India
1. Ghezzi D, Arzuffi P, Zordan M, Da Re C, Lamperti C, Benna C, et al. Mutations in TTC19 cause mitochondrial complex III deficiency and neurological impairment in humans and flies. Nat Genet 2011;43:259-63.
2. Koch J, Freisinger P, Feichtinger RG, Zimmermann FA, Rauscher C, Wagentristl HP, et al. Mutations in TTC19: Expanding the molecular, clinical and biochemical phenotype. Orphanet J Rare Dis 2015;10:40.
3. DiMauro S, Schon EA, Carelli V, Hirano M. The clinical maze of mitochondrial neurology. Nat Rev Neurol 2013;9:429-44.
4. Nogueira C, Barros J, Sa MJ, Azvedo L, Taipa R, Torraco A, et al. Novel TTC19 mutation in a family with severe psychiatric manifestations and complex III deficiency. Neurogenetics 2013;14:153-60.
5. Atwal PS. Mutations in the complex III assembly factor tetratricopeptide 19 gene TTC19 are a rare cause of Leigh syndrome. JIMD Rep 2014;14:43-5.
6. Morino H, Miyamoto R, Ohnishi S, Maruyama H, Kawakami H. Exome sequencing reveals a novel TTC19 mutation in an autosomal recessive spinocerebellar ataxia patient. BMC Neurol 2014;14:5.
7. Kunii M, Doi H, Higashiyama Y, Kugimoto C, Ueda N, Hirata J, et al. A Japanese case of cerebellar ataxia, spastic paraparesis and deep sensory impairment associated with a novel homozygous TTC19 mutation. J Human Genet 2015;14:43-5.
8. Habibzadeh P, Inaloo S, Silawi M, Dastsooz H, Farazi Fard MA, Sadeghipour F, et al. A novel TTC19 mutation in a patient with neurological, psychological and gastrointestinal impairment. Front Neurol 2019;10:944.