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.[1] 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.[2] 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 + 2T > A). She was treated with carnitine, coenzyme Q_{10}, 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-CYB*, *BCS1L*, *UQCRB*, *UQCRQ*, *UQCRC2*, *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.[1] 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.[5] 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 hyperintense 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]

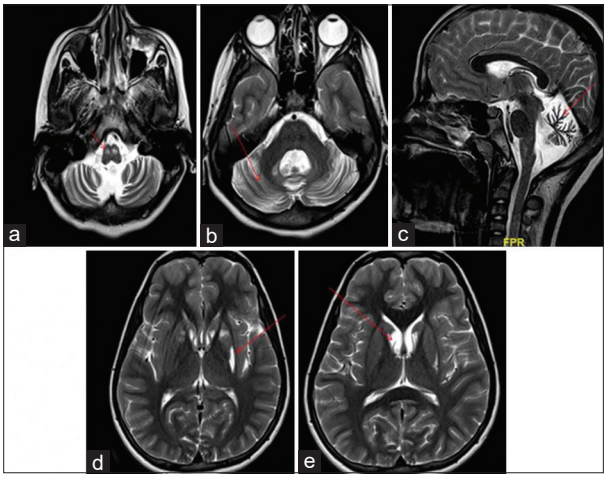

Figure 1: Brain MRI (a) and (b) axial T2 image showing hypertrophic olivary degeneration and cerebellar atrophy respectively (red arrow); (c) sagittal T2 image showing cerebellar atrophy (red arrow); (d), (e) axial T2 image showing caudate and putaminal hyperintensity (red arrow)

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 *TTC 19* 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.

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Conflicts of interest

There are no conflicts of interest.

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