Stress-induced Childhood Onset Neurodegeneration with Ataxia and Seizures (CONDSIAS) Presenting with Torticollis Attacks: Phenotypic Variability of the Same Mutation in Two Turkish Patients

Sir,

Two patients with the same genetic mutation in *ADPRHL2* gene, which takes a role in DNA repair, transcription, telomer function, and apoptosis are presented.[1] Developmental delay, intellectual disability, epilepsy, cerebral-cerebellar atrophy, neurogenic changes, sensorineural hearing loss, nystagmus, and dystonic ataxia have been reported and intrafamilial phenotypic variability has been defined in the literature.[2] Paroxysmal torticollis attacks have not been reported before.

The first case was a 20-month-old girl with normal motor development presenting with episodic torticollis attacks lasting from 2 h to 2 days for the last 20 days [Video]. She was the first child of parents with third-degree consanguinity. She had two febrile convulsions before 1-year old. She could not improve her language skills and developed aggressive behaviour and lack of communication after 18 months. She gradually developed ataxia, which worsened with infections. Dystonic posture, bradymimia, bradykinesia, nystagmus, spasticity of lower extremities and language delay were noticeable by 3 years of age. She had her first tonic focal seizure at age 4 with persistent perioral myoclonus. She presented with acute respiratory insufficiency and autonomic findings including lack of sweating, hyperthermia and tachycardia at 5 years of age and underwent mechanical ventilation after tracheostomy. Metabolic workup including cerebrospinal fluid lactate and amino acids nerve conduction studies, fundoscopic, audiological and cardiac evaluation, cranial (magnetic resonance imaging) MRI, and electroencephalogram (EEG) performed to rule out mitochondrial or heredodegenerative diseases were inconclusive [Table 1]. Her final EEG showed left frontotemporal spikes with generalized slowing and MRI showed prominent cerebral–cerebellar atrophy with T2 hyperintensity in the cervical region [Figure 1]. Nerve conduction study revealed severe axonal degeneration of all motor and sensory nerves. WES detected a previously defined homozygous p.T79P (c.235A > C) missense mutation of the ADPRHL2 gene (NM_017825.2) [Figure 2]. Her parents were heterozygous for this mutation. She also had homozygous p.N110S mutation in the palmitoyl protein thioesterase (PPT1) gene with her parents being heterozygous in Sanger sequencing. In silico analysis could not be performed because of financial concerns. The PPT1 level from dry blood was normal. She did not have any visual impairment. The patient was lost from sudden cardiac arrest at 5.5 years of age.

The second patient was a 3.5-year-old boy who presented with an acute attack of truncal ataxia, which resolved spontaneously. His ataxia recurred with infections and progressed with additional intentional tremor. His neuromotor development was normal till 3.5 years of age except for severe language

Table 1: Differential diagnosis of the presented patients and performed tests for diagnostic work up

Disease	Diagnostic Tests
Mitochondrial respiratory chain enzyme deficiency	Plasma/CSF amino acids, plasma/CSF lactate Nerve conduction Study Audiometry Cardiac evaluation Muscle biopsy (only second patient) Ophtalmologic examination EEG Cranial MRI
Spinocerebellar ataxia type 26	WES/Cranial-Spinal MRI
Ataxia-oculomotor apraxia	WES/Cranial/Spinal MRI
Neuronal ceroid lipofuscinosis	Palmitoyl protein thioesterase (PPT1) enzyme level, eye fundus examination

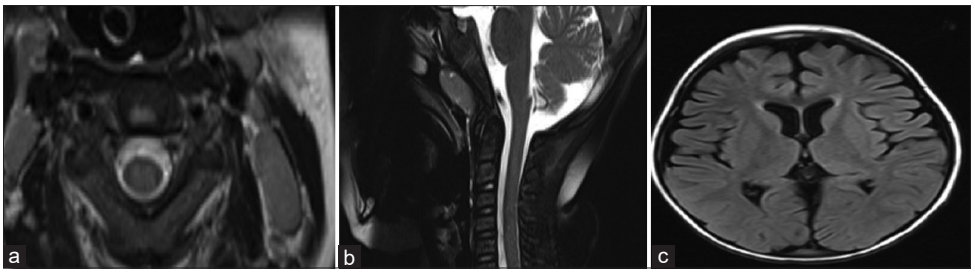

Figure 1: MRI findings of Patient 1. (a) Cervical T2 hyperintensity. (b) Cerebellar-cervical atrophy. (c) Cerebral atrophy

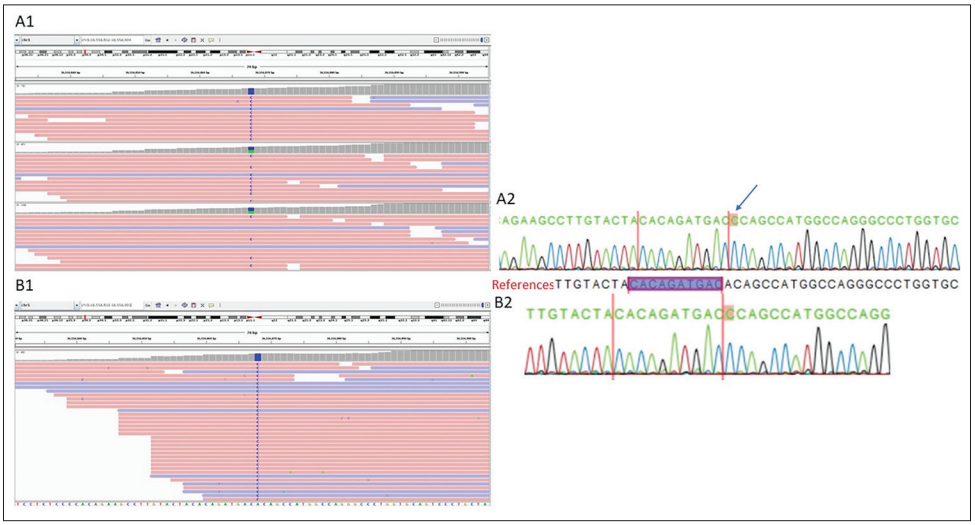

Figure 2: Genetic structure of identified variant in Patient 1 and 2 (a1) integrative genomics viewer (IGV) of ADPRHL2 gene mutation in Chr 1-patient1. (a2) Sanger view of the ADPRHL2 gene mutation in Chr 1-patient 1. (b1) Integrative genomics viewer (IGV) of ADPRHL2 gene mutation in Chr 1-patient 2. (b2) Sanger view of the ADPRHL2 gene mutation in Chr 1-patient 2

delay. His parents were third-degree relatives. His cranial MRI, EEG, and metabolic tests were normal. His nerve conduction study was normal. His muscle biopsy was inconclusive for mitochondrial disease. WES revealed a previously defined homozygous p.T79P (c. 235A > C) missense mutation in the ADPRHL2 gene (NM_017825.2). At 5 years of age, his clinical status was stable with only episodic ataxia and prominent language delay. He did not have any respiratory findings and his Cranial-spinal MRI was normal.

Discussion

Poly ADP polymerases add poly-ADP ribose (PAR) as a defense to cellular stressors and begin stress response pathways. PAR modification protects the cell from death due to stress; however, if there is a pathological mutation in the ADPRHL2 gene, which encodes one of the specific PAR-degrading enzymes, excessive PAR accumulation can trigger a cell-death response cascade.[3,4] Recently, mutations with different pathological variants of ADPRHL2 genes have been published.[3,5] A novel frameshift variant has recently been defined by Aryan *et al*.[6], which included gastrointestinal intolerance and white matter changes in the occipital area of the brain.

Our first patient's findings, including nystagmus, facial myoclonus, seizures, axonal polyneuropathy, cerebral/cerebellar and spinal atrophy, are very similar to the cases in literature except for earlier deterioration.[2] Ataxia accompanied by dystonic posture has been defined; however, paroxysmal torticollis attacks mimicking benign paroxysmal torticollis have not been reported before. Our second case has milder clinical findings with a better prognosis. Fifteen-year-old Turkish child with the same mutation as our patients who needed mechanical ventilation at the age of 10 was described by Ghosh *et al*.[3] All three patients had normal neurodevelopment before 18 months of age.

Epilepsy was defined as a component of the syndrome; however, not all patients reported have had seizures. Our first patient developed seizures at the age of 4, which was easily controlled with antiepileptics. She had a history of febrile convulsions. One patient in the literature deteriorated after febrile convulsions which started at age 4.[2] Our first patient had focal EEG findings different from the previously reported cases, but generalized slowing was similar.[2,3]

It has been speculated that cell death is responsible for disease mechanism through PAR signalling and accumulation;

however, different clinical presentations with variable severity of the same mutations still need to be further investigated.[3] In our first case, silent pathogenic mutation of PPT-1 gene on the same chromosome might be an additional factor for devastating clinical features and an early deterioration of the patient; further functional analysis would be informative.

ADPRHL2 has been shown to be the only PAR hydrolyzing enzyme located in mitochondria, and increased PARP1 activity was related to impaired mitochondrial metabolism, which could be a reason for deterioration with cellular stress.[7] White matter damage and loss have been attributed to axonal death due to mitochondrial dysfunction.[8] Hanzlikova *et al*.[9] showed that ADPRHL2-mutated human cells lead to mono (ADP-ribose) scar accumulation on core histones resulting in dysregulation of the transcription process. Progressive cerebellar ataxia and seizures have been attributed to this recently defined molecular mechanism. It has been speculated that PARP1 inhibitors might have a positive effect in attenuation of disease progression.[10]

CONDSIAS is a recently discovered clinical syndrome with a broad spectrum of clinical presentations and should be considered in differential diagnosis in cases with language delay, paroxysmal torticollis attacks aggravated by stress and complicated with progressive ataxia and truncal dystonia.

Consent for publication and ethics approval

Written informed consent was obtained from the patients' parents. Approval has been granted by the ethics board of Medipol University (22.10.2020-792).

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Conflicts of interest

There are no conflicts of interest.

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References

1. Hurwitz J. The discovery of RNA polymerase. J Biol Chem 2005;280:42477-85.
2. Danhauser K, Alhadded K, Makowski C. Bi-allelic ADPRHL2 mutations cause neurodegeneration with developmental delay, ataxia, and axonal neuropathy. Am J Hum Genet 2018;103:1-9.
3. Ghosh SG, Becker K, Huang H, Salazar TD, Chai G, Salpietro V, *et al*. Biallelic mutations in *ADPRHL*2, encoding ADP-ribosylhydrolase 3, lead to a degenerative pediatric stress-ınduced epileptic ataxia syndrome. Am J Hum Genet 2018;103:431-9.
4. Hanai S, Kanai M, Ohashi S, Okamoto K, Yamada M, Takahashi H, *et al*. Loss of poly (ADP-ribose) glycohydrolase causes progressive neurodegeneration in Drosophila melanogaster. Proc Natl Acad Sci USA 2008;101:82-6.
5. Mishra B, Fatima S, Agarwal A, Radhakrishnan DM, Garg A, Srivastava AK. Dystonia and myelopathy in a case of stress-ınduced childhood-onset neurodegeneration with ataxia and seizures (CONDSIAS). Mov Disord Clin Pract 2020;8:156-8.
6. Aryan H, Razmara E, Farhud D, Zarif-Yeganeh M, Zokaei S, Hassani AA. Novel imaging and clinical phenotypes of CONDSIAS disorder caused by a homozygous frameshipt variant of ADPRHL2: A case report. BMC Neurol 2020;20:291.
7. Schreiber V, Dantzer F, Ame JC, Murcia G. Poly (ADP-ribose): Novel functions for an old molecule. Nat Rev Mol Cell Biol 2006;7:517-28.
8. Gropman AL. Neuroimaging in mitochondrial disorders. Neurotherapeutics 2013;10273-85.
9. Hanzlikova H, Prokhorova E, Krejcikova K, Cihlarova Z, Kalasova I, Kubovciak J, *et al*. Pathogenic ARH3 mutations result in ADP-ribose chromatin scars during DNA strand break repair. Nat Commun 2020;11:3391.
10. Mashimo M, Bu X, Aoyama K, Kato J, Ishiwata-Endo H, Stevens LA, *et al*. PARP1 inhibition alleviates injury in ARH3-deficient mice and human cells. JCI Insight 2019;4:e124519.

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