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.

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

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 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

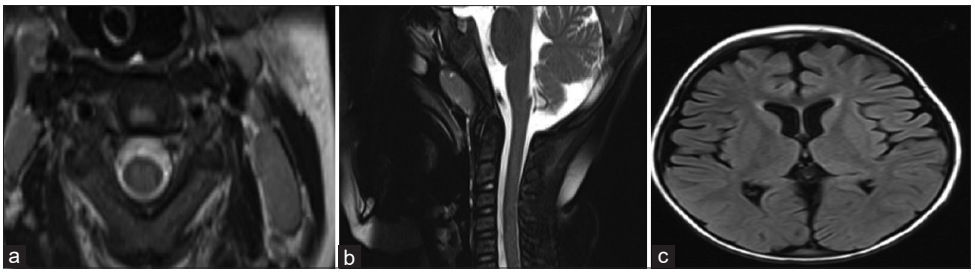

Figure 1: MRI findings of Patient 1. (a) Cervical T2 hyperintensity. (b) Cerebellar-cervical atrophy. (c) Cerebral atrophy

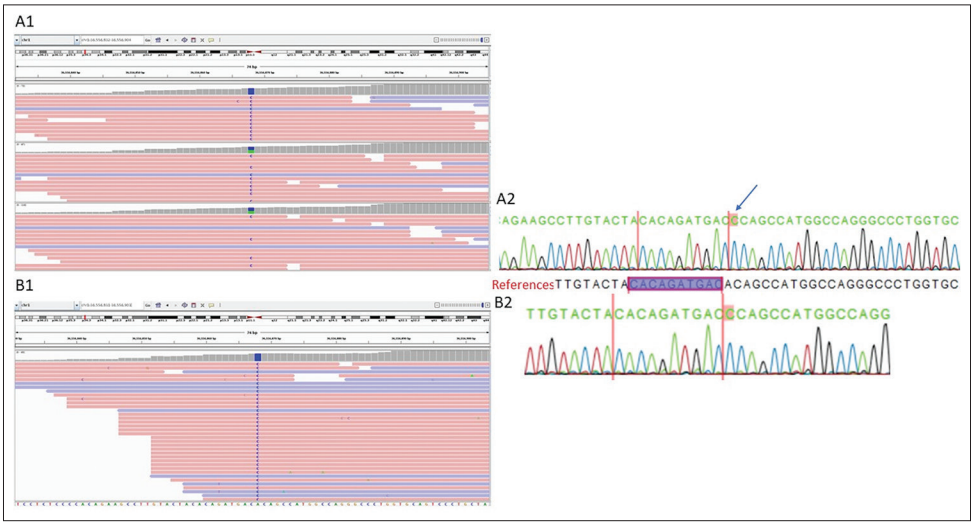

Figure 2: Genetic structure of identified variant in Patient 1 and 2 (a1) integrative genomics viewer (IGV) of ADPRHL2 gene mutation in Chr 1-patient1. (a2) Sanger view of the ADPRHL2 gene mutation in Chr 1-patient 1. (b1) Integrative genomics viewer (IGV) of ADPRHL2 gene mutation in Chr 1-patient 2.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

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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Supplementary: Summary of clinical and genetic findings of reported cases with *ADPRHL2* gene mutations

Literature	Country	Number of patients	Clinical characteristics	Exon	Mutation	MRI findings
Ghosh *et al*.[1]	United Arab Emirates	9	Normal early motor development: All patients Deterioration of motor milestones: All except two Speech: Two of them were normal till death, others deteriorated Intellectual ability: Six of them deteriorated Deterioration with stress: All of them Ataxia: All but two of them Seizures: All of them Respiratory insufficiency: Two of them Sudden death: Seven of them	Exon 6	c100C>T	Mild cerebellar atrophy
	Italy	1	Normal early motor development: Yes Deterioration of motor milestones: Yes Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: No Sudden death: No	Exon 3	c. 316C>T	Cerebellar vermis atrophy
	Turkey	1	Normal early motor development: Yes Deterioration of motor milestones: Yes Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: No Sudden death: No Claw hand and pes cavus deformities, scoliosis, sensorineural hearing loss tracheotomy, ventilator support	Exon 2	c. 235A>C	Mild cerebellar atrophy, spinal cord atrophy
	Pakistan	2	Normal early motor development: Yes Deterioration of motor milestones: Yes Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: No Sudden death: No Asthma	Exon 3	5-bp (c. 414-418delTGCCC)	Mild cerebellar atrophy
	Iran	2	Normal early motor development: Yes Deterioration of motor milestones: Yes	Exon 4	c. 530C>T	Female: normal (3 years) Male: N/A

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Literature	Country	Number of patients	Clinical characteristics	Exon	Mutation	MRI findings
			Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: No Sudden death: No Progressive weakness, tremors, frequent falling, progressive external ophthalmoplegia			
	Turkey	1	Normal early motor development: Yes Deterioration of motor milestones: Yes Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: No Sudden death: Yes Distal muscle atrophy, pes cavus deformity, toe abnormality, scoliosis, brisk deep tendon reflexes (DTRs), positive Babinski reflex, intentional tremor	Exon 1	c. 100G>A	Mild cerebellar vermis atrophy, spinal cord atrophy
	Germany	2	Normal early motor development: Yes Deterioration of motor milestones: Yes Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: Yes Facial myoclonia, diplopia, Neuropathy	Exon 6	c. 1004 T>G	Basal ganglia, cortex and cerebellum involvement
	Lebanon	1	Normal early motor development: Yes Deterioration of motor milestones: Yes Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: Yes Sudden death: Yes Neuropathy, facial myoclonia, Nystagmus	Exon 5	c. 744_746del	Corpus callosum, basal ganglia, cortex and cerebellum involvement
	N/A	1	Normal early motor development: Yes Deterioration of motor milestones: Yes	Exon 6	c. 1038C>G	Corpus callosum and cerebellum

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Literature	Country	Number of patients	Clinical characteristics	Exon	Mutation	MRI findings
			Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: Yes Sudden death: No Neuropathy, SNHL, strabismus, Microcephaly			involvement
Danhauser et al. [2]	N/A	2	Normal early motor development: Yes Deterioration of motor milestones: Yes Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: Yes Sudden death: No	Exon 6	c. 1004 T>G	Cerebellum involvement
	Kosovo	1	Normal early motor development: Yes Deterioration of motor milestones: Yes Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: Yes Sudden death: No Putative external ophthalmoplegia with ptosis, Impaired saccades Upward gaze and nystagmus, Putative retinal pigment epithelium anomalies, Neuropathy, Microcephaly	Exon 6	c. 1004 T>G	Cerebellum involvement
	Poland	1	Normal early motor development: Yes Deterioration of motor milestones: Yes Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: Yes Sudden death: No Neuropathy	Exon 6	c. 1004 T>G	N/A
	China	2	Normal early motor development: Yes Deterioration of motor milestones: Yes	N/A	c. 309-1G>T	Cerebellum involvement

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Literature	Country	Number of patients	Clinical characteristics	Exon	Mutation	MRI findings
			Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: Yes Sudden death: No Neuropathy			
	Turkey	2	Normal early motor development: Yes Deterioration of motor milestones: Yes Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: Yes Sudden death: No Microcephaly	Exon 2	c. 292delG	Basal ganglia involvement
Aryan *et al*.[3]	Iran	1	Normal early motor development: Yes Deterioration of motor milestones: Yes Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: Yes Sudden death: No General motor weakness and truncal hypotonia severe abdominal distension and GI intolerance, cardiorespiratory problems Sensorineural hearing loss	Exon 4	c. 636_639del	Mild supratentorial atrophy, progressive cerebral and cerebellar atrophy
Biswamohan *et al*.[4]	India	1	Normal early motor development: Yes Deterioration of motor milestones: Yes Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: No Severe cognitive involvement with apathy, aggression, irritability, delusions, visual and auditory hallucinations, jaw tremors, transverse myelopathy	Exon 1	c. 100G>A	
Present study	Turkey	2	Normal early motor development: Yes Deterioration of motor milestones: Yes	Exon 2	c. 235A>C	Cervical T2 hyperintensity

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Supplementary: Contd...

Literature	Country	Number of patients	Clinical characteristics	Exon	Mutation	MRI findings
			Speech: Normal Intellectual ability: Normal Deterioration with stress: Yes Ataxia: Yes Seizures: Yes Respiratory insufficiency: Yes Sudden death: Yes Paroxysmal torticollis attacks Progressive dystonia, focal seizures, myokymia, neuropathy, sensorineural hearing loss, nystagmus, bradymimia, bradykinesia, Autonomic dysregulation			Cerebellar-cervical atrophy, Cerebral atrophy