An Indian Child with CONDSIAS Due to a Novel Variant in *ADPRHL2* Gene

Dear Editor,

A male child of South-Asian descent, the first issue of a nonconsanguineous union, presented to us at 10.5 years age. The child was born full term, without any significant perinatal red flags. Frequent falls and gait instability were first noted at 2 years of age. The child also had history of poor grip over footwear, bilaterally, suggesting distal symmetrical weakness of the lower limbs. He gained the subsequent motor milestones with delay of 8–10 months. He did not achieve urinary or stool continence. There were no hearing or visual deficits, although he was noted to have convergent squint at 3 years of age. The distal-predominant weakness had a chronic progressive course to gradually involve the hand grip too, over the next 1 year. Further worsening of symptoms was noted at 9 years, following an intercurrent illness, to involve the proximal upper and lower limbs. He was now unable to lift his hand over the shoulders or get up from squatting position. The squint was noted to worsen too. At 10 years, following an episode of acute diarrheal illness, he regressed further. He was subsequently unable to self-feed, climb stairs or walk unassisted. Since the last 2 months, the child reported feeding and swallowing difficulties. Throughout the course, there were no seizures or sensory symptoms.

Examination revealed failure to thrive and short stature with normocephaly. He had bilateral convergent squint and nystagmus. His gait was unstable and ataxic. He had appendicular as well as axial hypotonia. The distal muscles of the hands as well the feet appeared wasted. His hand grip was weak with involvement of the intrinsic muscles of the hands. Bilateral symmetric distal-predominant (2/5) weakness along with proximal weakness (3/5) was appreciated. The deep tendon reflexes were elicitable normally, with the exception of bilateral well-sustained ankle clonus. Plantar response was absent. The joint position sense was impaired at bilateral great toes. Vibration sense was impaired at the medial malleoli. Rest of the sensory examination was normal. He had dysarthria and dysmetria. There was no weakness of the neck or the bulbar muscles. There were no behavioral or extrapyramidal abnormalities. Respiratory efforts were normal. Bilateral testes were undescended.

Review of previous investigations done at 6-years revealed normal blood parameters (*viz* complete blood count, creatinine-phosphokinase, lactate, liver function test, calcium, serum electrolytes, random blood sugar, thyroid function tests, and serum B12 level) and cerebellar atrophy on MRI brain. Neurophysiology evaluation consisted of electromyography (EMG), nerve conduction studies (NCS), somatosensory evoked potential (SEP), visual evoked potential (VEP), and brainstem electric response audiometry (BERA). All sensory conduction findings were normal. The compound muscle action potential amplitudes (CMAP) were grossly attenuated in the right median and left tibial nerves. Conduction times were mainly normal. Needle EMG revealed neurogenic changes that were mostly distal and symmetrical. The SSEP study showed delayed tibial responses and normal median latencies suggestive of posterior column dysfunction (PCD). The VEP and BERA were normal ruling out optic neuropathy and sensorineural deafness. In summary, neurophysiology evaluation showed evidence of a generalized pure motor, distal symmetrical axonopathy with posterior column involvement at dorsolumbar level.

Repeat MRI brain revealed periventricular and deep white matter abnormalities, superior vermis volume loss and parenchymal abnormalities in the spinal cord at the mid-thoracic level [Figure 1]. The clinico-electrophysiological correlation raised the suspicion of a hereditary motor axonopathy with PCD, likely of a genetic etiology given the early-onset and the chronic progressive course.[1] The variegate, potentially multisystemic spectrum, punctuated by worsening spells following stresses, made us consider mitochondrial

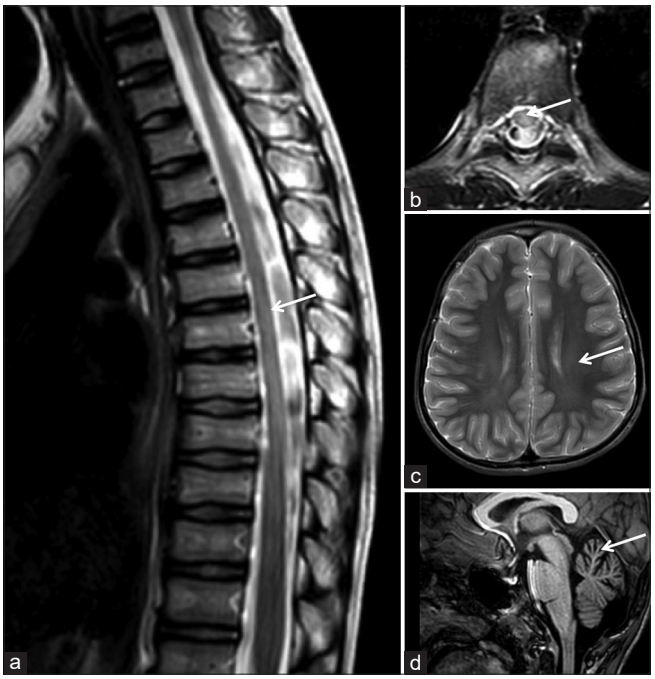

Figure 1: MRI spine and brain reveals diffuse ill-defined T2 hyperintense signal abnormality in the thoracic cord on T2 weighted sagittal (a) and axial (b) images. Diffuse subtle hyperintense signal is seen in the periventricular and deep white matter on T2 weighted axial images of the brain (c). Superior vermian volume loss is seen on mid-sagittal T1 weighted image (d)

disorders as a differential.[2] Juvenile amyotrophic lateral sclerosis was also suspected due to combination of upper motor and lower motor signs, however, the intercurrent worsening of features precipitated by illnesses, was not typical. Distal weakness due to hereditary motor sensory neuropathies or Charcot-Marie-Tooth disease was suspected, but could be differentiated on the basis of normal sensory NCS.

Next-generation sequencing (NGS) based whole-exome sequencing (WES) was ordered. It revealed a novel homozygous loss of function variant in the *ADPRHL2* gene [NM_017825.2:c.166C>T; p.(Gln56*)]. This variant is not present in the gnomAD database. It causes a premature stop codon, thus affecting the protein functioning. It was classified as likely pathogenic (class 2) according to the recommendations of the American College of Medical Genetics.[3] The variant was found to be segregating with the parents (both of them being heterozygous carriers for *ADPRHL2* gene variant, c.166C>T; p.(Gln56*). This confirmed a rare diagnosis of autosomal recessive *c*hildhood-*o*nset *n*euro*d*egeneration, *s*tress-*i*nduced, with variable *a*taxia and *s*eizures (CONDSIAS) in the child.[4]

CONDSIAS (OMIM #618170) is a rare, cyclically progressive, autosomal recessive neurodegenerative disorder, presenting usually in the first decade of life; the course often exacerbated by febrile illnesses and intercurrent stresses.[4-7] Literature review reveals our report to be the 33rd case reported globally, only the second one from the Indian Subcontinent.[4-7]

CONDSIAS, a condition first described as recently as 2018, includes a highly variable spectrum. We should suspect CONDSIAS in the clinical setting of cyclical/episodic worsening of neurodegeneration, ataxia, and seizures. The other clinico-radiological clues of CONDSIAS are summarised in Table 1. Evidence of myelopathy, present in our case (revealed by clinical features, SSEP findings, MRI spine findings) was reported only once earlier.[6]

The child was offered physiotherapy and occupational therapy. Role of routine vaccination to minimize intercurrent illnesses was also stressed upon. The parents were explained about the absence of any definitive treatment option for CONDSIAS. A confirmation of CONDSIAS helped the family attain closure to the diagnostic journey spanning over 8 years and understand the associated prognosis.

The child had a chronic gradually regressive course over the next 14-months. He had an acute diarrhoeal illness at 12-years, lasting for 3 days. During this period, he got increasingly incapacitated and nonambulatory; expiring suddenly on the 3rd day of illness.

The mother visited us 4 months later, desiring preconception genetic counseling. She was explained a 25% empiric risk of recurrence at each conception. Having established the causative variant in the proband, we could offer her the following reproductive options[8]:

(a) Natural conception and invasive testing for targeted *ADPRHL2*-gene by Sanger

Table 1: Typical features of CONDSIAS and the novel features of CONDSIAS present in our case[3-7]

Category	Details
Causative gene: *ADPRHL2*	Other reported variants' summary[17]
	Current case variant: novel*: homozygous nonsense variant c. 166C>T (chr1: 36554671C>T) in *ADPRHL2* gene
Typical features (variable)[14-18]	Usually childhood onset*
	Normal or delayed* development
	Neurodegeneration, neuroregression*
	Intellectual disability
	Autistic features
	Speech impairment
	Cyclical worsening during periods of fever/stress*
	Seizures
	Ataxia*, tremors, nystagmus, dysarthria*, dysmetria*
	Ptosis
	Ophthalmoplegia
	Strabismus*
	Sensorineural hearing impairment/loss
	Muscle weakness*
	Distal-muscle atrophy*
	Hypotonia*
	Tongue fasciculations
	Respiratory insufficiency
	Microcephaly
	Axonal neuropathy*
	Sensorimotor neuropathy
	Demyelination neuropathy
	Extensor plantar reflex
	Claw hand, pes cavus, scoliosis
	Sudden death may occur in childhood*
Rare features	Gastrointestinal intolerance[16]
	Recurrent attacks of torticollis[18]
	Retinal pigment epithelium anomalies[14]
	Psychosis[17]
	Dystonia[17]
	Quadriparesis[17]
Typical (variable)	Cerebellar atrophy (superior vermian* involvement in the current case)
	Spinal cord atrophy
	Cerebral atrophy
	Basal ganglia and corpus callosum involvement
Atypical/rare	Myelopathy*[17]
	Deep white matter signal abnormalities*

*Findings marked by asterisk were present in the current case

(b) In-vitro fertilization (IVF) and preimplantation genetic testing; selective implantation of the "healthy"/unaffected embryos.

The current case of CONDSIAS, the second only from the Indian subcontinent, highlights the strengths of new-age genetic tests in unravelling rare disease (RD) diagnosis and truncating these long diagnostic delays. It underlines the impact of a confirmed diagnosis, even in the absence of definite therapeutic options, in the form of being able to offer prognostication, closure, and reproductive counselling for the future pregnancies.

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Conflicts of interest
There are no conflicts of interest.

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