PHENOTYPIC EXPANSION OF VRK-1 RELATED DISORDERS: A CASE OF JUVENILE ONSET ALS

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Background :

Vaccinia-related kinase 1 (VRK1)-related disease is an extremely rare, autosomal recessive disorder affecting both the central and peripheral nervous systems. Pathogenic VRK1 variants have been associated with a wide phenotypic spectrum, including spinal muscular atrophy (SMA)-like phenotypes, hereditary motor and sensory neuropathies, and complex motor neuron disorders, with or without pontocerebellar hypoplasia or microcephaly.

Aim :

To describe the clinical, electrophysiological, and genetic characteristics of a 10-year-old male with progressive, symmetric distal weakness in his lower extremities due to a rare homozygous VRK1 splice-site mutation.

Case Report :

A 10-year-old boy, born to non-consanguineous parents, with unremarkable birth and developmental history, presented with a 6-month history of progressive, symmetric distal weakness of the lower limbs.

He reported foot dragging while walking and difficulty descending stairs. There were no family members with similar symptoms.

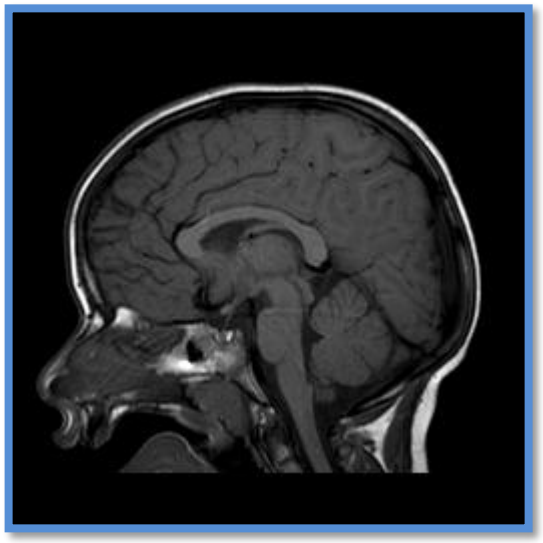
On examination, he had pes cavus and hammer toes. Extensor digitorum brevis was bilaterally atrophied, while no other muscle wasting or fasciculations were noted. Cranial nerves and cognitive function were normal. Muscle strength was graded 3/5 in ankle dorsiflexion and 4+/5 in plantarflexion; other muscles tested were 5/5. Deep tendon reflexes were brisk at the knees, 1+ at the ankles, with extensor bilateral plantar responses. Sensory and cerebellar examinations were normal. His gait was high-stepping.

Clinical differentials included distal spinal muscular atrophy , Juvenile ALS and hereditary neuropathies (Charcot–Marie–Tooth vs. hereditary motor neuropathy).

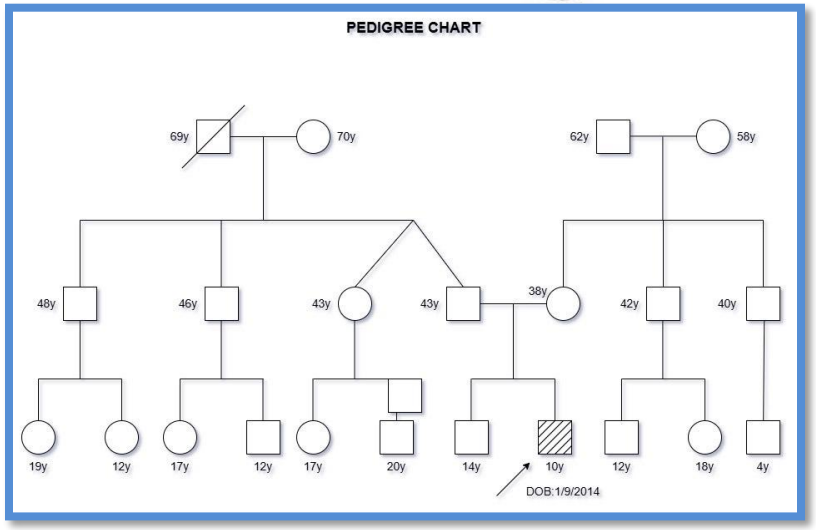
Results :

Electrodiagnostic studies showed normal sensory conductions of bilateral sural, left median, ulnar, and radial nerves. Motor conduction studies of bilateral peroneal/EDB, bilateral tibial, and median nerves showed reduced CMAP with normal latencies, velocities. Needle electromyographic examination shows neurogenic motor unit potentials in right dorsal interosseous, right biceps and right tibialis anterior with no features of denervation and reinnervations. Serum creatine kinase was mildly elevated (320 U/L). MRI brain and spine were normal. Genetic analysis was done by performing in proband along with both parents, singleton exome sequencing found to have splice site variant, c.1159+1G>A in intron 12 of VRK-1 in homozygous state in proband. Variant in Heterozygous state is found in his parents.

Gene Transcript	Location	Variant	Zygosity	ACMG classification	Disease (MIM#)	Inheritance	Parental origin
VRK1 NM_003384.3 NC_000014.9	Intron 12	c.1159+1G>A/ g.96876121G>A	Homozygous	Pathogenic	Neuronopathy, distal hereditary motor, autosomal recessive 10 (620542)	Autosomal recessive	Paternal and maternal



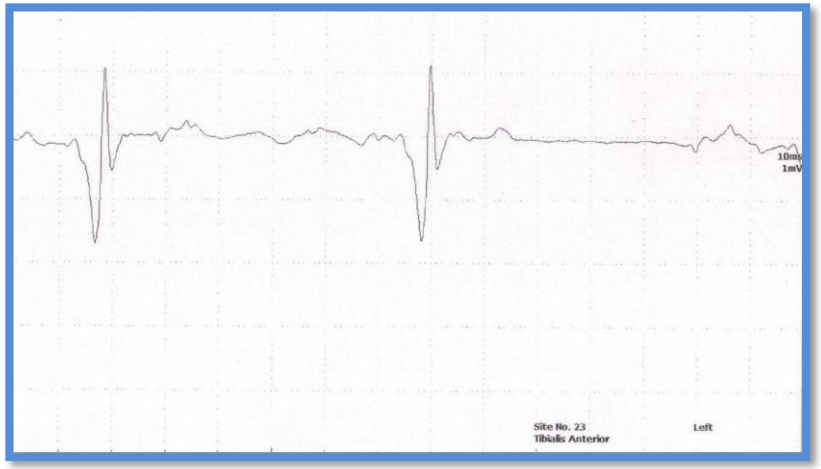
MRI : No Evidence Of Pontocerebellar Atrophy



Pedigree Chart

Common Peron Left								
Ankle	4.1	16.8	0.4mV	1.8mVm	*Ankle		4.1	
Head of fibula	11.1	15.5	0.4mV	2.0mVm	Ankle-Head of fibula	320	7.1	45.4
Popliteal	12.9	15.4	0.4mV	1.7mVm	Head of fibula-Popliteal	80	1.8	44.4
Tibial Right								
Ankle	4.4	16.6	5.4mV	15.1mV	*Ankle		4.4	
Popliteal	14.3	15.2	3.6mV	10.5mV	Ankle-Popliteal	400	9.9	40.4
Tibial Left								
Ankle	4.1	17.8	9.6mV	38.1mV	*Ankle		4.1	
Popliteal	12.6	15.4	4.8mV	18.7mV	Ankle-Popliteal	400	8.5	47.1
CPN - TIB.ANT Right								
Fib Head	3.2	12.5	1.9mV	6.4mVm	*Fib Head		3.2	
CPN - TIB.ANT Left								
Fib Head	3.3	17.2	2.6mV	11.3mV	*Fib Head		3.3	
Sensory Nerve Conduction Studies								

NCS : Motor axonal affection in tested nerves



EMG : Neurogenic Motor Unit Potentials

Discussion :

This patient with childhood-onset, distal lower extremity predominant, progressive weakness with upper and lower motor neuron signs would meet revised El Escorial criteria for clinically probable Amyotrophic lateral sclerosis[1]. On exome capture, he displayed homozygous splice site mutations in VRK1, which are suspected to be disease causing.

VRK1 encodes a serine/threonine kinase that interacts with p53 in an autoregulatory loop, potentially linking VRK1 dysfunction to motor neuron degeneration [2,3]. Previous reports have described VRK1 mutations in phenotypes ranging from slowly progressive adult-onset ALS to childhood-onset SMA or hereditary neuropathies with microcephaly and short stature. This case highlights a unique phenotype: a slowly progressive, ALS-like distal hereditary motor neuronopathy with brisk reflexes and onset in childhood.

VRK1 mutations were reported by Nguyen et al [4] (a case of slowly progressive adult-onset ALS) and Stoll et al.[5] reported two families: one with childhood-onset ALS with short stature and microcephaly, the other with childhood- onset SMA with mild to moderate generalized brain atrophy. Identification of VRK1 mutations among these various motor phenotypes, with clinical overlap among juvenile ALS, dHMN, and SMA, may serve to further unite concepts of pathogenesis among motor neuron disorders.

Conclusion :

We report a rare homozygous *VRK1* mutation (c.1159+1G>A) in a child with probable Juvenile ALS. This case broadens the phenotypic spectrum of VRK1-related disorders and underscores the importance of genetic testing in atypical presentations of motor neuron disease.

References :

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Thank You