Novel clinical findings of neurodevelopmental disorder linked to HPDL gene mutation: a case report from Saudi Arabia

Abdullah Musallam Alkhalaf,[1] Moayad Ahmed Alshaqaq,[2] Nadia Jradi,[3] Ahmad Hassan Aljaziri,[1] Essa Sultan Alsultan[1]

[1]College of Medicine, King Faisal University, Al-Ahsa; [2]Pediatric Neurology Consultant, Maternity and Children Hospital, Al-Ahsa; [3]Department of Pediatrics, College of Medicine, King Faisal University, Al-Ahsa, Saudi Arabia

Abstract

HPDL gene mutations have recently been linked to neurodevelopmental disorders with variable presentations, ranging from mild hereditary spastic paraplegia to severe infantile neurodegeneration. While the HPDL protein's role is unknown, it is highly expressed in brain mitochondria. Here we report a case of a 19-month-old male with a homozygous HPDL gene mutation presented with global developmental delay, epilepsy, laryngomalacia post-arytenoidectomy, swallowing dysfunction, and spasticity. He exhibited significant dysmorphic features and recurrent convulsions, and required nasogastric feeding due to oral feeding difficulties.

Introduction

The pathophysiology of neurodevelopmental impairments is complicated and involves both hereditary and environmental variables. These disabilities arise from improper development of the central nervous system. Recent research has demonstrated that biallelic variations in the 4-Hydroxyphenylpyruvate Dioxygenase-like (HPDL) gene may be the cause of neurodevelopmental disorders.[1] Biallelic variants in the HPDL gene have been described in 2020 as able to cause a progressive disorder with variable clinical presentation, ranging from milder manifestation of adolescent-onset pure Hereditary Spastic Paraplegia (HSP), classified as Autosomal recessive spastic paraplegia-83 (SPG83), to severe Neonatal-Onset Encephalopathy or infantile-onset Neurodegeneration with progressive Spasticity and brain White Matter Abnormalities (NEDSWMA).[2] Furthermore, affected patients with HPDL mutation typically develop spasticity, primarily in the lower limbs.[3] Still, the role of the HPDL protein remains unknown. HPDL is broadly expressed in tissues, with the most concentrated amounts found in the brain, and it is specifically located in mitochondria.[4]

Here, we report a patient with a novel clinical manifestation linked to an HPDL mutation. Comprehending these genetic foundations is essential for enhancing diagnostic precision and possibly directing treatment approaches in the future. This study was approved by the Ethics Committee of Maternity and Children's Hospital – Al Ahsa, with the IRB reference number (H-05-HS-137). Written informed consent was obtained from the father.

Case Report

Hereby, we report a 19-month-old male with global developmental delay, epilepsy, laryngomalacia, S/p arytenoidectomy, swallowing dysfunction, spasticity, thin corpus callosum on MRI brain, and confirmed homozygous HPDL gene mutation on genetic testing.

Detailed history taking reveals a full-term male infant who was born at 38 weeks of gestation to healthy first-degree cousins. The course of the pregnancy was uneventful. APGAR score was eight at 1 minute and 5 minutes. The delivery was complicated by meconium-stained amniotic fluid, leading to respiratory distress that resolved post-delivery. At birth, the infant presented with several dysmorphic features, including low-set ears, a depressed nasal bridge, micrognathia, clinodactyly, fixed flexion of the proximal interphalangeal joints of the 4th fingers bilaterally, and rocker-bottom feet.

The family consists of nine children in total, including the patient, who is the only one currently confirmed to have the disease. Two of the siblings, previously diagnosed with idiopathic brain atrophy of unknown etiology, are deceased. The remaining six children are alive and exhibit normal neurodevelopment. Whole Exome Sequencing (WES) has not been performed on any of the children.

Initial physical examination showed dysmorphic infant vitally

Correspondence: Nadia Jradi, Department of Pediatrics, College of Medicine, King Faisal University, Al-Ahsa, Saudi Arabia
Tel.: +966.569208088.
E-mail: Nadia.jradi@kfu.edu.sa

Key words: HPDL gene mutation, neurodevelopmental delay, spasticity, hypotonia, genetic neurodevelopmental disorders.

Conflict of interest: the authors do not have any conflict of interest or funding source to declare.

Ethics approval and informed consent to participate: this study was approved by the Ethics Committee of Maternity and Children's Hospital – Al Ahsa, with the IRB reference number (H-05-HS-137). Written informed consent was obtained from the father.

Availability of data and materials: all data underlying the findings are fully available.

Received: 29 November 2024.
Accepted: 10 June 2025.
Early access: 8 September 2025.

Healthcare in Low-resource Settings 2025; 13:13440
doi:10.4081/hls.2025.13440

stable. CNS examination showed open anterior fontanelle, a head circumference of 36 cm, high muscle tone (spasticity) in all extremities, axial hypotonia, Asymmetrical Moro reflex (sluggish on the left side) Intact, sucking, palmar, and plantar reflexes. Left upper limb internally rotated, extended at the elbow, flexed at the wrist with reduced movement. All other extremities moved freely. Chest, cardiovascular, and gastrointestinal were normal. Laboratory tests were unremarkable. Cranial ultrasound and brain MRI showed a bilateral germinal matrix subependymal cyst. No white matter abnormalities were detected. EEG showed no evidence of epileptiform discharge.

In the first month, the patient had axial hypotonia, poor head control, loss of ocular, pursuit and mild peripheral spasticity. By the second month, it was noted to have micrognathia, microcephaly (37 cm), peripheral spasticity, and central hypotonia. He developed recurrent episodes of convulsions, apnea, stridor, and cyanosis. Convulsions were in the form of generalized tonic-clonic movements. The EEG background shows diffuse slow 2-3 Hz delta activity, indicating a non-epileptiform pattern. The patient was then started on phenobarbitone.

Genetic testing using Whole Exome Sequencing (WES) identified a homozygous likely pathogenic variant in the *HPDL* gene, consistent with an autosomal recessive neurodevelopmental disorder characterized by progressive spasticity and brain white matter abnormalities. The specific variant detected was *HPDL*, c.788C>G p. (Thr263Arg), which results in an amino acid substitution from threonine to arginine at position 263.

At four months, the patient had global developmental delay and microcephaly. Although seizures were controlled, the episodes of frequent episodes of apnea with cyanosis and stridor persisted. The patient was then diagnosed to have laryngomalacia and underwent a micro laryngoscopy with arytenoidectomy. Apnea resolved after surgery.

At eight months old, the patient still showed profound developmental delay with no social smile, no sound imitation, and no interest in the surroundings. Axial hypotonia and peripheral spasticity increased in severity, with no improvement despite regular physiotherapy. Moreover, the patient failed to feed orally, which required feeding using a nasogastric tube. He then started to show a new form of abnormal movements while being on Levetiracetam. The EEG shows intermittent slow activity reflecting cerebral dysfunction. Sandifer phenomenon secondary to GERD was suspected; however, no fluoroscopic findings of GERD were detected on upper GI study, and the patient failed to improve on a one-month trial of omeprazole. Upper gastrointestinal endoscopy was then performed and revealed normal esophageal mucosa with a corkscrew appearance suggestive of diffuse esophageal spasm. Manometry studies were not available to confirm the diagnosis. The patient continues to be fed by nasogastric tube.

Discussion

Hereditary Spastic Paraplegia (HSP) is a collection of diseases that are mostly characterized by spasticity and paralysis in the lower extremities.[5] Today, there are more than 80 distinct forms of HSP, including a broad spectrum of molecular and metabolic aetiologies, that can be inherited in an autosomal dominant, recessive, or X-linked fashion.[6] In populations where there is parental consanguinity and/or a common set of founder mutations, autosomally recessively inherited illnesses are a significant source of both death and morbidity.[7] Although the consanguinity rates in Western and European countries are less than 0.5%, this rate is much higher in Arab countries, reaching 20-50% of marriages in Saudi Arabia.[8]

Both spastic paraplegia 83 (SPG83) and a Neuro-Developmental Disease with progressive Spasticity and brain White Matter Abnormalities (NEDSWMA) are the two primary phenotypes that clinically describe the HPDL-related neurodegenerative condition. SPG83 is characterized by spastic paraplegia in juveniles, whereas NEDSWMA often manifests as severe neurodevelopmental delay, brain atrophy, and spasticity in toddlers.[1] Previous studies have shown that probands with HPDL variations and early disease start had either a milder clinical course with mild to severe developmental delay and spasticity progression, or a severe newborn encephalopathy with little to no psychomotor development. Adolescent-onset illness, on the other hand, has not been linked to developmental problems.[4]

The range of neuroradiological findings linked to variations in HPDL was likewise quite high. They varied from no pathological findings to anomalies in the striatum and white matter.[9]

Our case is the second reported HPDL gene mutation case in Saudi Arabia. The first case was reported by Wiessner *et al.* in 2021.[6]

The dysmorphic features reported in our case share certain similarities with other reported cases.[6] However, our patient showed a set of unique dysmorphic features, including a depressed nasal bridge, micrognathia, clinodactyly, and rocker-bottom feet that were not previously reported. Other reported dysmorphic features, such as high-arched palates, hypertelorism and long philtrum were not detected in our case.[6]

The respiratory failure in this case was attributed to peripheral apnea caused by laryngomalacia. In contrast, the respiratory failure in the other reported cases was due to central apnea.[6]

Moreover, the highly suspected diagnosis of diffuse esophageal spasm is also a novel clinical finding, since it was not reported previously in similar patients. Although we acknowledge that Confirmation of the diagnosis with manometry studies is needed.

Conclusions

HPDL gene mutation is a rare white matter disease that typically presents as spastic quadriplegia with central hypotonia. Our patient exhibited novel clinical findings, including diffuse esophageal spasm and laryngomalacia. Additionally, unusual dysmorphic features were observed, such as micrognathia, clinodactyly, a depressed nasal bridge, and rocker-bottom feet.

References

1. Wang Y, Zheng X, Feng C, et al. HPDL mutations identified by exome sequencing are associated with infant neurodevelopmental disorders. Mol Genet Genomic Med 2022;10:2025.
2. Sartorelli J, Longo D, Travaglini L, et al. Acute ophthalmoplegia with Wernicke-like MRI pattern in a patient with HPDL-related disorder. Mov Disord Clin Pract 2024;11:1160-2.
3. Husain RA, Grimmel M, Wagner M, et al. Bi-allelic HPDL variants cause a neurodegenerative disease ranging from neonatal encephalopathy to adolescent-onset spastic paraplegia. Am J Hum Genet 2020;107:364–73.
4. Micule I, Lace B, Wright NT, et al. Case report: two families with HPDL related neurodegeneration. Front Genet

2022;13:780764.
5. Yu H, Wei Q, Luo WJ, Wu ZY. Novel bi-allelic HPDL variants cause hereditary spastic paraplegia in a Chinese patient. Clin Genet 2021;100:777–8.
6. Wiessner M, Maroofian R, Ni MY, et al. Biallelic variants in HPDL cause pure and complicated hereditary spastic paraplegia. Brain 2021;144:1422–34.
7. Morgan NV, Yngvadottir B, O'Driscoll M, et al. Evidence that autosomal recessive spastic cerebral palsy-1 (CPSQ1) is caused by a missense variant in HPDL. Brain Commun 2021;3:2.
8. Khayat AM, Alshareef BG, Alharbi SF, et al. Consanguineous marriage and its association with genetic disorders in Saudi Arabia: A review. Cureus 2024;16:e53888.
9. Numata-Uematsu Y, Uematsu M, Yamamoto T, et al. Leigh syndrome-like MRI changes in a patient with biallelic HPDL variants treated with ketogenic diet. Mol Genet Metab Reports 2021;29:100800.