Case Report

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Very rare Palestinian case report of PRUNE1 p. Asp106Asn mutation: a mutation of global developmental delay

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Introduction and importance: The PRUNE1 gene (prune exopolyphosphatase 1), situated on chromosome 1q21.3, encodes a protein crucial for early fetal brain development, regulating processes like the polymerization of microtubules, migration of cells, and proliferation. Common features of Neurodevelopmental disorder with microcephaly, hypotonia, and variable brain anomalies (NMIHBA) include progressive microcephaly, hypotonia, spastic quadriparesis, intellectual disability, and abnormal brain magnetic resonance imaging findings.

Case presentation: A 4-month-old male infant, born at 39 weeks and 2 days via Cesarean, prenatal ultrasound findings were positive for ventricular dilation (hydrocephalus). Postnatally, the infant required admission for transient tachypnea of the newborn. Developmental delays and limb stiffness were evident by 2 months of age, prompting neurological evaluation. Examination at 4 months revealed dysmorphic features, including frontal bossing, low-set, malformed ears, and dolichocephaly, alongside axial hypotonia, spasticity, and knee contractures. Genetic testing confirmed a c.316G>A mutation in the PRUNE1 gene, establishing the diagnosis of NMIHBA.

Clinical discussion: PRUNE1-related NMIHBA is a rare neurodevelopmental disorder characterized by profound developmental delays, microcephaly, and variable neurological findings. This case emphasizes the importance of early recognition and genetic testing in infants with suggestive dysmorphic and neurological features. While management remains supportive, early diagnosis aids in family counseling and long-term care planning.

Conclusion: This report describes a rare presentation of NMIHBA in a Palestinian infant with a PRUNE1 gene mutation, contributing to the limited literature on this disorder. Further studies are required to understand the phenotypic spectrum and molecular mechanisms underlying PRUNE1-related disorders.

Keywords: case report, neurodevelopmental disorder, NMIHBA, Palestine, PRUNE1 gene

Introduction

The PRUNE1 gene, located at 1q21.3, produces a protein belonging to the DHH (Asp-His-His) phosphoesterase family. This protein is widely expressed during early human fetal brain development and contributes to the polymerization of microtubules, cell migration, differentiation, and proliferation.[1].

NMIHBA (OMIM #617481) emerges as an autosomal recessive disorder caused by mutations in the PRUNE1 gene. Its prominent characteristics comprise global developmental delay, intellectual disability, progressive microcephaly, plagiocephaly, spastic quadriparesis, hypotonia, optic atrophy, and abnormal brain magnetic resonance imaging (MRI) findings, including delayed myelination, cerebral and cerebellar atrophy, and thin corpus callosum.[2].

Here, we describe one of the few reported cases of a c.316G>A mutation in the PRUNE1 gene, which presented with global developmental delay. The work has been reported per the SCARE criteria.[3]

Case presentation

Four-month-old male infant was delivered via Cesarean section at full term (39 weeks and 2 days of gestation) due to a history of a prior Cesarean delivery. His 28-year-old mother, a healthy gravida 5 para 4 abortion 1 woman, experienced an uneventful pregnancy. However, a detailed ultrasound raised concerns about brain ventricular dilation (hydrocephalus). The baby's birth parameters were within normal ranges, and he exhibited bilateral club foot.

Post-delivery, the infant developed transient tachypnea, requiring neonatal intensive care unit (NICU) admission for 2 days. After an episode of tachypnea and desaturation, he was diagnosed with Transient Tachypnea of the Newborn. At the 2-month follow-up, he displayed delayed developmental milestones and had stiff lower limbs, prompting a referral to a pediatric neurology center.

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Figure 1. Photographs of the patient reveal subtle dysmorphic characteristics, including frontal bossing, a low-set malformed ear, and dolichocephaly.

Upon admission to our hospital at the age of 4 months, the infant presented with dysmorphic features, including frontal bossing, low-set, malformed ears, and dolichocephaly (Fig. 1).

Neurological examination revealed axial hypotonia, spastic limbs, knee contracture, and poor eye contact. Laboratory results were within normal limits, including CBC, ammonia, CPK, calcium, CRP, electrolytes, magnesium, blood gas, and ALT (Table 1).

A brain MRI revealed mild cortical atrophy, thin corpus callosum, peri-cerebral effusion, wide opercles, and delayed myelination (Fig. 2).

Post-MRI, the infant experienced O_2 desaturation, leading to a 2-week requirement for oxygen support. A chest X-ray showed hypo-inflated lungs with no other significant findings (Fig. 3). The desaturation was attributed to pre-existing respiratory vulnerability, which was precipitated by anesthesia administered before the MRI.

Whole exome sequencing confirmed a homozygous mutation in the PRUNE1 gene (c.316G>A), establishing the diagnosis of NMIHBA. The sequencing utilized the IDT xGen Exome Research Panel v2.0 for protein-coding regions and the xGen Human mtDNA Research Panel v1.0 for mitochondrial DNA on the Illumina NOVASEQ 6000 platform, adhering to stringent European Molecular Genetics Quality Network (EMQN) standards. Variants were carefully filtered, excluding intronic variants >8 base pairs from splice sites, synonymous variants >3 base pairs from splice sites, and variants with >1% minor allele frequencies in the GnomAD database.[4] It uncovered a homozygous mutation in the PRUNE1 gene (c.316G>A), confirming the diagnosis of NMIHBA. Both parents whole-exome sequencing (WES) was advised to better understand the genetic contribution to the infant's condition and to evaluate potential carriers of the PRUNE1 p.Asp106Asn mutation. After 2 weeks, the patient was weaned from O_2 and discharged home with a plan to do physiotherapy.

The family continues to follow up with the physician for ongoing monitoring and management. However, as this represents a newly reported case, the long-term prognosis and potential complications remain undetermined. Future studies and extended follow-up are needed to better understand this rare mutation's clinical course and outcomes.

Discussion

The PRUNE1 gene on chromosome 1q21.3 governs the synthesis of 453 amino acid proteins that exhibit significant expression levels throughout fetal brain development. It regulates neuronal migration and proliferation and features DHH and DHHA2 domains.

However, disruptions, particularly in the DHH domain, have a significant impact on a conserved C-terminal motif.[2,5].

Beyond its role in brain development, PRUNE interacts with glycogen synthase kinase-3B, impacting neurite outgrowth and neurogenesis. Furthermore, it contributes to a sophisticated network that impacts cellular mobility and the expression of genes linked to cancer metastasis.[2].

NMIHBA is a progressive neurodegenerative and neurodevelopmental disorder characterized by developmental delay starting from early infancy that progresses over the age of 1-year patients usually have hypotonia and spastic quadriparesis, which makes them unable to ambulate[5].

c.316G>A variant in the PRUNE1 gene was previously described in Italian and Turkish cases[5-8]. The observed phenotypes in these cases encompassed intellectual disability, developmental delay, spastic quadriparesis, hypotonia, and abnormal brain MRI findings, aligning with the features observed in our case[2].

Furthermore, additional clinical manifestations such as gastrointestinal issues, involvement of the peripheral nervous system, and optic nerve atrophy have been documented in patients[9].

Table 1

Laboratory results

Parameters	Results	Normal value
ALT	48 U/L	7–55 U/L
Hemoglobin	10.9 g/dL	9.5–13 g/dL
Calcium	8 mg/dL	7–10 mg/dL
Magnesium	2.2 mg/dL	1.9–2.5 mg/dL
Sodium	136 mEq/L	132–148 mEq/L
Potassium	3.7 mEq/L	3.5–5 mEq/L
Chloride	102 mEq/L	99–110 mEq/L
CPK	35 U/L	30–190 U/L
Ammonia	30 µmol/L	<40 µmol/L
CRP	Negative	<6

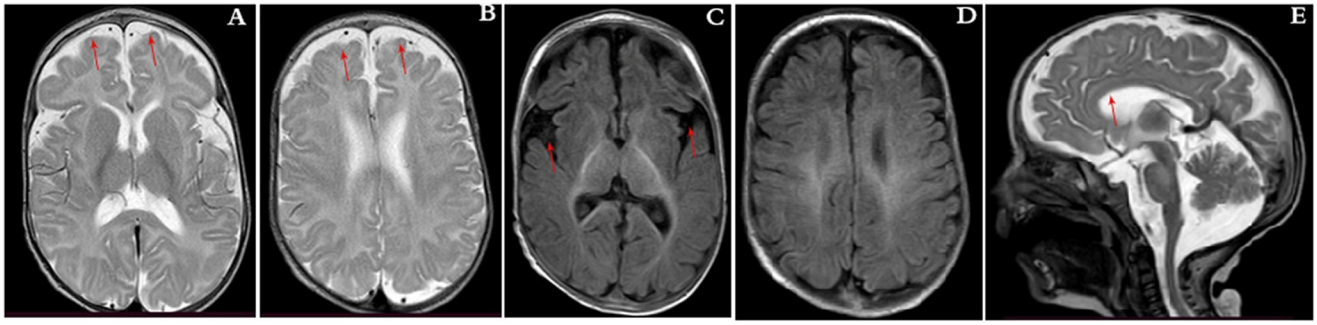

Figure 2. Brain MRI was done at the age of 4 months. A and B (T1-weighted) show an axial view of the brain with mild generalized volume loss and diffuse cortical thinning. Also, there is a slight lag in myelination and peri-cerebral effusion in red arrows. C and D (T2-weighted) showing an axial view of the brain also show diffuse cortical atrophy with wide brain operculum in the red arrow. E (T1-weighted) showing a sagittal view of the brain with thinning of the corpus callosum in red arrow.

Imaging of the brain in individuals with these conditions reveals cortical atrophy, a slender corpus callosum, cerebellar underdevelopment, and postponed myelination[2].

Most cases with PRUNE1 mutation present with microcephaly. However, in our case, the patient had macrocephaly, which had been previously reported in a Caucasian patient by Imagawa *et al*[8].

The global distribution of reported cases and disease-related genetic variations aligns with the hypothesis of clan genomics. This implies that uncommon genetic variations of notable consequences originating from recent ancestors are more probable factors in disease occurrence compared to prevalent variants with negligible impact on the populace[9].

Factors, including genetic drift within founder populations or consanguineous mating, contribute to the heightened homozygosity of these uncommon alleles within specific populations. For instance, the c.521-2A>G splicing variant has emerged as a founding allele within the Canadian Cree population, illustrating the genetic mechanisms at play. Similarly, the D30N allele, identified in individuals from Saudi Arabia and Oman, appears to be a founding allele within Middle Eastern populations.[9] Table 2 highlights the key differences between our case report and other published cases of PRUNE1 mutations[2,5,7-9].

Rare pathogenic alleles were documented in isolated families worldwide. Notably, the D106N variant is the most frequently reported pathogenic allele in patients with (NMIHBA), appearing across diverse ethnic backgrounds, including Lebanon, Turkey, Italy, Japan, and Sri Lanka. While it seems to be a founding allele within the Turkish population, its widespread occurrence suggests the possibility of the D106 residue serving as a recurring site of mutation, emerging independently within different population haplotypes[5-9].

The management of PRUNE1-related disorders predominantly involved supportive care depending on the patient's symptoms, without a specific treatment strategy. As in the Iranian, Italian, and Turkish cases [5,7]. Symptom management includes physiotherapy for spasticity and a multidisciplinary approach for all other symptoms including developmental ones. The same approach was adopted in other reports of Caucasians, Canadians, Saudi Arabia, and Oman cases [8,9]. For our case, the patient is under regular follow-up, with further interventions potentially informed as the prognosis evolves.

The prognosis across reported cases is generally poor, characterized by progressive neurodevelopmental impairment, significant delays, and limited functional improvement over time. Most cases, including the Iranian[2] and Italian and Turkish patients[5], presented with hypotonia, spastic quadriparesis, and microcephaly, contributing to severe functional limitations. The Caucasian case[8] followed a progressive course with developmental delays, while the Canadian Cree population[9] exhibited similar neurodevelopmental decline. Our case, however, remains novel, with prognosis yet to be determined.

Conclusion

In conclusion, our case contributes to the expanding understanding of PRUNE1-associated disorders, emphasizing the heterogeneity in phenotypic expressions and the global distribution of disease-related genetic variations. The diverse presentations and the identification of potential founder alleles underscore the complexity of the genetic landscape in NMIHBA, providing valuable insights for diagnosis, counseling, and future research endeavors. It's crucial to acknowledge that this disease is still not

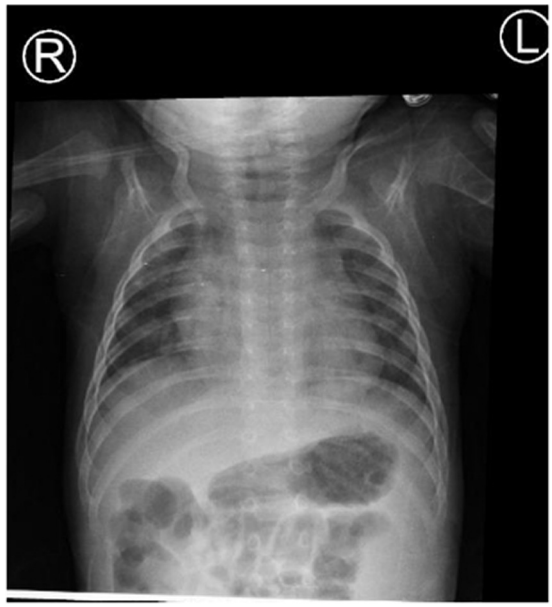

Figure 3. CXR of the patient showed hypo-inflated lungs with no other significant findings.

Table 2

Key differences between our case report and other published cases of PRUNE1 mutations[2,5,7-9]

Feature	Iranian case[2]	Italian & Turkish cases[5]	Imagawa *et al*[8]	Canadian cree population[9]	Saudi Arabia & Oman cases[9]	Our case
Mutation type	Homozygous start loss variant	c.316G>A (p.Asp106Asn)	c.316G>A (p.Asp106Asn)	c.521-2A > G (splicing variant)	D30N (missense variant)	c.316G>A (p.Asp106Asn)
Population documented	Iranian	Italian, Turkish	Caucasian	Canadian Cree	Saudi Arabia, Oman	Palestinian
Clinical features	Neurodevelopmental delay, hypotonia, microcephaly	Developmental delay, intellectual disability, spastic quadriparesis, hypotonia	Developmental delay, hypotonia	Neurodevelopmental delay, spasticity	Neurodevelopmental delay	Developmental delay, macrocephaly, hypotonia, spastic quadriparesis
Imaging findings	Variable brain anomalies	Cortical atrophy, thinning of corpus callosum, delayed myelination	Cortical atrophy, delayed myelination	Cortical and cerebellar atrophy and milder corpus callosum and brainstem atrophy	cortical and cerebellar atrophy and milder corpus callosum and brainstem atrophy	Cortical atrophy, thinning of corpus callosum, delayed myelination
Head size	Microcephaly	Microcephaly	Microcephaly[a]	Microcephaly	Microcephaly	Macrocephaly
Genetic mechanism	Homozygous start loss variant	Rare pathogenic D106N variant, recurrent mutation site	Rare pathogenic D106N variant, recurrent mutation site	Founder allele identified within Cree population	Founder allele identified within Middle Eastern population	Rare pathogenic D106N variant, possible founder mutation in Middle Eastern population

[a]Caucasian case had macrocephaly.

fully understood, highlighting the need for continued research to unravel its complexities and improve therapeutic strategies.

Ethical approval

Not applicable.

Consent

The authors declare that they have obtained all patient consent.

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Author's contributions

All authors have read and approved the final manuscript, and they are responsible for its content.

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The authors declare that they have no competing interests.

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